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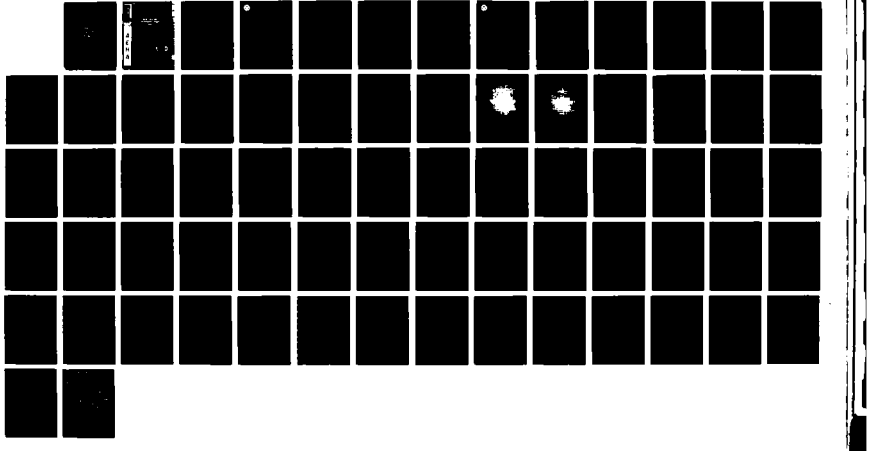

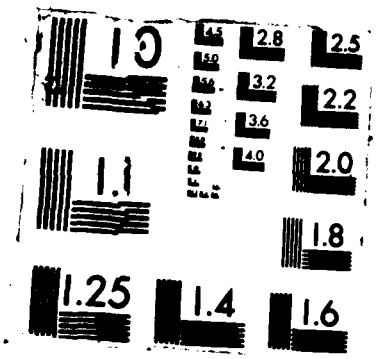
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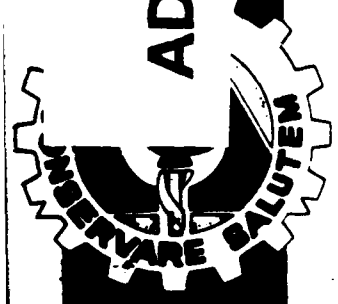

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UNITED STATES ARMY ENVIRONMENTAL HYGIENE AGENCY

ABERDEEN PROVING GROUND, MD 21010-5422

PHASE IV
RANGE FINDING 14-DAY AND 90-DAY SUBCHRONIC FEEDING STUDIES
WITH N,N-DIPROPYLCYCLOHEXANECARBOXAMIDE IN RATS
STUDY NO. 75-51-0233-86
DECEMBER 1986

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19 ABSTRACT (Continue on reverse if necessary and identify by block number) This study was conducted to determine the toxicity of N,N-Dipropylcyclohexanecarboxamide following repeated oral exposure to various doses of the technical grade compound. This evaluation will assist in advising on the health hazards associated with accidental oral exposure to this material. The low food consumption, probably due to the decreased rat body weight in high dose groups created great physiological stress and affected blood clinical chemistry values. Significant increases occurred in male rat liver organ-to-body weight ratios in all three dose levels at the 45 and 90 day necropsies during the 90-day feeding study. A no effect dose was not achieved during this study. Additional testing would be required to confirm a no effect dose level. It is concluded that a toxic hazard may exist from a prolonged significant oral exposure to N,N-Dipropylcyclohexanecarboxamide. It is recommended that further evaluation of this compound as a candidate insect repellent be discontinued due to the deleterious liver involvement caused by N,N-Dipropylcyclohexanecarboxamide at levels as low as 64 mg/Kg in male rats.

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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010-5422

REPLY TO ATTENTION OF

HSHB-MO-T

20 July 1987

Memorandum for: Executive Director, Armed Forces Pest Management Board, Forest Glen Section, Walter Reed Army Medical Center, Washington, DC 20307-5001

SUBJECT: Phase IV, Range Findings 14-Day and 90-Day Subchronic Feeding Studies, with N,N-Dipropylcyclohexanecarboxamide in Rats, Study No. 75-51-0233-86, December 1986

EXECUTIVE SUMMARY

The purpose and a summary of the recommendations of the enclosed report follow:

a. Purpose. This study was conducted to determine the toxicity of N,N-Dipropylcyclohexanecarboxamide following repeated oral exposure to various doses of the technical grade compound. This evaluation will assist in advising on the health hazards associated with accidental oral exposure to this material.

b. Essential Findings. The low food consumption, probably due to the unpalatability of the food mixture, definitely contributed to the decreased rat body weight in high dose groups throughout both studies. The prolonged fasting in the high dose groups created great physiological stress and affected blood clinical chemistry values. Significant increases occurred in male rat liver organ-to-body weight ratios in all three dose levels at the 45 and 90-day necropsies during the 90-day feeding study. A no effect dose was not achieved during this study. Additional testing would be required to confirm a no effect dose level. It is concluded that a toxic hazard may exist from a prolonged significant oral exposure to N,N-Dipropylcyclohexanecarboxamide.

c. Major Recommendations. It is recommended that further evaluation of this compound as a candidate insect repellent be discontinued due to the deleterious liver involvement caused by N,N-Dipropylcyclohexanecarboxamide at levels as low as 64 mg/Kg in male rats.

FOR THE COMMANDER:

for Donald R. Gilray, LTC

N. JOE THOMPSON
Colonel, MC
Director, Occupational and Environmental Health

Encl

CF:
HQDA(DASG-PSP E)(wo/encl)
Dir, Advisory Cen on Tox, NRC (2 cy) (w/encl)
Comdt, AHS, ATTN: HSHA IPM (w/encl)
USDA, ARS, ATTN: Dr. Terrence McGovern (w/encl)
USDA, ARS Southern Region (3 cy) (w/encl)
USDA, ARS Southern Region, ATTN: COL Moussa (w/encl)
Cdr, USAMRDC, ATTN: SGRD DPM/COL Reinert (w/encl)

Study No. 75-51-0233-86, Jun 84 - Dec 86

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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010-5422

REPLY TO ATTENTION OF

HSHB-MO-T

PHASE IV
RANGE FINDING 14-DAY AND 90-DAY SUBCHRONIC FEEDING STUDIES
WITH N,N-DIPROPYLCYCLOHEXANECARBOXAMIDE IN RATS
STUDY NO. 75-51-0233-86
DECEMBER 1986

1. AUTHORITY.

a. Memorandum of Understanding between the US Army Environmental Hygiene Agency; the US Army Health Services Command; the Department of the Army, Office of the Surgeon General; the Armed Forces Pest Management Board; and the US Department of Agriculture, Agricultural Research, Science and Education Administration, titled, Coordination of Biological and Toxicological Testing of Pesticides, effective 23 January 1979.

b. Letter, US Department of Agriculture, AFPCB, Armed Forces Pest Control Board, Washington DC, 9 March 1979 with inclosure thereto.

2. PURPOSE.

a. This 14-Day feeding study was designed to determine the toxicological effects in Sprague Dawley rats from a wide range of doses of the technical grade N,N-Dipropylcyclohexanecarboxamide received orally for a period of 14 days.*† It was designed as a range finding experiment, the results were to provide guidance in planning the dose levels for a subchronic 90-day feeding study.

b. The subchronic study was designed to examine the toxic effects associated with continuous oral exposure to N,N-Dipropylcyclo-hexanecarboxamide in Sprague-Dawley rats over a period of 90 days. It was designed to provide information on target organs, the possibilities of accumulation and for establishing safety criteria for human exposure.

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* In conduction the studies described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," US Department of Health Education and Welfare Publication No. (NIH) 78-23. revised 1978.
† The studies described in this report were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

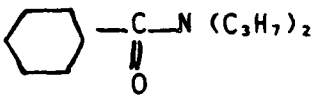
3. BACKGROUND.

a. N,N-Dipropylcyclohexanecarboxamide (AI3-36326) is a candidate insect repellent proposed for use by the US Army (paragraph 1a and 1b, this report). It has shown potential as a substitute or replacement for the current standard insect repellent N,N-diethyltoluamide (M-DET). This candidate insect repellent will be used either for topical application to human skin or as a clothing impregnant. Proposed usage concentrations range from 6.25 percent to 50 percent in liquid or cream formulations and/or aerosol sprays. (reference 1).

b. Previous studies performed by this Agency (reference 2 and 3) showed that technical grade carboxamide was not acutely toxic by ingestion (3,370 mg/Kg males and 2,400 mg/Kg females). Dermal exposure did not cause a phototoxic or skin sensitization reaction. It did produce mild primary skin irritation and slight to mild reversible injury to the cornea and conjunctiva of the eye.

4. MATERIAL AND METHODS.

a. Insect repellent AI3-36326, N,N-Dipropylcyclohexanecarboxamide was synthesized by Terrence P. McGovern, Ph.D., Organic Chemical Synthesis Laboratory, Agricultural Research Center, US Department of Agriculture, Beltsville, MD 20705. It is a light tan liquid with a molecular weight of 209, a chemical formula $C_{13}H_{25}NO$, and a slightly irritating odor. The batch samples "F" and "G" were analyzed upon receipt, using infrared (IR) spectrophotography and gas chromatography (GC) and was found to be free of any significant impurities (Appendix A). The chemical structure of AI3-36326 is as follows:



b. This report and the data generated in these studies are stored in Toxicology Division's files located in Room 3011, Building E2100, Aberdeen Proving Ground, in Edgewood, Maryland.

c. 14-Day Feeding

(1) This 14-day feeding study was performed with rats according to the Toxicology Division standing operating procedure for 14 and 90-Day Feeding Studies. (reference 4).

(2) Certified Purina Formulab Chow 5008 (Appendix B) was used as the diet for all rats in the 14-day feeding study. The feed was ground using a standard Oster® food grinder to a meal size texture and sealed in plastic bags.

(3) Ninety six rats, 48 male and 48 female Sprague Dawley, Caesarean-Derived, Barrier Restrained rats (6 to 8 weeks old) were purchased from Charles River Laboratories, Wilmington, Massachusetts.

(4) Animals were randomly divided into 8 groups of 6 each (male and female). All rats were then sequentially numbered by toe clip (reference 5). Animals were placed in feeding study cages and allowed to acclimate to their surroundings for a period of 19 days before to the test. During the acclimation period animals were allowed ground food and water ad libitum.

(5) Dose levels for the eight test groups of each sex were determined as fractions of the Oral LD_{50} values. Table 1 shows daily doses used for the test.

TABLE 1. PREDICTED DAILY DOSES (14-DAY FEEDING STUDY)

Group No.	Male Rats	Female Rats	Fraction of LD_{50}
1	6,740 mg/Kg	4,800 mg/Kg	2
2	3,370 mg/Kg	2,400 mg/Kg	1
3	1,685 mg/Kg	1,200 mg/Kg	1/2
4	843 mg/Kg	600 mg/Kg	1/4
5	422 mg/Kg	300 mg/Kg	1/8
6	211 mg/Kg	150 mg/Kg	1/16
7	105 mg/Kg	75 mg/Kg	1/32
8	(1 liter acetone)	(1 liter acetone)	Control

(6) Calculations of compound/food mixture were done in accordance with Toxicology Division SOP (reference 4) and recorded in laboratory notebook No. 85. The following is an example of the dosage calculation.

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Dose mg/Kg/day

Avg daily food consumption for female rats as determined during the control period = 15 g/rat/day

$$\frac{15 \text{ g/rat/day}}{0.335 \text{ Kg avg rat weight}} = 44.8 \text{ g/Kg/day}$$

$$\text{Dose} = \frac{1500 \text{ mg/Kg/day}}{44.8 \text{ g/Kg/day}} = 33.5 \text{ mg/g food}$$

67 g compound mixed in 2 Kg food.

This method of calculation was followed for each dose level except the control group which received ground food mixed with acetone only.

(7) The test diet was prepared according to the Toxicology Division SOP (reference 4), by mixing the required amount of test compound added to each 2.0 Kg of food in 1.0 liter of reagent grade acetone. This solution was added to 2.0 Kg of food in a commercial Hobart® food blender and agitated slowly for 15 minutes to be sure of a homogeneous mixture. The acetone was evaporated from the mixture on a steam table. The dry food was sifted through a fine wire mesh to break up any lumps. Prepared food was placed in large glass jars and sealed. Samples of each dose were level collected for analysis to assure proper concentration of test material. Samples from each batch were analyzed using liquid chromatography by the Organic Environmental Chemistry Division, US Army Environmental Hygiene Agency. Ground food and tap water were available ad libitum during the acclimation period and also during the entire study.

(8) There was a staggered introduction of test material to each sex. Test food was given initially to male rats on Monday and to the female rats on Tuesday of the initial test week.

(9) Body weight and food consumption were measured and recorded every other day throughout the 14-day study. At the time of weighing, food and water containers were refilled and reweighed. Animals were observed for signs of toxicity on a daily basis.

(10) On the final days of each study (male and female) blood samples were collected by intracardiac puncture from all rats from each dose group. Tables 2 and 3 list the clinical chemistry and hematological values that were examined on 3 rats from each dose group.

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TABLE 2. CLINICAL CHEMISTRY

SERUM GLUTAMIC OXALOACETIC TRANSAMINASE (SGOT)
SERUM GLUTAMIC PYRUVIC TRANSAMINASE (SGPT)
ALPHA-HYDROXYBUTYRIC DEHYDROGENASE (HBDH)
GLUTAML TRANSPEPTIDASE (GGTP)
ALKALINE PHOSPHATASE
TOTAL LACTIC DEHYDROGENASE (LDH)
BLOOD UREA NITROGEN (BUN)
BILIRUBIN
TOTAL SERUM PROTEIN

TABLE 3. HEMATOLOGY

HEMATOCRIT
HEMOGLOBIN
ERYTHROCYTE COUNT
TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS
PLATELET COUNT

(11) All surviving rats were sacrificed upon completion of the study by decapitation and necropsied. The brain, liver, kidney, testes (male) and spleen were weighed. Organ to body and organ to brain weight ratios were calculated. These organs plus bone marrow, thymus and lymph node, heart, sternum, tibia/femur, vertebra and ovary (females) were saved for histological examination.

d. 90-Day Feeding Study.

(1) This 90-day feeding study was performed in rats according to the Toxicology Division standing operating procedure for 14 and 90-Day Feeding Studies. (reference 4).

(2) NIH07 (rat food) from Agway, Inc. (Appendix A) was ground and used as the diet in this feeding study. The feed was ground using a standard Oster food grinder to a meal size texture and sealed in plastic bags, as in the previous 14-day feeding study.

(3) One hundred and thirty rats, (65 male and 65 female Sprague Dawley, Caesarean-Derived, Barrier Restrained rats (5 to 6 weeks old) were purchased from Charles River Breeding Laboratories, Wilmington, Massachusetts. These animals were randomly divided into test groups of 15 rats each (male and female). All rats were then sequentially numbered by toe clip (reference 5). Animals were placed in feeding study cages and allowed to acclimate to their surroundings for a period of 7-days before the test. During the acclimation period ground food and water were available ad libitum.

(4) Dose levels for the 90-day feeding study were determined from the 14-day preliminary feeding study. The high dose level (3,000 mg/Kg) was the highest expected concentration that would not cause death. The lowest dose level (120 mg/Kg) was the highest dose not expected to cause any effects. The middle dose level (600 mg/Kg) was the lowest dose where any significant weight changes occurred. Dose levels for the four test groups of each sex are listed in Table 4.

TABLE 4. DAILY DOSES (90-DAY FEEDING STUDY)

Group No.	# Male Rats	# Female Rats	Dose
1	15	15	3,000 mg/Kg
2	15	15	600 mg/Kg
3	15	15	120 mg/Kg
4	15	15	Control (acetone only)

(5) Calculations of compound/food mixture were done in accordance with Toxicology Division SOP (reference 5) and are recorded in laboratory notebook No. 99. An example of the dosage calculations can be found in the previous 14-day study (Paragraph 5, section c,(6)). This method of calculation was followed for each dose level except the control group which received ground food plus acetone only.

(6) The test diet was prepared as described in the proceeding 14-day feeding study (Paragraph 5, section c,(7)).

(7) There was a staggered introduction of test material to each sex. Test food was given introduced to male rats on Monday and to the female rats on Wednesday of the initial test week.

(8) Body weight and food consumption were measured and recorded three times a week (Monday, Wednesday and Friday). At the time of weighing, food and water containers were refilled and reweighed. Observations of animals for signs of toxicity were done on a daily basis.

(9) Appropriate action was taken to minimize the loss of animals during this study (e.g., necropsy or refrigeration of animals found dead and isolation or sacrifice of weak or moribund animals).

(10) Urine was collected from selected rats at the midpoint and termination of the study. Rats were randomly selected from each test group and placed in metabolism cages one day before necropsy. The parameters included in the analysis of the urine samples were specific gravity, pH, protein, glucose, ketones, bilirubin and urobilinogen.

(11) On the final days of the study (male and female) blood samples were collected by intracardiac puncture from all rats from each dose group. Tables 2 and 3 list the clinical chemistry and hematological values to be examined on rats from each dose group. The serums from the other rats from each dose group were frozen and saved for possible antibody titer.

(12) Selected rats (five from each test and control group) were necropsied on the 45th day of the study. All surviving rats were necropsied on the 90th exposure day. Animals were sacrificed by decapitation. The brain, liver, kidney, gonads, thymus, and spleen were weighed and organ-to-body weight ratios calculated. The following organs and tissues of each animal were harvested for processing and examination by light microscope (reference 5): all gross lesions, brain (at least 3 levels), eye, pituitary, salivary gland, heart, thyroid (with parathyroid), lungs with mainstem bronchi, lymph node, trachea, esophagus, stomach, small and large intestines, adrenals, pancreas, liver, kidneys. urinary bladder, testes, prostrate, ovaries, corpus and cervix uteri, bone (with marrow) and skeleton muscle. Sections of bone (with marrow when present) were taken from sternebrae, vertebrae, or the tibia-femoral joint (the last was also include attached muscle). Tissue slide preparation and histological examination were done by contract.

5. RESULTS.

a. 14-Day Feeding.

(1) Appendix B is a comparison of the predicted daily doses versus the actual daily doses for the 14-day feeding study. Rats in the highest dose groups lowered their food consumption considerably (Appendix D). The highest male dose group actually received 525 mg/Kg even though they had a predicted dose of 6,740 mg/Kg. The highest female dose group actually received 1,985 mg/Kg even though they had a predicted dose of 4,798 mg/Kg. The unpalatability of the food mixture may have been directly related to this result (paragraph 7, section b).

(2) Test data collected during this 14-day feeding study (body weights, food consumption, organ-to-body weight ratios, organ-to-brain weight ratios and blood chemistry values) were statistically compared with the data from their respective control groups using the Student "t" test at the .05 and .01 levels of significants (Appendix E to I).

(3) The highest test group of male rats (525 mg/Kg) exhibited minimal alopecia appearing about 12 days into the study.

(4) Table 5 displays the survival rate of the male and female rats during the 14-day feeding study.

TABLE 5. RAT SURVIVAL RATE (14-DAY FEEDING STUDY)

Group No.	Male Rats Predicted (Actual) Dose	Deaths/ Total Rats Per Group	Female Rats Predicted (Actual) Dose	Deaths/ Total Rats Per Group
1	6,740 (525) mg/Kg	6/6	4,800 (1,995) mg/Kg	6/6
2	3,370 (1,436) mg/Kg	1/6	2,400 (1,630) mg/Kg	0/6
3	1,685 (1,141) mg/Kg	0/6	1,200 (674) mg/Kg	0/6
4	843 (543) mg/Kg	0/6	600 (389) mg/Kg	0/6
5	422 (247) mg/Kg	0/6	300 (191) mg/Kg	0/6
6	211 (126) mg/Kg	0/6	150 (87) mg/Kg	0/6
7	105 (60) mg/Kg	0/6	75 (43) mg/Kg	0/6
8	(1 liter acetone)	0/6	(1 liter acetone)	0/6

(5) Blood clinical chemistry values (Appendix E) showed significant changes when compared to their respective control groups. These significant changes (SGOT, HBDH, GGTP, and BUN) were also found in the lowest dose group (60 mg/Kg) of the male rats. LDH values in the two highest surviving male groups (1,141 and 1,436 mg/Kg) were significantly decreased compared to the control values. Female rats also exhibited significant decreases in blood LDH values starting at the 300 mg/Kg dose group. These significant blood clinical chemistry changes were not dose related and could not be related to the ingestion of the test material.

(6) Examination of blood hematology values revealed significant changes mainly in the male rat WBC counts compared to control group values (Appendix F). Although these significant variations in the WBC values were found in the male rats as low as 126 mg/Kg they were not dose related.

(7) Significant decreases occurred in mean body weights in the two highest groups of male (1,436 and 525 mg/Kg) and female (1,630 and 1,986 mg/Kg) rats as compared with their controls throughout the study (Appendix G). Significant decreases in body weight also occurred in the male rats at 1,141 mg/Kg and female rats 191 and 674 mg/Kg on day 2 after the initial introduction of test compound.

(8) Significant liver organ-to-body weight ratios and organ-to-brain weight ratios occurred in all male rat test groups starting at 60 mg/Kg dose (Appendix H and I). Significant increases occurred in the female liver organ-to-body weight ratios in the top four dose groups (389, 674, 1,630 and 1,985 mg/Kg). Female rats showed significant organ-to-body

weight ratios as compared to controls for the brain at 1,630 and 1,985 mg/Kg, and for kidney and thymus at 1,985 mg/Kg. Significant female organ-to-brain weight ratios were also seen in kidney, spleen and thymus at 1985 mg/Kg.

(9) There was no consistent pattern of gross necropsy observations which could be associated with compound administration.

(10) The only histopathologic lesions which were considered to be associated with compound administration were in the hematopoietic system, specifically the bone marrow, spleen and thymus (reference 6).

(11) Bone marrow lesions consisted of fatty change, hemorrhage and hematopoietic atrophy. In fatty change, a portion of the marrow cavity was occupied by mature lipocytes, with resultant exclusion of hematopoietic elements. Bone marrow hemorrhage consisted of accumulations of freshly extravasated blood, sometimes to the extent that the entire marrow cavity was filled with blood. Less severe hemorrhages affected smaller areas of the marrow cavity. Hematopoietic atrophy was the term applied to a marrow lesion which involved loss of a substantial percentage of all cell types which are normally present in the marrow. Affected bone marrow was noticeably pancytopenic, with no discernible reduction in any specific cell type.

(12) Splenic lymphoid atrophy consisted of a marked reduction in the cellularity of the lymphoid follicles. Such changes were seen only in males of the two highest dose groups. Rats with splenic changes also exhibited severe hematopoietic atrophy of the bone marrow.

(13) Two of the examined high dose females had lymphoid atrophy of the thymus.

(14) Hematopoietic lesions suspected to be compound-related were seen only in the two highest dose groups (male 1,436 and 525 mg/Kg) (female 1,630 and 1,985 mg/Kg) of both sexes.

b. 90-Day Feeding Study.

(1) Appendix J is a comparison of the predicted daily doses verses the actual daily doses for the 90-day feeding study. Male and female rats in the highest dose groups, reduced their food consumption considerably during the first week of the 90-day study (Appendix K). The unpalatability of the food mixture may have been directly related to this result (paragraph 7, section b). The target doses for the three test groups were reduced one week into the study. Appendix J-1 is a comparison of predicted daily doses versus the actual daily doses during the first week of the 90-day study. Appendix J-2 is a comparison of the predicted daily doses versus the actual daily doses from week two throughout the remainder of the 90-day study.

(2) Test data collected during this 90-day feeding study (body weight, organ-to-body weight ratios, organ-to-brain weight ratios and blood chemistry values) were statistically compared with the data from their respective control groups using the Student "t" test at the .05 and .01 levels of significants (Appendix L to P).

(3) Table 6 displays the survival rate of the male and female rats during the 90-day feeding study.

(4) Blood clinical chemistry values (Appendix L) at the 45-day and 90-day examinations demonstrated some significant changes when compared to their respective control groups. Although changes were not dose related, the major deviations (HBDH, GGTP, ALK PHOS, LDH, BUN and Bilirubin) occurred in the high dose male (1,192 mg/Kg) and the high dose female (1,330 mg/Kg) rats. Significant changes were also seen at 90-days in SGOT, HBDH and BUN in the males and BUN and Bilirubin values in the females at 300 mg/Kg.

(5) The blood hematology values revealed no dose related significant changes in either the 45-day or 90-day female or 45-day male rats (Appendix M). The hematology values (Hct, Hgb, and RBC) of the 90-day males were significantly decreased in all three dose groups (64, 352 and 1,192 mg/Kg) when compared with their respective controls.

TABLE 6. RAT SURVIVAL RATE (90-DAY FEEDING STUDY)

Group No.	Male Rats Predicted (Actual) Dose	Deaths/ Total Rats Per Group	Female Rats Predicted (Actual) Dose	Deaths/ Total Rats Per Group
1	1,500 (1,192) mg/Kg	3/15*	1,500 (1,330) mg/Kg	0/15
2	300 (352) mg/Kg	0/15	300 (367) mg/Kg	0/15
3	60 (64) mg/Kg	0/15	60 (88) mg/Kg	0/15
4	(1 liter acetone)	1/15**	(1 liter acetone)	0/15

* Deaths occurred during the first week of 90-day Study.
** Rat found dead with head stuck in feeder.

(6) Three male rats died during the first week of the 90-day study. This was caused by the rats drastic decrease in food consumption The only toxic signs exhibited after the first week of the 90-day study were weight loss and slight alopecia. A significant decrease in body weight occurred in the high dose (1,192 mg/Kg) male rats starting

immediately following the introduction of test food and the medium dose (352 mg/Kg) on day +2 and +21, then starting again on day +26 and continuing throughout the 90-day study (Appendix N). Female rats showed a significant decrease in body weight in the high dose group (1,330 mg/Kg) starting immediately following the introduction of the test material and continuing throughout the study. These decreases in rat body weights can be directly correlated with decreased food consumption primarily during the first week of the study (Appendix K-1 and K-4).

(7) Dose related significant increases in liver organ-to-body weight ratios (Appendix O) occurred in all three male rat test groups at both the 45 and 90-day necropsies. These dose related increases were also seen in liver organ-to-brain weight ratios (Appendix P) in the medium and high (352 and 1,192 mg/Kg) 45-day and all three (64, 352 and 1,192 mg/Kg) 90-day male rat test groups. Significant brain and testes organ-to-body weight ratio increases at 45-day and brain, kidney and testes at 90-day occurred in the high dose male rats. These significant increases were also found in the high dose (1,330 mg/Kg) female brain and kidney organ-to-body weight ratios at the 45 and 90-day necropsies. Aside from the liver organ-to-brain ratios, only the female spleen organ-to-brain weight ratio in the high dose (1,330 mg/Kg) 90-day necropsy was significantly decreased compared to its control group.

(8) Urinalysis values were unremarkable and showed no significant dose related changes.

(9) There was no consistent pattern of gross necropsy observations which could be associated with compound administration.

(10) A large percentage of animals from both the 45- and 90-day sacrifices had mild centrilobular cytomegaly in the liver. This change consists of enlargement and tinctorial alteration of the centrilobular hepatocytes. The change included no overt evidence of necrosis. The highest incidence of centrilobular cytomegaly was seen in the highest dose groups, with an apparent dose-associated lower incidence in the lower dose groups (reference 7).

(11) Lymphoid depletion was seen in the thymus and spleen of a small number of rats, sacrificed at 45-days, in the high dose groups (1,192 mg/Kg male and 1,330 mg/Kg female) (reference 7).

(12) The kidneys of a few rats had interstitial infiltrations of lymphocytes and plasma cells, sometimes associated with atrophy of tubular epithelium and very mild interstitial fibroplasia. The lesions were graded as minimal in all cases, but there was an increased incidence in the dosed males of both the 45- and 90-day studies (reference 7).

6. DISCUSSION.

a. Throughout the 14- and 90-day feeding studies, it was difficult to successfully reach the predicted oral exposure of N,N-Dipropylcyclohexanecarboxamide in the high dose groups. This test material was not found to be acutely toxic by ingestion. The male and female oral LD^{50} values were 3,370 mg/Kg for male rats and 2,400 mg/Kg for female rats (reference 3). It was difficult to add sufficient test compound to the food during the feeding studies to reach the target oral doses. As the rats increased in weight and the addition of larger quantities of compound was necessary, the rats decreased their food consumption significantly.

b. The low food consumption due to the unpalatability of the food mixture definitely contributed to the significant differences in rat body weight gain in the high dose groups of the preliminary 14-day and the subchronic 90-day feeding studies. Prolonged fasting has also been shown to create great stress and affect blood clinical chemistry values. (reference 8)

c. The hepatic centilobular cytomegaly seen following the 90-day study was similar to that seen following administration of compounds which induce enzyme systems in the liver (reference 7). During the preliminary assessment of the relative toxicity of N,N-Dipropylcyclohexanecarboxamide (reference 3) evidence was also found suggesting the induction of microsomal enzymes by the action of this compound on the liver. The changes seen in the present study were considered to represent an adaptation on the part of the liver, rather than a degenerative change per se.

d. The kidney lesions found in the males rats sacrificed at 45- and 90-days, suggest that exposure to N,N-Dipropylcyclohexanecarboxamide may increase the incidence nephropathy (reference 7).

e. The lymphocytic changes seen in the thymus and spleen of intercurrent death rats were similar to those seen following severe stress, (reference 8) thus the lymphoid depletion/lymphocytolysis seen in the present study cannot be attributed to a direct effect of the compound. Rats which survived to termination of the study had no detectable residual lesions in the thymus or spleen.

7. CONCLUSION.

a. Food consumption decreased in the high dose rats causing a drastic decrease in body weight gain during the 14- and 90-day studies. This was probably due to the unpalatability of the compound food mixture.

b. Significant increases occurred in male rat liver organ-to-body weight ratios in all three dose levels at the 45- and 90-day necropsy during the 90-day feeding study. A no effect dose was not achieved during this study. Additional testing would be required to confirm a no effect dose level.

c. It is concluded that a toxic hazard may exist from an extended oral exposure to the candidate insect repellent N,N-Dipropylcyclohexanecarboxamide.

8. RECOMMENDATIONS. The following recommendations are based upon professional judgement of the investigators. Recommend discontinuation of further evaluation of this compound as a candidate insect repellent due to the deleterious liver involvement caused by N,N-Dipropylcyclohexanecarboxamide at levels as low as 64 mg/Kg.

9. REFERENCE. See Appendix Q for a listing of references.

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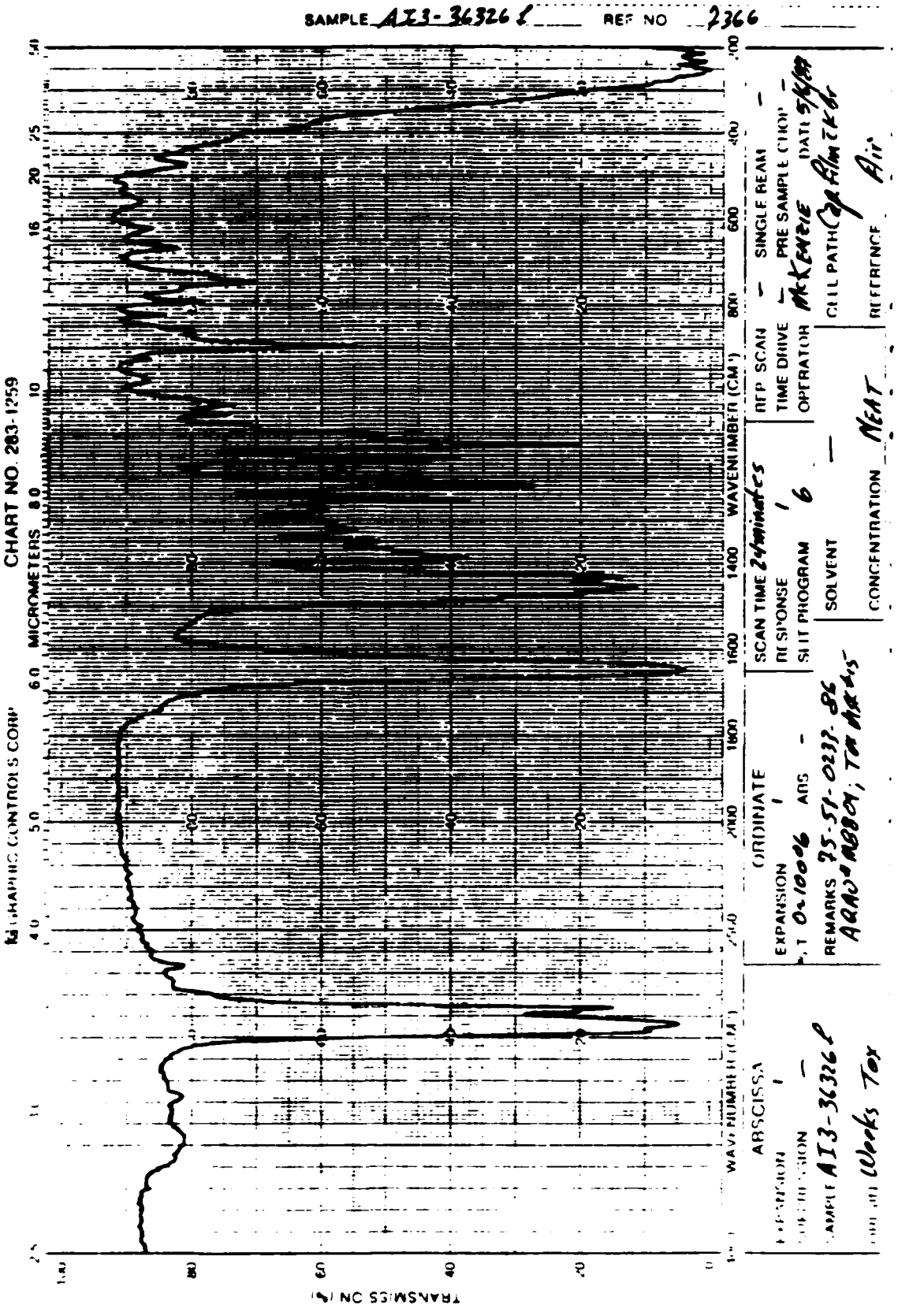
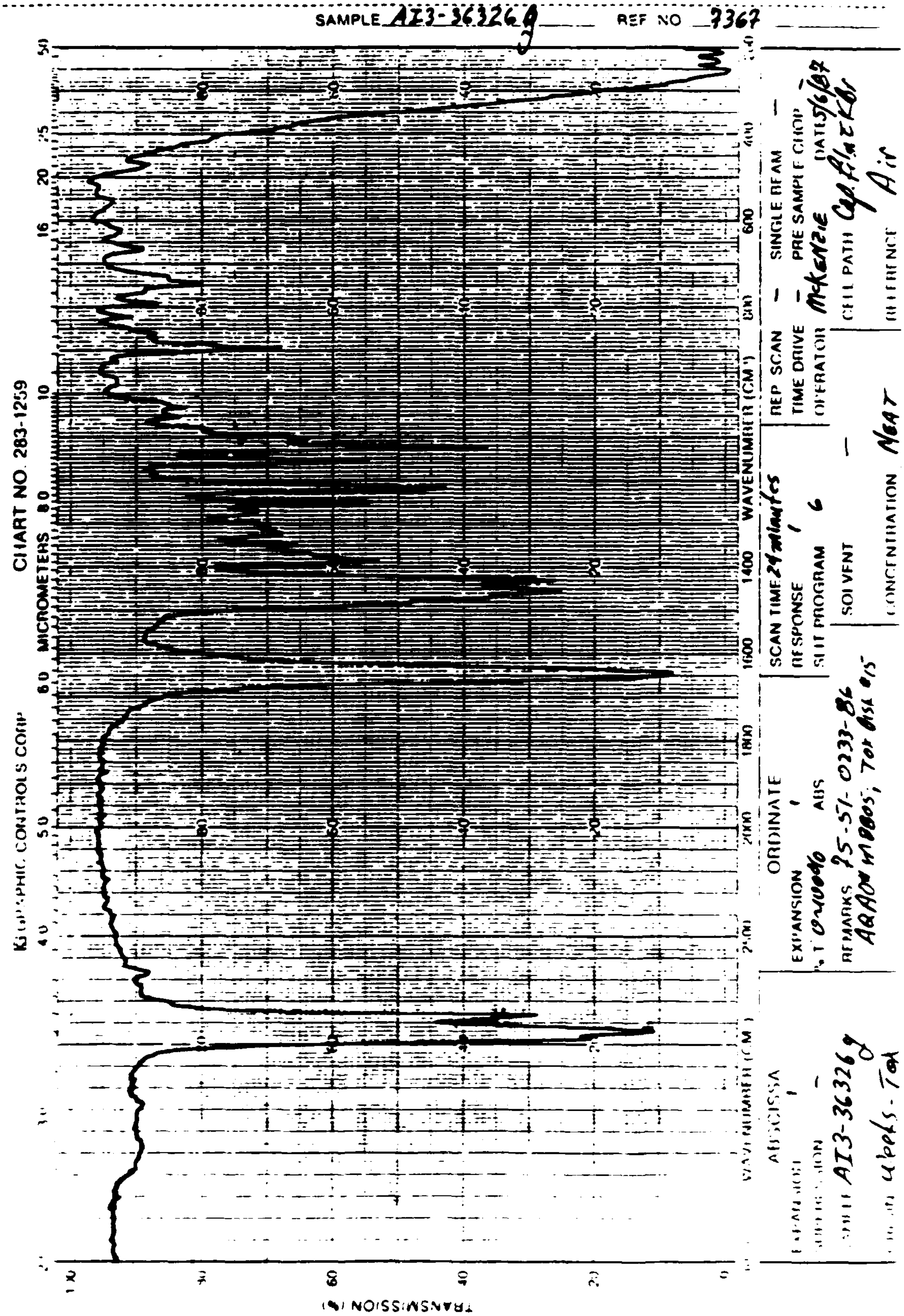
APPENDIX A

SAMPLE ANALYSIS USING INFRARED SPECTROPHOTOGRAPHY AND GAS CHROMATOGRAPHY


SAMPLE AI3-36326 ℓ
REF NO 2366
CHART NO. 283-1259
MICROMETERS
WAVENUMBER (CM⁻¹)
TRANSMISSION (%)
ABSCISSA
EXPANSION 1
ORDINATE
EXPANSION 1
SCAN TIME 24minutes
RESPONSE 1
SLIT PROGRAM 6
SOLVENT —
CONCENTRATION NEAT
REMARKS 75-51-0233-86 AGNOSTOG; TM Works
REP SCAN — SINGLE BEAM —
TIME DRIVE — PRE SAMPLE CHOP —
OPERATION McKenzie DATE 5/6/87
CELL PATH 6x Alum Tekk
REFERENCE Air


SAMPLE AI3-36326g
REF NO 7367
CHART NO. 283-1259
MICROMETERS
WAVENUMBER (CM⁻¹)
TRANSMISSION (%)
ORDINATE
ABSCISSA
SCAN TIME 24 minutes
RESPONSE
SLIT PROGRAM 6
SOLVENT
CONCENTRATION NEAT
REP SCAN
TIME DRIVE
OPERATOR McKenzie
SINGLE BEAM
PRE SAMPLE CHOP
CELL PATH Cap film KBr
REFERENCE Air
REMARKS 75-51-0233-86

APPENDIX B

STANDARD RAT CHOW
(LABEL INFORMATION)

NIH 07
Stock No. 63-8760
Bid No. 263-84-B(81)-0071
NiH-11-133i
GUARANTEED ANALYSIS

Crude Protein (min)	23.5%
Crude Fat (min)	4.5%
Crude Fiber (max)	4.5%

INGREDIENTS

Ground #2 yellow shelf corn, ground hard winter wheat, soy bean meal, fish meal, wheat midlings, dried skimmed milk, alfalfa meal, corn gluten meal, vegetable oil, brewers dried yeast, dried molasses, dicalcium phosphate, salt, vitamin A acetate, D-activated animal sterol (source of vitamin D3), vitamin E supplement, choline chloride, niacin, riboflavin, menadione sodium bisulfate complex (source of vitamin K activity), pyridoxine hydrochloride, thiamine mononitrate, calcium pantothenate, folic acid, biotin, vitamin b_{12} supplement, iron sulfate, manganous oxide, zinc oxide, copper sulfate, calcium iodate, cobalt carbonate.

NET WEIGHT 50 LBS.

Manufactured by
AGWAY, INC.
St. Marys, Ohio 45885

APPENDIX C

PREDICTED VERSUS ACTUAL DAILY DOSES (14-DAY FEEDING STUDY)

	Dose Male Rats mg/Kg/day		Dose Female Rats mg/Kg/day	
	Predicted	Actual	Predicted	Actual
1	6,744	525	4,798	1,985
2	3,372	1,436	2,399	1,630
3	1,686	1,141	1,200	674
4	843	543	600	389
5	422	247	300	191
6	211	126	150	87
7	105	60	75	43
8	Control	(acetone only)	Control	(acetone only)

APPENDIX D

FOOD CONSUMPTION (MALE RATS)
(14-DAY FEEDING STUDY)
g/rat/day

Dose (mg/Kg) Predicted (Actual)	Day -7 to -3	Day -3 to 0	Day 0 to 2	Day 2 to 4	Day 4 to 6	Day 6 to 8	Day 8 to 10	Day 10 to 12	Day 12 to 14
CONTROL	13.54	18.89	19.17	18.92	19.75	19.58	18.50	19.08	18.00
105 (60)	15.17	19.83	19.74	18.58	20.17	18.58	20.00	20.50	20.08
211 (126)	14.21	19.78	18.42	19.17	20.25	19.33	20.17	20.25	20.50
422 (247)	13.17	17.89	16.00	19.50	19.25	18.42	19.58	20.00	19.08
843 (543)	13.92	20.44	17.50	23.42	23.33	23.33	21.92	23.08	22.67
1,686 (1,141)	13.33	19.17	*	17.50	20.92	22.25	20.75	21.58	20.33
3,372 (1,436)	14.96	20.67	3.75	9.92	12.92	15.50	18.80	18.60	17.60
6,744 (525)	13.50	18.67	*	2.50	.75	4.75	.75	DEAD	0

* Missing Value

APPENDIX D

FOOD CONSUMPTION (FEMALE RATS)
(14-DAY FEEDING STUDY)
g/rat/day

Dose (mg/Kg) Predicted (Actual)		Day -8 to -4	Day -4 to 0	Day 0 to 2	Day 2 to 4	Day 4 to 6	Day 6 to 8	Day 8 to 10	Day 10 to 12	Day 12 to 14
CONTROL		14.33	14.46	14.42	13.42	15.33	14.00	15.58	14.50	14.42
75	(43)	12.04	13.13	12.83	12.67	13.17	12.08	13.33	13.42	14.00
150	(87)	14.08	15.29	14.33	13.83	15.08	13.42	15.00	13.58	15.83
300	(191)	10.17	15.58	13.92	14.25	14.08	16.00	15.75	13.83	15.08
600	(389)	15.00	14.25	10.25	17.33	17.00	15.50	16.83	16.00	16.33
1,200	(674)	13.29	13.33	5.17	13.33	15.08	14.08	13.83	13.75	13.75
2,399	(1,630)	12.25	15.21	12.33	11.67	15.58	13.83	13.33	15.25	13.83
4,798	(1,985)	*	14.46	2.58	9.08	12.33	8.08	8.75	10.90	13.25

* Missing Value

APPENDIX E

CLINICAL CHEMISTRY (MALE RATS)
(14-DAY FEEDING STUDY)

Dose (mg/Kg) Predicted (Actual)		SGOT IU/l	SGPT IU/l	HBDH IU/l	GGTP IU/l	ALK PHOS IU/l	LDH IU/l	BUN mg/dl	BLRBN mg/dl	TSP g/dl
CONTROL	x	340.67	42.67	589.00	0	379.33	1861.00	22.17	.80	7.42
	sd	100.95	8.08	137.36	0	79.32	234.34	.67	.10	.59
105	x	163.33	40.00	1006.67	4.33	638.33	1472.00	17.50	.60	7.55
(60)	sd	25.79	1.73	116.50	1.53	173.07	263.01	.56	.17	.32
	t	2.59*	.56	4.02*	4.91**	2.36	1.91	9.31**	1.73	.33
	df	4	4	4	4	4	4	4	4	4
211	x	195.00	47.00	820.67	8.00	487.00	1294.33	18.70	.60	7.75
(126)	sd	73.70	6.56	136.93	3.61	87.57	537.92	2.52	.17	.37
	t	2.02	.72	2.07	3.84*	1.58	1.67	2.31	.23	.84
	df	4	4	4	4	4	4	4	4	4
422	x	405.67	46.67	608.00	8.33	501.00	1691.67	19.03	.57	7.74
(247)	sd	162.72	7.77	362.89	7.09	93.40	226.89	1.80	.29	.32
	t	.59	.62	.08	2.03	1.72	.90	2.83*	.31	.83
	df	4	4	4	4	4	4	4	4	4
843	x	161.33	38.67	978.67	4.33	486.67	1235.67	19.97	.43	7.48
(543)	sd	.58	3.51	91.13	.58	111.79	388.60	1.82	.06	.09
	t	3.08*	.79	4.09*	13.00**	1.36	2.39	1.96	4.63**	.17
	df	4	4	4	4	4	4	4	4	4
1,686	x	164.67	38.67	756.33	6.33	455.33	725.33	18.97	.50	7.77
(1,141)	sd	39.15	4.93	132.26	1.53	75.72	152.13	3.10	.00	.47
	t	2.82*	.73	1.52	7.18**	1.20	7.04**	1.75	5.20**	.82
	df	4	4	4	4	4	4	4	4	4
3,372	x	153.00	43.33	598.00	12.00	554.00	523.00	16.13	.73	7.57
(1,436)	sd	39.60	4.93	344.07	6.93	159.29	250.28	2.05	.15	.17
	t	2.41	.12	.04	3.00**	1.70	6.71**	4.85**	.63	.90
	df	4	4	4	4	4	4	4	4	4

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX E

CLINICAL CHEMISTRY (FEMALE RATS)
(14-DAY FEEDING STUDY)

Dose (mg/Kg) Predicted (Actual)		SGOT IU/l	SGPT IU/l	HBDH IU/l	GGTP IU/l	ALK PHOS IU/l	LDH IU/l	BUN mg/dl	BLRBN mg/dl	TSP g/dl
CONTROL	x	149.67	44.33	930.67	2.33	384.67	1160.67	23.87	.47	7.68
	sd	17.95	1.53	69.41	2.52	99.38	103.85	2.31	.06	.33
75	x	287.33	44.33	773.67	3.67	392.33	1121.67	23.03	.63	8.37
(43)	sd	135.31	4.04	200.40	6.35	44.52	149.00	3.21	.15	.25
	t	1.75	.00	1.28	.34	.12	.37	.37	1.77	2.89*
	df	4	4	4	4	4	4	4	4	4
150	x	210.67	40.67	910.67	.67	469.00	930.67	21.57	.57	7.82
(87)	sd	13.65	10.69	102.48	.58	163.59	278.70	2.42	.21	.52
	t	4.68**	.59	.28	1.12	.76	1.34	1.19	.80	.37
	df	4	4	4	4	4	4	4	4	4
300	x	210.00	38.67	868.00	4.67	383.00	743.00	19.10	.43	8.08
(191)	sd	33.00	5.51	137.83	4.73	91.03	228.28	2.10	.15	.27
	t	2.78*	1.72	.70	.75	.02	2.88*	2.65	1.27	1.61
	df	4	4	4	4	4	4	4	4	4
600	x	113.67	33.67	760.00	0	398.00	633.67	16.37	.40	7.51
(389)	sd	14.57	2.08	108.04	0	91.89	51.55	.95	.00	.66
	t	2.70	7.16**	2.30	1.61	.17	7.87**	5.21**	2.00	.42
	df	4	4	4	4	4	4	4	4	4
1,200	x	192.67	36.67	907.33	3.00	420.00	865.00	17.50	.40	7.81
(674)	sd	45.94	2.52	123.33	1.00	91.85	274.07	2.33	.00	.65
	t	1.51	4.51*	.29	.43	.45	1.75	3.37*	2.00	.30
	df	4	4	4	4	4	4	4	4	4
2,399	x	210.67	39.00	794.00	12.00	377.33	856.00	17.40	.57	7.55
(1,630)	sd	125.30	13.53	101.15	3.61	50.12	191.28	3.48	.21	.54
	t	.83	.68	1.93	3.81*	.11	2.42	2.68	.80	.36
	df	4	4	4	4	4	4	4	4	4
4,798	x	193.50	47.50	792.50	33.50	462.50	663.50	23.15	.65	7.33
(1,985)	sd	88.39	6.36	239.71	.71	150.61	150.61	.07	.07	.23
	t	.90	.89	1.01	16.39**	.72	4.48*	.42	3.22*	1.29
	df	3	3	3	3	3	3	3	3	3

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX F

HEMATOLOGY (MALE RATS)
(14-DAY FEEDING STUDY)

Dose (mg/Kg) Predicted (Actual)		Hct %	Hgb g/dl	RBC $10^6/mm^3$	WBC $10^3/mm^3$	MCV u^3
CONTROL	x	41.36	15.04	7.23	7.32	56.80
	sd	2.36	.66	.41	.90	.84
105	x	38.83	14.87	6.75	7.00	57.00
(60)	sd	.74	.61	.32	2.56	1.73
	t	1.75	.37	2.04	.27	1.36
	df	6	6	6	6	6
211	x	39.50	15.27	6.98	10.73	56.67
(126)	sd	1.82	.60	.35	2.25	.58
	t	1.16	.48	1.18	3.13*	.24
	df	6	6	6	6	6
422	x	39.00	14.30	6.90	11.17	56.67
(247)	sd	1.25	.17	.13	3.16	1.53
	t	1.57	1.84	1.66	2.68*	.16
	df	6	6	6	6	6
843	x	41.30	15.07	6.92	12.00	60.00
(543)	sd	2.12	.84	.38	.36	.00
	t	.04	.05	1.37	8.40**	6.41**
	df	6	6	6	6	6
1,686	x	35.10	15.43	7.21	13.53	57.00
(1,141)	sd	18.00	.45	.25	6.38	.00
	t	.81	.90	.41	2.27	.40
	df	6	6	6	6	6
3,372	x	40.53	14.83	7.08	11.70	57.67
(1,436)	sd	1.31	.55	.25	3.10	1.53
	t	.55	.45	.88	3.10*	1.06
	df	6	6	6	6	6
6,744	x	All animals dead at conclusion of study				
(525)	sd					
	t					
	df					

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX F

HEMATOLOGY (FEMALE RATS)
(14-DAY FEEDING STUDY)

Dose (mg/Kg) Predicted (Actual)		Hct %	Hgb g/dl	RBC 10^6/mm^3	WBC 10^3/mm^3	MCV u^3
CONTROL	x	37.97	12.73	6.80	12.70	56.00
	sd	.75	4.02	.12	2.87	1.00
75	x	39.63	15.33	7.03	8.93	56.33
(43)	sd	1.44	.64	.35	1.56	1.15
	t	1.78	1.11	1.06	2.00	.38
	df	4	4	4	4	4
150	x	38.23	14.63	6.80	7.03	56.67
(87)	sd	1.33	.40	.17	3.67	2.08
	t	.30	.82	.06	2.11	.50
	df	4	4	4	4	4
300	x	37.33	14.77	6.73	7.53	56.00
(191)	sd	1.59	.31	.16	2.02	2.00
	t	.62	.87	.60	2.55	.00
	df	4	4	4	4	4
600	x	37.73	14.87	6.80	8.43	56.33
(389)	sd	1.00	.46	.30	1.27	1.15
	t	.32	.91	.04	2.35	.38
	df	4	4	4	4	4
1,200	x	37.97	14.93	6.80	11.[illegible]	56.33
(674)	sd	1.50	.61	.30	2.18	1.53
	t	.00	.94	.02	.40	.38
	df	4	4	4	4	4
2,399	x	40.30	16.15	7.14	14.80	56.50
(1,630)	sd	2.26	.64	.30	2.97	.71
	t	1.77	1.13	1.80	.79	.60
	df	3	3	3	3	3
4,798	x	35.60	16.25	6.68	14.75	54.00
(1,958)	sd	2.40	.78	.56	1.34	1.41
	t	1.71	1.16	.42	.91	1.90
	df	3	3	3	3	3

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX G

MEAN BODY WEIGHT (MALE RATS)
(14-DAY FEEDING STUDY)

Dose (mg/Kg) Proposed (Actual)		Day -10	Day -7	Day -3	Day 0	Day +2	Day +4	Day +6	Day +8	Day +10	Day +12	Day +14
CONTROL	x	187.83	204.33	231.00	253.83	268.00	276.00	290.83	302.17	311.00	318.00	327.33
		5.08	8.36	10.20	13.93	14.25	14.99	16.64	17.52	17.40	19.70	21.31
105	x	191.17	210.83	240.00	264.00	282.17	291.00	308.33	318.50	329.17	342.00	353.00
(60)	sd	16.47	16.04	17.81	17.72	18.00	20.43	20.85	21.16	22.33	23.84	23.58
	t	.47	.88	1.07	1.12	1.51	1.45	1.61	1.46	1.57	1.90	1.98
	df	10	10	10	10	10	10	10	10	10	10	10
211	x	193.00	209.83	235.50	258.67	271.17	281.00	295.50	304.17	315.33	323.67	335.83
(126)	sd	10.13	12.06	13.49	16.35	17.49	20.85	23.10	21.32	20.13	22.75	23.58
	t	1.11	.92	.65	.56	.34	.48	.40	.18	.40	.46	.65
	df	10	10	10	10	10	10	10	10	10	10	10
422	x	191.67	207.00	230.33	252.17	262.33	271.67	287.33	295.33	305.33	314.50	339.33
(247)	sd	12.64	16.15	16.40	17.59	20.53	21.04	23.04	22.51	24.37	23.95	36.74
	t	.69	.36	.08	.18	.56	.41	.30	.59	.46	.28	.69
	df	10	10	10	10	10	10	10	10	10	10	10
843	x	196.83	213.00	241.33	268.33	276.67	291.17	308.00	321.00	329.50	341.33	351.50
(543)	sd	10.52	11.61	8.43	11.93	13.08	12.84	17.75	15.39	18.85	16.45	16.45
	t	1.89	1.48	1.91	1.98	1.10	1.88	1.73	1.98	1.87	2.23*	2.20
	df	10	10	10	10	10	10	10	10	10	10	10
1,686	x	184.67	201.33	227.50	256.83	234.83	254.33	272.50	287.33	294.67	304.83	310.17
(1,141)	sd	14.43	17.93	15.54	15.18	14.08	20.54	16.60	14.92	18.77	21.61	22.89
	t	.51	.37	.46	.36	4.06	2.09	1.91	1.58	1.56	1.10	1.34
	df	10	10	10	10	10	10	10	10	10	10	10
3,372	x	193.50	212.17	241.50	263.33	230.17	224.83	230.83	233.00	253.40	256.00	262.20
(1,436)	sd	11.31	13.50	13.03	11.52	14.59	27.92	42.25	46.78	33.22	31.73	34.04
	t	1.12	1.21	1.55	1.32	4.54**	3.95**	3.24**	3.39**	3.71**	3.98**	3.88**
	df	10	10	10	10	10	10	10	10	9	9	9
6,744	x	190.00	205.67	231.83	254.67	221.83	202.67	186.50	169.00	167.75	158.00	DEAD
(525)	sd	10.20	12.97	15.45	9.79	9.97	10.27	10.13	14.39	7.41	1.41	
	t	.47	.21	.11	.12	6.50**	9.88**	13.12**	14.39**	15.32**	10.98**	
	df	10	10	10	10	10	10	10	10	8	6	

* Significantly different than controls (P-0.05)
** Significantly different than controls (P 0.01)
x Mean
sd Standard deviation
t t value
df degrees of freedom

APPENDIX G

MEAN BODY WEIGHT (FEMALE RATS)
(14 DAY FEEDING STUDY)

Dose (mg/Kg) Proposed (Actual)		Day 10	Day 7	Day 3	Day 0	Day +2	Day +4	Day +6	Day +8	Day +10	Day +12	Day +14
CONTROL	·	139.17	147.00	162.67	175.33	185.50	187.17	195.33	197.67	206.17	209.00	215.50
		2.64	3.74	2.73	4.68	4.68	5.98	5.72	5.65	5.53	6.96	7.23
75	·	135.67	141.17	153.17	164.83	172.17	176.33	181.00	184.50	190.33	195.50	200.67
(43)	sd	6.56	9.54	12.54	15.66	16.88	19.19	17.16	21.73	22.52	24.79	26.48
	t	1.21	1.39	1.81	1.57	1.86	1.32	1.94	1.44	1.67	1.28	1.32
	df	10	10	10	10	10	10	10	10	10	10	10
150	·	144.33	151.83	168.17	182.00	189.17	191.67	199.50	202.67	212.83	212.83	223.50
(87)	sd	9.75	10.65	8.70	7.04	9.06	6.65	8.50	9.16	10.63	10.07	13.20
	t	1.25	1.05	1.48	1.93	.88	1.23	1.00	1.14	1.36	.77	1.30
	df	10	10	10	10	10	10	10	10	10	10	10
300	·	134.67	141.33	148.17	168.83	174.33	178.67	183.67	188.33	196.50	198.17	204.17
(191)	sd	10.46	9.75	17.42	9.11	8.80	8.73	7.31	8.41	9.40	7.85	11.48
	t	1.02	1.33	2.01	1.56	2.74*	1.97	3.08*	2.26*	2.17	2.68*	2.85
	df	10	10	10	10	10	10	10	10	10	10	10
600	·	141.33	144.17	163.00	179.50	178.00	185.17	192.50	197.50	205.17	208.33	214.67
(389)	sd	9.58	23.09	15.90	16.77	13.81	14.91	13.61	16.40	13.53	16.01	14.62
	t	.53	.30	.05	.59	1.26	.31	.47	.02	.17	.09	.13
	df	10	10	10	10	10	10	10	10	10	10	10
1,200	·	133.67	145.50	160.00	173.17	164.67	176.17	180.83	186.67	192.67	195.33	200.50
(674)	sd	10.89	12.10	11.87	12.54	10.44	13.26	15.01	15.63	15.91	15.42	16.71
	t	1.20	.29	.54	.40	4.46**	1.85	2.21	1.62	1.96	1.98	2.02
	df	10	10	10	10	10	10	10	10	10	10	10
2,399	·	143.83	149.67	160.00	176.50	156.00	157.33	159.83	163.00	167.67	172.83	175.00
(1,630)	sd	6.05	5.05	9.12	7.31	6.03	6.31	7.49	7.40	10.07	13.29	13.99
	t	1.73	1.04	.69	.33	9.46**	8.40**	9.23**	9.12**	8.21**	5.91**	6.30**
	df	10	10	10	10	10	10	10	10	10	10	10
4,798	·	138.50	145.33	Missing	168.83	146.67	139.33	132.33	129.17	121.67	129.80	140.80
(1,985)	sd	6.92	7.61	Value	7.00	7.20	11.83	14.62	22.57	24.22	28.50	28.61
	t	.22	.48		1.89	11.08**	8.84**	9.83**	7.21**	8.33**	6.64**	8.44**
	df	10	10		10	10	10	10	10	10	9	8

* Significantly different than controls (P 0.05)
** Significantly different than controls (P 0.01)
· Mean
sd Standard deviation
t t value
df degrees of freedom

APPENDIx H

ORGAN-TO-BODY WEIGHT RATIOS
(MALE RATS)
(14 DAY FEEDING STUDY)

Dose (mg/Kg) Predicted (Actual)		Terminal Body Weights(Kg)	Mean Organ-to-Body Weight Ratios(gms/100gms body weight) BRAIN	KIDNEYS	LIVER	SPLEEN	TESTES	THYMUS
CONTROL	x	327.33	.61	.73	3.64	.20	.89	.17
	sd	21.31	.05	.10	.21	.01	.07	.05
105	x	353.00	.56	.71	3.95	.21	.86	.23
(60)	sd	23.58	.06	.04	.19	.01	.10	.03
	t	1.98	1.39	.45	2.66*	2.13	.61	2.49*
	df	10	10	10	10	10	10	10
211	x	335.83	.59	.76	4.25	.19	.91	.23
(126)	sd	23.58	.04	.08	.23	.03	.09	.04
	t	.65	.73	.58	4.79**	.28	.30	2.60*
	df	10	10	10	10	10	10	10
422	x	339.33	.60	.75	4.29	.20	.94	.23
(247)	sd	36.74	.05	.11	.57	.03	.13	.05
	t	.69	.42	.28	2.61*	.64	.76	2.41*
	df	10	10	10	10	10	10	10
843	x	351.50	.57	.77	5.05	.20	.94	.18
(543)	sd	16.45	.03	.05	.50	.02	.14	.05
	t	2.20	1.49	.83	6.30*	.59	.66	.44
	df	10	10	10	10	10	10	10
1,686	x	310.17	.64	.78	5.68	.19	.97	.22
(1,141)	sd	22.89	.05	.02	.32	.03	.07	.04
	t	1.34	1.38	1.19	12.88**	.28	1.87	2.12
	df	10	10	10	10	10	10	9
3,372	x	262.20	.70	.88	6.42	.18	.98	.17
(1,436)	sd	34.04	.13	.14	1.09	.04	.13	.04
	t	3.88**	1.55	2.00	6.14**	1.14	1.43	.00
	df	9	9	9	9	9	9	9
6,744	x	All Animals Dead						
(525)	sd							
	t							
	df							

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX H

ORGAN-TO-BODY WEIGHT RATIOS
(FEMALE RATS)
(14-DAY FEEDING STUDY)

Dose (mg/Kg) Predicted (Actual)		Terminal Body Weights	Mean Organ-to-Body Weights(gms/100gms body weight) BRAIN	KIDNEYS	LIVER	SPLEEN	THYMUS
CONTROL	x	215.50	.85	.75	3.97	.23	.27
	sd	7.23	.04	.06	.13	.04	.04
75	x	200.67	.92	.76	3.89	.24	.27
(43)	sd	26.48	.12	.05	.28	.05	.03
	t	1.32	1.47	.35	.63	.28	.34
	df	10	10	10	10	10	10
150	x	223.50	.86	.79	3.98	.22	.30
(87)	sd	13.20	.06	.08	.14	.03	.04
	t	1.30	.40	1.06	.13	.60	1.19
	df	10	10	10	10	10	10
300	x	204.17	.90	.80	4.16	.25	.30
(191)	sd	11.48	.05	.05	.30	.02	.04
	t	2.05	2.11	1.83	1.40	.89	1.07
	df	10	10	10	10	10	10
600	x	214.67	.85	.80	4.64	.23	.32
(389)	sd	14.62	.08	.01	.30	.05	.07
	t	.13	.09	2.03	5.00**	.00	1.33
	df	10	10	10	10	10	10
1,200	x	200.50	.93	.80	5.16	.23	.32
(674)	sd	16.71	.08	.06	.40	.03	.06
	t	2.02	2.00	1.63	6.95**	.18	1.50
	df	10	10	10	10	10	10
2,399	x	175.00	.96	.84	5.71	.23	.27
(1,630)	sd	13.99	.07	.09	.47	.04	.11
	t	6.30**	3.29**	1.99	8.80**	.07	.03
	df	10	9	9	9	9	9
4,798	x	140.00	1.23	.84	6.49	.18	.17
(1,985)	sd	20.61	.13	.07	.78	.03	.06
	t	8.44**	7.05**	2.60*	8.02**	2.20	3.36**
	df	8	8	8	8	8	8

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x Mean
sd Standard deviation
t t value
df degrees of freedom

APPENDIX I

ORGAN-TO-BRAIN WEIGHT RATIO
(MALE RATS)
(14-DAY FEEDING STUDY)

DOSAGE (mg/kg) Predicted (Actual)		Terminal Brain Weight	KIDNEYS	LIVER	SPLEEN	TESTES	THYMUS
CONTROL	x	1.98	1.21	6.02	.32	1.47	.28
	sd	.08	.18	.75	.03	.03	.08
105	x	1.98	1.28	7.07	.38	1.54	.41
(60)	sd	.10	.14	.57	.05	.12	.10
	t	.12	.76	2.71*	2.57*	1.37	2.51*
	df	10	10	10	10	10	10
211	x	1.97	1.30	7.28	.33	1.54	.40
(126)	sd	.06	.14	.78	.05	.09	.08
	t	.33	1.00	2.83*	.29	1.76	2.55*
	df	10	10	10	10	10	10
422	x	2.01	1.26	7.20	.34	1.57	.39
(247)	sd	.09	.17	.90	.04	.10	.08
	t	.50	.52	2.48*	.68	2.42*	2.44*
	df	10	10	10	10	10	10
843	x	2.01	1.35	8.82	.35	1.64	.32
(543)	sd	.11	.08	.78	.04	.29	.08
	t	.54	1.72	6.30**	1.38	1.42	.85
	df	10	10	10	10	10	10
1,686	x	1.99	1.22	8.88	.30	1.51	.35
(1,141)	sd	.06	.07	.87	.05	.13	.07
	t	.12	.11	6.10**	.85	.68	1.58
	df	10	10	10	10	10	9
2,733	x	1.91	1.27	9.39	.26	1.43	.25
(1,436)	sd	.04	.14	1.81	.07	.13	.07
	t	1.80	.65	4.18**	2.13	.80	.64
	df	9	9	9	9	9	9
6,744	x	ALL DEAD					
(525)	sd						
	t						
	df						
	sd						

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX I

ORGAN-TO-BRAIN WEIGHT RATIO
(FEMALE RATS)
(14-DAY FEEDING STUDY)

DOSAGE (mg/kg) Predicted (Actual)		Terminal Brain Weight	KIDNEYS	LIVER	SPLEEN	THYMUS
CONTROL	x	1.82	.88	4.70	.27	.32
	sd	.05	.04	.27	.04	.05
75	x	1.83	.83	4.31	.26	.30
(43)	sd	.08	.12	.90	.05	.07
	t	.22	.95	1.04	.51	.72
	df	10	10	10	10	10
150	x	1.91	.92	4.65	.26	.35
(87)	sd	.06	.09	.38	.05	.04
	t	2.93*	1.00	.26	.57	.99
	df	10	10	10	10	10
300	x	1.84	.90	4.63	.28	.33
(191)	sd	.08	.06	.48	.03	.03
	t	.39	.37	.32	.18	.26
	df	10	10	10	10	10
600	x	1.81	.95	5.52	.27	.38
(389)	sd	.08	.08	.72	.05	.10
	t	.18	1.66	2.60*	.13	1.29
	df	10	10	10	10	10
1,200	x	1.85	.86	5.62	.25	.35
(674)	sd	.05	.06	.82	.05	.10
	t	1.12	.70	2.59*	1.02	.57
	df	10	10	10	10	10
2,399	x	1.80	.87	5.95	.24	.28
(1,630)	sd	.05	.09	.73	.04	.12
	t	.87	.34	3.91**	1.47	.75
	df	9	9	9	9	9
4,798	x	1.71	.69	5 33	.15	.14
(1,985)	sd	.13	.05	.96	.05	.06
	t	1.99	6.41**	1.55	4.87**	4.95**
	df	8	8	8	8	8

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX J

PREDICTED VERSUS ACTUAL DAILY DOSES
(90-DAY FEEDING STUDY)
(Week One)

	Dose Male Rats mg/kg/day		Dose Female Rats mg/kg/day	
	Predicted	Actual	Predicted	Actual
1	3,000	1,230	3,000	563
2	600	468	600	398
3	120	64	120	109

APPENDIX J

PREDICTED VERSUS ACTUAL DAILY DOSES
(90-DAY FEEDING STUDY)
(Week Two Thur End of Study)

	Dose Male Rats mg/kg/day		Dose Female Rats mg/kg/day	
	Predicted	Actual	Predicted	Actual
1	1,500	1,192	1,500	1,330
2	300	352.	300	367
3	60	64	120	88

APPENDIX K

FOOD CONSUMPTION (MALE RATS)
(90-DAY FEEDING STUDY)
g/rat/day

Dose(mg/Kg) Predicted (Actual)	Day 0-2	Day 2-5	Day 5-7	Day 7-9	Day 9-12	Day 12-14	Day 14-16	Day 16-19	Day 19-21	Day 21-23	Day 23-26	Day 26-28	Day 28-30
CONTROL	24.57	23.07	23.93	22.20	24.40	24.57	24.83	26.04	23.77	23.37	24.80	22.93	23.70
60 (64)	22.60	22.67	23.63	22.40	25.11	25.13	24.97	25.02	24.27	24.03	23.78	23.67	24.43
300 (352)	17.70	22.09	23.10	22.73	24.20	23.93	24.57	24.40	23.50	23.63	24.78	22.20	23.93
1,500 (1,192)	2.27	7.78	15.05	14.91	26.12	26.59	28.45	26.52	24.91	25.86	26.58	24.73	25.27

APPENDIX K

FOOD CONSUMPTION (MALE RATS)
(90-DAY FEEDING STUDY)
g/rat/day

Dose(mg/Kg) Predicted (Actual)	Day 30-33	Day 33-35	Day 35-37	Day 37-40	Day 40-42	Day 42-44	Day 44-47	Day 47-49	Day 49-51	Day 51-54	Day 54-56	Day 56-58	Day 58-61
CONTROL	18.88	23.46	22.07	21.81	25.39	23.00	20.98	29.25	22.36	24.89	22.56	25.33	24.33
60 (64)	21.93	25.10	22.87	22.62	24.50	23.53	20.82	18.23	22.67	24.37	21.40	23.75	22.67
300 (353)	23.20	23.43	22.17	22.38	23.23	23.63	21.53	24.47	21.33	23.77	23.50	23.60	23.33
1,500 (1,192)	24.39	24.05	23.41	22.85	23.86	22.86	21.97	17.95	20.64	22.14	22.64	22.64	22.00

APPENDIX K

FOOD CONSUMPTION (MALE RATS)
(90-DAY FEEDING STUDY)
g/rat/day

Dose(mg/Kg) Predicted (Actual)	Day 61-63	Day 63-65	Day 65-68	Day 68-70	Day 70-72	Day 72-75	Day 75-77	Day 77-79	Day 79-82	Day 82-84	Day 84-86	Day 86-89
CONTROL	22.17	24.33	23.74	24.11	21.89	20.41	19.50	21.50	20.56	23.22	20.78	17.93
60 (64)	22.55	23.40	21.60	22.90	22.40	19.10	16.75	23.40	21.80	21.95	22.65	21.13
300 (352)	24.15	*	22.83	22.90	23.00	20.27	15.00	24.95	23.53	24.25	24.10	21.47
1,500 (1,192)	20.21	21.00	21.05	22.71	23.07	20.90	20.43	21.21	21.33	29.50	21.07	20.62

* Missing weight

APPENDIX K

FOOD CONSUMPTION (FEMALE RATS)
(90-DAY FEEDING STUDY)
g/rat/day

Dose(mg/Kg) Predicted (Actual)	Day 0-3	Day 3-5	Day 5-7	Day 7-10	Day 10-12	Day 12-14	Day 14-17	Day 17-19	Day 19-21	Day 21-24	Day 24-26	Day 26-28	Day 28-31
CONTROL	15.84	15.83	14.87	16.33	16.07	17.70	17.11	15.90	15.70	16.80	15.63	15.47	16.07
60 (88)	15.00	16.27	15.63	18.29	16.77	18.23	17.47	15.73	16.70	17.31	16.57	18.00	17.18
300 (367)	12.11	16.27	12.23	18.56	18.07	18.50	19.53	15.10	16.17	17.44	15.67	16.60	16.47
1,500 (1,330)	2.76	3.33	9.37	16.78	16.10	19.07	20.64	17.83	18.54	19.06	13.38	17.88	18.89

APPENDIX K

FOOD CONSUMPTION (FEMALE RATS)
(90-DAY FEEDING STUDY)
g/rat/day

Dose(mg/Kg) Predicted (Actual)	Day 31-33	Day 33-35	Day 35-38	Day 38-40	Day 40-42	Day 42-45	Day 45-47	Day 47-49	Day 49-52	Day 52-54	Day 54-56	Day 56-59	Day 59-61
CONTROL	17.27	15.60	16.16	17.10	16.67	16.18	16.37	15.10	16.79	17.90	18.25	16.83	16.15
60 (88)	17.30	16.47	16.93	17.27	16.63	16.51	19.50	15.63	15.78	16.40	17.90	16.87	18.15
300 (367)	18.00	17.40	19.20	19.80	17.33	18.76	14.93	15.60	14.89	16.80	16.35	15.33	16.15
1,500 (1,330)	19.96	17.58	18.61	17.67	16.46	18.00	17.88	16.00	16.81	15.81	15.80	15.67	16.44

APPENDIX K

FOOD CONSUMPTION (FEMALE RATS)
(90-DAY FEEDING STUDY)
g/rat/day

Dose(mg/Kg) Predicted (Actual)	Day 61-63	Day 63-66	Day 66-68	Day 68-70	Day 70-73	Day 73-75	Day 75-77	Day 77-80	Day 80-82	Day 82-84	Day 84-87	Day 87-89
CONTROL	16.90	16.57	17.05	17.40	15.90	16.45	16.65	17.40	17.35	15.00	17.50	15.70
60 (88)	16.20	16.90	18.35	16.25	17.10	15.05	18.26	17.80	17.65	15.20	15.90	17.10
300 (367)	16.85	16.20	17.40	16.25	17.13	15.20	16.20	15.67	15.55	13.95	15.20	14.75
1,500 (1,330)	18.25	16.13	14.63	14.31	15.08	14.75	16.19	17.08	14.75	15.25	15.13	14.56

APPENDIX L

CLINICAL CHEMISTRY (MALE RATS)
(45-DAY FEEDING STUDY)

Dose (mg/Kg) Predicted (Actual)		SGOT IU/l	SGPT IU/l	HBDH IU/l	GGTP IU/l	ALK PHOS IU/l	LDH IU/l	BUN mg/dl	BILIRUBIN mg/dl
CONTROL	x	227.40	61.40	712.40	2.00	400.20	1595.20	20.78	.66
	sd	76.22	5.08	135.59	.71	82.97	116.18	1.72	.05
60	x	236.60	57.00	730.20	2.60	535.60	1227.60	20.28	.76
(64)	sd	121.40	11.77	96.03	.55	174.46	292.56	3.36	.05
	t	.14	.77	.24	1.50	1.57	2.61*	.30	2.89*
	df	8	8	8	8	8	8	8	8
300	x	123.50	49.75	613.50	3.00	323.00	788.50	19.33	.68
(352)	sd	59.31	7.97	168.95	.02	102.51	230.59	2.10	.10
	t	2.23	2.68*	.98	1.97	1.11	6.71**	1.15	.30
	df	7	7	7	7	7	7	7	7
1,500	x	169.50	65.00	725.50	9.00	721.00	806.00	22.95	1.30
(1,192)	sd	98.29	8.49	163.34	4.24	124.45	123.04	2.05	.71
	t	.85	.73	.11	4.18**	4.13**	8.02**	1.45	2.39
	df	5	5	5	5	5	5	5	5

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX L

CLINICAL CHEMISTRY (FEMALE RATS)
(45-DAY FEEDING STUDY)

Dose (mg/Kg) Predicted (Actual)		SGOT IU/l	SGPT IU/l	HBDH IU/l	GGTP IU/l	ALK PHOS IU/l	IDH IU/l	BUN mg/dl	BILIRUBIN mg/dl
CONTROL	x	266.67	57.33	754.33	3.33	208.67	1143.33	24.50	.52
	sd	114.20	7.57	96.07	.58	22.81	272.59	3.30	.04
60	x	126.50	57.00	559.50	3.50	436.00	649.00	28.95	.64
(88)	sd	3.54	.00	24.75	.71	29.70	38.18	1.91	.11
	t	1.65	.06	2.68	.29	9.84**	2.42	1.67	2.19
	df	3	3	3	3	3	3	3	3
300	x	183.80	49.60	625.60	2.60	262.40	693.20	25.40	.38
(367)	sd	108.50	5.08	252.44	.55	115.67	295.12	2.09	.04
	t	1.03	1.76	.82	1.80	.77	2.14	.48	4.95*
	df	6	6	6	6	6	6	6	6
1,500	x	104.50	149.00	375.50	7.00	506.50	385.50	26.20	.63
(1,330)	sd	21.92	106.07	193.04	1.41	85.56	219.91	6.22	.32
	t	1.89	1.63	3.04	4.26*	6.18**	3.24*	.41	.74
	df	3	3	3	3	3	3	3	3

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX L

CLINICAL CHEMISTRY (MALE RATS)
(90-DAY FEEDING STUDY)

DOSAGE (mg/kg) Predicted (Actual)		SGOT IU/l	SGPT IU/l	HBDH IU/l	GGTP IU/l	ALK PHOS IU/l	LDH IU/l	BUN mg/dl	BILIRUBIN mg/dl
CONTROL	x	199.00	57.56	309.33	1.56	252.22	2261.00	21.56	.41
	sd	28.48	18.85	169.46	1.33	98.35	224.81	7.54	.08
60	x	186.10	55.60	510.80	1.60	328.60	1987.10	24.46	.47
(64)	sd	42.13	5.02	362.12	.84	126.46	611.90	4.33	.08
	t	.77	.32	1.52	.09	1.46	1.27	1.04	1.59
	df	17	17	17	17	17	17	17	17
300	x	154.10	50.80	809.40	2.40	364.20	1516.70	23.62	.34
(352)	sd	42.40	10.46	177.74	2.07	134.17	333.97	2.11	.13
	t	2.68	.98	6.26**	1.04	2.05	5.63**	.83	1.38
	df	17	17	17	17	17	17	17	17
1,500	x	166.00	53.14	772.14	6.86	503.43	1540.43	23.29	.33
(1,192)	sd	66.14	10.21	124.65	5.96	216.37	328.17	3.12	.08
	t	1.35	.56	6.05**	2.61*	3.12**	5.22**	.55	2.12
	df	14	14	14	14	14	14	14	14

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX L

CLINICAL CHEMISTRY (FEMALE RATS)
(90-DAY FEEDING STUDY)

DOSAGE (mg/kg) Predicted (Actual)		SGOT IU/l	SGPT IU/l	HBDH IU/l	GGTP IU/l	ALK PHOS IU/l	LDH IU/l	BUN mg/dl	BILIRUBIN mg/dl
CONTROL	x	162.44	57.11	761.56	.89	380.56	1607.33	35.33	.49
	sd	37.19	19.43	258.37	.60	158.19	412.85	4.98	.11
60	x	196.00	49.89	636.00	.56	306.89	1569.56	32.46	.41
(88)	sd	78.11	9.75	305.29	.53	132.69	542.30	5.33	.06
	t	1.16	1.00	.94	1.25	1.07	.17	1.18	1.92
	df	16	16	16	16	16	16	16	16
300	x	134.00	46.38	830.75	1.63	278.00	1259.13	26.14	.31
(367)	sd	27.66	12.20	103.53	1.06	141.80	389.36	4.11	.11
	t	1.77	1.34	.71	1.79	1.40	1.78	4.12**	3.34**
	df	15	15	15	15	15	15	15	15
1,500	x	161.33	43.67	865.00	17.67	410.00	1271.50	23.60	.45
(1,330)	sd	82.27	6.80	158.35	6.50	163.85	263.79	5.71	.10
	t	.04	1.61	.87	7.84**	.35	1.76	4.22**	.70
	df	13	13	13	13	13	13	13	13

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX M

HEMATOLOGY (MALE RATS)
(45-DAY FEEDING STUDY)

Dose (mg/Kg) Predicted (Actual)		Hct %	Hgb g/dl	RBC $10^6/mm^3$	WBC $10^3/mm^3$	MCV u^3
CONTROL	x	35.70	15.08	6.74	11.66	53.60
	sd	2.03	.81	.35	3.58	.89
60	x	36.42	15.32	6.87	7.60	53.60
(64)	sd	.64	.51	.08	.94	.55
	t	.76	.56	.82	2.45*	.00
	df	8	8	8	8	8
300	x	37.28	14.68	6.98	9.30	53.80
(352)	sd	2.00	.53	.35	2.06	.84
	t	1.24	.92	1.09	1.28	.37
	df	8	8	8	8	8
1,500	x	38.25	15.30	7.13	9.25	54.25
(1,192)	sd	2.95	.48	.34	2.52	1.26
	t	1.54	.48	1.72	1.13	.91
	df	7	7	7	7	7

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX M

HEMATOLOGY (FEMALE RATS)
(45-DAY FEEDING STUDY)

Dose (mg/Kg) Predicted Actual)		Hct %	Hgb g/dl	RBC $10^6/mm^3$	WBC $10^3/mm^3$	MCV u^3
CONTROL	x	36.74	14.70	6.84	5.52	54.00
	sd	2.17	.61	.33	.68	1.00
60	x	35.68	14.30	6.67	5.25	54.00
(88)	sd	1.47	.62	.24	2.58	.82
	t	.83	.97.	.86.	.23	.00
	df	7	7	7	7	7
300	x	34.22	14.22	6.45	7.38	53.00
(367)	sd	1.39	.44	.23	5.07	1.52
	t	2.19	1.42	2.18	.81	.49
	df	8	8	8	8	8
1,500	x	34.78	14.55	6.53	6.18	53.75
(1,330)	sd	1.49	.70	.24	1.18	.50
	t	1.53	.34	1.58	1.05	.45
	df	7	7	7	7	7

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX M

HEMATOLOGY (MALE RATS)
(90-DAY FEEDING STUDY)

Dose (mg/Kg) Predicted (Actual)		Hct %	Hgb g/dl	RBC $10^6/mm^3$	WBC $10^3/mm^3$	MCV u^3
CONTROL	x	40.10	16.21	7.59	8.38	53.67
	sd	2.50	.69	.36	2.03	1.00
60	x	37.52	15.29	7.17	7.04	53.20
(64)	sd	1.52	.53	.23	3.92	.92
	t	2.75*	3.28**	3.04**	.92	1.06
	df	17	17	17	17	17
300	x	35.94	15.15	6.89	9.44	53.10
(352)	sd	2.48	.53	.41	2.09	.88
	t	3.64**	3.76**	3.91**	1.12	1.32
	df	17	17	17	17	17
1,500	x	35.97	14.81	6.92	9.81	53.00
(1,192)	sd	1.09	.20	.19	2.38	.82
	t	4.06**	5.12**	4.38**	1.30	1.43
	df	14	14	14	14	14

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX M

HEMATOLOGY (FEMALE RATS)
(90-DAY FEEDING STUDY)

Dose (mg/Kg) Predicted (Actual)		Hct %	Hgb g/dl	RBC $10^6/mm^3$	WBC $10^3/mm^3$	MCV u^3
CONTROL	x	37.43	14.69	7.02	6.17	54.22
	sd	1.70	.59	.24	1.85	.67
60	x	36.95	14.54	6.90	4.21	54.50
(88)	sd	1.90	.96	.36	1.25	.85
	t	.58	.40	.84	2.72*	.79
	df	17	17	17	17	17
300	x	37.16	14.61	7.00	3.99	54.00
(367)	sd	1.98	.69	.32	1.40	.67
	t	.32	.27	.12	2.91**	.73
	df	17	17	17	17	17
1,500	x	35.20	14.30	6.68	5.66	53.50
(1,330)	sd	1.83	.60	.27	2.74	.76
	t	2.61*	1.35	.55	.54	2.09
	df	15	15	15	15	15

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX N

BODY WEIGHTS (MALE RATS)
(90-DAY FEEDING STUDY)
g

Dose (mg/Kg) Predicted (Actual)		Day 0	Day+2	Day+5	Day+7	Day+9	Day+12	Day+14	Day+16	Day+19	Day+21	Day+23	Day+26
CONTROL	x	225.00	244.93	266.67	282.93	296.07	315.47	329.67	342.80	360.73	372.27	379.40	393.20
	sd	13.23	11.34	11.39	11.50	13.39	13.78	15.91	17.01	17.89	18.61	20.94	21.49
60	x	223.07	239.40	263.40	279.13	292.67	312.47	326.07	335.53	354.60	365.67	374.27	383.93
(64)	sd	6.13	7.31	8.24	10.16	10.03	11.62	13.52	14.99	15.24	16.76	16.50	16.63
	t	.51	1.59	.90	.96	.79	.64	.67	1.24	1.01	1.02	.75	1.32
	df	28	28	28	28	28	28	28	28	28	28	28	28
300	x	226.80	234.80	251.13	275.40	288.67	307.67	319.60	331.07	346.93	355.67	364.00	375.47
(352)	sd	12.27	11.94	13.65	12.19	13.86	14.82	16.12	17.03	20.79	19.01	21.57	20.85
	t	.39	2.38*	1.21	1.74	1.49	1.49	1.72	1.89	1.95	2.42*	.80	2.29*
	df	28	28	28	28	28	28	28	28	28	28	28	28
1,500	x	223.20	188.87	179.13	198.45	224.73	253.18	268.73	285.36	307.00	316.73	327.18	342.38
(1,192)	sd	11.43	14.30	35.57	29.73	26.75	27.59	25.27	26.29	23.45	21.10	19.47	20.25
	t	.40	11.90**	5.39**	10.08**	8.95**	7.59**	7.55**	6.77**	6.64**	7.11**	4.06**	6.05**
	df	28	28	28	24	24	24	24	24	24	24	24	24

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX N

BODY WEIGHTS (MALE RATS)
(90-DAY FEEDING STUDY)
g

Dose (mg/Kg) Predicted (Actual)		Day+28	Day+30	Day+33	Day+35	Day+37	Day+40	Day+42	Day+44	Day+47	Day+49	Day+51	Day+54
CONTROL	x	404.07	411.87	421.71	426.07	435.14	440.71	446.21	454.00	450.43	465.71	473.36	488.33
	sd	22.74	22.00	23.44	25.29	25.40	23.57	26.10	26.08	23.85	28.90	28.53	21.28
60	x	395.93	405.00	410.87	417.93	424.20	432.20	442.27	448.60	449.87	448.40	463.13	468.60
(64)	sd	18.21	16.34	16.24	16.21	17.02	14.82	16.68	16.56	16.58	17.36	16.08	16.94
	t	1.08	.97	1.46	1.04	1.37	1.17	.49	.67	.07	1.97	1.20	2.25*
	df	28	28	27	27	27	27	27	27	27	27	27	17
300	x	383.73	392.27	401.60	405.00	409.80	418.53	425.80	433.80	434.40	444.53	451.13	457.30
(352)	sd	22.41	24.17	22.02	22.62	22.24	22.62	24.16	25.82	26.41	25.33	26.32	27.19
	t	2.47*	2.32*	2.38*	2.37*	2.86**	2.59*	2.19*	2.10*	1.71	2.10*	2.18*	2.75*
	df	28	28	27	27	27	27	27	27	27	27	27	17
1,500	x	352.64	362.45	374.55	375.18	380.45	386.64	392.73	394.82	396.73	395.00	398.09	405.43
(1,192)	sd	22.02	21.06	23.44	23.26	23.25	25.38	25.05	25.12	24.19	28.58	27.36	32.94
	t	5.77**	5.07**	4.99**	5.17**	5.54**	5.51**	5.18**	5.72**	5.55**	6.10**	6.67**	6.12**
	df	24	24	23	23	23	23	23	23	23	23	23	14

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX N

BODY WEIGHTS (MALE RATS)
(90-DAY FEEDING STUDY)
g

Dose (mg/Kg) Predicted (Actual)		Day+56	Day+58	Day+61	Day+63	Day+65	Day+68	Day+70	Day+72	Day+75	Day+77	Day+79	Day+82
CONTROL	x	490.78	498.00	505.56	506.00	512.56	516.78	522.00	520.22	521.11	525.56	528.22	527.00
	sd	21.26	22.68	20.93	19.53	25.23	21.51	20.54	20.21	20.34	18.05	20.15	19.40
60	x	471.40	476.50	480.80	488.50	487.90	492.00	496.60	500.60	497.40	491.70	499.80	503.30
(64)	sd	17.64	17.70	18.43	20.82	21.87	20.58	20.75	18.30	19.95	15.83	16.44	18.17
	t	2.17*	2.32*	2.74*	1.88	2.28*	2.57*	2.68*	2.22*	2.56*	4.36**	3.38**	2.75*
	df	17	17	17	17	17	17	17	17	17	17	17	17
300	x	464.80	466.10	470.40	478.50	479.20	483.60	487.20	488.20	484.10	476.60	485.30	487.30
(352)	sd	28.00	27.21	27.68	28.53	27.26	27.04	28.65	27.95	25.82	21.88	25.22	19.47
	t	2.26*	2.76*	3.09**	2.42*	2.76*	2.94**	3.01**	2.83*	3.44**	5.28**	4.07**	4.44**
	df	17	17	17	17	17	17	17	17	17	17	17	17
1,500	x	406.57	406.14	405.57	407.29	406.86	400.29	405.43	411.29	407.86	411.14	410.86	413.14
(1,192)	sd	32.37	30.10	31.56	33.28	32.69	33.74	33.25	36.57	35.75	35.28	36.89	39.03
	t	6.28**	6.98**	7.62**	7.44**	7.32**	8.43**	8.55**	7.61**	8.03**	8.46**	8.16**	7.67**
	df	14	14	14	14	14	14	14	14	14	14	14	14

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX N

BODY WEIGHTS (MALE RATS)
(90-DAY FEEDING STUDY)
g

Dose (mg/Kg) Predicted (Actual)		Day+84	Day+86	Day+89
CONTROL	x	533.56	533.78	525.44
	sd	20.53	25.94	20.49
60	x	509.32	510.20	515.00
(64)	sd	17.54	16.94	17.57
	t	2.78*	2.37*	.82
	df	17	17	17
300	x	493.40	498.10	502.70
(352)	sd	23.47	24.14	25.61
	t	3.95**	3.11**	2.12*
	df	17	17	17
1,500	x	415.71	414.43	416.57
(1,192)	sd	37.25	40.34	38.10
	t	8.09**	7.20**	7.36**
	df	14	14	14

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX N

BODY WEIGHTS (FEMALE RATS)
(90-DAY FEEDING STUDY)
g

Dose (mg/Kg) Predicted (Actual)		Day 0	Day+3	Day+5	Day+7	Day+10	Day+12	Day+14	Day+17	Day+19	Day+21	Day+24	Day+26
CONTROL	x	173.20	182.67	188.40	194.60	204.80	209.47	216.60	225.13	228.93	232.73	240.67	245.33
	sd	10.04	10.69	10.93	11.70	14.37	15.04	14.32	15.47	16.09	16.44	17.52	17.40
60	x	171.73	177.73	183.67	190.73	203.40	208.13	214.00	221.60	223.93	228.33	238.27	242.87
(88)	sd	11.10	12.81	13.48	14.83	19.36	22.32	23.99	23.22	25.82	22.76	25.78	24.38
	t	2.49*	1.15	1.06	.79	.22	.19	.36	.49	.64	.61	.30	.32
	df	28	28	28	28	28	28	28	28	28	28	28	28
300	x	178.13	177.33	183.80	195.33	203.47	211.40	215.60	227.87	227.27	233.00	240.80	243.60
(367)	sd	15.02	14.11	15.10	16.26	17.67	17.69	20.37	21.10	21.41	21.68	22.20	24.08
	t	1.06	1.17	.96	.14	.23	.32	.16	.40	.24	.04	.02	.23
	df	28	28	28	28	28	28	28	28	28	28	28	28
1,500	x	177.80	142.27	138.17	158.67	176.83	179.42	191.58	203.42	205.33	214.00	223.33	228.92
(1,330)	sd	10.45	11.27	16.25	14.25	11.94	11.23	11.70	10.87	13.14	13.87	15.42	13.62
	t	1.23	10.08**	9.58**	7.13**	5.41**	5.75**	4.88**	4.11**	4.10**	3.15**	2.69*	2.67*
	df	28	28	25	25	25	25	25	25	25	25	25	25

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX N

BODY WEIGHTS (FEMALE RATS)
(90-DAY FEEDING STUDY)
g

Dose (mg/Kg) Predicted (Actual)		Day+28	Day+31	Day+33	Day+35	Day+38	Day+40	Day+42	Day+45	Day+47	Day+49	Day+52	Day+54
CONTROL	x	247.13	253.73	257.13	259.40	267.27	267.93	272.80	276.87	278.87	281.13	285.67	283.90
	sd	15.12	17.73	17.36	18.69	17.15	20.86	18.27	22.05	21.58	22.73	22.82	18.94
60	x	232.47	252.27	253.53	256.27	262.73	264.33	268.40	269.73	274.80	276.07	281.33	280.00
(88)	sd	61.99	26.46	26.47	28.63	30.34	31.86	31.08	34.72	32.32	34.79	36.28	38.90
	t	.89	.18	.42	.35	.50	.37	.47	.67	.41	.47	.39	.29
	df	28	28	28	28	28	28	28	28	28	28	28	18
300	x	246.67	253.33	254.87	258.13	260.80	264.47	264.07	270.87	271.60	272.33	276.20	274.80
(367)	sd	23.14	21.80	25.12	23.23	22.74	21.71	23.23	21.78	21.45	22.73	23.57	27.21
	t	.07	.06	.29	.16	.88	.45	1.14	.75	.92	1.06	1.12	.87
	df	28	28	28	28	28	28	28	28	28	28	28	18
1,500	x	230.42	238.42	241.75	242.83	246.58	242.25	244.17	243.67	245.33	245.33	246.92	246.50
(1,330)	sd	14.44	16.04	15.97	16.47	17.55	17.65	18.76	18.81	19.62	20.00	19.83	14.57
	t	2.91**	2.33*	2.37*	2.41*	3.08**	3.40**	4.00**	4.14**	4.17**	4.28**	4.64**	4.59**
	df	25	25	25	25	25	25	25	25	25	25	25	16

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX N

BODY WEIGHTS (FEMALE RATS)
(90-DAY FEEDING STUDY)
g

Dose (mg/kg) Predicted (Actual)		Day+56	Day+59	Day+61	Day+63	Day+66	Day+68	Day+70	Day+73	Day+75	Day+77	Day+80	Day+82
CONTROL	x	283.50	288.90	290.20	290.90	295.00	294.70	297.70	299.20	302.70	302.40	306.70	308.30
	sd	17.51	17.84	18.53	20.13	18.68	19.92	18.44	19.83	18.90	21.18	22.50	21.41
60	x	284.20	284.00	287.30	288.10	288.80	291.10	290.00	296.60	295.20	298.80	301.80	302.60
(88)	sd	39.12	39.96	40.40	38.10	39.45	35.10	37.37	38.09	35.00	36.03	34.76	36.13
	t	.05	.35	.21	.21	.45	.28	.58	.19	.60	.27	.37	.43
	df	18	18	18	18	18	18	18	18	18	18	18	18
300	x	277.90	279.40	279.80	283.60	280.20	285.50	283.10	289.20	288.00	291.10	294.50	293.70
(367)	sd	23.94	26.90	25.50	25.57	26.20	26.58	28.31	28.39	29.46	28.32	27.86	29.40
	t	.60	.93	1.04	.71	1.45	.88	1.37	.91	1.33	1.01	1.08	1.27
	df	18	18	18	18	18	18	18	18	18	18	18	18
1,500	x	245.63	249.13	251.00	251.13	249.25	248.50	246.88	246.50	247.63	247.38	247.88	247.13
(1,330)	sd	14.04	14.80	16.70	16.15	15.48	16.87	18.30	16.46	18.66	17.54	18.89	20.12
	t	3.12**	5.06**	4.66**	4.53**	5.56**	5.22**	5.83**	6.03**	6.18**	5.90**	5.91**	6.18**
	df	16	16	16	16	16	16	16	16	16	16	16	16

* Significantly different than controls (P=0.05)
** Significantly different than controls (P=0.01)
x Mean
sd Standard deviation
t t value
df degrees of freedom

APPENDIX N

BODY WEIGHTS (FEMALE RATS)
(90-DAY FEEDING STUDY)
g

Dose (mg/Kg) Predicted (Actual)		Day+84	Day+87	Day+89
CONTROL	x	306.20	316.10	313.40
	sd	20.90	21.26	20.52
60	x	299.30	302.80	303.60
(88)	sd	34.89	34.40	34.72
	t	.54	1.04	.77
	df	18	18	18
300	x	292.70	295.50	294.40
(367)	sd	26.93	28.48	25.29
	t	1.25	1.83	1.84
	df	18	18	18
1,500	x	247.00	250.13	248.63
(1,330)	sd	20.04	18.98	20.19
	t	6.08**	6.85**	6.70**
	df	16	16	16

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX O

ORGAN-TO-BODY WEIGHT (MALE RATS)
(45 DAYS INTO 90-DAY FEEDING STUDY)

Dose (mg/kg) Predicted (Actual)		Terminal Body Weight	Mean Organ-to-Body Weight Ratios (gms/100gms body weight) BRAIN	KIDNEYS	LIVER	SPLEEN	TESTES	THYMUS
CONTROL	x	456.40	.45	.69	3.28	.15	.76	.12
	sd	35.82	.02	.08	.21	.01	.04	.04
60	x	469.00	.45	.67	3.74	.16	.70	.13
(64)	sd	21 17	.03	.04	.32	.02	.05	.03
	t	.68	.22	.57	2.77**	1.36	1.91	.25
	df	8	8	8	8	8	8	8
300	x	450.40	.46	.72	4.21	.17	.82	.15
(352)	sd	29.26	.03	.05	.24	.02	.10	.03
	t	.29	.64	.52	6.61**	1.91	1.31	1.04
	df	8	8	8	8	8	8	8
1,500	x	386.75	.52	.81	6.25	.17	.89	.13
(1,192)	sd	18.39	.04	.11	.30	.01	.03	.03
	t	3.50**	3.75**	1.91	17.60**	1.93	4.99**	.21
	df	7	7	7	7	7	7	7

* Significantly different than controls (P=0.05)
** Significantly different than controls (P=0.01)
x Mean
sd Standard deviation
t t value
df degrees of freedom

APPENDIX O

ORGAN-TO-BODY WEIGHT (FEMALE RATS)
(45-DAYS INTO 90-DAY FEEDING STUDY)

Dose (mg/Kg) Predicted (Actual)		Terminal Body Weight	Mean Organ-to-Body Weight Ratios (gms/100gms body weight) BRAIN	KIDNEYS	LIVER	SPLEEN	THYMUS
CONTROL	x	292.40	.64	.67	3.44	.20	.21
	sd	31.81	.05	.06	.36	.02	.02
60	x	280.20	.67	.66	3.82	.21	.18
(88)	sd	37.59	.07	.05	.18	.05	.04
	t	.55	.68	.34	2.18	.34	1.23
	df	8	8	8	8	8	8
300	x	273.60	.69	.65	4.24	.22	.20
(367)	sd	24.15	.05	.03	.35	.03	.05
	t	1.05	1.47	.53	3.51**	1.41	.25
	df	8	8	8	8	8	8
1,500	x	246.75	.83	.80	5.99	.20	.20
(1,330)	sd	31.21	.10	.04	.35	.03	.07
	t	2.16	3.68**	3.57**	10.65**	.33	.18
	df	7	7	7	7	7	7

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX O

ORGAN-TO-BODY WEIGHT (MALE RATS)
(90-DAY FEEDING STUDY)

Dose (mg/kg) Predicted (Actual)		Terminal Body Weight	Mean Organ-to-Body Weight Ratios (gms/100gms body weight) BRAIN	KIDNEYS	LIVER	SPLEEN	TESTES	THYMUS
CONTROL	x	525.44	.40	.62	2.59	.13	.16	.08
	sd	20.49	.01	.04	.19	.02	.08	.02
60	x	515.00	.41	.64	3.30	.15	.68	.10
(64)	sd	17.57	.02	.06	.28	.02	.03	.02
	t	1.20	.97	.72	6.49**	1.76	.12	1.71
	df	17	17	17	17	17	17	17
300	x	502.70	.41	.64	3.98	.16	.71	.09
(352)	sd	25.61	.02	.04	.24	.02	.05	.02
	t	2.12*	1.65	.72	13.78**	3.06**	.95	.50
	df	17	17	17	17	17	17	17
1,500	x	416.57	.49	.77	5.61	.15	.90	.10
(1,192)	sd	38.10	.04	.05	.33	.02	.08	.03
	t	7.36**	6.65**	6.16**	23.21**	1.92	5.56**	1.98
	df	17	17	17	17	17	17	17

* Significantly different than controls (P=0.05)
** Significantly different than controls (P=0.01)
x Mean
sd Standard deviation
t t value
df degrees of freedom

APPENDIX O

ORGAN-TO-BODY WEIGHT (FEMALE RATS)
(90 DAY FEEDING STUDY)

Dose (mg/kg) Predicted (Actual)		Terminal Body Weight	Mean Organ to Body Weight Ratios (gms/100gms body weight) BRAIN	KIDNEYS	LIVER	SPLEEN	THYMUS
CONTROL	x	313.40	.61	.60	3.19	.17	.13
	sd	20.52	.04	.04	.23	.01	.03
60	x	303.60	.62	.61	3.33	.18	.14
(88)	sd	34.72	.07	.04	.29	.02	.03
	t	.77	.61	.67	1.18	.47	.37
	df	18	18	18	18	18	18
300	x	294.40	.66	.66	3.83	.18	.13
(367)	sd	25.29	.07	.04	.38	.03	.03
	t	1.84	2.30*	2.99**	4.48**	.38	.64
	df	18	18	18	18	18	18
1,500	x	248.63	.79	.73	5.63	.18	.16
(1,330)	sd	20.19	.05	.06	.19	.02	.03
	t	6.70**	8.35**	5.46**	23.79**	.82	1.62
	df	16	16	16	16	16	16

* Significantly different than controls (P=0.05)
** Significantly different than controls (P=0.01)
x Mean
sd Standard deviation
t t value
df degrees of freedom

APPENDIX P

ORGAN-TO-BRAIN WEIGHT (MALE RATS)
(45 DAYS INTO 90-DAY FEEDING STUDY)

Dose (mg/Kg) Predicted (Actual)		Terminal Brain Weight	Organ-To-Brain Weight Ratios KIDNEYS	LIVER	SPLEEN	TESTES	THYMUS
CONTROL	x	2.05	154.02	730.41	33.40	168.18	26.79
	sd	0.09	13.72	67.70	1.69	10.31	7.90
60	x	2.12	148.64	829.88	36.04	156.49	28.12
(64)	sd	0.09	10.73	77.00	4.45	18.71	6.58
	t	1.16	0.68	2.17	1.24	1.22	0.29
	df	8	8	8	8	8	8
300	x	2.07	155.19	918.05	37.37	178.00	32.13
(352)	sd	0.07	2.43	84.22	5.89	19.49	6.34
	t	0.43	0.19	3.88**	1.45	1.00	1.18
	df	8	8	8	8	8	8
1,500	x	2.02	157.12	1203.45	31.58	171.08	23.89
(1,192)	sd	0.06	31.58	136.82	2.48	7.82	5.46
	t	0.62	0.20	6.84**	1.32	0.46	0.62
	df	7	7	7	7	7	7

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX P

ORGAN-TO-BRAIN WEIGHT (FEMALE RATS)
(45 DAYS INTO 90-DAY FEEDING STUDY)

Dose (mg/Kg) Predicted (Actual)		Terminal Brain Weight	Organ-to-Brain Weight Ratios KIDNEYS	LIVER	SPLEEN	THYMUS
CONTROL	x	1.86	105.21	539.76	31.05	32.37
	sd	0.07	11.51	69.62	3.02	2.72
60	x	1.82	99.68	580.14	31.34	27.87
(88)	sd	0.13	14.42	69.90	9.88	5.17
	t	0.18	0.67	0.91	0.06	1.72
	df	8	8	8	8	8
300	x	1.87	95.47	620.62	32.56	29.62
(367)	sd	0.04	7.97	79.39	5.60	9.10
	t	.17	1.56	1.71	0.53	0.65
	df	8	8	8	8	8
1,500	x	2.02	97.22	736.48	25.00	24.87
(1,330)	sd	0.09	14.16	127.04	5.68	9.95
	t	2.81*	0.94	2.98*	2.07	1.64
	df	7	7	7	7	7

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX P

ORGAN-TO-BRAIN WEIGHT (MALE RATS)
(90-DAY FEEDING STUDY)

Dose (mg/Kg) Predicted (Actual)		Terminal Brain Weight	Organ-To-Brain Weight Ratios KIDNEYS	LIVER	SPLEEN	TESTES	THYMUS
CONTROL	x	2.11	155.16	646.42	32.33	169.43	20.13
	sd	0.08	13.52	49.90	4.59	17.60	3.58
60	x	2.11	157.05	820.65	35.76	167.84	22.52
(64)	sd	0.10	19.49	105.62	5.74	14.25	4.26
	t	0.06	0.24	4.51	1.40	0.21	1.26
	df	17	16	16	16	16	15
300	x	2.08	153.06	958.14	33.99	170.13	20.44
(352)	sd	0.06	9.59	56.32	12.62	14.89	4.70
	t	0.76	0.39	12.91	0.37	0.09	0.16
	df	17	17	17	17	17	17
1,500	x	2.04	157.10	1134.79	29.89	182.32	19.72
(1,192)	sd	0.05	14.77	123.27	7.11	13.39	6.00
	t	1.90	0.26	10.88**	0.81	1.52	0.17
	df	14	13	13	13	13	13

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX P

ORGAN-TO-BRAIN WEIGHT (FEMALE RATS)
(90-DAY FEEDING STUDY)

Dose (mg/Kg) Predicted (Actual)		Terminal Brain Weight	Organ-To-Brain Weight Ratios KIDNEYS	LIVER	SPLEEN	THYMUS
CONTROL	x	1.92	98.46	527.59	28.29	22.05
	sd	0.09	55.63	9.20	3.08	3.61
60	x	1.87	99.02	542.20	28.68	22.26
(88)	sd	0.11	12.56	80.23	3.90	4.70
	t	0.97	0.11	0.47	0.25	0.11
	df	18	18	18	18	18
300	x	1.95	99.04	578.37	26.51	19.24
(367)	sd	0.11	8.49	73.23	4.63	4.32
	t	0.77	0.15	1.75	1.01	1.58
	df	18	18	18	18	18
1,500	x	1.97	92.89	714.28	22.69	19.94
(1,330)	sd	0.09	5.96	57.78	2.56	3.87
	t	1.06	1.48	6.95**	4.12**	1.19
	df	16	16	16	16	16

* - Significantly different than controls (P=0.05)
** - Significantly different than controls (P=0.01)
x - Mean
sd - Standard deviation
t - t value
df - degrees of freedom

APPENDIX Q

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