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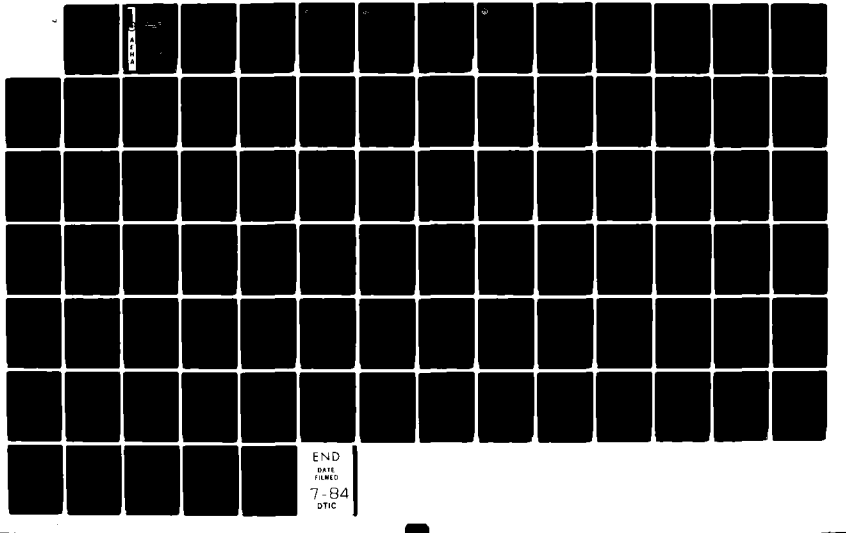

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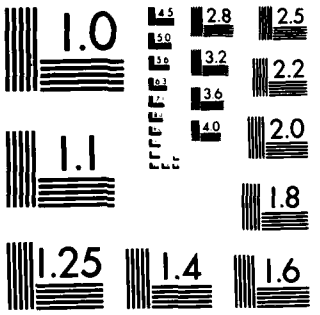

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UNITED STATES ARMY ENVIRONMENTAL HYGIENE AGENCY

ABERDEEN PROVING GROUND, MD 21010

ASSESSMENT OF THE RELATIVE TOXICITY OF N,N-DIPROPYLCYCLO-HEXANECARBOXAMIDE, AI3-36326
STUDY NO. 75-51-0233-84
PHASE 3
AUGUST 1982 - APRIL 1983

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AI3-36326	Insect Repellent
Aquatic	Irritation
Avian	Mutagenicity
Dominant Lethal	N,N-Dipropylcyclohexanecarboxamide
In-Vitro	Toxicity

20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)*

Repeated applications of the high dose concentration (450 mg/kg) of technical grade carboxamide produced moderate to severe erythema on the skin of rabbits. Application of the expected human dermal dosage concentration (9 mg/kg) in a 25 percent (w/v) ethanol solution for 21 days produced mild to moderate skin irritation in rabbits. Toxicity studies performed for this Agency indicate that AI3-36326 was found relatively innocuous to Bobwhite quail and Mallard ducks during an eight day dietary LC50 study up to concentrations greater than 5000 ppm. This insect repellent was found to be slightly toxic during 96 hour LC50 studies

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20. performed on Bluegill sunfish (28 mg/L) and Rainbow trout (42 mg/L). Caution should be exercised when handling large quantities of technical grade material.

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

Mr. Macko/orl/AUTOVON
584-3980

REPLY TO
ATTENTION OF

HSHB-OT/WP

18 MAY 1983

SUBJECT: Assessment of The Relative Toxicity of N,N-Dipropylcyclohexanecarboxamide, AI3-36326 Study No. 75-51-0233-84, Phase 3, August 1982 - April 1983

Executive Secretary
Armed Forces Pest Management Board
Forest Glen Section, WRAMC
Washington, DC 20307

Copies of subject report with Executive Summary are inclosed.

FOR THE COMMANDER:

LTC, MC

1 Incl
as (5 cy)

JOEL C. GAYDOS, M.D.
Colonel, MC
Director, Occupational and
Environmental Health

CF:
HQDA (DASG-PSP) wo incl
Cdr, HSC (HSPA-P)
Comdt, AHS (HSHA-IPM)
Dir, Advisory Ctr on Tox, NRC (2 cy)
USDA, ARS, Southern Region
USDA, ARS (Dr. Tarrence McGovern)

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

REPLY TO
ATTENTION OF

HSHB-OT/WP

EXECUTIVE SUMMARY
ASSESSMENT OF THE RELATIVE TOXICITY OF N,N-DIPROPYLCYCLO-HEXANECARBOXAMIDE, AI3-36326
STUDY NO. 75-51-0233-84
PHASE 3
AUGUST 1982 - APRIL 1983

1. PURPOSE. The purpose of this study was to determine the toxicity of N,N-dipropylcyclohexanecarboxamide (AI3-36326) following repeated dermal exposure to the technical grade repellent. This report will also present results from toxicity studies performed for this Agency by outside contracting laboratories.

2. ESSENTIAL FINDINGS. Repeated applications of the high dose concentration (450 mg/kg) of technical grade carboxamide produced moderate to severe erythema on the skin of rabbits. Application of the expected human dermal dosage concentration (9 mg/kg) in a 25 percent (w/v) ethanol solution for 21 days produced mild to moderate skin irritation in rabbits. Toxicity studies performed for this Agency indicate that AI3-36326 was found relatively innocuous to Bobwhite quail and Mallard ducks during an eight day dietary LC_{50} study up to concentrations greater than 5000 ppm. This insect repellent was found to be slightly toxic during 96 hour LC_{50} studies performed on Bluegill sunfish (28 mg/L) and Rainbow trout (42 mg/L).

3. MAJOR RECOMMENDATIONS. The dominant lethal study of AI3-36326 should be repeated to clarify the near dominant lethal effects exhibited by the negative controls. Essential additional tests should include a rodent teratology study, a 90-day rabbit dermal response study and a 14-day feeding study to be used as a range finder for a 90-day test. Caution should be exercised when handling large quantities of technical grade material.

Study No. 75-51-0233-84, Aug 82 - Apr 83

CONTENTS

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

REPLY TO ATTENTION OF
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ASSESSMENT OF THE RELATIVE TOXICITY OF N,N-DIPROPYLCYCLO-HEXANECARBOXAMIDE, AI3-36326
STUDY NO. 75-51-0233-84
PHASE 3
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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 Control Board; and the US Department of Agriculture, Agricultural Research, Science and Education Administrations; 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. REFERENCES. See Appendix A for a listing of references.

3. PURPOSE. The purpose of this study was to determine the toxicity of N,N-dipropylcyclohexanecarboxamide (AI3-36326) following repeated dermal exposures to the technical grade repellent.*† This report will also present results from toxicity studies performed for this Agency by outside contracting laboratories.†

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* In conducting 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 21-Day Dermal Study reported herein was performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care. This report and data generated in this study are stored in Toxicology's file located in Room 3011, Building E2100, Aberdeen Proving Ground, in Edgewood, Maryland.

‡ Wildlife International Ltd., East Kennedy Street, Easton, Maryland 21601, (301) 822-8600; Analytical Bio-Chemistry Laboratories, Inc., P.O. Box 1097, Columbia, Missouri, (314) 474-8579; Litton Bionetics, Inc., 5516 Nicholson Lane, Kensington, Maryland, (301) 881-5600; and Omni Research Laboratories, Inc., 4800 Roland Avenue, Baltimore, Maryland.

4. 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 by spray or total emersion. Proposed usage concentrations may range from 6.25 percent to 50 percent in ethanol (reference 1, Appendix A).

b. Previous studies performed by this Agency (references 2 and 3, Appendix A) showed that technical grade carboxamide was not acutely toxic by ingestion or by dermal exposure nor did it cause a phototoxic or skin sensitization reaction. It did produce mild primary skin irritation and slight to mild reversible injury to the cornea and conjuntiva.

5. MATERIALS AND METHODS.

a. The candidate insect repellent AI3-36326, N,N-dipropylcyclohexane-carboxamide was synthesized in three batches (c, d, e) by Terrence P. McGovern, Ph.D., Organic Chemical Synthesis Laboratory, Agricultural Research Center, US Department of Agriculture, Beltsville, Maryland 20705 (reference 4, Appendix A). This light tan liquid with a slightly irritating odor, specific gravity of 0.94, molecular weight of 209, and a boiling point of 128-129°/0.7 mm, is soluble in general polar solvents (ether, acetone, alcohol etc.) but only slightly soluble in water. Each batch sample was analyzed upon receipt using infrared (IR) spectrophotography (Appendix B) and gas chromatography (GC) and was found free of any significant impurities or variations. The chemical structure of AI3-36326 is represented below:

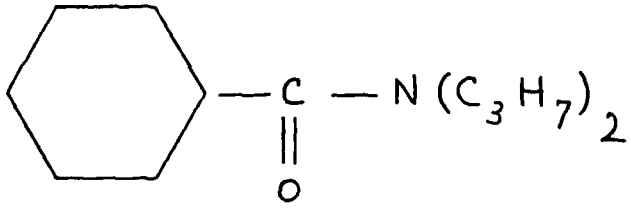

Figure 1. N,N-dipropylcyclohexanecarboxamide

b. Subchronic Dermal Toxicity.

(1) The subchronic dermal toxicity study was performed to evaluate the relative toxicity of N,N-dipropylcyclohexanecarboxamide through the dermal route of exposure and to identify target organs to establish appropriate dose levels for a future 90-day study. This study was performed using male and female New Zealand White rabbits by the application of the test material to a shaven area of abraded skin 5 days per week for 3 consecutive weeks.

(2) Two separate shipments of 90 and 40 animals were obtained approximately 120 days apart§. Upon arrival to this Agency, the first group of rabbits was assigned a Toxicology Issue Number and labeled with a felt tip marker (numbering both ears). Each animal was housed individually in 45 x 60 x 38 cm stainless steel cages with food|| and water available ad libitum. During the first 14-day period, rabbits were quarantined and their drinking water contained sodium sulfa quinoxaline** for the treatment and control of coccidiosis. Treated drinking water was used during the entire testing period. Rabbits were housed in rooms with 12-hour, light-dark sequence under ambient conditions of 24°C±2°C and 40-45 percent relative humidity.

(3) The 21-day dermal study was conducted according to Toxicology's Standing Operating Procedure (SOP) (reference 5, Appendix A). Rabbits were shaved, weighed and bled weekly during the pretest and testing period. The hematology and blood chemistry parameters listed in Tables 1 and 2 were analyzed according to Toxicology's SOP (reference 5, Appendix A).

(4) Following the final pretest bleedings, the rabbits were randomly divided into 4 groups of 20 rabbits each (10 male and 10 female) using the short table of random numbers from the Experimental Statistics National Bureau of Standards Handbook 91, 1961. Experimental dose group levels were multiples of the expected human usage dose. The calculations for the dose in group 1 are listed below:

Expected human usage calculations

250 mg/forearm of 25% in ethanol x 2	=	500 mg
250 to 500 mg/face, neck and bottom of pants	=	250 to 500 mg
		750 to 1000 mg of insect repellent

750 mg/70 kg man of insect repellent = 9 mg/kg
Therefore 9 mg/kg is the expected human usage dose.

---

§ The first order of 90 rabbits (45 male and 45 female) was obtained from Dutchland Farms, Denver, Pennsylvania and ranged in weight from 1.8 to 2.3 kg. The second order of 40 rabbits (20 male and 20 female) was obtained from Hill Top Lab Animal Inc, P.O. Box 195, Scottsdale, Pennsylvania, and ranged in weight from 1.36 to 1.81 kg.

|| Rabbits were fed Purina Certified Rabbit Chow (No. 5322), Ralston Purina Company, Saint Louis Missouri.

** Sulfaquinoxaline (20 percent S.Q. Solution) manufactured by MSD AGVET, Division of Merck and Company, Inc., Rahway, New Jersey.

TABLE 1. HEMATOLOGY MEASUREMENTS††

Hematocrit
Hemoglobin
Total red blood cell count (RBC)
Total white blood cell count (WBC)
Differential leucocyte count
Reticulocyte count

†† Hematological parameters, except differential WBC were analysed on a Coulter Counter Model 010ZBI and Hemoglobinometer, Coulter Electronics, Inc., Hialeah, Florida. Stains for differential WBC were done according to the Toxicology Division SOP (reference 5, Appendix A).

TABLE 2. CLINICAL CHEMISTRY MEASUREMENTS‡‡

Sodium
Calcium
Potassium
Serum lactic dehydrogenase (LDH)
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Glucose
Blood urea nitrogen (BUN)
Total bilirubin
Total Cholesterol
Serum alkaline phosphatase
Total protein
Gamma-glutamyl transferase
Triglycerides
alpha hydroxybutyric dehydrogenase (HBDH)
Creatine Phosphokinase (CPK)

‡‡ Serum clinical chemistry were performed using the Abbott Bichromatic Analyzer 100 (ABA-100), Abbott Diagnostics, South Pasadena, California. The Instrumentation Laboratory Flame Photometer Model 143, Instrumentation Laboratory Inc., Lexington, Massachusetts, was used in analyzing for sodium and potassium.

The chosen experimental dose groups are listed in Table 3.

TABLE 3. SUBCHRONIC DERMAL STUDY (TECHNICAL GRADE MATERIAL) INITIAL EXPERIMENTAL DOSE TREATMENT GROUPS

Exposure Group			Treatment
1	Low Dose	Expected Human Dose (EHD)	9 mg/Kg
2	Medium Dose	10 x (EHD)	90 mg/Kg
3	High Dose	50 x (EHD)	450 mg/Kg
4	Control	Skin shaved, abraded and pad covered compound not applied	

The technical grade material was applied over the shaven area (mid-lumbar region) of the abraded skin (reference 5, Appendix A). The treated area of the rabbit was then surrounded with a foam rectangular hollow pad (6 inches 8 inches) covered by a piece of screen and secured in place with surgical adhesive tape. The test material was applied 5 days per week for 3-consecutive weeks. The adhesive strips on one side of the protective pad were removed each Monday. The rabbits were reshaved, graded for irritation (Draize Method, Appendix C), abraded, compound applied and protective pad reattached. Compound was applied using a 21-gauge 1 1/2-inch needle and 5 cc glass syringe through the screen on the next 4 days. A concurrent wrapped but untreated control group of 10 male and 10 female rabbits were handled identically as described above. During the treatment period, a record of food consumption was kept for the treated and control animals.

(5) Three days after the final application all animals were bled, weighed and then sacrificed by injection of 2 ml of T-61 Euthanasia Solution, Taylor Pharmacal Company, Decatur, Illinois, into the marginal ear vein. Each rabbit was necropsied; and selected organs and tissues were prepared for routine histopathologic examination and evaluated by Findley Research, Inc., PO Box 375, Assonet, Massachusetts, 4 December 1980, under contract No. DAAD05-80-D-0481. The organ-to-body weight ratios were calculated for the kidneys, liver, spleen, heart, testes, adrenals, pituitary and thyroid.

(6) During the 3 weeks of the initial 21-day dermal study with N,N-Dipropylcyclohexanecarboxamide, the low dose (expected human dose 9 mg/Kg) of technical grade compound caused slight to moderate erythema and very slight to moderate edema. Due to the irritation caused at this dose, a second group of 40 rabbits was purchased for additional testing. These rabbits were assigned to two treatment groups (10 male and 10 female per group) using a table of ascending body weights and sequentially dividing them into dose groups described in Table 4. The rabbits were handled similarly to the rabbits in the initial study. The compound was applied and animals wrapped as previously described.

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TABLE 4. SUBCHRONIC DERMAL STUDY ON RABBITS - ADDITIONAL EXPERIMENTAL DOSE TREATMENT GROUPS

Exposure Group		Treatment
1	AI3-36326 (25 % in ethanol)	9 mg/Kg (250 mg/ml wt/volume)
2	ethanol control	(0.1 ml/Kg)

(7) Following the 21-day dermal exposure, all surviving rabbits were necropsied and treated the same as the initial study.

c. Avian Toxicity Studies.[1,2,3] Preliminary wildlife hazard evaluation studies were conducted using two captive reared avian species, the wild mallard duck (Anas platyrhynchos) and the native bobwhite quail, (Colinus virginianus). First, a study[1] was performed to evaluate technical grade AI3-36326-c for acute oral toxicity. Birds were randomly assigned to one of six treatment groups with (398, 631, 1000, 1590 and 2510 mg/Kg of AI3-36326-c or a corn oil control) five birds of each sex per group. The birds were individually weighed and dosed on the basis of milligram of material per kilogram of body weight. The test compound was dissolved in corn oil and a single dose intubated directly into the crop via a stainless steel catheter. Control birds received equivalent volumes of corn oil only. Signs of toxicity and mortality were recorded daily throughout the study. The LD_{50}'s were analyzed statistically by probit analysis. A feeding study[2] was then performed to determine the subacute toxicity of AI3-36326-c in the Mallard duck through a dietary exposure to the test material. The birds were randomly assigned to the treatment groups outlined in Table 5 without regard to sex. The experimental material and the lab standard dieldrin§§ were dissolved in corn oil in concentrations such that the addition of two parts (by weight) of each solution to 98 parts of the standard game bird starter ration resulted in the logarithmic series of dosage levels listed below. The ducks were exposed to the appropriate dietary concentrations for 5 days and then basal diet only for an additional 3-day observation period. The control birds received the basal diet throughout the study. Body weights were recorded at the start and termination of the study and feed consumption was also measured. The LD_{50}'s were analyzed statistically by probit analysis. A study[3] was also conducted to determine the subacute toxicity of AI3-36326-c

§§ There is a significant historical data base for a dieldrin standard in acute avian toxicology research. Wildlife International utilizes this standard periodically throughout the year to characterize variations in population sensitivity.

in the Bobwhite quail through dietary exposure to the test material. The test material was prepared, the quail treated and experimental data handled similarly as described in the previous Mallard Duck Dietary LC_{50} study. Test birds were randomly assigned to the treatment groups outlined in Table 6 without regard to sex.

TABLE 5. EIGHT-DAY DIETARY LC_{50} IN MALLARD DUCK EXPERIMENTAL DOSE TREATMENT GROUPS

Treatment	Birds Per Group	Dietary Concentration (ppm)
Control	10	Basal Diet Only[1]
Lab Standard (dieldrin)	10	72, 100, 139, 193, and 269
AI3-36326-c	10	562, 1000, 1780, 3160 and 5620

TABLE 6. EIGHT-DAY DIETARY LC_{50} IN BOBWHITE QUAIL EXPERIMENTAL DOSE TREATMENT GROUPS

Treatment	Birds Per Group	Dietary Concentration (ppm)
Control	10	Basal Diet Only[1]
Lab Standard (dieldrin)	10	15.9, 25.1, 39.8, 63.1 and 100
AI3-36326-c	10	562, 1000, 1780, 3160 and 5620

d. Aquatic Toxicity Studies. Preliminary acute toxicity tests[4,5,6] were conducted with AI3-36326 on warm and cold water fish species, bluegill sunfish (*Lepomis macrochirus*) and rainbow trout (*Salmo gairdneri*). An additional study[7,8] was performed to evaluate the acute toxicity of the candidate insect repellent with the invertebrate *Daphnia magna* cultured at the ABC facility. The toxicity evaluation was performed by determining the LC_{50} levels of the candidate compound during 48, 72 and 96 hours, static chamber, exposure periods. The trout used in these tests were obtained from Spring Creek Trout Hatchery in Lewistown, Montana. The bluegill sunfish used in the tests were obtained from Aquatic Control, Inc. in Seymour, Indiana. The static fish bioassays were conducted in 5-gallon glass vessels containing 15 liters of soft reconstituted water. The water was composed of the following compounds in the amounts stated per liter of deionized water:

48 mg $NaHCO_3$
30 mg $CaSO_4$
30 mg $MgSO_4$
2 mg KCl

Test concentrations were obtained by transferring appropriate aliquots from a working solution of AI3-36326, prepared in nanograde acetone warmed to room temperature (22°C), directly into the test chambers. Control chambers received a 10 ml aliquot of nanograde acetone (quantity received by the high test concentration). Based on 48-hour, range-finding exposures, five concentrations of the test compound, ranging in a logarithmic series from 10 to 100 mg/l, with 10 fish per concentration per species were selected for definitive bioassay. The fish were added to the test chambers by random assignment within 30 minutes after addition of test material aliquots. Daphnia magna were used in the invertebrate aquatic toxicity study. Bioassays were conducted in 250 ml glass beakers containing 200 ml of ABC well water. Vessels were maintained at 20°C(±1.0). Photoperiods were controlled to give 16-hours daylight and 8-hours darkness. Based on initial range finding experiments, six concentrations were selected for the bioassay. Test concentrations were a logarithmic series ranging from 5.6 to 100 mg/l. Nanograde acetone was used in the preparation of all working stock solutions from which all test concentrations were prepared.

e. In Vitro Mutagenicity Studies. A study[9,10] was performed to evaluate AI3-36326-d for its ability to induce forward mutation in the L5178Y TK+/-mouse lymphoma cell line, as assessed by colony growth in the presence of 5-bromo-2' deoxyuridine (BrD U) or 5-trifluorothymidine (TFT). The test material was examined directly and in the presence of liver homogenates prepared from Fisher 344 adult male rat livers induced by Aroclor® 1254 and necessary Cofactors (CORE). The CORE consists of NADP (sodium salt) and isocitric acid. Following preliminary cytotoxicity testing, it was decided that the mutation assay would be initiated with a series of concentrations ranging from 3.13 nL/mL to 400.00 nL/mL. The positive control articles were ethylmethane sulfonate (EMS) at 0.5 uL/mL for nonactivation studies and Dimethlynitrosamine (DMN) at 0.3 uL/mL for assays performed with activation. A negative (untreated) control and solvent control were included with both tests. A study[11,12] was also performed to establish whether AI3-36326-d or its metabolites would induce gross chromosomal changes in Chinese Hamster Ovary (CHO) cells with or without an in vitro metabolic activation system. The in vitro metabolic activation system was composed of rat liver enzymes and an energy producing system. The enzymes were contained in a preparation of liver microsomes (S9 fraction)|| from rats treated with an alkylating agent, Aroclor, to induce enzymes capable of transforming chemicals to more active forms. Cells were examined 10 to 12 hours following treatment when entering mitosis for the first time after chemical exposure. Cells used in this assay (CHO-WB1) were obtained from Dr. S. Wolff, University of California, San Francisco, and were cloned in the laboratory of Dr. A. Bloom, Columbia University, New York. The original cells were obtained from an ovarian biopsy of a Chinese hamster. Test compound stock solution was

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® Aroclor is a registered trademark of the Monsanto Company, St. Louis, Missouri.

|| The S9 fraction from male Fisher or Sprague Dawley rats induced with Aroclor 1254, was purchased from Litton Biological Products, Inc., Kensington, MD 20795.

prepared in dimethylsulfoxide (DMSO). Serial dilutions were carried out to achieve the desired final concentrations by the addition of 0.1 mL of test solution per 10 mL culture (Table 7). Negative controls contained only CHO cells and culture medium. Solvent controls contained solvent for the test article (DMSO) at a final concentration of 1 percent. The positive control agents were triethylenemelamine (TEM) dissolved in H_2O at 0.5 ug/mL for nonactivation studies and cyclophosphamide (CP) dissolved in H_2O at 25 ug/mL for assays performed with activation. Table 7 lists the dose treatment groups used during this study.

TABLE 7. CHROMOSOME ABBERRATIONS IN CHO CELLS AI3-36326-D EXPERIMENTAL DOSE TREATMENT GROUPS

Test No. 1	Test No. 2
Without Activation	
0.94 nL/mL	46.88 nL/mL
3.75	93.75
15.00	187.50
60.00	200.00
240.00	250.00
With Activation	
0.8 nL/mL	15.0 nL/mL
4.0	30.0
20.0	60.0
100.0	75.0
500.0	100.0
	120.0
	150.0

An unscheduled DNA synthesis (UDS) assay using rat liver cell cultures was performed to detect DNA damage caused by AI3-36326-d measuring UDS in primary rat hepatocytes in vitro.[13,14] The existence and degree of DNA damage was inferred from an increase in nuclear grain counts compared to untreated hepatocytes. The indicator cells for this assay were hepatocytes obtained from adult, male, Fisher 344 rats purchased from Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Following a preliminary cytotoxicity test, the USD assay was initiated with a series of 8 concentrations from 7.8 nL/mL to 400.0 nL/mL. Dimethylsulfoxide was chosen as the diluent for the test solution. The DMSO (1 percent) was also the negative control. The positive control for this assay was 2-acetly aminofluorene (2-AAF) at 50 ug/ml.

f. Dominant Lethal Studies in Mice. An acute toxicity study[15] was performed to define the acute oral LD_{50} in male mice. This information was necessary to determine dose group concentrations for a dominant lethal study. The animals used in these studies were 8-10 week old CF-1 mice from a closed colony maintained at OMNI Research Labs. Mice were randomly divided into treatment groups, six mice to a group. The test compound (2000, 2510, 3160, 3980 and 5010 mg/Kg) was administered by gavage. The negative control group

received 0.20 ml of corn oil. Food was withheld for 4 hours prior to dosing. Animals were observed for toxic signs and or death for 14 days following dosing. A dominant lethal study was performed with mice to determine whether N,N-dipropylcyclohexanecarboxamide would produce a mutagenic reaction in male germ cells[15]. The male mice were randomly divided into 5 groups (10 per group). The negative control received 0.20 mL of corn oil. The test animals received 1/5, 1/10 and 1/100 of the LD_{50}, (560, 280 and 28 mg/Kg) administered daily for 5 days by gavage. On the fifth day, the positive control group received triethylenemelamine (TEM) 0.30 mg/Kg, i.p. Males were rested for 2 days and then sequentially co-housed with two females per week for 7 weeks. Each mating period was 5 days. Females were sacrificed by cervical dislocation 13 days after the midweek of their cohabitation. Each uterus was examined for living and dead implants. Dead implants were further divided into early and late fetal implants. The following is a list of parameters calculated for each dosage each week.

(a) Fertility Index (pregnant females per mated females).

(b) Implantations per pregnant female.

(c) Number of early fetal death implants per pregnant female.

(d) Number of late fetal death implants per pregnant female.

(e) Number of females with one or more early fetal death implants per pregnant female.

(f) Number of females with two or more early fetal death implants per pregnant female.

(g) Early fetal death implants/total implants.

Student's t-test was used to compare each treatment group to the negative control.

6. RESULTS.

a. Subchronic dermal study

(1) Test data collected during this 21-day dermal study (skin irritation, body weight, food consumption, organ-to-body weight ratios and blood chemistry values) were statistically compared with the data from their respective control groups using the Student "t" test (Tables D-1 to D-14, Appendix D) for a summary of data. N,N-dipropylcyclohexanecarboxamide applied for 7 days at the EHD level (9 mg/Kg technical grade solution) to the shaved backs of both male and female rabbits caused slight to well defined erythema and very slight to moderate edema. This candidate compound exhibited a dose dependent irritation reaction during the 21-day study (Tables D-1 and D-2, Appendix D). Due to the dermal irritation produced by the technical grade material, two additional groups of each sex were added to the study, 9 mg/Kg (25 percent in ETOH) and an ETOH control. After 7 days of application no to well defined erythema and no to slight edema were observed in the 25 percent ETOH solution groups (Table D-1 and D-2, Appendix D). Almost no response was observed in the untreated or ETOH control groups (Tables D-1 and D-2, Appendix D).

(2) The body weights of the male high dose group (450 mg/Kg technical grade) were the only weights significantly lower as compared with control rabbits after the first week of application. This groups' mean body weight remained significantly lower during the entire 21-day study. A significant decrease in food consumption per gram body weight occurred in the female high dose group (450 mg/Kg technical grade) for the first 10 days of the study while a significant decrease occurred during the entire study in the male high dose group.

(3) At the time of necropsy, the organ-to-body weight ratios of the heart, kidney, pituitary and thyroid of the male high dose group (450 mg/Kg technical grade) were significantly higher when compared to the control group. The kidney organ to body weight ratios of the female rabbits were significantly higher in all three technical grade dose groups and increased directly with the increase in dose of test material applied.

(4) Results of hematology and clinical chemistry tests described earlier are listed in Tables E-1 to E-41, Appendix E. Gamma glutamyl transferase (GGT), an enzyme found mainly in the kidneys, increased in value as compared to controls in the technical grade high dose groups (Tables E-12 and E-13, Appendix E). These values increase to a statistically significant level in the female rabbits during weeks two and three and male rabbits during week three. Other variations were sporadic in nature and not felt to be caused by the administration of the test compound.

(5) Gross and microscopic evaluation of tissues from these rabbits revealed no histological evidence of a systemic compound related effect other than skin irritation. Compound related skin irritation was present in treated sections from rabbits at all technical grade dosage levels. Epithelial necrosis with re-epithelialization was observed at the high dose level. Other changes observed in a dose dependent fashion either by increased incidence and/or severity when compared to control animals were acanthosis, hyperkeratosis, parakeratosis, papillary epithelial hyperplasia, dermal scarring and edema of the tips of dermal papillae. Other microscopic tissue changes were either sporadic or occurred with approximately equal frequency and degree in controls and test rabbits and were judged unrelated to the experimental compound.[16]

b. Avian Toxicity Study. In the acute oral LD_{50} in Bobwhite quail, the candidate insect repellent was dissolved in corn oil and intubated directly into the crop via a stainless steel catheter. Toxic signs exhibited by the birds at the lethal doses of 1590 and 2510 mg/Kg were depression, reduced reaction to external stimuli (sound and movement), wing droop, loss of coordination, lower limb weakness, dyspnea, prostrate posture, loss of righting reflex and lower limb rigidity. All birds in the 398 and 631 mg/Kg groups and the negative controls were normal in appearance and behavior throughout the test period. There was a dose related loss of body weight at the 1590 and 2510 mg/Kg levels through day 3 of the study and slight reduction in food consumption for the first 7 days at these dose levels. The oral LD_{50} for Bobwhite quail was calculated following a 14-day observation period and is listed in Table 8[1]. In the two dietary 8-day LC_{50} studies, with Bobwhite quail and Mallard ducks, the test material and the positive control (dieldrin) were dissolved in corn oil before their addition to the standard game bird starter ration. Toxic signs noted in the quail prior to

death in the 39.8, 63.1 and 100.0 ppm dosage levels of the dieldrin included reduced reaction to external stimuli (sound and movement), wing droop, loss of coordination, lower limb weakness, prostrate posture and loss of the righting reflex. A slight reduction in body weight gain at 15.9 ppm, and a dose related reduction in food consumption at 39.8 ppm through 100 ppm was also observed. There were no deaths at any dose level (562 ppm to 5620 ppm) and no overt symptoms of toxicity exhibited in Bobwhite's with the experimental material (AI3-36236). However, a dose related reduction in food consumption was seen in the 3160 ppm and 5620 ppm dose groups. In the Mallard duck study toxic signs in the 100 ppm positive control group included lethargy with a few birds displaying wing drop, loss of coordination, lower limb weakness and possible hyperexcitability. In the 139 and 193 ppm dose groups the birds also exhibited some depression and a reduced reaction to sound and movement. Muscle tremors were added to the list of signs described above at the 269 ppm dose level. A slight reduction of body weight gain was observed at all dose levels and a reduction in food consumption at 193 and 269 ppm dose groups. In the test material group only one duck was found dead at 3160 ppm. Autolysis precluded determination of the cause of death. No other deaths occurred in the Mallard duck at any level tested. The appearance, behavior, food consumption and weight gain were also not affected in these birds at any dose level tested. All control birds in both studies were normal in appearance and behavior throughout the test periods. The LC_{50} concentrations were calculated for each study following the 5-day exposure and the 3-day observation period and are listed in Table 8.[2,3]

c. Aquatic Toxicity Studies. An acute toxicity study of AI3-36326 was performed with a warm water fish Bluegill sunfish and a cold water fish, Rainbow Trout. Water quality parameters of temperature, dissolved oxygen and pH were measured at the termination of the test and were within acceptable limits. The predicted, LC_{50} values and their 95 percent confidence intervals for the candidate repellent AI3-36326 and the reference material Antimycin A***, a piscicide, are listed in Table 9.[5,6] A static bioassay of AI3-36326 on Daphnia magna was performed to determine the 24- and 48-hour LC_{50} levels. Water quality parameters of temperature, dissolved oxygen and pH were measured at the termination of the test and were within acceptable limits. The predicted LC_{50} values and the 95 percent confidence intervals for the candidate repellent AI3-36326 are listed in Table 10. Some abnormal behavior was observed in all the test exposure concentrations as compared to the acetone control. The immobilization of organisms and surfacing behavior was attributed to the presence of AI3-36326 in the water.[7,8]

*** Antimycin A is a reference standard obtained from Sigma Chemical Company, Type III, crystalline, Lot No. 125c-0152 used to characterize variations in population sensitivity.

TABLE 8. COMPARISON OF TOXIC RESPONSES IN BOBWHITE QUAIL AND THE MALLARD DUCK

Animal	Test Compound	Treatment	Diluent	Lethal Value	95% C.L.	Slope
Bobwhite Quail	AI3-36326	Oral LD_{50}	Corn Oil	2199 (mg/Kg)	(1866 - 2592 mg/kg)	9.2
Bobwhite Quail	AI3-36326	Dietary LC_{50}	Corn Oil	>5620 ppm	-	-
Bobwhite Quail	Lab Standard*	Dietary LC_{50}	Corn Oil	32 ppm	(28 - 36 ppm)	12.8
Mallard Duck	AI3-36326	Dietary LC_{50}	Corn Oil	>5620 ppm	-	-
Mallard Duck	Lab Standard*	Dietary LC_{50}	Corn Oil	217 ppm	(171-274 ppm)	5.0

TABLE 9. COMPARISON OF TOXIC RESPONSES IN BLUEGILL SUNFISH AND RAINBOW TROUT

Species	Test Compound	Treatment	LC_{50} mg/L (ppm)	95% C.L
Bluegill Sunfish	AI3-36326	24 hr LC_{50}	36	18-56
Bluegill Sunfish	AI3-36326	48 hr LC_{50}	36	18-56
Bluegill Sunfish	AI3-36326	96 hr LC_{50}	28	18-56
Bluegill Sunfish	AI3-36326	96 hr (No observable effect)	18	
Bluegill Sunfish	Antimycin A	24 hr LC_{50}	0.00012	
Bluegill Sunfish	Antimycin A	48 hr LC_{50}	0.00011	0.000075-0.00014
Bluegill Sunfish	Antimycin A	96 hr LC_{50}	0.00010	0.000082-0.00013
Rainbow Trout	AI3-36326	24 hr LC_{50}	42	32-56
Rainbow Trout	AI3-36326	48 hr LC_{50}	42	32-56
Rainbow Trout	AI3-36326	96 hr LC_{50}	42	32-56
Rainbow Trout	AI3-36326	96 hr (No observable effect)	18	
Rainbow Trout	Antimycin A	24 hr LC_{50}	0.00010	0.000075-0.00014
Rainbow Trout	Antimycin A	48 hr LC_{50}	0.000091	0.000042-0.00014
Rainbow Trout	Antimycin A	96 hr LC_{50}	0.000056	0.000042-0.000075

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TABLE 10. THE ACUTE TOXICITY OF AI3-36326 TO DAPHNIA MAGNA

Test Compound	Treatment	LC_{50} mg/L(ppm)	95% C.L.
AI3-36326	24 hours	70.0	58 - 89
AI3-36326	48 hours	29.0	24 - 34
AI3-36326	48 hour (no effect level)	5.6	-

d. In Vitro Mutagenicity Studies.

(1) The L5178Y TK +/- mouse lymphoma forward mutation assay with AI3-36326-d was performed with stock solutions (100 nL/mL) prepared in DMSO just prior to use. These stock solutions were diluted 1:100 into tubes of culture medium containing the cells in order to initiate the treatments. In the preliminary cytotoxicity testing, the 24-hour cell growth was reduced by exposures to 25 nL/mL, and treatments with 500 nL/mL were completely lethal. No evidence for mutagenesis by the test material was obtained with or without metabolic activation. All of the assayed treatments from 3.13 nL/mL to 300 nL/mL were moderately toxic but not dose related. Treatments with 400 nL/mL under both test conditions were completely lethal to the cells. The average cloning efficiencies of the negative controls (solvent and untreated) varied from 73 percent without activation to 91 percent with activation. The negative control mutant frequencies were in the normal range, and the positive control compounds induced normal mutant frequencies that were greatly in excess of the negative controls.[10]

(2) A mutagenicity evaluation was performed in CHO Cells. The candidate insect repellent was diluted with dimethylsulfoxide (24 nL/mL). No aberrations were found in cultures without metabolic activation exposed to concentrations of 0.94 to 15.0 nL/mL and the slight increase at 60 nL/mL was not significant. However, 19.8 percent abnormal cells were present in the 240 nL/mL cultures. Ten of these were endoreduplicated cells ("E"). Endoreduplication is a disturbance of the cell division process rather than direct chromosomal damage. These cells occur at a frequency of approximately 1 in 50 to 1 in 1000 in untreated cultures and the appearance of 10 such cells here is unusual. There were also 11 chromatid breaks and fragments, only a slight increase over control levels. The test was repeated to examine the top dose ranges more closely. In the second test the negative control was again normal and positive controls exhibited large amounts of damage. No increase in aberrations was found at doses from 46.9 to 200 nL/mL without metabolic activation. The compound was toxic at 250 nL/mL and 13 readable cells were found. No increase in endoreduplication over normal levels was found. In cultures exposed to the test compound with a metabolic activation system, no significant increases in aberrations were found in doses ranging from 15 to 150 nL/mL. Doses above this level were found to be toxic.[12]

(3) A study was performed to evaluate AI3-36326-d's potential to cause DNA damage in primary rat liver cells. In preliminary cytotoxicity testing, no apparent toxicity was caused by treatments with concentrations up

to 62.5 nL/mL. Some morphological evidence of toxicity was observed at 125 to 250 nL/mL however, complete lethality was obtained within 2 hours at 500 nL/mL. The test material AI3-36326-d, did not induce a detectable level of unscheduled DNA synthesis in primary rat hepatocytes for an applied concentration range of 7.8 nL/mL to 300 nL/mL. Treatment with 400 nL/mL was excessively toxic.[14]

e. Dominant Lethal Studies in Mice.

(1) Preliminary to the dominant lethal study, an acute oral LD_{50} in male mice, was determined to be 2790 mg/Kg with a slope of 7.5. Toxic signs exhibited by the mice at lethal dosages were ataxia and bradypnea. These signs were also exhibited by several surviving mice in the first few hours of dosing. A decrease in body weight gain occurred in surviving mice in all treatment groups compared to the negative control group.

(2) During the dominant lethal study, the test compound, AI3-36326, had no effect on the fertility index or number of total or live implants per pregnancy. The data indicated an increased incidence of early fetal deaths around weeks 4-7 postexposure. None of the weekly means of early fetal deaths per pregnancy or per total implants was statistically significantly different from the negative control. Using the criteria proposed by Epstein[15] the test compound exerted a dominant lethal effect during weeks 4, 5 and 7 posttreatment in the 1/5 LD_{50} group and week 5 in the 1/10 LD_{50} treatment group. There was no dominant lethal effect in male mice treated with 1/100 of the calculated LD_{50}.[15]

7. DISCUSSION.

a. Previous studies performed by this Agency have demonstrated that AI3-36326 caused moderate irritation on the shaved skin of rabbits following a single application of technical grade material or a 25 percent (w/v) ethanol solution (reference 3, Appendix A). The repeated application of N,N-dipropylcyclohexanecarboxamide in this study produced moderate to severe erythema in the technical grade high dose concentration (450 mg/Kg). Repeated dermal exposure to large quantities of the technical grade material would be expected to cause human skin irritation if left unwashed. Repeated application of the EHD concentration (14.3 mg/Kg) 25 percent (w/v) ethanol solution represents a mild to moderate skin irritant in the rabbit under the conditions of this test.

b. There was a significant decrease in rabbit body weight and food consumption during the 21-day Dermal Study and an increase in kidney organ-to-body weight ratios following the study in the male and female technical grade high dose group rabbits. However, no evidence of compound related effects, other than skin alterations, were seen during the histological examination of tissue samples collected following this subchronic dermal study. There was a significant increase in GGT in blood samples analysed toward the conclusion of this 21-day study. Since GGT is a microsomal enzyme, its tissue levels increase in response to microsomal enzyme induction.

c. Epstein et.al.,[15] has suggested that a dominant lethal effect has occurred if in any week, the early fetal death (EFD) per pregnancy is greater than 1.00 and greater than 55 percent of pregnant females had one or more early fetal deaths. According to these criteria, in a study performed for this Agency by Omni Research Laboratories Inc., AI3-36326 exerted a dominant lethal effect during weeks 4, 5, and 7 posttreatment in the 1/5 LD_{50} group and Week 5 in the 1/10 LD_{50} treatment group even though none of the weekly means of EFD/pregnancy or per total implants was statistically significantly different from the negative control. There was no dominant lethal effect in male mice treated with 1/100 of the LD_{50} (27.90 mg/Kg). The test compound had no effect on the fertility index or number of total or live implants per pregnancy.[15]

d. The oral LD_{50} in Bobwhite quail and the 8-day dietary LC_{50}'s in the Bobwhite quail and the Mallard duck were found to be greater than 2000 and 5000 ppm, respectively.[1,2,3] These values have been suggested in literature on avian toxicology as exposure cut-off levels for relatively innocuous compounds[17,18]. It has also been suggested by the Environmental Protection Agency[19] that few (if any) pesticides will be applied at a labeled rate that will result in residues equal to or greater than these values.

e. According to the toxicity studies performed with Bluegill sunfish and Rainbow trout, the test compound AI3-36326 may be slightly toxic to aquatic life. The 96-hour LC_{50}'s (28 mg/L Bluegill sunfish and 42 mg/L Rainbow trout) were used to provide the basis for this rating.[5,6] Hann and Jensin rate the aquatic toxicity of a chemical with a 96-hour LC_{50} between the values of 10 and 100 mg/L as slightly toxic.[20]

8. CONCLUSION. It is concluded that N,N-dipropylcyclohexanecarboxamide has the potential to produce moderate to severe dermal irritation within 7 days when applied daily at 450 mg/Kg to the shaved, unwashed skin of rabbits. AI3-36326, at the projected human use level of (9 mg/Kg), as a technical grade material and as a 25 percent (w/v) ethanol solution, represents a mild to moderate skin irritant in the rabbit under the conditions stated above. Care is necessary for use of this compound around eyes. It is not expected that exposure to small amounts of this candidate insect repellent by oral and or dermal routes would present a toxic hazard to man.

9. RECOMMENDATIONS. The following recommendations are based upon good toxicological practices.

a. Recommend further evaluation of this compound with emphasis in the following areas.

(1) Continuation of subchronic studies to evaluate rodent teratology responses.

(2) Development of a subchronic study to evaluate 90-day rabbit dermal responses.

(3) Development of a preliminary 14-day feeding study to be used as a range finder for a 90-day test.

(4) Repeat the dominant lethal study of AI3-36326. The negative control during the original study exhibited results close to meeting the definition of dominant lethal effects.

b. Recommend exercising caution when handling large quantities of technical grade material. Immediate rinsing with copious amounts of water should help prevent or diminish dermal or ocular irritation from accidental exposure to the technical grade material.

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APPENDIX A

REFERENCES

1. Letter, AFPCB, Armed Forces Pest Control Board, Washington, DC, 29 November 1979, subject: Toxicological Testing of Candidate Repellant Compounds.

2. Letter, HSE-LT/WP, USAEHA, 18 July 1980, subject: Topical Hazard Evaluation Program of Candidate Insect Repellents AI3-36325, 1-(cyclohexylcarbonyl)hexahydro-1H-Azepine, AI3-36326, N,N-dipropyl-cyclohexanecarboxamide, and AI3-36328, 1-[(6 - methyl-3-cyclohexen-1-yl)carbonyl]-Pyrrolidine, Study Nos. 75-51-0833-80, 75-51-0834-80, 75-51-0835-80, October 1975 - April 1980.

3. Letter, HSHB-OT/WP, USAEHA, 31 March 1983, subject: Phase I, Preliminary Assessment of the Relative Toxicity of N,N-Dipropylcyclohexanecarboxamide, AI3-36326, in Laboratory Animals, Study No. 75-51-0233-83, November 1979 - August 1982.

4. Letter, Agriculture Research, Northeastern Region, February 14, 1980, subject: Requested Synthesis Procedure.

5. Toxicology Division Standing Operating Procedures, US Army Environmental Hygiene Agency (USAEHA), 1980 - 1982.

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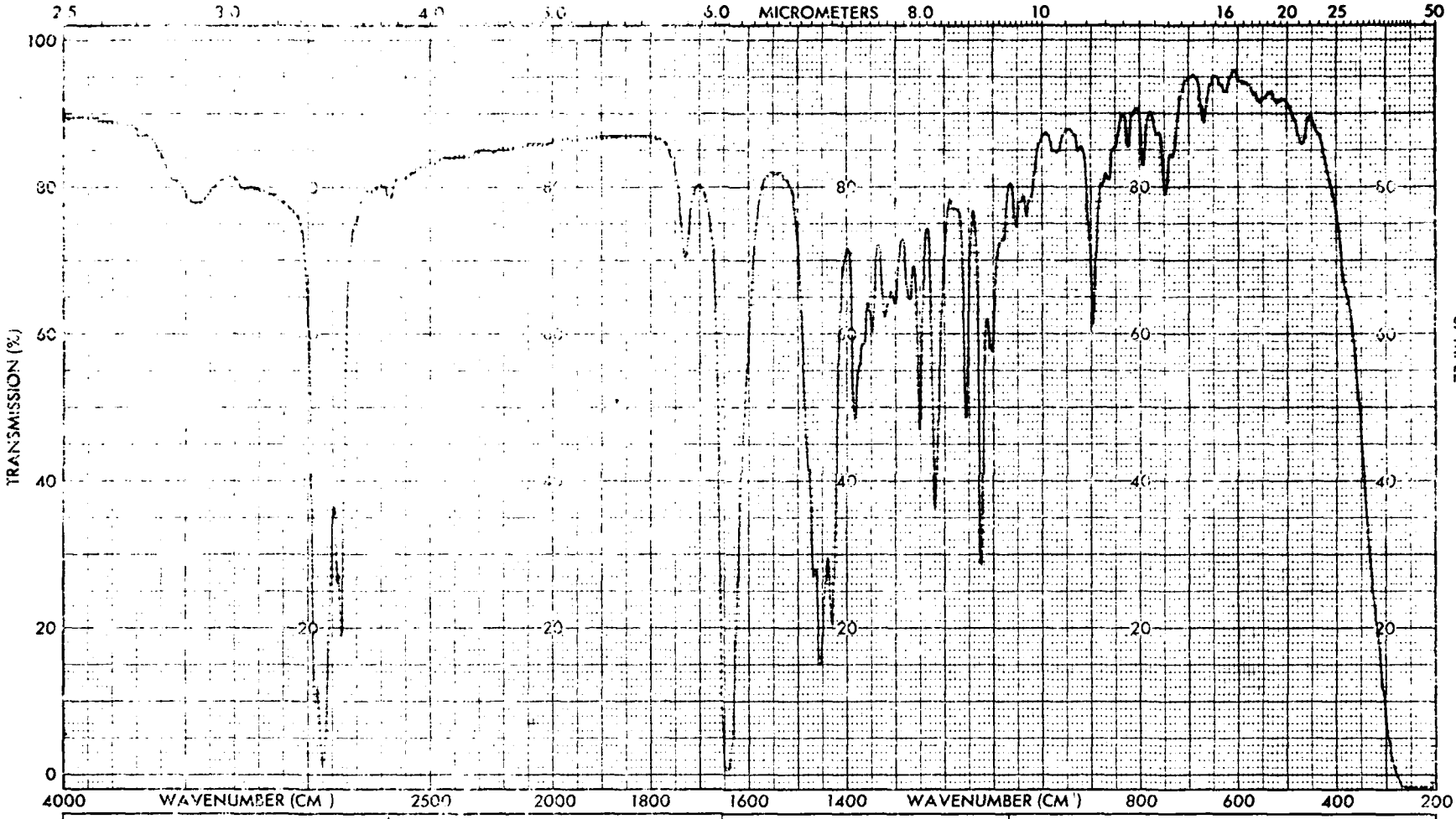
APPENDIX B

SAMPLE ANALYSIS USING INFRARED SPECTROPHOTOGRAPHY AND GAS CHROMATOGRAPHY

PERKIN-ELMER ®

CHART NO. 283-1259



ABSCISSA	ORDINATE		
EXPANSION 1	EXPANSION 1	SCAN TIME 24 min.	REP. SCAN — SINGLE BEAM —
SUPPRESSION —	% T 0-100% ABS —	RESPONSE 1	TIME DRIVE — PRE SAMPLE CHOP —
		SLIT PROGRAM 6	OPERATOR McKenzie DATE 11/26/82

SAMPLE AI3-36326C 85-SI-0233-89	REMARKS Disc T001	SOLVENT —	CELL PATH Cap. film = KBr
ORIGIN Weeks-Tox		CONCENTRATION Neat	REFERENCE Air

SAMPLE AI3-36326C REF. NO. 5727

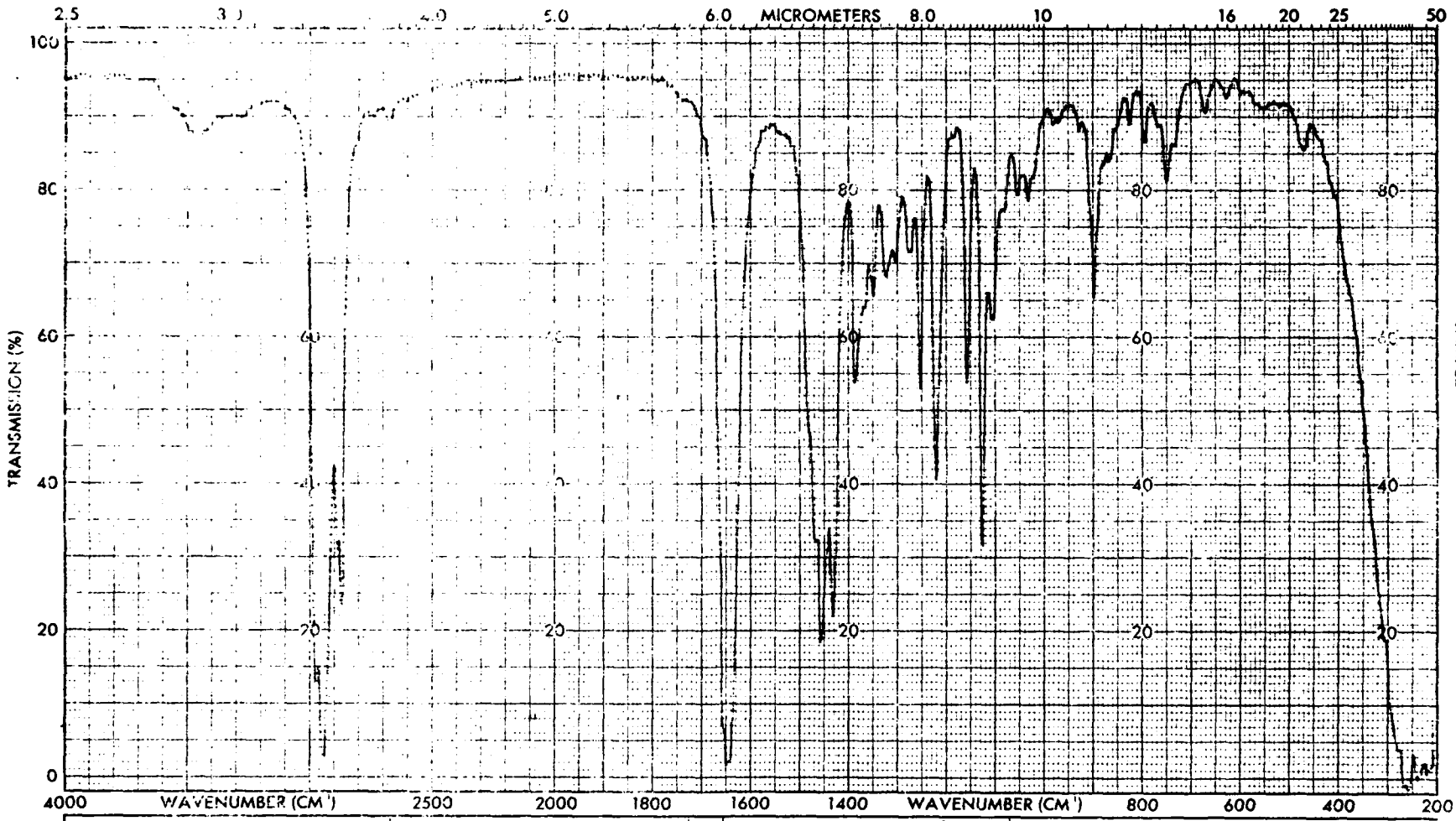
B-2.

G1

03

PERKIN ELMER ®

CHART NO. 283-1259

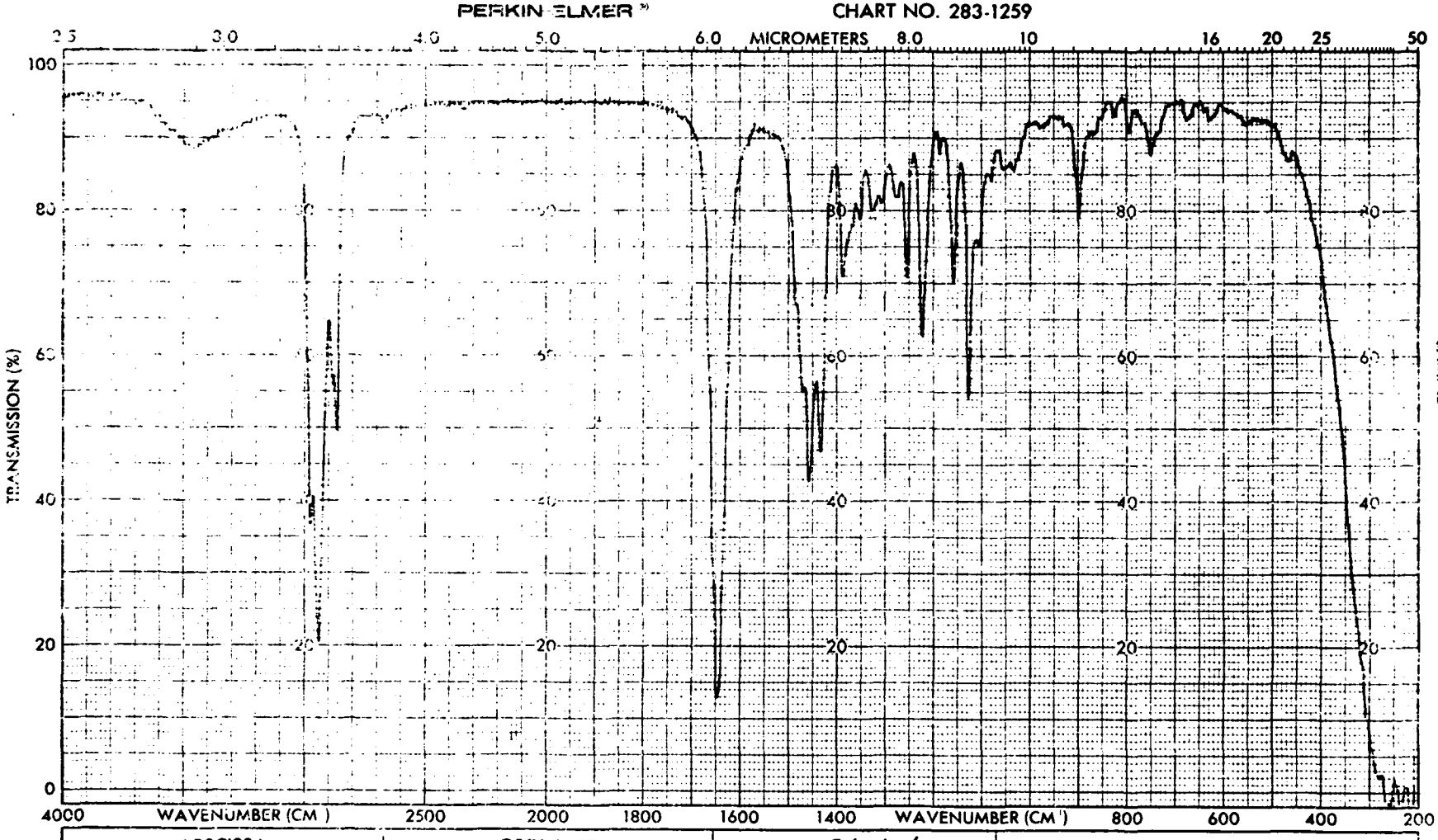


SAMPLE AI3-36326D REF NO. 5996

ABSCISSA	ORDINATE		
EXPANSION 1	EXPANSION 1	SCAN TIME 24 minutes	REP. SCAN — SINGLE BEAM —
SUPPRESSION —	% T 0 to 100 % ABS —	RESPONSE 1	TIME DRIVE — PRE SAMPLE CHOP —
		SLIT PROGRAM 6	OPERATOR McKenzie DATE 9/18/80
SAMPLE AI3-36326D	REMARKS	SOLVENT —	CELL PATH Cap film KBr
ORIGIN Weeks-Tox		CONCENTRATION Neat	REFERENCE Air

B-3

B-2



ABSCISSA	ORDINATE		
EXPANSION 1	EXPANSION 1	SCAN TIME 24 minutes	REP. SCAN — SINGLE BEAM —
SUPPRESSION —	%T 0-100% AES —	RESPONSE 1	TIME DRIVE — PRE SAMPLE CHOP —
		SLIT PROGRAM 6	OPERATOR McKenzie DATE 9/30/81
SAMPLE AI3-36326E 25-51-0233-81	REMARKS	SOLVENT —	CELL PATH Cap. film KBr
ORIGIN Weeks-Tox		CONCENTRATION Neat	REFERENCE Air

SAMPLE AI3-36326 E REF. NO. 60161

B-4

APPENDIX C

EVALUATION OF SKIN REACTIONS*

Erythema and Eschar Formation

No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate-to-severe erythema	3
Severe erythema (beet redness to slight eschar formation)	4

Edema Formation

No edema	0
Very slight (barely perceptible)	1
Slight edema (edges or area well defined by definite raising)	2
Moderate edema (edges raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4

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* An individual irritation score is equal to the sum of the scores for edema formation and erythema and eschar formation.

APPENDIX D

SUMMARY OF DATA

TABLE D-1. SKIN REACTIONS FOLLOWING DAILY SUBCHRONIC DERMAL APPLICATIONS (MALE RABBITS)

DOSE GROUP		Erythema					Edema				
		Pre	Day + 1	Day + 7	Day + 14	Day + 21	Pre	Day + 1	Day + 7	Day + 14	Day + 21
Control (untreated)	$\bar{x}$	0	-	0	0.1	0	0	-	0	0	0
	OE	0	-	0	(0-1)	0	0	-	0	0	0
9 (mg/Kg) (Tech Grade)	$\bar{x}$	0	-	1.5	1.6	1.6	0	-	2.1	2.0	1.9
	OE	0	-	(1-2)	(1-2)	(1-2)	0	-	(1-3)	(0-3)	(1-3)
90 (mg/Kg) (Tech Grade)	$\bar{x}$	0	-	1.9	1.8	1.5	0	-	2.1	2.0	1.9
	OE	0	-	(1-2)	(1-2)	(1-2)	0	-	(1-3)	(0-3)	(1-3)
450 (mg/Kg) (Tech Grade)	$\bar{x}$	0	-	2.3	2.2	2.6	0	-	3.6	3.5	3.8
	OE	0	-	(2-3)	(2-3)	(2-3)	0	-	(3-4)	(3-4)	(3-4)
9 (mg/Kg) (25% ETOH)	$\bar{x}$	0	0.3	0.4	0.9	1.9	0	0	0	0.5	1.7
	OE	0	(0-2)	(0-1)	(0-1)	(1-2)	0	0	(0-1)	(0-1)	(0-3)
ETOH Control	$\bar{x}$	0	0	0	0	0.3	0	0	0	0	0
	OE	0	0	0	0	(0-1)	0	0	0	0	0

$\bar{x}$ - mean erythema or edema score
OE - observed extremes (highest and lowest value recorded)

TABLE D-2. SKIN REACTIONS FOLLOWING DAILY SUBCHRONIC DERMAL APPLICATIONS (FEMALE RABBITS)

DOSE GROUP		Erythema					Edema				
		Pre	Day + 1	Day + 7	Day + 14	Day + 21	Pre	Day + 1	Day + 7	Day + 14	Day + 21
Control	$\bar{x}$	0	-	0	0	0	0	-	0	0	0
	OE	0	-	0	0	0	0	-	0	0	0
9 (mg/Kg)	$\bar{x}$	0	-	1.6	1.5	1.5	0	-	1.1	1.2	1.1
	OE	0	-	(1-2)	(1-2)	(1-2)	0	-	(0-2)	(0-3)	(0-3)
90 (mg/Kg)	$\bar{x}$	0	-	1.2	1.8	1.8	0	-	1.7	1.9	1.9
	OE	0	-	(1-2)	(1-2)	(1-2)	0	-	(1-3)	(1-3)	(1-3)
450 (mg/Kg)	$\bar{x}$	0	-	2.4	2.5	2.2	0	-	3.6	3.7	1.3
	OE	0	-	(2-3)	(2-3)	(2-3)	0	-	(2-4)	(2-4)	(2-4)
9 (mg/Kg) (25% ETOH)	$\bar{x}$	0	0.2	0.8	0.8	1.3	0	0	0.1	0.5	1.7
	OE	0	(0-1)	(0-2)	(0-2)	(1-2)	0	0	(0-2)	(0-2)	(1-3)
ETOH Control	$\bar{x}$	0	0	0	0	0.4	0	0	0	0	0
	OE	0	0	0	0	(0-2)	0	0	0	0	0

$\bar{x}$ - mean erythema or mean edema score
OE - observed extremes (highest and lowest value recorded)

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TABLE D-3. FOOD CONSUMPTION (FEMALE RABBITS) TECHNICAL GRADE SOLUTION

DOSE GROUP		DAY -3 to 1	DAY 1-4	DAY 4-8	DAY 8-11	DAY 11-15	DAY 15-18	DAY 18-22
Control	$\bar{x}$	43.6	31.8	44.8	31.2	40.3	30.2	37.3
		± 4.3	± 5.1	± 5.0	± 4.6	± 4.6	± 6.0	± 7.3
9 (mg/Kg)	$\bar{x}$	50.3	42.2	49.2	37.4	41.1	37.9	43.0
		± 9.6	±13.4	± 6.2	± 4.2	±15.0	± 3.2	± 4.8
	t	2.01	2.29*	1.83	3.16*	2.17	3.60	2.06
	df	18.0	18.0	18.0	18.0	18.0	18.0	18.0
	$\bar{x}$	43.7	32.4	46.0	33.9	44.7	35.3	44.4
		± 7.7	± 5.5	± 6.8	± 6.3	± 4.8	± 4.2	± 4.0
	t	0.03	0.25	0.52	1.09	2.10	2.21*	-2.70*
	df	18.0	18.0	18.0	18.0	18.0	18.0	18.0
450 (mg/Kg)	$\bar{x}$	46.4	17.6	35.6	23.3	40.4	30.7	39.2
		± 8.5	± 6.8	±10.5	± 6.7	± 7.1	± 5.7	± 7.2
	t	0.92	± 5.3*	2.45*	3.07*	0.04	0.19	0.59
	df	18.0	18.0	18.0	18.0	18.0	18.00	18.0

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
- standard deviation
t - t value
df- degrees of freedom

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TABLE D-4. FOOD CONSUMPTION (MALE RABBITS) TECHNICAL GRADE SOLUTION

DOSE GROUP		DAY -3 to 1	DAY 1-4	DAY 4-8	DAY 8-11	DAY 11-15	DAY 15-18	DAY 18-22
Control	$\bar{x}$	39.0	33.3	41.2	32.4	41.8	33.0	41.1
		±9.8	±8.7	±5.5	±6.6	±5.2	±7.1	±5.3
9 (mg/Kg)	$\bar{x}$	32.6	27.0	36.6	27.1	40.4	30.6	41.0
		±7.5	±9.1	±7.7	±3.5	±3.9	±5.9	±4.9
	t	1.64	1.58	1.53	2.22*	0.68	0.82	0.04
	df	18.0	18.0	18.0	18.0	18.0	18.0	18.0
90 (mg/Kg)	$\bar{x}$	35.5	22.9	38.1	27.8	40.8	29.5	42.8
		±6.2	±5.2	±6.9	±5.2	±5.8	±3.5	3.5
	t	0.96	3.24*	0.96	1.72	0.41	1.39	0.84
	df	18.0	18.0	18.0	18.0	18.0	18.0	18.0
450 (mg/Kg)	$\bar{x}$	37.7	7.6	15.2	14.4	34.2	25.8	32.9
		±8.6	±4.6	±10.4	±8.9	±6.3	±7.1	±10.5
	t	0.31	8.24*	6.99*	5.11*	2.87*	2.22*	2.19*
	df	18.0	18.0	18.0	18.0	17.0	17.0	17.0

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
  - standard deviation
t - t value
df- degrees of freedom

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TABLE D-5 FOOD CONSUMPTION (MALE RABBITS) 25 PERCENT in ETOH

DOSE GROUP		DAY -2 to 1	DAY 1-6	DAY 6-9	DAY 9-13	DAY 13-16	DAY 16-20
Control (ETOH)	$\bar{x}$	62.5 ±23.9	87.2 ±18.6	79.8 ±12.8	75.7 ±14.1	70.7 ±10.8	68.2 ± 9.2
9 (mg/Kg) (25% ETOH)	$\bar{x}$	62.9 ±14.2	84.3 ±14.2	71.8 12.4	71.5 ±12.9	67.1 ±13.3	64.4 ± 8.8
	t	0.05	0.40	1.43	0.83	0.66	0.96
	df	18.0	18.0	18.0	18.0	18.0	18.0

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
- standard deviation
t - t value
df- degrees of freedom

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TABLE D-6. FOOD CONSUMPTION (FEMALE RABBITS) 25 PERCENT in ETOH

DOSE GROUP		DAY -2 to 1	DAY 1-6	DAY 6-9	DAY 9-13	DAY 13-16	DAY 16-20
Control (ETOH)	$\bar{x}$	71.2 ±17.1	84.8 ±15.3	78.4 ±16.2	73.1 ±11.8	72.3 ±17.3	64.8 ±13.8
9 (mg/Kg) (25% ETOH)	$\bar{x}$	80.1 ±18.2	93.1 ±16.4	81.9 ±14.1	76.8 ±12.9	75.1 ±13.5	70.0 ±10.8
	t	1.10	1.2	0.50	0.66	0.39	0.90
	df	17.0	17.0	17.0	17.0	17.0	17.0

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - value
df - degrees of freedom

TABLE D-7. MEAN BODY WEIGHTS (Kg) SUBCHRONIC DERMAL (MALE RABBITS) TECHNICAL GRADE SOLUTION

DOSE GROUP		WEEK -6	WEEK -5	WEEK -4	WEEK -3	WEEK -2	WEEK -1	WEEK 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	2.38	2.51	2.69	2.89	3.07	3.14	3.22	3.24	3.33	3.38
		±0.19	±0.20	±0.19	±0.20	±0.20	±0.23	±0.24	±0.23	±0.23	±0.25
9 (mg/Kg)	$\bar{x}$	2.44	2.56	2.73	2.92	3.08	3.15	3.27	3.29	3.37	3.52
		±0.15	±0.15	±0.16	±0.20	±0.22	±0.23	±0.25	±0.28	±0.27	±0.25
	t	0.79	0.57	0.54	0.35	0.10	0.12	0.42	0.39	0.35	1.20
	df	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0
90 (mg/Kg)	$\bar{x}$	2.40	2.55	2.75	2.91	3.10	3.15	3.27	3.27	3.35	3.47
		±0.11	±0.13	±0.17	±0.20	±0.22	±0.22	±0.24	±0.21	±0.24	±0.24
	t	0.30	0.57	0.75	0.28	0.34	0.18	0.48	0.28	0.14	0.77
	df	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0
450 (mg/Kg)	$\bar{x}$	2.35	2.53	2.71	2.91	3.10	3.12	3.22	3.00	2.98	3.02
		±0.11	±0.15	±0.19	±0.25	±0.27	±0.27	±0.27	±0.28	±0.21	±0.21
	t	0.48	0.25	0.33	0.26	0.33	0.14	0.03	2.14*	3.48*	3.21*
	df	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
  - standard deviation
t - t value
df- degrees of freedom

TABLE D-8. MEAN BODY WEIGHTS (Kg) SUBCHRONIC DERMAL (FEMALE RABBITS) TECHNICAL GRADE SOLUTION

DOSE GROUP		WEEK -6	WEEK -5	WEEK -4	WEEK -3	WEEK -2	WEEK -1	WEEK 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	2.45	2.64	2.81	3.00	3.18	3.32	3.46	3.49	3.60	3.68
		±0.22	±0.25	±0.24	±0.28	±0.25	±0.29	±0.33	±0.31	±0.33	±0.35
9 (mg/Kg)	$\bar{x}$	2.29	2.55	2.77	3.00	3.22	3.36	3.43	3.57	3.70	3.86
		±0.22	±0.33	±0.34	±0.40	±0.45	±0.49	±0.66	±0.50	±0.52	±0.53
	t	1.80	0.68	0.31	0.01	0.22	0.26	0.14	0.45	0.50	0.89
	df	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0
90 (mg/Kg)	$\bar{x}$	2.42	2.58	2.76	2.99	3.19	3.35	3.56	3.51	3.63	3.77
		±0.20	±0.25	±0.30	±0.36	±0.39	±0.40	±0.27	±0.40	±0.42	±0.42
	t	0.33	0.59	0.37	0.04	0.02	0.20	0.79	0.16	0.17	0.52
	df	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0
450 (mg/Kg)	$\bar{x}$	2.22	2.63	2.84	3.03	3.26	3.34	3.43	3.33	3.39	3.51
		±0.75	±0.18	±0.21	±0.24	±0.26	±0.23	±0.25	±0.28	±0.33	±0.33
	t	0.93	0.14	0.29	0.30	0.64	0.15	0.20	1.18	1.46	1.12
	df	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df - degrees of freedom

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TABLE D-9. MEAN BODY WEIGHT (Kg) SUBCHRONIC DERMAL (MALE RABBITS) 25 PERCENT IN ETOH

DOSE GROUP		-1 DAY PRE-EXPOSURE	+1 WEEK	+2 WEEKS	+3 WEEKS
Control (ETOH)	$\bar{x}$	1.47 ±0.14	1.84 ±0.10	2.02 ±0.11	2.20 ±0.19
9 (mg/Kg) (25 PERCENT ETOH)	$\bar{x}$	1.45 ±0.15	1.84 ±0.17	2.01 ±0.19	2.15 ±0.21
	t	0.22	0.05	0.17	0.53
	df	18.0	18.0	18.0	18.0

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
  - standard deviation
t - t value
df- degrees of freedom

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TABLE D-10. MEAN BODY WEIGHTS (Kg) SUBCHRONIC DERMAL (FEMALE RABBITS) 25% in ETOH

DOSE GROUP		-1 DAY PRE-EXPOSURE	+1 WEEK	+2 WEEKS	+3 WEEKS
Control (ETOH)	$\bar{x}$	1.50 ±0.11	1.86 ±0.16	2.03 ±0.18	2.16 ±0.17
9 (mg/Kg) (25% ETOH)	$\bar{x}$	1.50 ±0.11	1.89 ±0.14	2.07 ±0.15	2.21 ±0.14
	t	0.06	0.50	0.58	0.73
	df	18.0	17.0	17.0	17.0

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df - degrees of freedom

TABLE D-11. MEAN ORGAN-TO-BODY WEIGHT RATIOS (g/100g) SUBCHRONIC DERMAL (MALE RABBITS) TECHNICAL GRADE SOLUTION

DOSE GROUP		LIVER	SPLEEN	HEART	KIDNEYS	TESTES	ADRENALS	PITUITARY	THYROID
Control	$\bar{x}$	35.04	0.43	2.11	6.24	1.43	0.10	0.006	0.09
		±5.86	±0.16	±0.19	±0.82	±0.24	±0.02	±0.002	±0.02
9 (mg/Kg)	$\bar{x}$	31.99	0.37	2.09	5.50	1.38	0.08	0 007	0.08
		±5.61	±0.20	±0.17	±0.35	±0.18	±0.02	±0.002	±0.01
	t	1.19	0.76	0.36	2.61*	0.55	1.57	1.344	2.53*
	df	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0
90 (mg/Kg)	$\bar{x}$	31.63	0.34	2.19	6.59	1.46	0.10	0.007	0.12
		±4.67	±0.14	±0.25	±1.05	±0.24	±0.03	±0.001	±0.03
	t	1.44	1.39	0.81	0.84	0.25	0.75	1.376	2.38*
	df	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0
450 (mg/Kg)	$\bar{x}$	34.03	0.52	2.46	9.67	1.62	0.11	0.009	0.13
		±4.04	±0.24	±0.23	±1.05	±0.22	±0.02	±0.002	±0.02
	t	0.14	1.00	3.49*	7.78*	1.76	0.89	3.691*	3.52*
	df	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
  - standard deviation
t - t value
df- degrees of freedom

TABLE D-12. MEAN ORGAN-TO-BODY WEIGHT RATIOS (g/100g) SUBCHRONIC DERMAL (FEMALE RABBITS) TECHNICAL GRADE SOLUTION

DOSE GROUP		LIVER	SPLEEN	HEART	KIDNEYS	ADRENALS	PITUITARY	THYROID
Control	$\bar{x}$	29.83	0.38	2.32	4.99	0.11	0.009	0.10
		±5.80	±0.12	±0.40	±0.40	±0.03	±0.002	±0.03
9 (mg/Kg)	$\bar{x}$	28.94	0.35	2.30	5.62	0.10	0.008	0.12
		±4.54	±0.08	±0.54	±0.83	±0.02	±0.001	±0.02
	t	0.38	0.66	0.11	2.14*	1.30	1.987	1.44
	df	18.0	18.0	18.0	18.0	17.0	18.0	18.0
90 (mg/Kg)	$\bar{x}$	29.34	0.37	2.12	5.97	0.09	0.01	0.11
		±4.70	±0.11	±0.34	±1.16	±0.02	±0.00	±0.02
	t	0.21	0.10	1.25	2.51*	2.15*	1.30	0.25
	df	18.0	18.0	18.0	18.0	17.0	18.0	18.0
450 (mg/Kg)	$\bar{x}$	29.80	0.45	2.73	8.14	0.11	0.010	0.11
		±3.92	±0.10	±0.99	±0.90	±0.02	±0.001	±0.01
	t	0.02	1.46	1.21	10.10*	0.67	2.064	0.58
	df	18.0	18.0	18.0	18.0	17.0	18.0	18.0

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df- degrees of freedom

TABLE D-13. MEAN ORGAN-TO-BODY WEIGHT RATIOS (g/100g) SUBCHRONIC DERMAL (MALE RABBITS) 25 PERCENT in ETOH

DOSE GROUP		LIVER	SPLEEN	HEART	KIDNEYS	ADRENALS	PITUITARY	THYROID
Control (ETOH)	$\bar{x}$	46.89	0.53	2.51	6.85	0.09	0.020	0.93
		± 8.95	±0.20	±0.38	±0.75	±0.02	±0.025	±0.17
9 (mg/Kg) (25% in ETOH)	$\bar{x}$	48.07	0.72	2.50	7.69	0.10	0.011	0.80
		± 7.33	±0.57	±0.25	± 1.63	±0.21	±0.002	±0.24
	t	0.32	1.011	0.02	1.49	0.74	1.17	1.42
	df	18.00	18.00	18.00	18.00	18.00	18.00	18.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
- standard deviation
t - t value
df- degrees of freedom

TABLE D-14. MEAN ORGAN-TO-BODY WEIGHT RATIOS (g/100g) SUBCHRONIC DERMAL (FEMALE RABBITS) 25 PERCENT in ETOH

DOSE GROUP		LIVER	SPLEEN	HEART	KIDNEYS	ADRENALS	PITUITARY	TYROID
Control (ETOH)	$\bar{x}$	44.70	0.42	2.52	6.79	0.12	0.013	0.16
		± 6.46	±0.10	±0.24	±0.55	±0.02	±0.006	±0.03
9 (mg/Kg) (25% in ETOH)	$\bar{x}$	44.33	0.70	2.53	7.46	0.11	0.012	0.19
		± 5.89	±0.42	±0.40	±1.45	±0.04	±0.002	±0.07
	t	0.13	2.00	0.05	1.36	0.43	0.69	1.54
	df	17.00	17.00	17.00	17.00	17.00	17.00	17.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
  - standard deviation
t - t value
df- degrees of freedom

APPENDIX E

MEAN BLOOD VALUES

TABLE E-1. MEAN BLOOD VALUES - ASPARTATE AMINOTRANSFERASE - (IU/1) SUBCHRONIC DERMAL (MALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	17.75	9.06	14.6	12.0	21.0	16.6	12.4	19.4
		±4.03	±4.03	±1.81	±5.33	±3.08	± 3.57	±3.36	±2.7
9 (mg/Kg)	$\bar{x}$	18.66	10.00	16.4	10.2	18.6	15.0	11.8	20.4
		±8.14	±2.44	±3.50	±5.44	±5.85	±6.55	± 4.14	± 8.7
	t	0.19	0.18	1.01	0.52	0.81	0.47	0.25	0.25
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	17.25	11.00	16.2	11.4	19.4	19.8	17.6	22.2
		±1.70	±6.89	±4.08	±5.45	±7.50	±12.45	±15.40	± 10.4
	t	0.22	0.39	0.8	0.17	0.44	0.55	0.73	0.58
	df	6.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
450 (mg/Kg)	$\bar{x}$	20.5	15.00	20.2	20.6	24.4	31.2	23.4	29.2
		±4.94	±6.78	±4.20	±9.39	±3.84	±17.00	±10.08	± 14.3
	t	0.74	1.52	2.73*	1.77	1.54	1.87	2.31*	1.50
	df	4.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df- degrees of freedom

TABLE E-2. MEAN BLOOD VALUES - ASPARTATE AMINOTRANSFERASE (IU/1) SUBCHRONIC DERMAL (FEMALE) RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	17.5	17.8	10.6	12.4	11.4	16.6	17.4	25.0
		±2.64	±7.98	±2.50	±2.07	±4.72	±4.39	±6.26	±4.0
9 (mg/Kg)	$\bar{x}$	13.6	15.25	20.4	12.2	11.25	21.25	21.25	20.4
		±7.09	±5.56	±14.06	±8.55	±1.70	±19.31	±9.04	±4.4
	t	1.03	0.53	1.53	0.05	0.05	0.52	0.44	0.63
	df	7.00	7.00	8.00	8.00	7.00	7.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	22.4	14.4	11.8	14.00	12.6	18.75	19.00	16.5
		±10.50	±2.30	±2.28	±3.36	±2.96	±7.54	±7.17	±8.6
	t	0.89	0.91	0.79	0.88	0.48	0.53	0.37	1.99
	df	7.00	8.00	8.00	7.00	8.00	7.00	8.00	7.00
450 (mg/Kg)	$\bar{x}$	21.00	13.6	11.4	16.2	17.2	14.5	15.6	18.4
		±10.36	±4.27	±1.94	±10.70	±4.65	±3.69	±4.03	±6.0
	t	0.65	1.03	0.56	0.77	1.95	0.76	0.53	2.05
	df	7.00	8.00	8.00	8.00	8.00	7.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df- degrees of freedom

TABLE E-3. MEAN BLOOD VALUES - ALANINE AMINOTRANSFERASE (IU/1) SUBCHRONIC DERMAL (MALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	41.0	31.4	34.4	38.6	38.0	28.6	34.2	39.6
		±10.98	±6.10	±7.36	±7.79	±10.83	±3.64	±6.18	±7.5
9 (mg/Kg)	$\bar{x}$	32.3	31.6	33.6	36.2	31.2	29.4	36.6	42.6
		±4.93	±10.23	±4.50	±5.93	±3.89	±6.46	±2.61	±10.2
	t	1.25	0.03	0.20	0.54	1.31	0.24	0.50	0.53
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	35.25	35.8	39.4	50.0	42.2	44.6	51.0	71.0*
		±3.09	±13.38	±8.76	±17.87	±13.12	±21.96	±22.53	±49.6
	t	1.00	0.66	0.97	1.30	0.55	1.60	1.60	1.40
	df	6.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
450 (mg/Kg)	$\bar{x}$	34.0	36.2	40.0	50.0	37.8	39.2	44.4	64.8*
		±14.14	±11.21	±10.27	±10.86	±6.01	±12.63	±14.97	±27.2
	t	0.68	0.84	0.99	1.90	0.03	1.80	1.40	2.00
	df	4.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df- degrees of freedom

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TABLE E-4. MEAN BLOOD VALUES - ALANINE AMINOTRANSFERASE (IU/l) SUBCHRONIC DERMAL (FEMAL RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	24.75 ±9.32	39.4 ±27.92	35.4 ±15.48	35.0 ±12.32	41.2 ±16.11	38.6 ±11.97	27.4 ±11.54	37.6 ±14.9
9 (mg/Kg)	$\bar{x}$	44.2 ±24.99	33.5 ±10.01	50.6 ±22.34	39.4 ±12.83	42.5 ±11.09	50.75 ±25.7	47.8 ±19.61	47.2 ±14.6
	t	1.46	0.39	1.25	0.55	0.13	0.94	2.00	1.03
	df	7.00	7.00	8.00	8.00	7.00	7.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	27.4 ±16.31	35.0 ±9.89	33.8 ±6.14	27.5 ±8.73	37.0 ±10.67	44.75 ±11.67	36.4 ±15.51	34.7 ±14.8
	t	0.28	0.33	0.21	1.02	0.48	0.77	1.04	0.29
	df	7.00	8.00	8.00	7.00	8.00	7.00	8.00	7.00
450 (mg/Kg)	$\bar{x}$	40.6 ±33.26	36.0 ±14.12	38.2 ±14.66	46.62 ±20.17	44.0 ±16.65	46.75 ±7.93	30.75 ±10.01	42.8 ±18.9
	t	0.91	0.24	0.29	1.15	0.27	1.16	0.45	0.48
	df	7.00	8.00	8.00	8.00	8.00	7.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df- degrees of freedom

TABLE E-5. MEAN BLOOD VALUES ALPHA-HYDROXYBUTYRIC DEHYDROGENASE (HBDH) (IU/l) SUBCHRONIC DERMAL (MALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	254.5 ±112.93	277.2 ±126.78	155.4 ±38.95	189.6 ±52.3	261.4 ±107.23	269.4 ±179.11	181.0 ±105.8	299.4 ±143.2
9 (mg/Kg)	$\bar{x}$	147.0 ±94.17	193.4 ±82.54	185.8 ±81.8	169.8 ±61.15	204.2 ±119.47	216.4 ±151.32	111.8 ±38.00	183.6 ±79.8
	t	1.20	1.23	0.75	0.55	0.79	0.50	1.37	1.58
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	209.0 ±129.03	265.6 ±105.95	157.0 ±57.93	218.2 ±112.91	203.6 ±116.16	294.4 ±113.94	230.4 ±95.86	256.2 ±137.2
	t	0.49	0.15	0.05	0.51	0.81	0.26	0.77	0.49
	df	6.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
450 (mg/Kg)	$\bar{x}$	117.5 ±33.23	205.6 ±45.01	157.8 ±75.63	159.6 ±50.69	164.2 ±44.50	349.0 ±311.71	312.6 ±93.67	194.4 ±191.0
	t	1.38	1.18	0.06	0.92	1.87	0.49	2.08	1.63
	df	4.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
  - standard deviation
t - t value
df- degrees of freedom

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TABLE E-6. MEAN BLOOD VALUES ALPHA-HYDROXYBUTRIC DEHYDROGENASE (IU/l) SUBCHRONIC DERMAL (FEMALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	226.5 ±60.22	226.8 ±109.48	160.2 ±43.28	265.6 ±81.6	168.8 ±59.12	305.2 ±243.02	258.8 ±198.4	375.60* ±144.1
9 (mg/Kg)	$\bar{x}$	146.8 ±61.05	226.5 ±210.13	126.00 ±51.43	200.80 ±133.58	238.25 ±128.72	194.75 ±96.92	117.2 ±31.26	276.4 ±76.5
	t	1.95	0.00	-1.13	0.92	1.08	0.84	1.57	1.36
	df	7.00	7.00	8.00	8.00	7.00	7.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	116.4 ±12.17	140.0 ±33.64	83.2 ±19.74	140.75 ±65.81	186.8 ±53.14	173.5 ±82.69	131.8 ±22.79	181.0 ±79.9
	t	4.05*	1.69	3.61*	2.47*	0.50	1.02	1.42	2.40*
	df	7.00	8.00	8.00	7.00	8.00	7.00	8.00	7.00
450 (mg/Kg)	$\bar{x}$	157.4 ±37.58	152.8 ±31.82	17.66 ±96.55	180.4 ±40.41	261.8 ±134.36	201.0 ±87.48	168.2 ±57.21	305.2 ±115.9
	t	2.11	1.45	0.34	2.09	1.41	0.80	0.98	0.85
	df	7.00	8.00	8.00	8.00	8.00	7.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df- degrees of freedom

TABLE E-7. MEAN BLOOD VALUES CREATINE PHOSPHOKINASE (IU/l) SUBCHRONIC DERMAL (MALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	633.25	709.2	400.8	414.00	605.0	610.00	391.20	631.8
		±226.58	±156.0	±78.33	±56.91	±130.21	±245.27	±177.66	±172.8
9 (mg/Kg)	$\bar{x}$	385.0	734.6	539.0	528.8	634.00	841.8	465.00	690.8
		±130.98	±193.51	±129.51	±201.8	±285.48	±404.4	±132.94	±414.0
	t	1.67	0.22	2.04	1.22	0.20	1.09	.74	0.29
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	601.0	828.2	484.4	524.8	774.0	801.8	624.2	813.6
		±199.32	±340.53	±138.92	±190.22	±499.00	±306.24	±240.03	±431.5
	t	0.21	0.71	1.17	1.24	0.73	1.09	1.74	0.87
	df	6.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
450 (mg/Kg)	$\bar{x}$	657.0	609.6	581.4	609.2	656.4	1,851.37*	765.2	553.8
		±175.36	±100.92	±115.71	±251.09	±372.3	±2,702.87	±303.40	±105.5
	t	0.12	1.19	2.58	1.69	0.29	1.00	2.37*	0.86
	df	4.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df- degrees of freedom

TABLE E-8. MEAN BLOOD VALUES CREATINE PHOSPHOKINASE (IU/l) SUBCHRONIC DERMAL (FEMALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	607.0 ±113.26	777.8 ±501.62	474.8 ±129.55	959.8 ±690.84	705.4 ±446.2	874.0 ±339.33	705.6 ±379.56	803.8 ±215.4
9 (mg/Kg)	$\bar{x}$	507.6 ±84.22	673.0 ±377.87	701.2 ±725.02	446.8 ±193.81	570.0 ±242.64	696.75 ±113.51	579.4 ±125.56	808.8 ±271.8
	t	1.51	0.34	0.68	1.59	0.54	0.98	0.70	0.03
	df	7.00	7.00	8.00	8.00	7.00	7.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	513.8 ±161.58	442.8 ±82.46	364.0 ±50.99	474.0 ±139.87	1,000.6 ±614.19	782.25 ±302.15	658.8 ±244.85	642.5 ±352.3
	t	0.97	1.47	1.77	1.36	0.80	0.42	0.23	0.85
	df	7.00	8.00	8.00	7.00	8.00	7.00	8.00	7.00
450 (mg/Kg)	$\bar{x}$	716.2 ±354.07	568.2 ±244.54	619.8 ±209.04	811.6 ±409.87	1,324.6 ±526.56	974.75 ±204.38	796.4 ±192.26	935.6 ±262.1
	t	0.58	0.83	1.31	0.41	2.00	0.51	0.47	0.87
	df	7.00	8.00	8.00	8.00	8.00	7.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
  - standard deviation
t - t value
df- degrees of freedom

TABLE E-9. MEAN BLOOD VALUES LACTIC DEHYDROGENASE (IU/l) SUBCHRONIC DERMAL (MALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	166.2	172.4	99.6	112.4	132.4	139.0	99.8	165.0
		±80.9	±79.2	±25.7	±27.3	±61.2	±86.2	±51.3	±74.8
9 (mg/Kg)	$\bar{x}$	66.3	117.8	111.8	102.8	116.2	117.6	66.8	123.0
		±8.0	±37.6	±47.6	±36.4	±65.4	±79.3	±19.6	±77.8
	t	2.1	1.39	0.50	0.47	0.40	0.41	1.34	0.87
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	153.2	160.2	103.0	124.0	117.0	154.2	127.2	155.4
		±91.9	±65.1	±33.7	±59.8	±61.3	±59.5	±55.3	±73.1
	t	0.21	0.27	0.18	0.39	0.40	0.32	0.81	0.21
	df	6.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
450 (mg/Kg)	$\bar{x}$	96.5	126.4	102.4	106.2	97.6	337.00*	167.2	120.8
		±12.0	±29.0	±39.5	±26.7	±24.5	±491.1	±45.6	±19.4
	t	1.15	1.22	0.13	0.36	1.18	0.89	2.20	1.28
	df	4.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df- degrees of freedom

TABLE E-10. MEAN BLOOD VALUES LACTIC DEHYDROGENASE (IU/l) SUBCHRONIC DERMAL (FEMALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	140.5	152.0	116.0	148.4	97.2	156.0	142.4	222.40*
		±33.0	±69.9	±27.3	±38.1	±25.7	±119.3	±108.6	±82.7
9 mg/kg	$\bar{x}$	100.2	154.5	106.0	115.8	125.0	105.5	75.4	160.8
		±38.4	±120.0	±44.7	±68.1	±64.8	±42.3	±15.8	±43.4
	t	1.66	0.04	0.43	0.93	0.89	0.80	1.37	1.47
	df	7.00	7.00	8.00	8.00	7.00	7.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	87.6	88.0	64.0	82.5	101.2	92.5	80.2	106.7
		±16.7	±25.4	±13.2	±29.2	±29.2	±42.2	±11.3	±44.8
	t	3.15*	1.92	3.83*	2.84*	0.23	1.00	1.27	2.50*
	df	7.00	8.00	8.00	7.00	8.00	7.00	8.00	7.00
450 (mg/Kg)	$\bar{x}$	107.6	104.4	123.0	105.8	146.2	106.5	97.8	186.8
		±27.2	±18.4	±59.6	±26.3	±66.3	±42.3	±31.9	±49.6
	t	1.64	1.47	0.24	2.06	1.54	0.78	0.88	0.83
	df	7.00	8.00	8.00	8.00	8.00	7.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df- degrees of freedom

TABLE E-11. MEAN BLOOD VALUES ALKALINE PHOSPHATASE (IU/l) SUBCHRONIC DERMAL (MALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	291.2	254.6	219.8	199.4	191.0	167.0	145.2	149.4
		±43.7	±33.7	±37.8	±33.5	±39.2	±39.3	±19.0	±21.9
9 (mg/Kg)	$\bar{x}$	366.7	380.0	301.0	267.6	261.2	201.2	193.0	210.8
		±65.2	±129.4	±66.1	±50.1	±51.0	±69.8	±42.1	±35.2
	t	1.85	2.10	2.38*	2.53*	2.44*	0.95	2.31*	3.31*
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	289.5	235.4	214.2	183.6	183.2	161.6	163.0	161.6
		±35.7	±24.2	±19.8	±17.5	±11.6	±33.7	±45.6	±35.0
	t	0.06	1.03	0.29	0.94	0.43	0.23	0.81	0.66
	df	6.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
450 (mg/Kg)	$\bar{x}$	330.0	259.8	217.6	177.6	177.2	110.0	144.2	129.0
		±113.1	±69.4	±73.7	±60.0	±62.1	±34.2	±57.6	±39.89
	t	0.66	0.15	0.06	0.73	0.42	2.44*	0.04	1.00
	df	4.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df- degrees of freedom

TABLE E-12. MEAN BLOOD VALUES ALKALINE PHOSPHATASE (IU/l) SUBCHRONIC DERMAL (FEMALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	323.5	379.4	364.2	288.2	305.4	256.8	231.8	258.4
		±51.9	±46.5	±93.9	±75.1	±74.2	±91.7	±94.8	±122.9
9 (mg/Kg)	$\bar{x}$	287.8	291.0	322.6	211.2	223.5	172.7	196.4	200.8
		±146.0	±97.1	±91.6	±40.6	±45.3	±44.5	±59.8	±61.4
	t	0.46	1.81	0.71	2.02	1.92	1.67	0.71	0.94
	df	7.00	7.00	8.00	8.00	7.00	7.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	215.6	243.2	244.4	191.2	192.2	141.5	140.8	161.7
		±46.1	±50.3	±35.6	±34.7	±19.15	±24.8	±22.8	±42.3
	t	3.31*	4.44*	2.67*	2.36*	3.30*	2.41*	2.09	1.49
	df	7.00	8.00	8.00	7.00	8.00	7.00	8.00	7.00
450 (mg/Kg)	$\bar{x}$	250.6	253.8	236.2	179.6	183.8	116.5	113.2	130.6
		±104.0	±74.5	±66.7	±51.4	±63.7	±62.2	±40.9	±40.2
	t	1.27	3.20*	2.48*	2.67*	2.78*	2.60*	2.57*	2.21
	df	7.00	8.00	8.00	8.00	8.00	7.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df- degrees of freedom

TABLE E-13. MEAN BLOOD VALUES - GAMMA-GLUTAMYL TRANSFERASE (Iu/l) SUBCHRONIC DERMAL (MALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	3.5	7.0	6.4	8.4	4.6	4.4	4.8	5.4
		±0.58	±2.8	±2.9	±3.9	±2.1	±1.8	±1.6	±1.8
9 (mg/Kg)	$\bar{x}$	5.0	8.4	7.8	7.4	5.0	4.8	4.6	6.4
		±2.0	±1.1	±1.5	±0.9	±1.9	±0.8	±1.3	±1.7
	t	1.46	1.03	0.97	0.56	0.32	0.45	0.21	0.91
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	5.7	9.4	6.0	10.8	5.6	5.8	5.8	7.8
		±1.7	±1.8	±1.7	±1.6	±1.9	±1.5	±0.8	±1.3
	t	2.50*	1.6	0.27	1.26	0.79	1.33	1.21	2.40*
	df	6.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
450 (mg/Kg)	$\bar{x}$	5.0	7.6	7.4	9.2	6.2	8.0	6.4	12.0
		±0.0	±2.7	±2.4	±2.2	±2.9	±3.5	±3.6	±3.2
	t	3.46*	0.34	0.6	0.4	0.99	2.03	0.91	4.05*
	df	4.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
  - standard deviation
t - t value
df- degrees of freedom

TABLE E-14. MEAN BLOOD VALUES - GAMMA-GLUTAMYL TRANSFERASE (IU/l) SUBCHRONIC DERMAL (FEMALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	6.2	5.8	7.8	3.8	6.2	7.8	3.6	7.8
		±1.7	±0.8	±2.2	±2.3	±2.7	±2.4	±2.7	±1.3
9 (mg/Kg)	$\bar{x}$	5.0	4.7	8.4	2.2	5.7	7.7	4.4	8.8
		±1.2	±0.5	±1.5	±1.9	±1.0	±2.8	±0.6	±0.8
	t	1.3	2.20	0.51	1.2	0.32	0.03	0.65	1.44
	df	7.00	7.00	8.00	8.00	7.00	7.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	7.4	7.0	9.6	1.7	4.6	7.0	4.0	8.7
		±0.9	±1.4	±0.9	±2.8	±1.7	±0.8	±1.6	±1.0
	t	1.31	1.6	1.72	1.20	1.13	0.63	0.29	1.21
	df	7.00	8.00	8.00	7.00	8.00	7.00	8.00	7.00
450 (mg/Kg)	$\bar{x}$	7.2	7.0	9.0	3.4	4.8	10.5	7.2	11.2
		±3.1	±2.4	±2.3	±3.0	±2.2	±1.3	±1.10	±1.3
	t	0.54	1.08	0.84	0.24	0.91	2.02	2.76*	4.12*
	df	7.00	8.00	8.00	8.00	8.00	7.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df- degrees of freedom

TABLE E-15. MEAN BLOOD VALUES - TOTAL BILIRUBIN (mg/dl) SUBCHRONIC DERMAL (MALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	0.38	0.30	0.34	0.32	0.32	0.32	0.20	0.24
		±0.10	±0.07	±0.11	±0.08	±0.04	±0.04	±0.07	±0.05
9 (mg/Kg)	$\bar{x}$	0.40	0.38	0.36	0.38	0.36	0.32	0.20	0.22
		±0.10	±0.08	±0.05	±0.04	±0.09	±0.04	±0.07	±0.11
	t	0.34	1.63	0.35	1.41	0.89	0.00	0.00	0.37
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	0.35	0.32	0.30	0.32	0.34	0.30	0.22	0.24
		±0.06	±0.04	±0.07	±0.08	±0.05	±0.00	±0.04	±0.09
	t	0.45	0.53	0.67	0.00	0.63	1.00	0.53	0.00
	df	6.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
450 (mg/Kg)	$\bar{x}$	0.55	0.32	0.32	0.30	0.38	0.33	0.22	0.22
		±0.35	±0.08	±0.08	±0.07	±0.08	±0.05	±0.08	±0.04
	t	1.03	0.41	0.32	0.41	1.41	0.16	0.41	0.63
	df	4.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df- degrees of freedom

TABLE E-16. MEAN BLOOD VALUES - TOTAL BILIRUBIN (mg/dl) SUBCHRONIC DERMAL (FEMALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	0.30	0.22	0.26	0.30	0.52*	0.30	0.26	0.24
		±0.00	±0.04	±0.05	±0.00	±0.08	±0.00	±0.09	±0.05
9 (mg/Kg)	$\bar{x}$	0.32	0.30	0.26	0.30	0.48	0.30	0.22	0.24
		±0.04	±0.00	±0.05	±0.07	±0.10	±0.00	±0.04	±0.05
	t	0.88	3.53*	0.00	0.00	0.75	0.00	0.89	0.00
	df	7.00	7.00	8.00	8.00	7.00	7.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	0.32	0.30	0.28	0.30	0.46	0.35	0.22	0.25
		±0.04	±0.07	±0.04	±0.08	±0.09	±0.06	±0.08	±0.06
	t	0.88	2.14	0.63	0.00	1.10	1.97	0.73	0.27
	df	7.00	8.00	8.00	7.00	8.00	7.00	8.00	7.00
450 (mg/Kg)	$\bar{x}$	0.32	0.28	0.26	0.28	0.46	0.30	0.20	0.24
		±0.04	±0.04	±0.05	±0.04	±0.09	±0.00	±0.00	0.05
	t	0.88	2.12	0.00	1.00	1.10	0.00	1.50	0.00
	df	7.00	8.00	8.00	8.00	8.00	7.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
  - standard deviation
t - t value
df- degrees of freedom

TABLE E-17. MEAN BLOOD VALUES - TOTAL PROTEIN (g/dl) SUBCHRONIC DERMAL (MALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	6.35	5.81	6.34	5.68	5.94	5.94	6.63	5.67
		±0.34	±0.44	±0.44	±1.17	±0.17	±0.73	±0.46	±0.77
9 (mg/Kg)	$\bar{x}$	6.84	6.11	6.69	5.51	5.97	6.24	6.90	5.22
		±0.71	±0.70	±0.44	±0.59	±0.40	±0.62	±0.26	±1.13
	t	1.23	0.80	1.28	0.31	0.17	0.70	1.15	0.73
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	6.16	5.90	6.55	6.44	5.81	6.22	7.40	5.62
		±0.47	±0.37	±0.38	±0.68	±0.51	±0.31	±1.00	±0.64
	t	0.68	0.33	0.81	1.25	0.54	0.77	1.58	0.10
	df	6.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
450 (mg/Kg)	$\bar{x}$	6.70	5.87	6.47	6.17	5.41	6.16	6.91	5.84
		±0.19	±0.56	±0.17	±0.68	±0.74	±0.18	±0.43	±0.74
	t	1.29	0.19	0.63	0.80	1.56	0.64	1.00	0.36
	df	4.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df- degrees of freedom

TABLE E-18. MEAN BLOOD VALUES - TOTAL PROTEIN (g/dl) SUBCHRONIC DERMAL (FEMALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	6.43 ±0.46	6.02 ±0.63	6.61 ±0.59	6.22 ±0.55	6.31 ±0.84	6.56 ±0.59	5.81 ±0.47	6.34 ±0.80
9 (mg/Kg)	$\bar{x}$	6.50 ±0.22	5.90 ±0.17	6.46 ±0.19	6.06 ±0.36	6.26 ±0.67	6.04 ±0.30	5.82 ±0.28	6.65 ±0.48
	t	0.32	0.35	0.53	0.54	0.11	1.59	0.03	0.75
	df	7.00	7.00	8.00	8.00	7.00	7.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	6.31 ±0.75	5.88 ±0.29	6.63 ±0.47	6.08 ±0.65	6.66 ±0.51	6.56 ±0.34	6.06 ±0.48	6.69 ±0.56
	t	0.27	0.45	0.06	0.36	0.80	0.01	0.83	0.74
	df	7.00	8.00	8.00	7.00	8.00	7.00	8.00	7.00
450 (mg/Kg)	$\bar{x}$	6.56 ±0.62	6.03 ±0.54	6.47 ±0.20	6.32 ±0.39	6.54 ±0.21	6.12 ±0.09	5.75 ±0.22	6.52 ±0.64
	t	0.36	0.05	0.50	0.32	0.58	1.47	0.25	0.38
	df	7.00	8.00	8.00	8.00	8.00	7.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
  - standard deviation
t - t value
df- degrees of freedom

TABLE E-19. MEAN BLOOD VALUES - CALCIUM (mg/dl) SUBCHRONIC DERMAL (MALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	14.29	14.75	15.28	14.74	14.86	14.51	14.48	15.55
		±0.49	±1.00	±0.61	±0.58	±0.39	±0.46	±0.75	±0.79
9 (mg/Kg)	$\bar{x}$	14.77	15.61	16.09	14.86	15.84	14.81	15.21	15.45
		±0.99	±1.24	±0.70	±0.78	±0.66	±0.93	±0.39	±0.42
	t	0.86	1.20	1.96	0.29	2.88*	0.64	1.91	0.25
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	13.82	14.83	15.17	15.31	14.69	14.37	14.79	15.41
		±1.06	±0.93	±0.43	±0.36	±0.40	±0.44	±0.52	±0.72
	t	0.80	0.12	0.32	1.87	0.65	0.50	0.74	0.29
	df	6.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
450 (mg/Kg)	$\bar{x}$	15.43	15.25	15.36	14.96	14.85	13.81	14.60	15.14
		±0.86	±0.85	±0.67	±0.05	±0.89	±0.89	±0.98	±0.36
	t	2.17	0.85	0.21	0.51	0.01	1.55	0.21	1.07
	df	4.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df- degrees of freedom

TABLE E-20. MEAN BLOOD VALUES - CALCIUM (mg/dl) SUBCHRONIC DERMAL (FEMALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	15.40	14.77	14.67	15.38	15.45	14.79	14.28	15.17
		±0.78	±0.83	±0.62	±1.13	±0.97	±1.04	±0.75	±0.80
9 (mg/Kg)	$\bar{x}$	15.04	15.04	14.81	15.66	15.22	14.33	14.51	15.41
		±0.34	±1.01	±0.59	±0.77	±0.75	±0.62	±1.15	±1.11
	t	0.91	0.45	0.38	0.47	0.38	0.77	0.37	0.39
	df	7.00	7.00	8.00	8.00	7.00	7.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	15.33	15.02	15.05	15.35	15.53	14.89	14.70	15.28
		±0.87	±0.51	±0.63	±0.65	±0.71	±0.42	±0.85	±0.13
	t	0.12	0.57	0.96	0.04	0.15	0.18	0.82	0.27
	df	7.00	8.00	8.00	7.00	8.00	7.00	8.00	7.00
450 (mg/Kg)	$\bar{x}$	15.79	15.09	14.78	15.00	15.14	14.65	13.94	15.23
		±0.48	±0.35	±0.23	±0.57	±0.44	±0.28	±0.36	±0.38
	t	0.93	0.80	0.38	0.66	0.64	0.26	0.92	0.16
	df	7.00	8.00	8.00	8.00	8.00	7.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
  - standard deviation
t - t value
df- degrees of freedom

TABLE E-21. MEAN BLOOD VALUES - CHOLESTEROL (mg/dl) SUBCHRONIC DERMAL (MALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	64.0	66.0	68.0	75.2	76.8	63.2	56.4	44.0
		±6.3	±13.3	±8.1	±8.8	±15.8	±9.5	±13.3	±13.0
9 (mg/Kg)	$\bar{x}$	71.7	60.4	53.8	75.6	67.0	54.4	53.6	43.2
		±29.9	±4.2	±6.5	±14.7	±10.7	±3.21	±9.2	±7.6
	t	0.57	0.90	3.06*	0.05	1.15	1.97	0.39	0.12
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	72.2	72.6	77.2	97.2	80.6	83.6	69.8	54.8
		±13.6	±22.1	±25.4	±26.1	±18.6	±24.5	±19.3	±20.9
	t	1.10	0.57	0.77	1.78	0.35	1.74	1.28	0.98
	df	6.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
450 (mg/Kg)	$\bar{x}$	47.5	67.2	66.8	103.0	89.8	103.6	106.2	78.0
		±10.6	±35.0	±28.5	±54.7	±45.9	±26.0	±51.1	±19.3
	t	2.51	0.07	0.09	1.12	0.60	3.30*	2.11	3.26*
	df	4.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df- degrees of freedom

TABLE E-22. MEAN BLOOD VALUES - CHOLESTEROL (mg/dl) SUBCHRONIC DERMAL (FEMALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	88.2	105.8	154.0	153.0	176.6	137.4	131.2	145.2
		±30.7	±38.7	±57.3	±74.8	±72.3	±49.7	±60.1	±53.9
9 (mg/Kg)	$\bar{x}$	101.4	107.2	152.4	168.8	157.7	139.5	146.0	153.0
		±38.0	±18.8	±42.8	±56.5	±11.8	±30.4	±44.3	±72.3
	t	0.56	0.07	0.05	0.38	0.51	0.07	0.44	0.19
	df	7.00	7.00	8.00	8.00	7.00	7.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	88.6	107.4	127.4	107.7	130.8	105.5	107.8	112.5
		±14.7	±28.7	±22.0	±19.4	±25.6	±53.2	±50.7	±65.9
	t	0.02	0.07	0.97	1.16	1.34	0.93	0.67	0.82
	df	7.00	8.00	8.00	7.00	8.00	7.00	8.00	7.00
450 (mg/Kg)	$\bar{x}$	92.6	101.0	146.8	133.6	149.8	177.5	122.8	124.8
		±32.7	±37.2	±72.4	±28.1	±45.1	±43.2	±16.7	±18.5
	t	0.20	0.20	0.17	0.54	0.70	1.27	0.30	0.80
	df	7.00	8.00	8.00	8.00	8.00	7.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df- degrees of freedom

TABLE E-23. MEAN BLOOD VALUES - GLUCOSE (mg/dl) SUBCHRONIC DERMAL (MALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	225.2	218.2	182.0	155.0	133.8	132.6	147.4	149.4
		±44.7	±99.8	±20.4	±12.5	±14.5	±9.7	±14.1	±11.9
9 (mg/Kg)	$\bar{x}$	204.0	205.8	206.8	172.4	171.2	160.2	174.2	191.4
		±22.5	±34.9	±18.2	±17.2	±33.6	±19.5	±27.0	±85.3
	t	0.74	0.26	2.03	1.83	2.28	2.84*	1.97	1.09
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	178.2	184.6	170.2	167.8	141.6	138.4	156.8	140.2
		±31.2	±7.4	±8.6	±6.8	±9.4	±11.2	±14.1	±14.6
	t	1.72	0.75	1.19	2.02	1.01	0.87	1.05	1.09
	df	6.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
450 (mg/Kg)	$\bar{x}$	186.5	190.4	163.8	166.8	145.4	152.8	154.6	151.4
		±4.9	±35.6	±9.0	±21.7	±13.6	±25.5	±19.4	±33.3
	t	1.15	0.59	1.82	1.05	1.30	1.66	0.67	0.13
	df	4.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df- degrees of freedom

TALBE E-24. MEAN BLOOD VALUES - GLUCOSE (mg/dl) SUBCHRONIC DERMAL (FEMALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	192.5	192.0	167.2	161.8	166.6	146.8	152.4	148.8
		±67.0	±53.1	±11.1	±18.5	±19.1	±7.3	±25.6	±19.1
9 (mg/Kg)	$\bar{x}$	177.9	189.0	192.2	184.4	167.0	153.0	146.8	149.2
		±30.0	±31.6	±34.4	±19.3	±18.0	±11.5	±19.8	±22.3
	t	0.47	0.10	1.55	1.89	0.03	0.99	0.39	0.03
	df	7.00	7.00	8.00	8.00	7.00	7.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	167.6	157.6	167.6	184.0	164.2	159.2	152.6	158.5
		±13.3	±23.2	±22.1	±14.8	±13.4	±34.1	±24.3	±29.9
	t	0.82	1.33	0.04	1.94	0.23	0.81	0.01	0.59
	df	7.00	8.00	8.00	7.00	8.00	7.00	8.00	7.00
450 (mg/Kg)	$\bar{x}$	189.2	174.0	176.4	168.0	178.6	164.7	154.0	156.0
		±±18.6	±23.9	±15.0	±10.8	±13.8	±18.3	±26.7	±19.0
	t	0.11	0.69	1.10	0.65	1.14	2.03	0.10	0.60
	df	7.00	8.00	8.00	8.00	8.00	7.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df- degrees of freedom

TABLE E-25. MEAN BLOOD VALUES BLOOD UREA NITROGEN (mg/dl) SUBCHRONIC DERMAL (MALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	19.2	20.4	22.3	19.3	18.4	15.42	18.3	17.9
		±1.6	±4.5	±3.2	±2.2	±2.3	±0.94	±2.9	±3.0
9 (mg/Kg)	$\bar{x}$	21.8	20.7	21.0	19.9	20.2	15.6	22.1	19.1
		±1.6	±2.1	±3.1	±1.6	±2.7	±1.9	±2.2	±1.6
	t	2.15	0.13	0.66	0.49	1.2	0.17	2.30*	0.78
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	20.0	22.2	21.4	20.8	19.02	17.5	21.7	20.7
		±1.3	±3.2	±2.5	±3.1	±1.30	±2.1	±0.63	±1.9
	t	0.8	0.73	0.54	0.88	0.52	1.99	2.53*	1.76
	df	6.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
450 (mg/Kg)	$\bar{x}$	20.8	21.0	22.2	18.5	18.9	18.1	22.3	24.9
		±0.4	±2.9	±1.5	±3.1	±2.4	±5.7	±4.8	±5.1
	t	1.36	0.25	0.11	0.49	0.31	1.05	1.59	2.66*
	df	4.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df- degrees of freedom

TABLE E-26. MEAN BLOOD VALUES - BLOOD UREA NITROGEN (mg/dl) SUBCHRONIC DERMAL (FEMALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	18.15	21.3	20.5	20.0	21.0	20.5	16.6	20.7
		±1.50	±3.9	±1.4	±1.7	±2.1	±2.2	±0.9	±2.9
9 (mg/Kg)	$\bar{x}$	16.58	17.9	19.3	22.6	23.2	22.8	18.8	22.7
		±3.0	±5.8	±2.7	±4.4	±2.2	±3.6	±3.0	±4.0
	t	0.95	1.05	0.83	1.20	1.55	1.20	1.6	0.92
	df	7.00	7.00	8.00	8.00	7.00	7.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	21.0	22.8	23.3	24.6	26.1	24.4	22.4	25.9
		±6.1	±6.7	±4.4	±6.3	±6.4	±4.4	±7.4	±6.0
	t	0.90	0.42	1.38	1.58	1.69	1.75	1.74	1.73
	df	7.00	8.00	8.00	7.00	8.00	7.00	8.00	7.00
450 (mg/Kg)	$\bar{x}$	18.1	20.3	19.6	23.2	21.3	22.5	19.1	27.0
		±2.8	±2.4	±3.9	±4.4	±4.1	±4.6	±3.9	±6.1
	t	0.06	0.48	0.48	1.46	0.16	0.85	1.40	2.09
	df	7.00	8.00	8.00	8.00	8.00	7.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df- degrees of freedom

TABLE E-27. MEAN BLOOD VALUES - TRIGLYCERIDES (mg/dl) SUBCHRONIC DERMAL (MALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	255.5	216.0	193.6	164.0	147.2	129.4	147.4	153.6
		±123.9	±77.9	±116.7	±66.7	±92.6	±62.9	±44.1	±45.7
9 (mg/Kg)	$\bar{x}$	203.7	236.0	174.8	185.6	206.2	165.0	170.8	222.8
		±85.6	±103.1	±62.2	±63.5	±149.0	±71.2	±75.3	±144.9
	t	0.62	0.35	0.32	0.52	0.75	0.84	0.60	1.02
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	166.2	161.0	146.4	166.2	132.6	123.4	145.6	165.6
		±23.3	±32.4	±19.4	±45.8	±36.4	±44.9	±46.4	±45.1
	t	1.42	1.46	0.89	0.06	0.33	0.17	0.06	0.42
	df	6.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
450 (mg/Kg)	$\bar{x}$	317.5	233.8	207.6	162.2	194.8	225.8	235.4	177.4
		±222.7	±59.2	±88.2	±58.0	±119.1	±93.2	±114.1	±53.6
	t	0.46	0.41	0.21	0.05	0.71	1.92	1.61	0.76
	df	4.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df- degrees of freedom

TABLE E-28. MEAN BLOOD VALUES - TRIGLYCERIDES (mg/dl) SUBCHRONIC DERMAL (FEMALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	106.2	151.2	124.6	118.4	126.4	103.4	133.2	104.6
		±48.5	±35.6	±41.0	±34.9	±35.3	±35.7	±51.8	±37.1
9 (mg/Kg)	$\bar{x}$	84.3	177.5	152.0	124.8	104.7	69.2	123.6	93.0
		±48.1	±49.0	±84.2	±24.1	±14.1	±12.4	±28.4	±36.7
	t	0.59	0.94	0.65	0.34	1.14	1.81	0.36	0.50
	df	5.00	7.00	8.00	8.00	7.00	7.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	78.5	136.8	111.0	123.7	111.2	113.7	111.0	104.5
		±27.3	±16.1	±28.9	±26.8	±42.9	±34.1	±19.8	±22.9
	t	1.00	0.82	0.61	0.25	0.61	0.44	0.89	0.01
	df	6.00	8.00	8.00	7.00	8.00	7.00	8.00	7.00
450 (mg/Kg)	$\bar{x}$	139.2	185.8	139.6	118.8	119.2	170.7	136.4	145.6
		±41.6	±23.5	±20.5	±31.5	±18.2	±76.5	±18.1	±49.9
	t	1.03	1.82	0.73	0.02	0.40	1.77	0.13	1.47
	df	6.00	8.00	8.00	8.00	8.00	7.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
± - standard deviation
t - t value
df- degrees of freedom

TABLE E-29. MEAN BLOOD VALUES - POTASSIUM (mEq/l) SUBCHRONIC DERMAL (MALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	6.0	6.1	5.7	5.2	5.7	4.7	5.10	5.1
		±0.6	±0.9	±0.9	±0.2	±0.5	±0.3	±0.6	±0.9
9 (mg/Kg)	$\bar{x}$	6.7	6.3	6.0	5.6	5.94	5.1	5.6	5.14
		±0.5	±1.4	±1.2	±0.7	±0.6	±1.1	±0.5	±0.5
	t	1.59	0.29	0.51	1.21	0.72	0.63	1.31	0.09
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	5.7	5.94	6.0	5.8	5.3	5.2	5.6	5.4
		±0.5	±0.70	±0.3	±0.8	±0.7	±0.6	±0.4	±0.5
	t	0.95	0.27	0.62	1.80	1.11	1.50	1.45	0.62
	df	6.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
450 (mg/Kg)	$\bar{x}$	6.5	6.3	5.7	5.5	5.3	4.4	5.0	5.1
		±0.7	±0.7	±0.6	±0.6	±0.3	±0.8	±0.4	±0.9
	t	0.82	0.4	0.08	1.15	1.80	0.89	0.14	0.03
	df	4.00	8.00	8.00	8.00	8.00	8.00	7.00	8.00

* - Significantly different than controls ($P<0.05$)
$\bar{x}$ - mean
  - standard deviation
t - t value
df- degrees of freedom

TABLE E-30. MEAN BLOOD VALUES - POTASSIUM (mEq/l) SUBCHRONIC DERMAL (FEMALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	5.3 ±0.2	4.5 ±0.5	4.4 ±0.3	5.2 ±0.6	5.3 ±1.0	4.9 ±0.9	4.74 ±0.6	4.3 ±0.5
9 (mg/Kg)	$\bar{x}$	5.1 ±0.8	5.5 ±0.6	5.1 ±0.7	5.6 ±1.0	5.3 ±0.6	4.7 ±0.7	5.7 ±1.9	4.6 ±1.3
	t	0.56	2.97*	2.03	0.69	0.07	0.29	1.08	0.50
	df	7.00	7.00	8.00	8.00	7.00	7.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	5.2 ±0.4	5.6 ±0.5	5.6 ±0.6	5.0 ±0.3	5.1 ±0.9	4.7 ±0.6	5.3 ±1.0	4.8 ±0.7
	t	0.46	3.38*	3.95*	0.62	0.32	0.30	1.03	1.21
	df	7.00	8.00	8.00	7.00	8.00	7.00	8.00	7.00
450 (mg/Kg)	$\bar{x}$	5.3 ±0.7	5.1 ±0.2	5.2 ±0.3	4.8 ±0.2	5.0 ±0.6	4.9 ±0.4	4.5 ±0.6	4.4 ±0.3
	t	0.19	2.46*	4.73*	1.37	0.42	0.18	0.55	0.50
	df	7.00	8.00	8.00	8.00	8.00	7.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
x- mean
  - standard deviation
t - t value
df- degrees of freedom

TABLE E-31. MEAN BLOOD VALUES - HEMATOCRIT (g/dl) SUBCHRONIC DERMAL (MALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	35.4 ±3.4	36.2 ±2.7	37.7 ±3.0	36.8 ±1.3	37.0 ±1.3	38.0 ±0.88	37.8 ±1.2	39.2 ±2.2
9 (mg/Kg)	$\bar{x}$	40.9 ±3.2	39.1 ±2.2	39.5 ±1.1	37.2 ±1.2	37.0 ±1.8	37.8 ±1.1	38.2 ±1.7	38.3 ±2.5
	t	2.16	1.86	1.23	0.54	0.04	0.25	0.38	0.59
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	37.0 ±1.2	37.2 ±1.9	39.1 ±2.7	39.3 ±2.1	37.9 ±1.8	38.4 ±1.7	39.8 ±1.5	40.7 ±1.1
	t	0.79	0.70	0.75	2.28	0.91	0.47	2.29	1.35
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
450 (mg/Kg)	$\bar{x}$	37.5 ±1.1	38.9 ±3.6	37.4 ±0.9	36.3 ±2.8	36.0 ±2.7	34.9 ±2.8	37.5 ±2.5	37.8 ±1.7
	t	0.84	1.33	0.27	0.33	0.74	2.32*	0.26	1.11
	df	4.00	8.00	8.00	8.00	8.00	7.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
x- mean
  - standard deviation
t - t value
df- degrees of freedom

TABLE E-32. MEAN BLOOD VALUES - HEMATOCRIT (g/dl) SUBCHRONIC DERMAL (FEMALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	33.7 ±2.5	35.7 ±2.0	35.8 ±2.2	35.7 ±2.5	36.5 ±2.0	36.4 ±1.1	35.0 ±2.5	35.1 ±1.2
9 (mg/Kg)	$\bar{x}$	33.3 ±1.7	34.9 ±1.1	34.4 ±1.7	35.9 ±1.8	34.4 ±2.0	37.3 ±1.0	36.6 ±1.5	36.5 ±0.7
	t	0.25	0.74	1.07	0.16	1.52	1.15	1.20	2.25
	df	6.00	7.00	8.00	8.00	7.00	6.00	7.00	8.00
90 (mg/Kg)	$\bar{x}$	32.0 ±3.7	35.0 ±4.1	33.7 ±3.9	35.5 ±2.0	33.3 ±1.7	36.8 ±2.1	35.3 ±2.3	35.0 ±0.62
	t	0.82	0.35	1.05	0.12	2.65*	0.38	0.21	0.16
	df	7.00	7.00	8.00	7.00	8.00	6.00	7.00	7.00
450 (mg/Kg)	$\bar{x}$	34.4 ±2.2	36.9 ±2.9	35.6 ±2.5	36.5 ±2.3	34.1 ±1.6	35.1 ±2.1	35.6 ±1.9	34.9 ±2.4
	t	0.46	0.78	0.13	0.55	2.07	1.16	0.43	0.18
	df	7.00	8.00	8.00	8.00	8.00	7.00	7.00	8.00

* - Significantly different than controls ($P<0.05$)
x- mean
  - standard deviation
t - t value
df- degrees of freedom

TABLE E-33. MEAN BLOOD VALUES - HEMOGLOBIN (g/dl) SUBCHRONIC DERMAL (MALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	12.4	12.1	12.4	12.7	13.1	13.7	13.1	13.3
		±1.1	±0.9	±1.0	±0.4	±0.4	±0.2	±0.4	±0.7
9 (mg/Kg)	$\bar{x}$	13.9	13.0	13.2	13.0	13.2	13.2	13.3	12.9
		±1.2	±0.8	±0.4	±0.4	±0.8	±0.4	±0.6	±0.9
	t	1.7	1.73	1.57	1.39	0.3	2.29*	0.58	0.7
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	12.9	12.4	13.1	13.9	13.7	13.8	14.2	13.9
		±0.8	±0.5	±0.9	±0.8	±0.6	±0.8	±0.5	±0.4
	t	0.72	0.63	1.08	2.99*	1.59	0.21	3.44*	1.63
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
450 (mg/Kg)	$\bar{x}$	13.1	13.0	12.4	12.5	12.7	12.2	12.9	12.7
		±0.6	±0.9	±0.3	±0.9	±0.9	±0.9	±0.8	±0.3
	t	0.87	1.55	0.04	0.30	0.82	3.77*	0.42	1.66
	df	4.00	8.00	8.00	8.00	8.00	7.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
x- mean
  - standard deviation
t - t value
df- degrees of freedom

TABLE E-34. MEAN BLOOD VALUES - HEMOGLOBIN (g/dl) SUBCHRONIC DERMAL (FEMALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	11.9 ±0.7	11.9 ±0.6	12.2 ±0.6	12.4 ±0.8	12.7 ±0.7	13.2 ±0.4	12.5 ±0.9	12.9 ±0.4
9 (mg/Kg)	$\bar{x}$	11.9 ±0.6	11.6 ±0.4	11.8 ±0.7	12.4 ±0.6	12.6 ±0.9	13.2 ±0.3	12.9 ±0.5	13.0 ±0.4
	t	0.0	0.83	0.85	0.09	0.18	0.19	0.80	0.52
	df	6.00	7.00	8.00	8.00	7.00	6.00	7.00	3.00
90 (mg/Kg)	$\bar{x}$	11.5 ±1.3	11.9 ±0.6	11.5 ±1.2	12.2 ±0.8	12.2 ±0.7	13.1 ±1.0	12.5 ±0.8	12.6 ±0.3
	t	0.58	0.16	1.08	0.32	1.07	0.16	0.05	0.86
	df	7.00	7.00	8.00	7.00	8.00	6.00	7.00	7.00
450 (mg/Kg)	$\bar{x}$	12.4 ±1.0	12.2 ±1.0	12.1 ±0.9	12.2 ±0.8	12.2 ±0.7	12.8 ±1.0	12.7 ±0.7	12.7 ±1.1
	t	0.80	0.48	0.2	0.27	1.13	0.85	0.29	0.43
	df	7.00	8.00	8.00	8.00	8.00	7.00	7.00	8.00

* - Significantly different than controls ($P<0.05$)
x- mean
  - standard deviation
t - t value
df- degrees of freedom

TABLE E-35. MEAN BLOOD VALUES - RED BLOOD COUNT (RBC) (mm^3) SUBCHRONIC DERMAL (MALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	5.55 ±0.61	5.63 ±0.50	5.79 ±0.66	5.84 ±0.26	5.85 ±0.29	6.02 ±0.23	6.00 ±0.30	6.12 ±0.40
9 (mg/Kg)	$\bar{x}$	6.02 ±0.35	6.04 ±0.44	5.99 ±0.24	5.80 ±0.26	5.72 ±0.29	5.80 ±0.30	5.90 ±0.35	5.79 ±0.35
	t	1.19	1.36	0.63	0.24	0.68	1.28	0.51	1.37
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	5.72 ±0.40	5.64 ±0.22	5.84 ±0.45	6.08 ±0.39	5.92 ±0.38	5.98 ±0.32	6.23 ±0.36	6.23 ±0.16
	t	0.41	0.02	0.13	1.10	0.35	0.24	1.08	0.57
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
450 (mg/Kg)	$\bar{x}$	5.82 ±0.46	5.88 ±0.44	5.63 ±0.30	5.54 ±0.58	5.50 ±0.56	5.37 ±0.66	5.77 ±0.45	5.74 ±0.35
	t	0.53	0.82	0.52	1.08	1.24	2.07	0.98	1.62
	df	3.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
x- mean
  - standard deviation
t - t value
df- degrees of freedom

TABLE E-36. MEAN BLOOD VALUES - RED BLOOD COUNT (mm^3) SUBCHRONIC DERMAL (FEMALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	5.04	5.27	5.29	5.30	5.43	5.64	5.33	5.57
		±0.27	±0.19	±0.23	±0.36	±0.25	±0.15	±0.31	±0.13
9 (mg/Kg)	$\bar{x}$	5.21	5.38	5.29	5.54	5.41	5.95	5.85	5.94
		±0.32	±0.12	±0.23	±0.35	±0.44	±0.41	±0.20	±0.30
	t	0.81	0.96	0.06	1.06	0.06	1.63	3.03	2.56
	df	6.00	7.00	8.00	8.00	7.00	6.00	7.00	8.00
90 (mg/Kg)	$\bar{x}$	4.69	5.01	4.84	5.15	5.00	5.59	5.35	5.42
		±0.55	±0.64	±0.62	±0.41	±0.35	±0.44	±0.38	±0.21
	t	1.17	0.89	1.52	0.58	2.21	0.23	0.06	1.38
	df	7.00	7.00	8.00	7.00	8.00	6.00	7.00	7.00
450 (mg/Kg)	$\bar{x}$	5.15	5.44	5.27	5.49	5.19	5.54	5.54	5.59
		±0.27	±0.34	±0.31	±0.35	±0.28	±0.30	±0.29	±0.33
	t	0.61	0.95	0.08	0.81	1.39	0.65	1.03	0.11
	df	7.00	8.00	8.00	8.00	8.00	7.00	7.00	8.00

* - Significantly different than controls ($P<0.05$)
x- mean
  - standard deviation
t - t value
df- degrees of freedom

TABLE E-37. MEAN BLOOD VALUES - WHITE BLOOD CELLS (mm^3) SUBCHRONIC DERMAL (MALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	6.8 ±1.0	8.6 ±1.4	7.9 ±1.8	7.4 ±2.1	7.7 ±1.8	7.8 ±4.1	8.4 ±1.6	8.5 ±2.4
9 (mg/Kg)	$\bar{x}$	7.0 ±2.6	8.5 ±2.1	8.1 ±2.5	6.4 ±1.0	6.7 ±1.4	8.1 ±1.1	7.6 ±2.1	8.4 ±1.7
	t	0.08	0.12	0.13	0.88	0.99	0.16	0.60	0.03
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	9.5 ±3.9	7.2 ±1.1	8.5 ±2.0	9.0 ±3.2	8.1 ±2.1	9.4 ±2.4	9.8 ±2.7	9.5 ±2.6
	t	1.34	1.85	0.55	0.96	0.32	0.73	1.01	0.66
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
450 (mg/Kg)	$\bar{x}$	7.0 ±3.0	9.7 ±2.8	7.3 ±1.9	7.1 ±1.9	7.7 ±2.3	11.6 ±3.5	9.2 ±1.7	8.8 ±1.9
	t	0.13	0.78	0.53	0.17	0.06	1.49	0.85	0.22
	df	4.00	8.00	8.00	8.00	8.00	7.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
x- mean
  - standard deviation
t - t value
df- degrees of freedom

TABLE E-38. MEAN BLOOD VALUES - WHITE BLOOD CELLS (WBC) (mm^3) SUBCHRONIC DERMAL (FEMALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	6.4 ±1.9	7.3 ±1.1	6.5 ±0.8	6.9 ±1.2	6.8 ±0.5	6.9 ±1.3	6.8 ±1.1	7.0 ±1.5
9 (mg/Kg)	$\bar{x}$	6.0 ±1.9	6.9 ±0.8	6.2 ±0.8	7.3 ±1.5	7.7 ±1.5	7.6 ±1.3	7.8 ±1.6	6.4 ±0.4
	t	0.35	0.51	0.52	0.46	1.23	0.79	1.02	0.76
	df	6.00	7.00	8.00	8.00	7.00	6.00	7.00	8.00
90 (mg/Kg)	$\bar{x}$	6.2 ±1.2	7.5 ±0.9	6.9 ±0.9	6.5 ±1.2	8.0 ±1.2	6.5 ±0.1	6.9 ±1.3	6.5 ±1.1
	t	0.26	0.25	0.84	0.54	2.0	0.52	0.14	0.48
	df	7.00	7.00	8.00	7.00	8.00	6.00	7.00	7.00
450 (mg/Kg)	$\bar{x}$	5.9 ±0.8	7.9 ±1.2	6.7 ±0.9	7.7 ±1.2	7.5 ±1.0	9.4 ±2.3	8.3 ±1.3	6.7 ±1.1
	t	0.54	0.80	0.42	1.0	1.39	2.13	1.76	0.26
	df	7.00	8.00	8.00	8.00	8.00	8.00	7.00	8.00

* - Significantly different than controls ($P<0.05$)
x- mean
  - standard deviation
t - t value
df- degrees of freedom

TABLE E-39. MEAN BLOOD VALUES - MEAN CELL VOLUME (um^3) SUBCHRONIC DERMAL (MALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	63.7	64.6	65.8	64.4	64.0	63.8	63.6	64.4
		±1.5	±2.5	±3.5	±2.3	±2.1	±2.2	±1.5	±1.7
9 (mg/Kg)	$\bar{x}$	67.7	64.8	66.4	65.0	65.2	65.8	65.8	66.4
		±1.5	±3.3	±3.8	±3.0	±3.0	±2.9	±2.9	±2.9
	t	3.39	0.11	0.26	0.35	0.72	1.22	1.48	1.34
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
90 (mg/Kg)	$\bar{x}$	65.0	66.2	67.2	65.6	64.8	64.8	64.6	65.4
		±2.6	±2.9	±2.6	±2.3	±2.2	±2.5	±2.4	±2.4
	t	0.80	0.94	0.72	0.82	0.59	0.68	0.79	0.76
	df	5.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
450 (mg/Kg)	$\bar{x}$	64.5	66.2	67.0	66.4	66.2	65.7	65.8	66.2
		±3.5	±2.5	±2.0	±3.4	±3.8	±4.5	±3.6	±2.8
	t	0.39	1.01	0.67	1.08	1.14	0.86	1.27	1.24
	df	4.00	8.00	8.00	8.00	8.00	7.00	8.00	8.00

* - Significantly different than controls ($P<0.05$)
x- mean
  - standard deviation
t - t value
df- degrees of freedom

Study No. 75-51-0233-84, Aug 82 - Apr 83

TABLE E-40. MEAN BLOOD VALUES - MEAN CELL VOLUME (MCV) (μm^3) SUBCHRONIC DERMAL (FEMALE RABBITS)

DOSE GROUP		WEEK -5	WEEK -4	WEEK -3	WEEK -1	DAY 0	WEEK +1	WEEK +2	WEEK +3
Control	$\bar{x}$	66.0 ±2.6	67.8 ±2.2	68.2 ±2.2	67.2 ±1.9	67.8 ±1.9	65.2 ±1.6	66.0 ±1.6	64.2 ±1.9
9 (mg/Kg)	$\bar{x}$	63.5 ±2.1	65.0 ±2.2	65.2 ±1.7	65.0 ±1.6	64.2 ±2.2	63.0 ±2.6	63.0 ±1.9	62.6 ±1.8
	t	1.51	1.93	2.22	1.98	2.58	1.48	2.52	1.35
	df	6.00	7.00	8.00	8.00	7.00	6.00	7.00	8.00
90 (mg/Kg)	$\bar{x}$	67.6 ±1.5	70.0 ±1.4	69.8 ±1.9	69.5 ±1.9	66.6 ±0.6	66.3 ±1.5	66.6 ±1.1	66.0 ±1.6
	t	1.17	1.74	1.23	1.79	1.34	0.97	0.65	1.49
	df	7.00	7.00	8.00	7.00	8.00	6.00	7.00	7.00
450 (mg/Kg)	$\bar{x}$	66.2 ±2.2	67.8 ±1.9	67.8 ±1.5	66.8 ±1.3	66.2 ±0.8	63.7 ±2.2	64.8 ±1.8	63.6 ±1.8
	t	0.13	0.0	0.34	0.38	1.71	1.13	1.04	0.51
	df	7.00	8.00	8.00	8.00	8.00	7.00	7.00	8.00

* - Significantly different than controls ($P<0.05$)
x- mean
  - standard deviation
t - t value
df- degrees of freedom

APPENDIX F

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