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Final Report

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TOXIC EVALUATION OF INHALED CHLOROBENZENE (MONOCHLOROBENZENE)

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ABSTRACT OF FINAL REPORT ON

CONTRACT/IA #: 210-76-0126

CONTRACT/IA TITLE: Toxic Evaluation of Inhaled Chlorobenzene (Monochlorobenzene)

CONTRACTOR/COOP. AGENCY: Stanford Research Institute

PROJECT OFFICER: Trent R. Lewis, Ph.D.

PURPOSE: To evaluate hematology clinical chemistry & gross histopathologic changes resulting from chlorobenzene exposure.

DURATION: 6/19/76 - 6/18/77

COST: $ 68,120

ABSTRACT: Male rats and rabbits were exposed to 0, 75, or 250 ppm chlorobenzene vapors for 7 hours daily, 5 days/week, for up to 120 exposure days (24 weeks). Groups of animals from both species were sacrificed after 5 and 11 weeks of treatment and examined for hematology, clinical chemistry, and gross and histopathological changes resulting from the chlorobenzene treatment. A statistical analysis of the data suggests some treatment-related effect on the red cell parameters. There appeared to be a small effect on food utilization in rats. Pathological changes were mostly found in rats, where occasional focal lesions in the adrenal cortex, tubular lesions in the kidneys, and congestion in the liver and kidneys suggested a treatment relationship.

The subtle changes observed in rats at 75 and 250 ppm suggest that the current maximum permissible concentration for chlorobenzene of 75 ppm may be too high and that 5 to 10 ppm may be a better working level.

Final report received December 5, 1977.

ABSTRACT

Male rats and rabbits were exposed to 0, 75, or 250 ppm chlorobenzene vapors for 7 hours daily, 5 days/week, for up to 120 exposure days (24 weeks). Groups of animals from both species were sacrificed after 5 and 11 weeks of treatment and examined for hematology, clinical chemistry, and gross and histopathological changes resulting from the chlorobenzene treatment. A statistical analysis of the data suggests some treatment-related effect on the red cell parameters. There appeared to be a small effect on food utilization in rats. Pathological changes were mostly found in rats, where occasional focal lesions in the adrenal cortex, tubular lesions in the kidneys, and congestion in the liver and kidneys suggested a treatment relationship.

The subtle changes observed in rats at 75 and 250 ppm suggest that the current maximum permissible concentration for chlorobenzene of 75 ppm may be too high and that 5 to 10 ppm may be a better working level.

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INTRODUCTION

Chlorobenzene (monochlorobenzene, benzyl chloride) is extensively used by industry as a solvent and as a chemical intermediate, but relatively little information has been published on its toxicity. Rozenbaum et al.[1] reported that the absolute toxic dose of chlorobenzene vapor in mice was 20 mg/liter. Irish[2] cited a report on the acute toxicity of chlorobenzene vapor to rats, in which mortality was produced by exposure to 37 mg/liter for 0.5 hour or to 17 mg/kg for 7 hours. Rats, rabbits, and guinea pigs were chronically exposed to chlorobenzene vapor for 7 hours/day, 5 days/week, for 32 exposures (44 days). At 1000 ppm, histological changes occurred in the lung, liver, and kidney of all animals. Also, mortality in guinea pigs was increased. At 475 ppm, liver weight and histological changes in the liver were increased only slightly. At 200 ppm, all the animals appeared to be normal.

The acute oral LD_{50}s for rats and rabbits were determined to be 2.91 g/kg and 2.83 g/kg, respectively.[2] Repeated daily doses, totaling 137 doses over 192 days, did not produce any observable effect in rats at 14.4 mg/kg. However, at 144 and 288 mg/kg, their liver and kidney weight increased significantly. Some liver lesions were observed in both rats and rabbits, but blood and bone marrow were normal.

Williams[3] has summarized metabolism studies with chlorobenzene and the dichlorobenzenes. In rabbits, 30% of an oral dose (150 mg/kg) of chlorobenzene was excreted unchanged. In rats, 20 to 30% and in dogs about 35% of the dose was excreted as p-chlorophenyl-mercapturic acid. (No ortho or meta isomers were formed.) Chlorobenzene is sufficiently volatile (vapor pressure, 11.8 mm Hg at 25° C) that 20 to 30% of a dose in dogs was eliminated unchanged in the expired air;[4] the rest of the compound was oxidized to phenols and excreted in the urine as glucuronide and sulfate conjugates. The major phenol formed was 4-chlorocatechol.

In April 1959, the American Conference of Government Industrial Hygienists established the threshold limit value of chlorobenzene at 75 ppm (350 mg/m^3). Because of the lack of information on the inhalation of chlorobenzene vapors, additional dose-response data are needed to determine whether 75 ppm is a safe concentration for the work environment.

Under Contract No. 210-76-0126 with the National Institute for Occupational Safety and Health (NIOSH), SRI International (Stanford Research Institute) evaluated the toxicity of inhaled chlorobenzene in male rats and rabbits. The animals were exposed to 0, 75, or 250 ppm chlorobenzene for 7 hours daily, 5 days/week, for 120 exposure days (24 weeks). After 25, 55, and 120 exposure days, groups of animals from both species were sacrificed. They were evaluated for hematology, clinical chemistry, and gross and histopathological changes that resulted from the chlorobenzene exposures.

MATERIALS AND METHODS

Animals

Adult male Sprague-Dawley rats, weighing 125 ± 10 g, were obtained from Simonsen Laboratories, Gilroy, California. Adult male rabbits, weighing 2.0 to 2.5 kg, were obtained from L.I.T. Rabbitry, Aptos, California. The animals were isolated for 1 week after their arrival in the laboratory to ensure that only healthy animals were used for this study. After isolation, the animals were randomized into three groups, each containing 32 male rats and 32 male rabbits (30 animals plus 2 extra to allow for a small attrition expected during the project). Rats were housed two per cage, and rabbits were housed singly. All animals were provided with food and water ad libitum when they were not in the exposure chamber.

All animals were weighed weekly for the first 5 weeks, biweekly for 4 weeks, and monthly thereafter. The food consumption of the rats was measured for 13 weeks and biweekly thereafter. All animals were observed daily throughout the experiment.

Exposure Chambers

The animals were exposed to chlorobenzene in cylindrical stainless-steel chambers. The chambers are 122 cm in diameter and have a total volume of approximately 2.3 m^3. Animals were placed in cages on the four shelves, which are approximately 38 cm apart. Filtered, conditioned intake air and chlorobenzene vapor were introduced at the top of the chamber through a diffusing apparatus that ensured uniform distribution of the test material throughout the chamber. The chamber atmospheres were exhausted from the bottom of the chamber, through an absolute filter, and out a stack through the roof. Chamber flow rates, monitored by water manometers, were approximately ten chamber volumes per hour.

Vapor Generation

Chlorobenzene vapors were generated by passing breathing-quality air through a scintered-glass tube that was immersed in a chlorobenzene-containing Erlenmeyer flask. The vapor was carried from the flask to the chamber induction system by glass tubing. The flask was immersed in a Precision Labs water bath during generation to maintain the temperature of the chlorobenzene and compensate for the evaporative cooling that occurs during generation.

Chlorobenzene Analysis

Chlorobenzene concentrations were determined with a Varian Model 1700 gas chromatograph equipped with a flame ionization detector. The 183 cm x 0.48 cm glass column was packed with 10% QFI on Chromosorb W-HP. The column temperature was 60° C, the injector temperature was 250° C, and the carrier gas (nitrogen) flow was 35 ml/min. Under these conditions, the daily standards varied less than 2%.

Chlorobenzene (J. T. Baker Chemical Company, Phillipsburg, New Jersey) was obtained from a local supplier. Analysis of this material indicated that it contained 99%+ chlorobenzene. The principal contaminant was probably benzene.

Serial Sacrifices

After 25, 55, or 120 exposures to chlorobenzene, animals were anesthetized with chloroform for sacrifice. Blood was collected for hematology and clinical chemistry studies by cardiac puncture. Any observations of gross changes were recorded; if the organs were normal, this was also recorded. The brain, heart, lungs, liver, spleen, kidneys, and gonads of each animal were weighed. In addition, adrenal glands, bone marrow (sternum), eye, skin, and any abnormal tissue were collected. All tissues were immediately fixed in 10% neutral buffered formalin, stained with hematoxylin and eosin, and evaluated by a board-certified veterinary pathologist.

Clinical Chemistry and Hematology

Clinical chemistry determinations were made with a Technicon SMAC high-speed, computer-controlled biochemical analyzer. The methods used for each determination were those recommended by Technicon Instruments Corporation, Tarrytown, New Jersey.

Cell counts and micro-parameters were determined using a Model MHR Coulter counter. Differential counts, platelets, and reticulocytes were determined by standard hand methods.

Data Analysis

Body weights and organ weights and hematology and clinical chemistry parameters were tested for statistical significance by an analysis of variance (ANOVA),[5] followed by a Dunnett's test,[6,7] to determine which, if any, group was different.

Because this experiment was designed to detect subtle effects of chlorobenzene vapor inhalation, additional statistical methods were also applied to the data. Bartlett's chi-square statistic was used to test the hypothesis that the group variances were equal. If Bartlett's chi-square is significantly large, the indication is that the variances within each group are unequal; unequal variances of and by themselves are indicators of unequal group effects. In addition, the analysis of variance and subsequent t-tests (Dunnett's) assume equal variances; a significantly large value of Bartlett's statistic indicates possible violation of that assumption.

Other statistical evaluations of the data were directed to elucidation of the average treatment effect. This is the sample mean value of two treatment groups minus the control mean group value. The linear trend statistic represents the average change per unit of increase in the log-dose level for the two treatment groups. This latter statistic suggests which parameters would be expected to change with increasing dosages.

RESULTS*

Chamber Concentrations

Figure 1 shows the analytical concentrations of chlorobenzene in the exposure chamber, as determined by gas chromatography of 1.0-ml chamber air samples. The chambers were sampled daily at the beginning of the exposure, at midday, and just before the end of the daily exposure. If the chamber for exposure to 250 ppm chlorobenzene was off by more than 6 ppm, the flow was adjusted and the chamber was sampled again. The chamber containing 75 ppm was adjusted and sampled again if it was off by more than 3 ppm. The grand analytical mean (± standard deviation) was 248 ± 19 ppm for the high exposure and 73 ± 8 ppm for the low exposure of both rats and rabbits.

Occasionally during the inhalation exposures, leaks developed because of a deteriorating gasket, an improperly sealed door, a chamber drain left open, or other factors. Leaks were detected and corrected after the first sampling that indicated the chamber concentrations were at considerable variance from the desired amount. These minor problems did contribute greatly to the large standard deviations occasionally seen with the weekly chamber concentrations.

General Observations of Rats

Nothing unusual was noted in any of the rats during daily observations. No rats died during the entire exposure period.

Body Weights and Food Consumption of Rats

The body weights of the treated and control groups of rats did not differ significantly during the 24 weeks of exposure to chlorobenzene, as shown in Tables 1 through 3. The low-dose group (75 ppm)

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* Tables presenting the complete statistical evaluations of the body weights and absolute and relative organ weights and of the hematology and clinical chemistry parameters are appended.

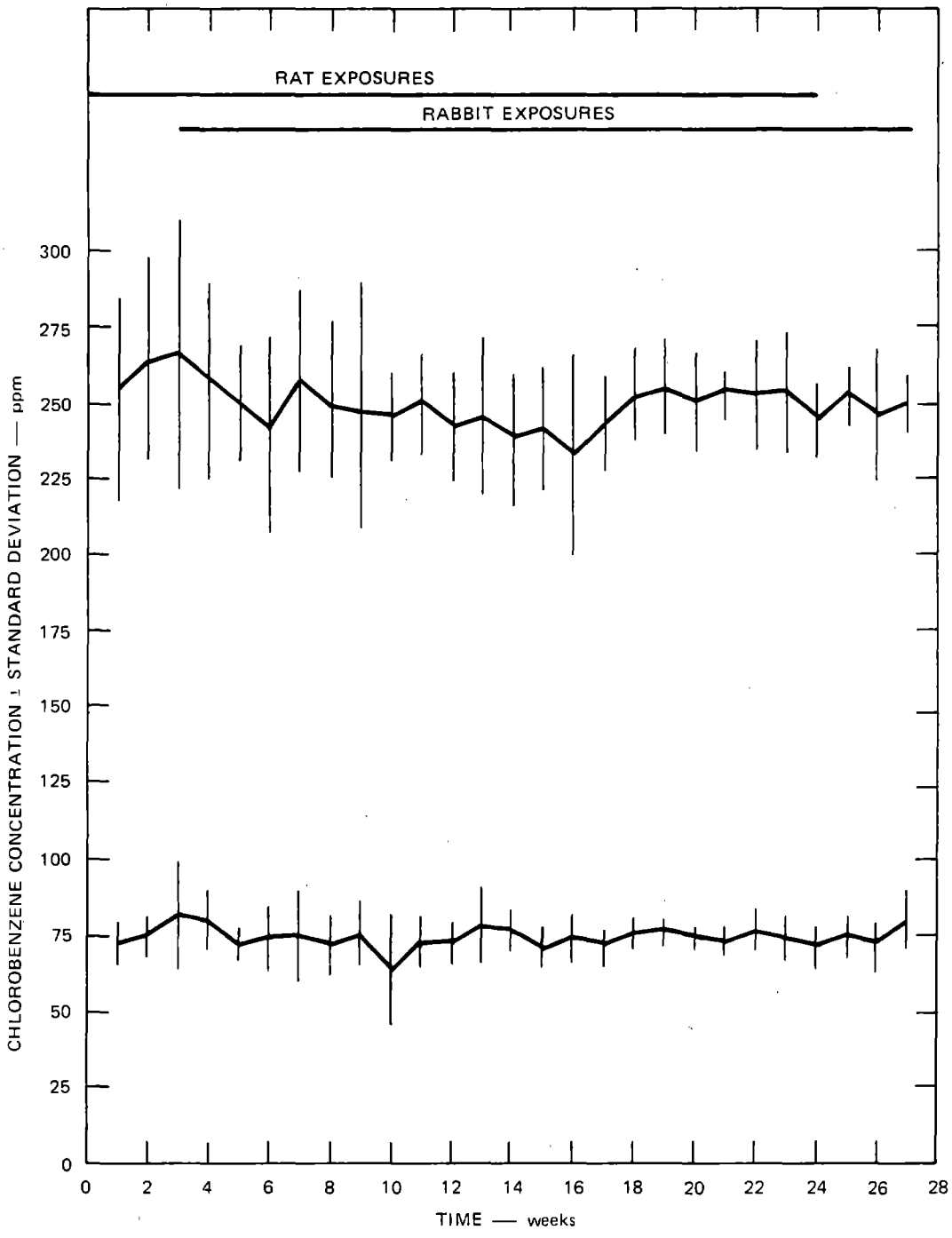

FIGURE 1 WEEKLY CHAMBER CONCENTRATIONS OF CHLOROBENZENE

Table 1

EFFECTS OF CHLOROBENZENE ON BODY WEIGHTS OF RATS
AFTER 5 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE=75 PPM (3)	DOSE=250 PPM (4)
INITAL	152.7(1.28)	153.0(5.28)	153.0(2.72)
WEEK 1	203.8(2.31)	198.8(5.34)	195.7(4.82)
WEEK 2	249.9(5.31)	240.3(6.04)	244.6(5.91)
WEEK 3	290.5(7.32)	274.0(7.21)	286.3(8.06)
WEEK 5	302.3(9.25)	277.6(5.93)	288.5(10.2)

ENTRIES ARE MEAN + STANDARD ERROR

Table 2

EFFECTS OF CHLOROBENZENE ON BODY WEIGHTS OF RATS
AFTER 11 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE=75 PPM (3)	DOSE=250 PPM (4)
INITAL	158.7(1.44)	155.8(2.63)	157.0(2.11)
WEEK 1	201.4(5.09)	204.3(4.25)	199.3(3.05)
WEEK 2	247.9(6.82)	247.9(4.21)	245.1(3.13)
WEEK 3	291.0(5.12)	287.8(4.43)	284.7(5.26)
WEEK 5	337.7(5.06)	337.7(8.16)	337.0(8.45)
WEEK 7	379.2(6.29)	380.6(8.90)	368.7(10.5)
WEEK 11	390.5(8.92)	400.3(9.08)	371.4(5.99)

ENTRIES ARE MEAN + STANDARD ERROR

Table 3

EFFECTS OF CHLOROBENZENE ON BODY WEIGHTS OF RATS
AFTER 24 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE= 75 PPM (3)	DOSE= 250 PPM (4)
INITAL	150.5(4.32)	152.0(1.89)	158.9(3.54)
WEEK 1	197.6(6.46)	197.9(3.54)	205.6(4.48)
WEEK 2	235.7(8.30)	240.8(4.83)	248.7(4.13)
WEEK 3	271.1(9.10)	277.9(6.80)	284.2(4.08)
WEEK 5	317.5(12.0)	319.9(6.59)	329.7(4.82)
WEEK 7	354.8(14.4)	307.8(8.41)	362.2(5.37)
WEEK 11	404.5(16.6)	414.9(9.28)	420.3(13.2)
WEEK 15	432.8(19.8)	444.7(10.3)	449.0(16.6)
WEEK 19	450.3(19.9)	464.2(11.5)	465.8(18.2)
WEEK 24	467.1(20.7)	479.1(13.5)	479.8(18.4)

ENTRIES ARE MEAN + STANDARD ERROR

showed an apparent weight loss at the seventh week because of a malfunction in the automatic watering system on their cage rack. Once this was remedied, the rats regained the weight within a few days.

Table 4 shows the food consumption of the rats. Note that the treated groups generally had a higher daily food consumption.

General Observations of Rabbits

The rabbits were occasionally observed to have diarrhea during the course of this study, but it was not treatment-related since it was observed in the control animals as well as in the treated groups. One rabbit (#89) was found dead in the chamber at the end of the 23rd exposure. Autopsy failed to reveal anything that would cause death. Another rabbit (#125) was found dead at the end of the 26th exposure. Again, no cause of death could be established at autopsy. One rabbit (#146) was sacrificed after the 32nd exposure when he was found to have a leg injury either from fighting or from getting caught in the cage flooring in the chamber. One rabbit (#1) broke his food on the 41st exposure day, and #134 lost a testicle while fighting between cages in the chamber.

Body Weights of Rabbits

Tables 5 through 7 present the body weights of the rabbits after 5, 11, and 24 weeks of treatment. No differences were noted between the treated and control groups during the exposure period.

Absolute and Relative Organ Weights of Rats

Tables 8 through 10 show the absolute and relative organ weights of rats sacrificed after 25, 55, and 120 exposures, respectively. An analysis of variance showed no significant difference between the organ weights of control and exposed rats sacrificed after 25 exposures. However, Bartlett's chi-square statistic did indicate a significant difference in the variances of the absolute weights of heart, liver, and spleen as well as in the relative weights of these organs to body and brain weights.

Table 4

FOOD CONSUMPTION (GRAMS) OF TREATED AND CONTROL RATS

Week	Control	Exposed	
		75 ppm	250 ppm
1	19.1	19.4	19.0
2	22.9	24.4	24.9
3	25.0	26.3	26.9
4	26.7	27.0	27.3
5	25.3	25.6	25.6
6	25.0	27.1	25.9
7	24.1	22.0*	26.4
8	25.1	28.0	26.0
9	24.1	26.6	25.4
10	27.4	29.0	27.3
11	23.7	25.7	25.4
12	25.4	28.6	28.9
13	25.8	22.3	24.7
15	25.9	28.0	27.9
17	23.9	26.7	27.7
19	27.9	27.0	26.3
21	26.0	28.0	27.9

* Without water for 1 day due to malfunction of automatic watering system on cage rack.

Table 5

EFFECTS OF CHLOROBENZENE ON BODY WEIGHTS OF RABBITS
AFTER 5 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE= 75 PPM (3)	DOSE= 250 PPM (4)
INITAL	2.4(.038)	2.2(.060)	2.3(.058)
WEEK 1	2.4(.056)	2.2(.081)	2.4(.063)
WEEK 2	2.5(.090)	2.4(.085)	2.6(.061)
WEEK 3	2.4(.134)	2.5(.089)	2.7(.072)
WEEK 5	2.5(.098)	2.7(.081)	2.7(.092)

ENTRIES ARE MEAN + STANDARD ERROR

Table 6

EFFECTS OF CHLOROBENZENE ON BODY WEIGHTS OF RABBITS
AFTER 11 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE=75 PPM (3)	DOSE=250 PPM (4)
INITAL	2.3(.044)	2.3(.059)	2.2(.042)
WEEK 1	2.4(.052)	2.3(.062)	2.4(.042)
WEEK 2	2.6(.100)	2.6(.056)	2.6(.048)
WEEK 3	2.7(.081)	2.7(.065)	2.7(.048)
WEEK 5	3.0(.103)	2.9(.076)	2.9(.060)
WEEK 7	3.1(.130)	3.1(.091)	3.1(.043)
WEEK 11	3.2(.142)	3.1(.150)	3.1(.087)

ENTRIES ARE MEAN + STANDARD ERROR

Table 7

EFFECTS OF CHLOROBENZENE ON BODY WEIGHTS OF RABBITS
AFTER 24 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE= 75 PPM (3)	DOSE= 250 PPM (4)
INITAL	2.2(.049)	2.3(.051)	2.2(.060)
WEEK 1	2.4(.029)	2.4(.082)	2.3(.072)
WEEK 2	2.5(.065)	2.7(.089)	2.6(.070)
WEEK 3	2.7(.060)	2.7(.073)	2.8(.089)
WEEK 5	2.9(.041)	2.9(.079)	3.0(.091)
WEEK 7	3.2(.041)	3.1(.081)	3.2(.120)
WEEK 11	3.5(.079)	3.4(.095)	3.6(.081)
WEEK 15	3.6(.109)	3.6(.096)	3.8(.097)
WEEK 19	3.5(.144)	3.6(.128)	4.0(.100)
WEEK 23	3.7(.118)	3.7(.150)	4.1(.110)
WEEK 24	3.7(.109)	3.7(.119)	4.1(.096)

ENTRIES ARE MEAN + STANDARD ERROR

Table 8

EFFECTS OF CHLOROBENZENE ON ORGAN WEIGHTS OF RATS
AFTER 5 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE= 75 PPM (3)	DOSE= 250 PPM (4)
BRAIN	1.99(.033)	2.01(.043)	1.89(.050)
HEART	1.15(.032)	1.11(.036)	1.14(.073)
LUNG	1.79(.139)	1.70(.127)	1.77(.108)
LIVER	10.10(.381)	9.98(.324)	9.67(.994)
SPLEEN	.64(.020)	.56(.017)	.66(.103)
KIDNEY	2.62(.090)	2.62(.086)	2.79(.132)
GONAD	3.10(.093)	2.91(.085)	2.99(.145)
BRAIN/BYWT	6.61(.159)	7.27(.133)*	6.67(.172)
HEART/BYWT	3.82(.077)	4.02(.121)	3.94(.180)
LUNG/BYWT	5.90(.385)	6.16(.518)	6.10(.225)
LIVER/BYWT	33.40(.576)	35.90(.601)	33.77(3.25)
SPLEEN/BYWT	2.14(.050)	2.02(.054)	2.35(.445)
KIDNEY/BYWT	8.68(.169)	9.44(.202)	9.66(.245)*
GONAD/BYWT	10.30(.331)	10.51(.313)	10.43(.502)
HEART/BRAIN	.58(.016)	.55(.020)	.59(.034)
LUNG/BRAIN	.90(.069)	.85(.075)	.92(.047)
LIVER/BRAIN	5.08(.166)	4.96(.131)	5.01(.549)
SPLEEN/BRAIN	.32(.010)	.28(.008)	.35(.065)
KIDNEY/BRAIN	1.32(.037)	1.30(.041)	1.45(.056)
GONAD/BRAIN	1.56(.050)	1.45(.038)	1.58(.104)

BYWT=BODY WEIGHTS

ENTRIES ARE MEAN + STANDARD ERROR

*$P < .05$

Table 9

EFFECTS OF CHLOROBENZENE ON ORGAN WEIGHTS OF RATS
AFTER 11 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE= 75 PPM (3)	DOSE= 250 PPM (4)
BRAIN	2.19(.033)	2.12(.031)	2.13(.039)
HEART	1.38(.048)	1.75(.156) *	1.40(.035)
LUNG	1.88(.132)	1.69(.042)	1.84(.097)
LIVER	11.31(.356)	13.65(.474) **	12.31(.364)
SPLEEN	.73(.026)	.77(.032)	.70(.041)
KIDNEY	3.10(.109)	3.40(.149)	3.32(.104)
GONAD	3.26(.127)	3.33(.081)	3.26(.063)
BRAIN/BYWT	5.63(.141)	5.31(.111)	5.74(.084)
HEART/BYWT	3.53(.094)	4.37(.363)	3.78(.106)
LUNG/BYWT	4.80(.295)	4.26(.156)	4.93(.216)
LIVER/BYWT	29.04(.965)	34.06(.718) **	33.13(.701) **
SPLEEN/BYWT	1.86(.064)	1.92(.093)	1.89(.104)
KIDNEY/BYWT	7.96(.242)	8.49(.276)	8.92(.200)
GONAD/BYWT	8.36(.295)	8.32(.171)	8.79(.166)
HEART/BRAIN	.63(.017)	.82(.067) *	.66(.016)
LUNG/BRAIN	.85(.052)	.80(.025)	.86(.040)
LIVER/BRAIN	5.16(.150)	6.45(.237) **	5.79(.152)
SPLEEN/BRAIN	.33(.012)	.36(.018)	.33(.019)
KIDNEY/BRAIN	1.42(.042)	1.60(.054) *	1.56(.045)
GONAD/BRAIN	1.49(.049)	1.57(.035)	1.53(.033)

BYWT=BODY WEIGHTS

ENTRIES ARE MEAN + STANDARD ERROR

*P < .05

**P < .01

Table 10

EFFECTS OF CHLOROBENZENE ON ORGAN WEIGHTS OF RATS
AFTER 24 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE=75 PPM (3)	DOSE=250 PPM (4)
BRAIN	2.16(.066)	2.25(.031)	2.20(.036)
HEART	1.58(.060)	1.77(.041)	1.63(.062)
LUNG	2.77(.890)	1.90(.094)	2.06(.140)
LIVER	15.81(.842)	17.91(.875)	21.48(1.74)*
SPLEEN	.73(.034)	.75(.033)	.81(.106)
KIDNEY	3.50(.198)	3.69(.124)	4.05(.186)
GONAD	3.24(.092)	3.28(.122)	3.41(.091)
BRAIN/BYWT	4.68(.175)	4.73(.189)	4.65(.171)
HEART/BYWT	3.40(.125)	3.74(.107)	3.40(.070)
LUNG/BYWT	6.31(2.34)	3.95(.173)	4.31(.301)
LIVER/BYWT	33.75(.623)	37.56(1.19)	44.30(1.93)**
SPLEEN/BYWT	1.59(.080)	1.56(.078)	1.65(.146)
KIDNEY/BYWT	7.48(.222)	7.86(.165)	8.45(.234)*
GONAD/BYWT	7.02(.242)	6.90(.335)	7.20(.297)
HEART/BRAIN	.73(.032)	.79(.022)	.74(.023)
LUNG/BRAIN	1.26(.383)	.85(.043)	.94(.070)
LIVER/BRAIN	7.33(.354)	7.97(.427)	9.73(.769)*
SPLEEN/BRAIN	.34(.018)	.33(.015)	.37(.048)
KIDNEY/BRAIN	1.62(.077)	1.64(.057)	1.84(.077)
GONAD/BRAIN	1.51(.039)	1.46(.062)	1.55(.051)

BYWT=BODY WEIGHTS

ENTRIES ARE MEAN + STANDARD ERROR

*P < .05

**P < .01

The control and exposed rats sacrificed after 55 exposures (11 weeks) had a statistically significant increase in the absolute weights of heart and liver. The 75-ppm dose group also had an increase in the relative liver-to-body weight and heart-, liver-, and kidney-to-brain weight ratios. The high-dose group had an increase only in the relative liver- and kidney-to-body weight ratios. Bartlett's statistic indicated wide variances in the absolute heart and lung weights as well as in the relative heart-to-body weight and heart-to-brain weight ratios.

After 120 exposures (24 weeks), the rats in the high-dose group had an increased absolute and relative liver weight as well as an increased kidney-to-body weight ratio. Bartlett's statistic indicated increased variances in the absolute weights of the brain, lung, liver, and spleen, as well as in the relative lung, liver, and spleen weights.

Absolute and Relative Organ Weights of Rabbits

Dunnett's test showed a significant difference only in the liver-to-brain weight ratios of the rabbits in the 250-ppm group sacrificed after 5 treatment weeks (25 exposures); Table 11 shows these data. This statistical method showed no differences in the group sacrificed after 11 weeks (55 exposures), as indicated in Table 12. In the 250-ppm group, in the rabbits sacrificed after 24 weeks (120 exposures) the absolute lung and liver weights were increased, as were the relative liver- and lung-to-brain weight ratios; Table 13 presents these data.

In the groups sacrificed after 5 weeks (25 exposures), Bartlett's chi-square statistic indicated significant differences between control and exposed rats in the variances of the absolute weights of the spleen and gonads and of the relative weights of the brain, heart, and spleen. The variances of the absolute gonad-to-body weight ratio and of the spleen-to-brain weight ratio also were significantly different in the treated groups.

Table 11

EFFECTS OF CHLOROBENZENE ON ORGAN WEIGHTS OF RABBITS
AFTER 5 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE= 75 PPM (3)	DOSE=250 PPM (4)
BRAIN	9.96(.260)	9.98(.209)	9.58(.243)
HEART	6.58(.348)	6.84(.319)	7.28(.314)
LUNG	13.13(1.02)	12.97(1.16)	12.82(.625)
LIVER	85.67(4.15)	95.77(6.86)	108.96(7.18)
SPLEEN	1.18(.110)	1.15(.128)	1.54(.244)
KIDNEY	15.87(.932)	16.48(1.03)	17.41(.900)
GONAD	3.75(.491)	4.97(.612)	4.18(.227)
BRAIN/BYWT	4.08(.210)	4.11(.359)	3.60(.141)
HEART/BYWT	2.69(.143)	2.86(.282)	2.76(.142)
LUNG/BYWT	5.40(.516)	5.28(.513)	4.88(.294)
LIVER/BYWT	34.59(1.23)	38.93(2.14)	40.64(2.10)
SPLEEN/BYWT	.47(.037)	.48(.053)	.61(.118)
KIDNEY/BYWT	6.42(.340)	6.79(.434)	6.66(.509)
GONAD/BYWT	1.49(.174)	1.89(.247)	1.56(.078)
HEART/BRAIN	.66(.034)	.68(.025)	.76(.030)
LUNG/BRAIN	1.31(.083)	1.30(.112)	1.35(.064)
LIVER/BRAIN	8.64(.467)	9.60(.647)	11.62(.672) **
SPLEEN/BRAIN	.12(.012)	.12(.012)	.17(.028)
KIDNEY/BRAIN	1.60(.104)	1.65(.096)	1.84(.117)
GONAD/BRAIN	.38(.052)	.51(.074)	.43(.029)

BYWT=BODY WEIGHTS

ENTRIES ARE MEAN + STANDARD ERROR

** $P < .01$

Table 12

EFFECTS OF CHLOROBENZENE ON ORGAN WEIGHTS OF RABBITS
AFTER 11 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE= 75 PPM (3)	DOSE= 250 PPM (4)
BRAIN	10.55(.371)	9.72(.216)	9.95(.270)
HEART	9.45(1.11)	9.05(.895)	8.56(.533)
LUNG	16.17(2.32)	13.19(.833)	11.85(.628)
LIVER	98.18(9.74)	109.76(4.63)	103.81(4.33)
SPLEEN	1.77(.208)	1.49(.202)	1.41(.136)
KIDNEY	14.71(2.54)	15.00(2.62)	18.54(.976)
GONAD	5.56(.686)	4.88(.506)	5.79(.428)
BRAIN/BYWT	3.32(.135)	3.15(.123)	3.18(.103)
HEART/BYWT	2.89(.221)	2.90(.249)	2.72(.140)
LUNG/BYWT	4.92(.504)	4.36(.501)	3.78(.191)
LIVER/BYWT	30.03(1.68)	35.24(1.13)	33.17(1.56)
SPLEEN/BYWT	.55(.065)	.47(.054)	.45(.045)
KIDNEY/BYWT	4.75(.814)	4.97(.843)	5.96(.414)
GONAD/BYWT	1.76(.213)	1.57(.154)	1.82(.101)
HEART/BRAIN	.89(.092)	.93(.083)	.87(.061)
LUNG/BRAIN	1.52(.196)	1.37(.107)	1.19(.056)
LIVER/BRAIN	9.24(.755)	11.29(.423)	10.49(.499)
SPLEEN/BRAIN	.17(.020)	.15(.018)	.14(.015)
KIDNEY/BRAIN	1.41(.240)	1.56(.269)	1.87(.104)
GONAD/BRAIN	.53(.067)	.50(.051)	.58(.038)

BYWT=BODY WEIGHTS

ENTRIES ARE MEAN + STANDARD ERROR

Table 13

EFFECTS OF CHLOROBENZENE ON ORGAN WEIGHTS OF RABBITS
AFTER 24 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE= 75 PPM (3)	DOSE= 250 PPM (4)
BRAIN	11.07(.307)	11.24(.373)	11.46(.315)
HEART	9.68(.535)	9.53(.441)	11.09(.436)
LUNG	12.98(.707)	15.27(1.14)	18.76(1.66)*
LIVER	94.18(4.38)	91.07(2.78)	116.61(5.52)**
SPLEEN	1.57(.173)	1.93(.232)	3.02(.551)
ADRENAL	.53(.049)	.48(.024)	.53(.047)
KIDNEY	20.42(.726)	20.71(1.21)	24.17(1.26)
GONAD	6.81(.449)	7.19(.333)	6.99(.285)
BRAIN/BYWT	3.03(.134)	3.07(.113)	2.84(.115)
HEART/BYWT	2.65(.163)	2.61(.148)	2.73(.096)
LUNG/BYWT	3.57(.250)	4.20(.388)	4.65(.456)
LIVER/BYWT	25.52(.563)	24.99(1.14)	28.68(1.18)
SPLEEN/BYWT	.44(.056)	.53(.067)	.74(.131)
ADRENAL/BYWT	.14(.009)	.13(.008)	.13(.011)
KIDNEY/BYWT	5.58(.222)	5.63(.262)	5.93(.258)
GONAD/BYWT	1.85(.109)	1.96(.092)	1.72(.067)
HEART/BRAIN	.88(.053)	.85(.036)	.97(.038)
LUNG/BRAIN	1.18(.069)	1.36(.097)	1.63(.125)*
LIVER/BRAIN	8.56(.444)	8.18(.406)	10.20(.422)
SPLEEN/BRAIN	.14(.014)	.17(.020)	.26(.043)
ADRENAL/BRAIN	.05(.005)	.04(.003)	.05(.005)
KIDNEY/BRAIN	1.85(.060)	1.84(.079)	2.12(.104)
GONAD/BRAIN	.61(.035)	.65(.049)	.61(.018)

BYWT=BODY WEIGHTS

*P < .05

**P < .01

After 11 weeks (55 exposures), rabbits sacrificed showed a significant variance of the absolute weights of the lung, liver, and kidney and of the lung-to-body weight and lung- and kidney-to-brain weight ratios.

After 24 weeks, the variance of the absolute weights of the lung, liver, spleen, and adrenals of exposed rabbits was significantly greater than that of the controls. The relative liver- and spleen-to-body weight ratios and spleen- and gonad-to-brain weight ratios were significantly different also.

Rat Hematology

Hematological changes in rats after 5 weeks of treatment were limited to an increase in the total RBC count and in the microhematocrit count of both treatment groups over the controls, as shown in Table 14. This suggested a possible bone marrow stimulation when reticulocyte and platelet counts were added to subsequent hematology measurements.

As Table 15 shows, after 11 weeks of treatment, significant changes were seen, especially in the high-dose group. These changes included a decrease in hematocrit and microcell volume, and in the high-dose group the total WBC counts were increased, as was the relative percentage of polymorphonuclear leukocytes. In both treatment groups, the platelet and reticulocyte counts were significantly different from those of the controls.

After 24 weeks, only the reticulocyte counts in the high-dose group were significantly different from those of the controls, as shown in Table 16.

Table 14

EFFECTS OF CHLOROBENZENE ON HEMATOLOGY OF RATS
AFTER 5 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE= 75 PPM (3)	DOSE=250 PPM (4)
RBC X 10^6	7.4(.154)	7.9(.090)	8.0(.114)
HB, G %	14.3(.297)	15.1(.181)	15.1(.133)
HCT, %	41.3(.795)	42.2(.462)	42.5(.449)
MCV, U	54.7(.818)	53.8(.559)	52.9(.482)
MCH, UUg	19.2(.204)	19.1(.195)	18.8(.216)
MCHC, %	34.7(.202)	35.8(.192) **	35.5(.181) *
WBC X 10^3	8.2(.963)	11.8(1.06)	9.8(.870)
PMN, %	13.5(1.50)	10.2(1.50)	8.5(1.26)
BANDS, %	.6(.375)	1.4(.460)	.9(.314)
LYMPH, %	83.6(1.85)	86.3(2.02)	89.6(1.52)
MONO, %	2.0(.567)	1.3(.313)	.6(.306)
EOSIN, %	.3(.164)	.9(.398)	.4(.306)
BASO, %	0.0(0.00)	0.0(0.00)	0.0(0.00)

ENTRIES ARE MEAN + STANDARD ERROR

*P < .05

**P < .01

Table 15

EFFECTS OF CHLOROBENZENE ON HEMATOLOGY OF RATS
AFTER 11 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE= 75 PPM (3)	DOSE= 250 PPM (4)
RBC X 10^6	8.4(.180)	8.3(.106)	8.4(.134)
HB, G %	15.3(.213)	15.0(.186)	14.9(.176)
HCT, %	46.5(.707)	44.3(.708)	43.4(.514)*
MCV, U	53.9(.515)	52.2(.359)	51.0(.715)**
MCH, UUg	18.0(.207)	18.0(.119)	17.7(.234)
MCHC, %	33.1(.169)	34.1(.143)**	34.5(.130)**
WBC X 10^3	12.3(1.44)	10.7(.921)	7.8(.863)*
PMN, %	8.1(1.62)	11.0(1.37)	16.5(2.03)*
BANDS, %	0.0(0.00)	.1(.100)	.3(.153)
LYMPH, %	89.1(1.88)	87.6(1.31)	82.7(1.98)
MONO, %	1.3(.250)	.8(.249)	.1(.100)**
EOSIN, %	1.5(.500)	.5(.224)	.4(.221)
BASO, %	0.0(0.00)	0.0(0.00)	0.0(0.00)
PLATELETS, X 10^5	3.8(.712)	8.9(1.10)**	8.9(.530)**
RETIC, %	3.1(.425)	1.2(.334)**	1.2(.323)**

ENTRIES ARE MEAN + STANDARD ERROR

*$P < .05$

**$P < .01$

Table 16

EFFECTS OF CHLOROBENZENE ON HEMATOLOGY OF RATS
AFTER 24 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE= 75 PPM (3)	DOSE= 250 PPM (4)
RBC X 10^6	8.5(.132)	8.7(.348)	8.1(.223)
HB, G %	14.6(.216)	15.2(.665)	14.1(.299)
HCT, %	41.5(.293)	43.3(2.12)	39.9(.687)
MCV, U	49.5(.401)	50.4(.542)	50.9(.722)
MCH, UUg	17.0(.175)	17.2(.187)	17.3(.169)
MCHC, %	35.0(.277)	35.0(.149)	35.1(.200)
WBC X 10^3	8.3(.490)	10.8(.757)	10.0(1.19)
PMN, %	19.0(2.19)	15.7(1.31)	15.1(1.90)
BANDS, %	0.0(0.00)	0.0(0.00)	.5(.269)
LYMPH, %	78.7(2.08)	81.2(1.06)	82.9(1.78)
MONO, %	1.4(.340)	1.7(.423)	.6(.163)
EOSIN, %	.9(.348)	1.4(.427)	.9(.277)
BASO, %	0.0(0.00)	0.0(0.00)	0.0(0.00)
PLATELETS, X 10^5	8.6(1.18)	10.0(.442)	9.9(.369)
RETIC, %	.3(.070)	.4(.093)	1.1(.265) **

ENTRIES ARE MEAN + STANDARD ERROR

** $P < .01$

Bartlett's chi-square statistic indicated that variances in the treatment groups were significant only in the groups sacrificed at 24 weeks. These changes occurred in the RBCs, hemoglobin, hematocrit, platelets, and reticulocytes.

Rabbit Hematology

Rabbit hematology was essentially unchanged during the study, as indicated by an analysis of variance and Dunnett's test. Tables 17 through 19 present the data. However, Bartlett's chi-square statistic suggested significant differences between treated and control groups treated for 11 weeks and 24 weeks. These changes included differences in RBCs, hemoglobin, hematocrit, and WBCs after 11 weeks and in RBCs, microcell volume, microhemoglobin, WBCs, and platelets after 24 weeks.

Rat Clinical Chemistry

The only consistent significant changes in the rat clinical chemistry profile was reduced SGOT activity in the high-dose group at all three times of sacrifice, as shown in Tables 20 through 22. Bartlett's chi-square test also suggested that the variance of the SGOT determinations in the treated groups was significantly greater than that of controls at all three sacrifice times. This statistical test also showed that the calcium variance at 11 weeks and the variances of cholesterol, albumin, globulin, and A/G ratio at 24 weeks were significantly different between the treated and control rats.

Table 17

EFFECTS OF CHLOROBENZENE ON HEMATOLOGY OF RABBITS
AFTER 5 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE= 75 PPM (3)	DOSE= 250 PPM (4)
RBC X 10^6	5.9(.300)	6.0(.195)	6.7(.215)
HB, G %	12.7(.614)	12.9(.509)	14.1(.633)
HCT, %	36.8(1.69)	37.6(1.05)	40.5(1.31)
MCV, U	61.0(.986)	60.9(.857)	59.8(1.02)
MCH, UUg	21.3(.296)	21.2(.296)	21.0(.419)
MCHC, %	34.4(.314)	34.3(.434)	34.7(.430)
WBC X 10^3	7.7(.530)	6.6(.737)	10.2(.437)*
PMN, %	0.0(0.00)	0.0(0.00)	0.0(0.00)
BANDS, %	0.0(0.00)	0.0(0.00)	0.0(0.00)
LYMPH, %	42.6(4.57)	43.7(4.77)	37.6(6.35)
MONO, %	.7(.236)	0.0(0.00)	0.0(0.00)
EOSIN, %	56.7(4.64)	56.3(4.77)	62.4(6.35)
BASO, %	.1(.111)	0.0(0.00)	0.0(0.00)

ENTRIES ARE MEAN + STANDARD ERROR

*$P < .05$

Table 18

EFFECTS OF CHLOROBENZENE ON HEMATOLOGY OF RABBITS
AFTER 11 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE= 75 PPM (3)	DOSE= 250 PPM (4)
RBC X 10^8	6.5(.193)	5.8(.447)	6.6(.146)
HB, G %	13.7(.403)	12.3(1.07)	14.4(.350)
HCT, %	39.8(1.07)	36.0(2.86)	41.3(.936)
MCV, U	62.0(.843)	61.6(1.48)	63.0(.745)
MCH, UU	21.0(.400)	20.8(.572)	21.6(.264)
MCHC, %	34.2(.261)	33.9(.379)	34.6(.165)
WBC X 10^3	12.4(2.70)	11.6(1.14)	9.6(.780)
PMN, %	1.9(.849)	1.8(1.20)	1.0(.394)
BANDS, %	0.0(0.00)	0.0(0.00)	0.0(0.00)
LYMPH, %	43.6(6.25)	30.3(5.68)	38.2(4.39)
MONO, %	1.1(.379)	1.0(.289)	2.2(.611)
EOSIN, %	53.3(5.64)	66.9(5.68)	58.1(4.60)
BASO, %	.1(.100)	0.0(0.00)	.5(.307)
PLATELETS, X 10^5	4.3(1.12)	5.4(.536)	5.4(.633)
RETIC, %	2.2(.484)	2.6(.596)	2.1(.469)

ENTRIES ARE MEAN + STANDARD ERROR

Table 19

EFFECTS OF CHLOROBENZENE ON HEMATOLOGY OF RABBITS
AFTER 24 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE= 75 PPM (3)	DOSE= 250 PPM (4)
RBC X 10^6	6.5(.098)	6.4(.264)	6.5(.086)
Hb, G %	14.2(.337)	14.0(.465)	14.9(.168)
HCT, %	41.4(.850)	40.7(1.13)	43.1(.492)
MCV, U	65.0(1.76)	65.1(.990)	66.7(.607)
MCH, UUg	21.6(.633)	21.7(.245)	22.4(.203)
MCHC, %	34.0(.215)	34.1(.205)	34.3(.186)
WBC X 10^3	8.2(.771)	9.2(.664)	8.7(.488)
PMN, %	0.0(0.00)	.3(.164)	1.8(.605) *
BANDS, %	0.0(0.00)	0.0(0.00)	.1(.083)
LYMPH, %	46.8(4.88)	46.3(6.12)	55.4(2.48)
MONO, %	1.8(.521)	3.5(.707)	1.5(.399)
EOSIN, %	51.4(4.58)	49.7(6.29)	40.8(2.56)
BASO, %	0.0(0.00)	.3(.250)	.4(.288)
PLATELETS, X 10^5	5.2(1.12)	4.2(.202)	4.7(.525)
RETIC, %	1.2(.264)	.9(.220)	1.2(.244)

ENTRIES ARE MEAN + STANDARD ERROR

*$P < .05$

Table 20

EFFECT OF CHLOROBENZENE ON CLINICAL CHEMISTRY OF RATS
AFTER 5 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE= 75 PPM (3)	DOSE= 250 PPM (4)
GLUCOSE, MG %	116.1(7.91)	127.2(5.65)	127.9(1.66)
BUN, MG %	18.0(.978)	18.9(.564)	19.4(.733)
CREAT, MG %	.6(.029)	.7(.024) **	.6(.025)
URIC ACID, MG %	1.9(.134)	2.0(.118)	1.6(.147)
NA, MEQ/L	145.5(.401)	141.8(.324) **	141.7(.367) **
K, MEQ/L	5.3(.174)	6.0(.213)	5.9(.198)
CO_2, MEQ/L	25.6(.636)	23.3(.601)	25.7(.943)
CL, MEQ/L	99.6(.499)	101.6(.626) *	100.8(.416)
CA, MG %	10.9(.151)	10.8(.084)	11.1(.144)
P, MG %	8.0(.177)	7.3(.159) *	7.9(.098)
NA-(CL+CO_2)	20.3(.746)	16.9(.611) **	15.2(.512) **
CHOL, MG %	48.2(1.67)	43.0(1.31)	35.6(1.83) **
TRIG, MG %	29.8(3.60)	28.1(3.60)	13.6(4.07) *
BILI, MG %	.1(0.00)	.1(.011)	.1(.015)
SGOT, MU/ML	182.3(31.8)	157.6(12.2)	102.0(5.17) *
SGPT, MU/ML	54.8(13.9)	38.9(3.45)	40.1(3.33)
LDH, MU/ML	1643.5(122.)	1280.6(154.)	595.0(114.) **
ALK-P, MU/ML	293.4(26.1)	238.8(19.9)	256.9(22.2)
IRON, MCG %	148.4(17.4)	132.4(5.28)	159.4(12.1)
PROTEIN, GM %	6.3(.092)	6.1(.091)	6.0(.082)
ALBUMIN, GM %	5.6(.077)	5.5(.090)	5.4(.073)
GLOBULIN, GM %	.7(.064)	.6(.059)	.7(.072)
A/G, RATIO	8.3(.933)	10.0(.996)	9.1(1.01)

ENTRIES ARE MEAN + STANDARD ERROR
*P < .05
**P < .01

Table 21

EFFECT OF CHLOROBENZENE ON CLINICAL CHEMISTRY OF RATS
AFTER 11 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE=75 PPM (3)	DOSE=250 PPM (4)
GLUCOSE, MG %	135.3(11.2)	157.5(7.85)	115.3(4.80)
BUN, MG %	14.4(.812)	17.4(.792)	15.0(*907)
CA, MG %	10.0(.134)	10.2(.100)	9.4(.563)
P, MG %	7.1(.177)	7.3(.159)	7.2(.151)
CHOL, MG %	42.9(2.38)	42.6(1.67)	45.6(3.19)
BILI, MG %	.1(0.00)	.1(0.00)	.1(.013)
SGOT, MU/ML	142.1(14.4)	100.9(4.26)*	87.2(7.44)**
LDH, MU/ML	1402.0(116.)	1150.8(164.)	1035.5(255.)
ALK-P, MU/ML	154.1(12.0)	171.3(16.0)	150.7(16.1)
PROTEIN, GM %	6.2(.149)	6.2(.078)	6.1(.080)
ALBUMIN, GM %	2.9(.057)	2.9(.033)	2.9(.049)
GLOBULIN, GM %	3.2(.102)	3.2(.065)	3.2(.054)
A/G, RATIO	.9(.021)	.9(.020)	.9(.021)

ENTRIES ARE MEAN + STANDARD ERROR

*P < .05

**P < .01

Table 22

EFFECT OF CHLOROBENZENE ON CLINICAL CHEMISTRY OF RATS
AFTER 24 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE= 75 PPM (3)	DOSE= 250 PPM (4)
GLUCOSE, MG %	141.8(6.51)	148.3(3.24)	152.8(4.83)
BUN, MG %	16.6(.499)	17.0(1.05)	16.2(.772)
URIC ACID, MG %	1.7(.143)	1.8(.102)	2.1(.224)
CA, MG %	10.1(.071)	10.0(.111)	10.1(.105)
P, MG %	5.8(.228)	5.9(.125)	5.8(.174)
CHOL, MG %	52.2(1.83)	53.4(3.35)	55.3(6.18)
BILI, MG %	.1(0.00)	.1(0.00)	.1(0.00)
SGOT, MU/ML	139.1(5.64)	122.5(6.32)	104.7(9.31)*
LDH, MU/ML	1688.5(58.1)	1446.5(151.)	1295.9(216.)
ALK-P, MU/ML	242.5(27.2)	269.8(26.4)	275.6(26.4)
PROTEIN, GM %	6.4(.124)	6.4(.059)	6.2(.087)
ALBUMIN, GM %	2.9(.063)	3.1(.035)	3.0(.026)
GLOBULIN, GM %	3.4(.168)	3.3(.042)	3.2(.073)
A/G, RATIO	.9(.047)	.9(.014)	.9(.019)

ENTRIES ARE MEAN + STANDARD ERROR

*$P < .05$

Rabbit Clinical Chemistry

Rabbit clinical chemistry data are shown in Tables 23 through 25. Lower uric acid levels were evident in the treated groups at 5 and 11 weeks, and LDH activity was elevated in the 75-ppm group at 5 and 24 weeks. These differences were statistically significant.

Bartlett's chi-square test suggested significant changes in BUN, uric acid, SGOT, and LDH after 5 weeks of treatment. After 11 weeks, significant changes were indicated in calcium, phosphorus, bilirubin, LDH, globulin, and A/G ratio; at 24 weeks, significant changes were suggested in uric acid, SGOT, LDH, and protein.

Histopathologic Examination of Rats

Rats Sacrificed After 5 Weeks

The ten rats from each group sacrificed after 25 exposures revealed no important histopathological differences among groups. Adrenals, bone, bone marrow, eye, heart, liver, and skin were all within normal limits in all groups. The following histological lesions were identified:

- Brain--Slight, focal hemorrhage in one control.
- Kidney--Regenerating cortical tubules that exhibited basophilic cytoplasm that may be cuffed with lymphocytes; elsewhere, interstitial foci of lymphocytes were present in one control, one low-dose, and one high-dose rat.
- Lung

	Control	75 ppm	250 ppm
Atelectasis	3/10	4/10	4/10
Emphysema	0	1/10	0
Atelectasis and emphysema	4/10	4/10	4/10
Edema	0	1/10	0
Focal hemorrhage	2/10	1/10	2/10
Chronic respiratory disease	10/10	10/10	10/10

Lung lesions were generally focal, of mild to moderate severity, and were found in every lung. Significant differences among groups were not evident. By their nature and incidence, the lesions encountered in rats sacrificed at 25 days were not considered to be treatment related.

Table 23

EFFECT OF CHLOROBENZENE ON CLINICAL CHEMISTRY OF RABBITS
AFTER 5 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE= 75 PPM (3)	DOSE=250 PPM (4)
GLUCOSE, MG %	126.9(6.59)	123.7(4.00)	136.9(6.97)
BUN, MG %	26.1(4.10)	20.6(1.47)	22.3(1.18)
URIC ACID, MG %	1.3(.180)	.1(.088) **	.2(.041) **
CA, MG %	12.9(.392)	13.9(.228)	13.7(.318)
P, MG %	6.7(.139)	6.2(.246)	6.4(.195)
CHOL, MG %	57.2(6.41)	52.0(6.78)	68.6(11.7)
BILI, MG %	.2(.016)	.2(.010)	.3(.022)
SGOT, MU/ML	33.6(3.46)	79.3(19.0)	49.3(14.9)
LDH, MU/ML	81.8(7.98)	306.7(67.5) *	138.2(35.4)
ALK-P, MU/ML	119.2(16.3)	140.6(9.93)	105.6(14.8)
PROTEIN, GM %	6.0(.151)	6.1(.153)	6.4(.207)
ALBUMIN, GM %	3.5(.158)	3.7(.162)	3.9(.125)
GLOBULIN, GM %	2.5(.112)	2.4(.107)	2.5(.122)
A/G, RATIO	1.4(.099)	1.6(.118)	1.6(.067)

ENTRIES ARE MEAN + STANDARD ERROR

*P < .05

**P < .01

Table 24

EFFECT OF CHLOROBENZENE ON CLINICAL CHEMISTRY OF RABBITS
AFTER 11 WEEKS OF INHALATION TREATMENTS

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE= 75 PPM (3)	DOSE= 250 PPM (4)
GLUCOSE, MG %	132.9(8.77)	131.0(10.4)	133.9(4.43)
BUN, MG %	23.0(1.44)	27.0(1.89)	21.5(.847)
URIC ACID, MG %	.6(.033)	0.0(0.00) **	.2(0.00) **
CA, MG %	13.3(.685)	13.2(.359)	14.0(.302)
P, MG %	6.2(.285)	5.5(.084)	6.1(.192)
SGOT, MU/ML	58.5(19.8)	61.1(32.2)	48.4(20.5)
LDH, MU/ML	218.7(24.6)	258.7(66.2)	471.0(306.)
ALK-P, MU/ML	108.0(17.8)	77.8(12.4)	111.3(12.9)
PROTEIN, GM %	6.7(.104)	7.0(.118)	6.9(.206)
ALBUMIN, GM %	4.2(.083)	4.4(.143)	4.4(.174)
GLOBULIN, GM %	2.5(.059)	2.7(.181)	2.6(.185)
A/G, RATIO	1.7(.051)	1.7(.152)	1.8(.156)

ENTRIES ARE MEAN + STANDARD ERROR

** $P < .01$

Table 25

EFFECT OF CHLOROBENZENE ON CLINICAL CHEMISTRY OF RABBITS
AFTER 24 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE (1)	DOSE=CONTROL (2)	DOSE= 75 PPM (3)	DOSE= 250 PPM (4)
GLUCOSE, MG %	114.2(6.15)	138.0(11.1)	120.0(5.17)
BUN, MG %	20.2(.909)	20.7(1.56)	20.7(.993)
URIC ACID, MG %	.4(.103)	.4(.041)	.4(.039)
CA, MG %	14.3(.126)	13.9(.288)	14.7(.155)
P, MG %	5.0(.157)	4.7(.219)	5.1(.152)
CHOL, MG %	33.0(2.66)	34.3(2.09)	36.6(1.90)
BILI, MG %	.2(0.00)	.2(.015)	.2(.008)
SGOT, MU/ML	56.3(11.0)	47.1(6.17)	29.4(3.25) *
LDH, MU/ML	305.4(67.2)	86.9(19.2) **	172.2(29.1)
ALK-P, MU/ML	59.6(6.06)	51.2(4.45)	70.5(6.32)
PROTEIN, GM %	7.2(.099)	6.6(.550)	7.4(.087)
ALBUMIN, GM %	2.7(.047)	2.5(.048)	2.7(.053)
GLOBULIN, GM %	4.6(.128)	4.5(.144)	4.8(.074)
A/G, RATIO	.6(.022)	.5(.021)	.6(.015)

ENTRIES ARE MEAN + STANDARD ERROR

*$P < .05$

**$P < .05$

Rats Sacrificed After 11 Weeks

Ten control rats and 10 rats each from the low-dose and high-dose groups were sacrificed after 55 days. Vacuolated cortical adrenal cells were seen only in treated animals, and the incidence of tubular and interstitial kidney lesions was much higher in the treated than in the control animals. Therefore, a relationship to the treatment is suggested.

The following tissues were examined and found to be within normal limits: bone, bone marrow, brain, eye, heart, liver, skin, and testes.

The following lesions were identified:

- Adrenal--Vacuolation of some cells in the zone fasciculata was present in three low-dose rats and in one high-dose rat.

- Kidney--Regenerating cortical tubules that exhibited basophilic cytoplasm and that were often cuffed with lymphocytes were seen in one control, two low-dose, and five high-dose rats.

- Lung

	Control	75 ppm	250 ppm
Atelectasis	0	2/10	2/10
Emphysema	1/10	1/10	1/10
Atelectasis and emphysema	7/10	4/10	5/10
Focal hemorrhage	3/10	0/10	1/10
Alveolar histiocytosis	0/10	1/10	0/10
Chronic respiratory disease	8/10	10/10	8/10

  Lung lesions were generally focal, usually of slight to moderate severity, and were found in all lungs except in those from one high-dose animal.

The increased incidence of lesions in the adrenal cortex and the tubular and interstitial lesions in the kidneys of the treated animals suggests that the lesions are treatment related.

Rats Sacrificed After 24 Weeks

The remaining rats were sacrificed after 24 weeks (120 exposures). The sections of bone, bone marrow, brain, eye, skin, and spinal cord were all within normal limits. The following histological lesions were noted:

- Adrenals--Vacuolization of cells of the zona fasciculata was slight to moderate in four controls, five low-dose, and six high-dose rats.

- Heart--A small focus of fibrosis was noted in one high-dose rat.

- Kidney--Focal paravascular lymphocytes were seen in five controls, five low-dose (including one case of interstitial lymphocytes), and three high-dose rats.

  Regenerating cortical tubules were seen in four controls, two low-dose, and five high-dose rats. Slight focal infarcts were present in both kidneys of one low-dose rat and in one kidney of one high-dose rat. A few hyaline casts were seen in the convaluted tubules of one low-dose rat.

- Liver--Foci of lymphocytes in paravascular or parenchymal location were seen in two controls and in two low-dose rats. Slight bile duct hyperplasia was seen in one low-dose rat.

- Lung

	Control	75 ppm	250 ppm
Atelectasis	3/10	4/10	4/10
Atelectasis and emphysema	3/10	2/10	4/10
Congestion	0/10	0/10	2/10
Hemorrhage	2/10	1/10	2/10
Parenchymal lymphocytes	1/10	0/10	0/10
Chronic respiratory disease	10/10	10/10	9/10

- Testes--One low-dose rat had a marked atrophy of one testis, but the other was normal.

Generally, no lesions were recognized as being treatment-related in the rats sacrificed at 24 weeks.

Histopathologic Examination of Rabbits

Rabbits Sacrificed After 5 Weeks

Ten rabbits in each of three groups were sacrificed after 25 exposures to chlorobenzene. No important differences existed among the groups, but congestion of kidneys and liver occurred more often in the high-dose group. Bone, brain, eye, and skin were all normal in all animals. The following tissues exhibited some histological lesions:

- Adrenal--One high-dose animal had a solitary focus of congestion.

- Bone marrow--Slight atrophy was seen in one control and in one high-dose animal. One high-dose rabbit had a moderate hyperplasia.

- Testes--Immaturity of varying degrees was seen in three controls and in one high-dose rabbit; testicular atrophy was seen in one high-dose rabbit.

- Kidneys--Nephrocalcinosis was apparent in one low-dose rabbit. Slight or moderate focal congestion occurred in three controls, four low-dose, and nine high-dose rabbits.

  Foci of lymphocytes were seen in the parenchyma and/or in portal areas in one control, in one low-dose, and in two high-dose rabbits.

- Heart--Slight hemorrhage was found in one low-dose rabbit.

- Lung

	Control	75 ppm	250 ppm
Atelectasis	0/10	2/10	0/10
Congestion	3/10	1/10	3/10
Edema	1/10	1/10	3/10
Atelectasis and emphysema	8/10	4/10	8/10
Hemorrhage	0/10	3/10	0/10
Perivascular lymphocytes	10/10	8/10	9/10

  Lung lesions were generally focal, most often slight or moderate in severity, and were found in every lung. Important differences were not recognized.

Generally, no important differences existed among groups, but congestion of the kidneys and liver occurred more often in the high-dose group.

Rabbits Sacrificed After 11 Weeks

Eleven rabbits in the 75- and 250-ppm groups and ten controls were sacrificed after 11 weeks of exposure (55 exposure days). The adrenals, bone, bone marrow, and eyes of all these animals were normal. In addition, the gall bladder was normal in those sections where it was attached to the liver.

The following lesions were noted:

- Brain--Lesions of encephalitozoonosis (cause, E. cuniculi) were seen in three controls and in one low-dose rabbit. Perivascular lymphocytic cuffing was present in two of the three aforementioned controls and in another control rabbit. A small single hemorrhage was observed in the pons of one low-dose rabbit.

- Heart--Recent and solitary hemorrhage was seen in the myocardium of three low-dose rabbits and in one high-dose rabbit. A small thrombus was seen in one low-dose rabbit.

- Kidney--Interstitial lymphocytic foci were seen in three controls and in one low-dose and one high-dose rabbit.

- Liver--Congestion was seen in two control, seven low-dose, and six high-dose rabbits. Slight focal hemorrhages were seen in one control. Foci of perivascular lymphocytes were seen in five control, three low-dose, and one high-dose rabbit.

- Lungs

	Control	75 ppm	250 ppm
Atelectasis and emphysema	8/10	9/11	10/11
Lymphocytic foci near bronchi, bronchioles, blood vessels	10/10	8/11	9/11
Focal hemorrhage	1/10	0/11	0/11
Focal edema	1/10	0/11	0/11
Congestion	2/10	1/11	1/11

- Skin--A large, solitary hemorrhage was deep in the submucosa of one high-dose rabbit.

- Testes--Atrophy of the seminiferous tubules was diffuse in one testis of one control rabbit and focal in both testes of another control. The atrophy was accompanied by cellular debris and giant cell formation. One testis of one low-dose rabbit was moderately atrophic.

Encephalitozoonosis often affects brain, kidney, liver, spleen, and sometimes other organs of rabbits. Some of the brain lesions seen here were undoubtedly caused by this disease, while others in the brain, liver, and kidneys were compatible with it.

Generally, the lesions observed in the animals sacrificed at this time were spontaneous and sporadic and, therefore, not related to the treatment.

Rabbits Sacrificed After 24 Weeks

Ten rabbits each remaining in the low-dose, high-dose, or control groups were sacrificed after 24 weeks (120 exposures). Bone, bone marrow, eyes, and skin were within normal limits in every rabbit. The following lesions were noted:

- Adrenals--A moderate focal hemorrhage was present in the cortex of one control rabbit. Congestion was observed in two low-dose animals and three high-dose rabbits.

- Brain--Paravascular foci of lymphocytes were found in four control rabbits. Encephalitozoonosis was evident in three control, six low-dose, and eight high-dose rabbits.

- Heart--Intramyocardial foci of lymphocytes were observed in four controls and in one low-dose and two high-dose rabbits. A moderate focus of hemorrhage was seen in the myocardium of one low-dose rabbit.

- Kidneys--Congestion of the kidneys was evident in nine controls and in eight low-dose and eight high-dose rabbits. Interstitial foci of lymphocytes were seen in six controls and in six low-dose and eight high-dose rabbits. Tubular adenoma, small and well circumscribed, was diagnosed in one control rabbit. A micro-abcess was in the kidney of one low-dose rabbit. Dilated convoluted tubules were focal and prominent in one low-dose and in one high-dose rabbit. Regenerative cortical tubule foci were seen in one low-dose rabbit.

- Liver--Parenchymal lymphocytic foci were observed in the livers of seven control, seven low-dose, and seven high-dose rabbits. Two high-dose rabbits had a slight to moderate congestion of the liver.

- Lung

	Control	75 ppm	250 ppm
Atelectasis	4/10	3/10	2/10
Emphysema	0/10	1/10	0/10
Atelectasis and emphysema	5/10	2/10	6/10
Congestion	0/10	1/10	1/10
Edema	0/10	0/10	1/10
Hemorrhage	1/10	0/10	0/10
Lymphocytic foci*	10/10	9/10	10/10
Bronchopneumonia	0/10	0/10	1/10

* Around blood vessels, bronchi, and bronchioles.

- Testes--A few interstitial lymphocytic foci appeared in the testes of two controls and one low-dose rabbit. One testis was markedly atrophic in one high-dose rabbit; the other testis was normal.

Generally, the lesions observed in the rabbits sacrificed after 24 weeks of treatment can be explained on the basis of the encephalitozoonosis found in every treatment group and in the controls. Therefore, the effects found in the rabbits sacrificed at that time were not necessarily treatment-related.

DISCUSSION AND CONCLUSIONS

Earlier Irish[2] reported histological changes in the lungs, liver, and kidneys of rats, rabbits, and guinea pigs after repeated inhalation exposures to 1000 ppm chlorobenzene for 32 days. However, no changes were seen at levels of 200 ppm. The findings in this study suggest that, with longer exposure, damage may occur in the liver and kidneys of rats. For example, rats sacrificed at 11 weeks (55 exposures) had an increase in the liver-to-body weight ratio ($p < .01$). In addition, the kidneys were in the upper normal weight range. At the end of 24 weeks (120 exposures), both the liver- and kidney-to-body weight ratios were significantly larger in the 250-ppm treatment group. Significant weight changes occurred only in the liver of rabbits after 24 weeks of treatment, although there was also an absolute increase in kidney weight in the treatment groups.

Histological changes were seen in rat kidneys after 11 and 24 weeks of treatment and consisted of regenerating cortical tubules with cells that had basophilic cytoplasms that were often cuffed with lymphocytes. There was also liver congestion. In the rabbits, the "background pathology" in the controls was such that no changes could be determined in the treatment groups. Other histological findings that suggest a treatment relationship were seen in the adrenals of rats. After 11 and 24 weeks of treatment, there was vacuolization of some cells in the zona fasciculata that was found more frequently in the treated than the control rats.

Hematology changes were more apparent in the rats than in the rabbits. Small differences in red cell parameters including an increase in microhematocrit (MCHC) and a decrease in micro cell volume (MCV) were seen in rats. An increase in platelets in both the treated groups of rats and rabbits after 11 weeks of chlorobenzene exposure

suggests some stimulation of the bone marrow megakaryocytes. However, the platelets were normal at the end of 24 treatment weeks.

Clinical chemistry changes in both rats and rabbits were generally random and nonspecific. However, there was a decrease in SGOT activity in the rats at all three sacrifice periods and in rabbits at the 24-week sacrifice. LDH activity was less affected but exhibited the same trend in decreased activity. These observations are difficult to interpret by themselves. However, when they are considered in the light of the other observations, a picture of a rather subtle toxicity emerges. If we consider the slight decrease in food utilization in the two treatment groups of rats and the enlarged liver in rats and rabbits, perhaps protein synthesis is being impaired, resulting in a decreased synthesis of SGOT (and possibly LDH) in the liver.

In conclusion, exposure of rats and rabbits to 75 or 250 ppm chlorobenzene for 7 hours/day, 5 days/week for up to 24 weeks results in a decrease in food utilization in rats, increased liver and kidney weights in rats and rabbits, histopathological changes in the kidneys and adrenals of rats, possibly some changes in red cell microparameters and bone marrow, and a decrease in SGOT and LDH activity. The sum of these observations suggests that 75 ppm may be a marginal toxic concentration for the chronic daily inhalation of chlorobenzene vapors. Therefore, allowing for some safety margin, it is suggested that the safe working level be dropped tenfold to 5 to 10 ppm until such time that a lifespan study can be done to ensure the safety of the present working level of 75 ppm.

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Appendix A

STATISTICAL EVALUATION OF DATA COLLECTED FROM
ANIMALS DURING INHALATION OF 0, 75, OR 250 PPM CHLOROBENZENE

Table A-1

EFFECTS OF CHLOROBENZENE ON BODY WEIGHTS OF RATS
AFTER 5 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITH CONTROL		OVERALL EFFECTS	
			DOSE= 75 PPM	DOSE= 250 PPM	AVERAGE EFFECTS	LINEAR TREND
WEEK 1	2.33	4.25	5.30(3.94)	8.40(3.94)	6.85(3.41)	1.55(1.97)
WEEK 2	1.12	2.22	9.90(6.65)	5.60(6.65)	7.75(5.76)	-2.15(3.32)
WEEK 3	1.62	.47	16.80(9.68)	4.50(9.68)	10.65(8.38)	-6.15(4.84)
WEEK 5	2.44	1.25	25.00(11.3)	14.10(11.3)	19.55(9.83)	-5.45(5.67)

*P < .05

**P < .01

Table A-2

EFFECTS OF CHLOROBENZENE ON BODY WEIGHTS OF RATS
AFTER 11 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITH CONTROL		OVERALL EFFECTS	
			DOSE=75 PPM	DOSE=250 PPM	AVERAGE EFFECTS	LINEAR TREND
WEEK 1	1.14	12.22**	-5.80(4.60)	.40(4.60)	-2.70(3.98)	3.10(2.30)
WEEK 2	.22	9.45**	-2.90(6.20)	1.10(6.20)	-.90(5.37)	2.00(3.10)
WEEK 3	.31	2.71	.30(6.58)	4.60(6.58)	2.45(5.70)	2.15(3.29)
WEEK 5	.04	4.36	-2.90(11.1)	-1.00(11.1)	-1.95(9.57)	.95(5.53)
WEEK 7	.54	3.84	-4.30(12.8)	8.80(12.8)	2.25(11.1)	6.55(6.41)
WEEK 11	3.42*	1.50	-12.70(11.6)	17.40(11.6)	2.35(10.0)	15.05(5.78)*

*P < .05

**P < .01

Table A-3

EFFECTS OF CHLOROBENZENE ON BODY WEIGHTS OF RATS
AFTER 24 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITH CONTROL		OVERALL EFFECTS	
			DOSE= 75 PPM	DOSE= 250 PPM	AVERAGE EFFECTS	LINEAR TREND
WEEK 1	.06	4.62	1.20(3.54)	.40(3.54)	.80(3.06)	-.40(1.77)
WEEK 2	.23	1.35	-3.60(7.15)	-4.60(7.15)	-4.10(6.19)	-.50(3.57)
WEEK 3	.23	.26	-5.30(8.53)	-4.70(8.53)	-5.00(7.39)	.30(4.26)
WEEK 5	.07	1.93	-.90(10.8)	-3.80(10.8)	-2.35(9.37)	-1.45(5.41)
WEEK 7	6.83**	2.43	48.50(13.2)**	1.00(13.2)	24.75(11.4)*	-23.75(6.59)**
WEEK 11	.16	1.86	-8.90(17.1)	-7.40(17.1)	-8.15(14.8)	.75(8.53)
WEEK 15	.13	2.59	-10.40(20.9)	-7.80(20.9)	-9.10(18.1)	1.30(10.4)
WEEK 19	.14	2.93	-12.40(23.8)	-7.10(23.8)	-9.75(20.6)	2.65(11.9)
WEEK 24	.11	2.29	-11.73(25.3)	-4.30(24.6)	-8.02(21.5)	3.72(12.7)

*P < .05

**P < .01

Table A-4

FOOD CONSUMPTION OF TREATED AND CONTROL RATS

This was not evaluated statistically.

Table A-5

EFFECTS OF CHLOROBENZENE ON BODY WEIGHTS OF RABBITS
AFTER 5 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITH CONTROL		OVERALL EFFECTS	
			DOSE= 75 PPM	DOSE= 250 PPM	AVERAGE EFFECTS	LINEAR TREND
WEEK 1	1.43	4.72	.04(.064)	-.07(.066)	-.02(.056)	-.05(.033)
WEEK 2	.73	5.44	-.07(.093)	-.11(.096)	-.09(.082)	-.02(.048)
WEEK 3	3.26*	10.91**	-.26(.128)	-.31(.131)	-.28(.112)*	-.02(.066)
WEEK 5	3.66*	.45	-.33(.129)	-.24(.125)	-.29(.110)*	.05(.064)

*P < .05

**P < .01

Table A-6

EFFECTS OF CHLOROBENZENE ON BODY WEIGHTS OF RABBITS
AFTER 11 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITN CONTROL		OVERALL EFFECTS	
			DOSE= 75 PPM	DOSE= 250 PPM	AVERAGE EFFECTS	LINEAR TREND
WEEK 1	1.39	14.10**	.07(.051)	-.00(.050)	.04(.044)	-.04(.025)
WEEK 2	.35	.44	-.06(.081)	-.05(.079)	-.06(.069)	.00(.039)
WEEK 3	.09	.46	.02(.083)	-.01(.081)	.01(.071)	-.02(.040)
WEEK 5	.18	1.07	.01(.103)	.06(.100)	.03(.088)	.02(.050)
WEEK 7	.14	4.81	.03(.134)	-.04(.130)	-.01(.115)	-.03(.065)
WEEK 11	.04	4.10	.05(.190)	.02(.186)	.04(.163)	-.02(.093)

*P < .05
**P < .01

Table A-7

EFFECTS OF CHLOROBENZENE ON BODY WEIGHTS OF RABBITS
AFTER 24 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITH CONTROL		OVERALL EFFECTS	
			DOSE= 75 PPM	DOSE= 250 PPM	AVERAGE EFFECTS	LINEAR TREND
WEEK 1	.68	4.49	.08(.067)	.02(.065)	.05(.057)	-.03(.034)
WEEK 2	.64	6.87*	-.10(.091)	-.06(.088)	-.08(.077)	.02(.045)
WEEK 3	1.11	10.22**	.08(.082)	-.04(.080)	.02(.070)	-.06(.041)
WEEK 5	2.92*	.76	.16(.074)	.00(.072)	.08(.063)	-.08(.037)*
WEEK 7	.39	10.97**	.12(.136)	.08(.132)	.10(.116)	-.02(.068)
WEEK 11	1.58	.51	.16(.137)	-.08(.133)	.04(.116)	-.12(.068)
WEEK 15	1.52	.68	.03(.182)	-.25(.176)	-.11(.154)	-.14(.091)
WEEK 19	2.25	.51	.01(.215)	-.38(.209)	-.19(.183)	-.20(.107)
WEEK 23	2.52	.03	.11(.212)	-.34(.206)	-.12(.180)	-.23(.106)*
WEEK 24	3.62*	.34	.08(.182)	-.38(.177)	-.15(.155)	-.23(.091)*

*P < .05

**P < .01

Table A-8

EFFECTS OF CHLOROBENZENE ON ORGAN WEIGHTS OF RATS
AFTER 5 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITH CONTROL		OVERALL EFFECTS	
			DOSE= 75 PPM	DOSE= 250 PPM	AVERAGE EFFECTS	LINEAR TREND
BRAIN	2.26	1.03	.03(.059)	-.10(.060)	-.03(.051)	-.06(.030)
HEART	.16	7.21*	-.04(.071)	-.01(.071)	-.03(.062)	.01(.036)
LUNG	.15	.56	-.09(.177)	-.02(.177)	-.06(.154)	.03(.089)
LIVER	.12	13.30**	-.12(.909)	-.44(.909)	-.28(.787)	-.16(.454)
SPLEEN	.76	33.22**	-.08(.087)	.02(.087)	-.03(.075)	.05(.043)
KIDNEY	.87	2.01	.00(.148)	.17(.148)	.09(.128)	.08(.074)
GONAD	.71	3.00	-.19(.157)	-.11(.157)	-.15(.136)	.04(.078)
BRAIN/BYWT	5.62**	.39	.65(.215)*	.06(.221)	.36(.188)	-.30(.111)*
HEART/BYWT	.54	5.73	.19(.188)	.12(.188)	.16(.163)	-.04(.094)
LUNG/BYWT	.12	5.40	.26(.558)	.20(.558)	.23(.484)	-.03(.279)
LIVER/BYWT	.48	32.58**	2.50(2.74)	.37(2.74)	1.43(2.37)	-1.06(1.37)
SPLEEN/BYWT	.41	47.41**	-.11(.368)	.22(.368)	.05(.319)	.16(.184)
KIDNEY/BYWT	6.22**	1.17	.76(.293)	.99(.293)*	.87(.254)**	.11(.147)
GONAD/BYWT	.07	2.43	.21(.553)	.13(.553)	.17(.479)	-.04(.277)
HEART/BRAIN	.66	4.24	-.03(.033)	.01(.034)	-.01(.029)	.02(.017)
LUNG/BRAIN	.29	2.13	-.05(.092)	.02(.094)	-.02(.080)	.03(.047)
LIVER/BRAIN	.04	18.49**	-.13(.445)	-.07(.457)	-.10(.389)	.03(.228)
SPLEEN/BRAIN	1.03	40.28**	-.05(.050)	.03(.051)	-.01(.043)	.04(.025)
KIDNEY/BRAIN	3.07*	1.16	-.01(.062)	.13(.064)	.06(.054)	.07(.032)*
GONAD/BRAIN	1.12	8.15*	-.11(.093)	.01(.095)	-.05(.081)	.06(.048)

*P < .05

**P < .01

Table A-9

EFFECTS OF CHLOROBENZENE ON ORGAN WEIGHTS OF RATS
AFTER 11 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITH CONTROL		OVERALL EFFECTS	
			DOSE= 75 PPM	DOSE= 250 PPM	AVERAGE EFFECTS	LINEAR TREND
BRAIN	1.24	.47	-.07(.049)	-.06(.049)	-.07(.042)	.01(.024)
HEART	4.76**	21.33**	.38(.136)*	.02(.136)	.20(.118)	-.18(.068)*
LUNG	.97	9.32**	-.18(.138)	-.04(.138)	-.11(.120)	.07(.069)
LIVER	8.54**	.92	2.34(.568)**	1.01(.568)	1.67(.492)**	-.67(.284)*
SPLEEN	.89	1.26	.04(.046)	-.02(.047)	.01(.040)	-.03(.024)
KIDNEY	1.59	1.38	.30(.173)	.21(.173)	.26(.150)	-.04(.087)
GONAD	.16	4.34	.06(.133)	-.00(.133)	.03(.115)	-.03(.067)
BRAIN/BYWT	3.74*	2.17	-.32(.162)	.10(.162)	-.11(.140)	.21(.081)*
HEART/BYWT	3.67*	19.97**	.84(.319)	.25(.319)	.54(.276)	-.30(.159)
LUNG/BYWT	2.41	3.33	-.55(.324)	.12(.324)	-.21(.281)	.33(.162)
LIVER/BYWT	11.04**	1.14	5.02(1.14)**	4.09(1.14)**	4.56(.985)**	-.47(.568)
SPLEEN/BYWT	.13	1.62	.06(.122)	.02(.125)	.04(.107)	-.02(.063)
KIDNEY/BYWT	4.01*	.90	.53(.341)	.96(.341)*	.75(.296)*	.22(.171)
GONAD/BYWT	1.39	3.92	-.04(.310)	.43(.310)	.20(.268)	.23(.155)
HEART/BRAIN	6.52**	22.98**	.19(.058)*	.03(.058)	.11(.050)*	-.08(.029)*
LUNG/BRAIN	.65	4.33	-.05(.057)	.01(.057)	-.02(.049)	.03(.028)
LIVER/BRAIN	12.18**	2.49	1.29(.261)**	.62(.261)	.96(.226)**	-.33(.130)*
SPLEEN/BRAIN	1.34	1.59	.03(.023)	-.00(.023)	.01(.020)	-.02(.012)
KIDNEY/BRAIN	4.16*	.60	.19(.067)*	.14(.067)	.16(.058)*	-.02(.034)
GONAD/BRAIN	1.12	1.62	.08(.056)	.05(.056)	.06(.048)	-.02(.028)

*P < .05

**P < .01

Table A-10

EFFECTS OF CHLOROBENZENE ON ORGAN WEIGHTS OF RATS
AFTER 24 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITH CONTROL		OVERALL EFFECTS	
			DOSE= 75 PPM	DOSE= 250 PPM	AVERAGE EFFECTS	LINEAR TREND
BRAIN	.95	5.74	.09(.067)	.04(.067)	.07(.058)	-.03(.033)
HEART	3.24*	1.72	.19(.078)	.05(.078)	.12(.068)	-.07(.039)
LUNG	.78	44.11**	-.86(.739)	-.71(.739)	-.79(.640)	.08(.370)
LIVER	5.45**	6.24*	2.10(1.74)	5.67(1.74)*	3.88(1.50)*	1.78(.868)
SPLEEN	.34	16.18**	.01(.094)	.07(.094)	.04(.082)	.03(.047)
KIDNEY	2.65	1.96	.20(.244)	.55(.244)	.37(.211)	.18(.122)
GONAD	.76	1.05	.03(.145)	.17(.145)	.10(.126)	.07(.073)
BRAIN/BYWT	.05	.02	.05(.254)	-.03(.247)	.01(.216)	-.04(.127)
HEART/BYWT	3.47*	2.72	.34(.147)	-.00(.143)	.17(.125)	-.17(.073)*
LUNG/BYWT	.81	51.44**	-2.36(2.02)	-1.99(1.97)	-2.18(1.72)	.18(1.01)
LIVER/BYWT	15.61**	9.84**	3.80(1.96)	10.54(1.91)**	7.17(1.67)**	3.37(.981)**
SPLEEN/BYWT	.16	4.96	-.03(.154)	.06(.150)	.02(.131)	.04(.077)
KIDNEY/BYWT	5.45**	1.36	.38(.303)	.97(.295)*	.67(.258)*	.29(.152)
GONAD/BYWT	.26	.64	-.12(.416)	.18(.405)	.03(.354)	.15(.208)
HEART/BRAIN	1.30	1.43	.05(.037)	.00(.037)	.03(.032)	-.02(.018)
LUNG/BRAIN	.92	40.40**	-.41(.320)	-.32(.320)	-.37(.277)	.04(.160)
LIVER/BRAIN	5.16**	5.93	.64(.774)	2.40(.774)*	1.52(.671)*	.88(.387)*
SPLEEN/BRAIN	.32	14.51**	-.01(.043)	.02(.043)	.01(.038)	.02(.022)
KIDNEY/BRAIN	2.84	.97	.02(.101)	.22(.101)	.12(.087)	.10(.050)
GONAD/BRAIN	.87	1.76	-.05(.072)	.05(.072)	-.00(.063)	.05(.036)

*P < .05

**P < .01

Table A-11

EFFECTS OF CHLOROBENZENE ON ORGAN WEIGHTS OF RABBITS
AFTER 5 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITH CONTROL		OVERALL EFFECTS	
			DOSE= 75 PPM	DOSE= 250 PPM	AVERAGE EFFECTS	LINEAR TREND
BRAIN	.85	.27	.02(.328)	-.38(.344)	-.18(.291)	-.20(.168)
HEART	1.10	.13	.26(.458)	.70(.480)	.48(.409)	.22(.229)
LUNG	.02	3.86	-.16(1.38)	-.31(1.45)	-.24(1.22)	-.07(.709)
LIVER	3.36*	2.99	10.09(8.80)	23.28(9.01)	16.69(7.74)*	6.60(4.40)
SPLEEN	1.68	5.10	-.03(.226)	.36(.237)	.17(.200)	.19(.116)
KIDNEY	.60	.48	.61(1.34)	1.54(1.41)	1.07(1.19)	.47(.688)
GONAD	1.72	7.37*	1.22(.667)	.43(.667)	.82(.578)	-.40(.334)
BRAIN/BYWT	1.18	7.42*	.03(.361)	-.48(.371)	-.23(.316)	-.26(.186)
HEART/BYWT	.17	6.23*	.17(.292)	.08(.300)	.12(.257)	-.05(.146)
LUNG/BYWT	.33	3.25	-.12(.644)	-.52(.662)	-.32(.563)	-.20(.331)
LIVER/BYWT	2.78	2.94	4.34(2.65)	6.05(2.65)	5.19(2.29)*	.86(1.32)
SPLEEN/BYWT	1.02	10.44**	.01(.103)	.13(.106)	.07(.090)	.06(.053)
KIDNEY/BYWT	.19	1.01	.36(.595)	.23(.611)	.30(.520)	-.06(.306)
GONAD/BYWT	1.43	8.49*	.40(.249)	.08(.243)	.24(.212)	-.16(.125)
HEART/BRAIN	2.84	.46	.02(.040)	.10(.044)	.06(.036)	.04(.021)
LUNG/BRAIN	.05	3.76	-.01(.128)	.03(.139)	.01(.115)	.02(.068)
LIVER/BRAIN	5.99**	1.30	.96(.833)	2.98(.876)**	1.97(.740)*	1.01(.429)*
SPLEEN/BRAIN	2.92*	6.12*	-.00(.023)	.05(.025)	.02(.021)	.03(.012)*
KIDNEY/BRAIN	1.33	.01	.05(.142)	.24(.154)	.14(.128)	.10(.075)
GONAD/BRAIN	1.45	6.81*	.13(.078)	.05(.080)	.09(.068)	-.04(.040)

*P < .05

**P < .01

Table A-12

EFFECTS OF CHLOROBENZENE ON ORGAN WEIGHTS OF RABBITS
AFTER 11 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITH CONTROL		OVERALL EFFECTS	
			DOSE=75 PPM	DOSE=250 PPM	AVERAGE EFFECTS	LINEAR TREND
BRAIN	2.08	2.46	-.83(.419)	-.60(.409)	-.71(.360)	.11(.205)
HEART	.28	4.06	-.40(1.24)	-.90(1.21)	-.65(1.06)	-.25(.604)
LUNG	2.40	16.66**	-2.98(2.05)	-4.31(2.00)	-3.64(1.76)	-.67(1.00)
LIVER	.75	7.28*	11.58(9.46)	5.63(9.24)	8.60(8.13)	-2.98(4.62)
SPLEEN	1.11	1.08	-.28(.263)	-.36(.250)	-.32(.224)	-.04(.125)
KIDNEY	1.04	8.10*	.29(3.05)	3.83(2.98)	2.06(2.62)	1.77(1.49)
GONAD	.75	1.78	-.68(.782)	.23(.764)	-.23(.672)	.45(.382)
BRAIN/BYWT	.55	.48	-.17(.173)	-.14(.168)	-.15(.148)	.02(.084)
HEART/BYWT	.26	2.53	.00(.295)	-.18(.288)	-.09(.253)	-.09(.144)
LUNG/BYWT	1.91	8.06*	-.56(.594)	-1.14(.581)	-.85(.511)	-.29(.290)
LIVER/BYWT	3.03*	1.59	5.22(2.13)	3.15(2.08)	4.18(1.83)*	-1.03(1.04)
SPLEEN/BYWT	.90	.63	-.08(.079)	-.10(.076)	-.09(.068)	-.01(.038)
KIDNEY/BYWT	.87	4.34	.22(1.01)	1.21(.986)	.72(.867)	.50(.493)
GONAD/BYWT	.71	4.28	-.20(.229)	.06(.224)	-.07(.197)	.13(.112)
HEART/BRAIN	.15	1.21	.03(.113)	-.03(.111)	.00(.097)	-.03(.055)
LUNG/BRAIN	1.62	12.22**	-.15(.186)	-.33(.181)	-.24(.159)	-.09(.091)
LIVER/BRAIN	3.15*	3.03	2.05(.823)	1.25(.804)	1.65(.707)*	-.40(.402)
SPLEEN/BRAIN	.53	.30	-.02(.025)	-.02(.024)	-.02(.021)	-.00(.012)
KIDNEY/BRAIN	1.27	7.05*	.15(.303)	.46(.296)	.30(.261)	.16(.148)
GONAD/BRAIN	.59	2.41	-.03(.075)	.05(.074)	.01(.065)	.04(.037)

*P < .05

**P < .01

Table A-13

EFFECTS OF CHLOROBENZENE ON ORGAN WEIGHTS OF RABBITS
AFTER 24 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITH CONTROL		OVERALL EFFECTS	
			DOSE= 75 PPM	DOSE= 250 PPM	AVERAGE EFFECTS	LINEAR TREND
BRAIN	.36	.34	.18(.496)	.39(.464)	.28(.421)	.11(.232)
HEART	3.62*	.30	-.14(.701)	1.41(.656)	.63(.594)	.78(.328)*
LUNG	4.88**	7.92*	2.29(2.02)	5.78(1.89)*	4.03(1.71)*	1.75(.943)
LIVER	9.48**	5.40	-3.11(7.00)	22.43(6.55)**	9.66(5.94)	12.77(3.28)**
SPLEEN	3.56*	15.82**	.37(.616)	1.45(.576)	.91(.522)	.54(.288)
ADRENAL	.36	4.97	-.05(.065)	-.00(.060)	-.03(.055)	.02(.030)
KIDNEY	3.57*	3.73	.29(1.71)	3.74(1.60)	2.02(1.45)	1.73(.799)*
GONAD	.26	1.08	.38(.523)	.18(.489)	.28(.443)	-.10(.245)
BRAIN/BYWT	1.13	.28	.04(.180)	-.19(.169)	-.08(.153)	-.12(.084)
HEART/BYWT	.24	1.39	-.04(.197)	.08(.184)	.02(.167)	.06(.092)
LUNG/BYWT	1.89	4.32	.63(.594)	1.08(.555)	.85(.503)	.22(.278)
LIVER/BYWT	3.87*	5.68	-.53(1.57)	3.16(1.47)	1.31(1.33)	1.85(.734)*
SPLEEN/BYWT	2.39	10.18**	.10(.152)	.30(.143)	.20(.129)	.10(.071)
ADRENAL/BYWT	.45	1.72	-.01(.015)	-.01(.014)	-.01(.013)	-.00(.007)
KIDNEY/BYWT	.61	.72	.05(.377)	.35(.353)	.20(.320)	.15(.176)
GONAD/BYWT	1.96	1.03	.11(.130)	-.13(.122)	-.01(.110)	-.12(.061)
HEART/BRAIN	2.39	1.06	-.03(.063)	.09(.059)	.03(.054)	.06(.030)
LUNG/BRAIN	4.82**	4.62	.18(.160)	.46(.149)*	.32(.135)*	.14(.075)
LIVER/BRAIN	6.72**	.29	-.38(.638)	1.63(.597)*	.63(.541)	1.01(.299)**
SPLEEN/BRAIN	3.72*	14.20**	.03(.048)	.12(.045)	.07(.041)	.04(.023)
ADRENAL/BRAIN	.28	4.43	-.01(.007)	-.00(.007)	-.00(.006)	.00(.003)
KIDNEY/BRAIN	3.36*	4.32	-.01(.133)	.27(.124)	.13(.113)	.14(.062)*
GONAD/BRAIN	.41	6.15*	.04(.050)	-.00(.046)	.02(.042)	-.02(.023)

*P < .05
**P < .01

Table A-14

EFFECTS OF CHLOROBENZENE ON HEMATOLOGY OF RATS
AFTER 5 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITH CONTROL		OVERALL EFFECTS	
			DOSE= 75 PPM	DOSE= 250 PPM	AVERAGE EFFECTS	LINEAR TREND
RBC X 10^6	5.99**	1.80	.43(.179)	.58(.170)*	.50(.152)**	.07(.085)
HB, G %	4.37*	3.91	.77(.302)	.75(.287)	.76(.257)**	-.02(.143)
HCT, %	1.23	2.52	.93(.844)	1.23(.800)	1.08(.718)	.15(.400)
MCV, U	2.31	1.62	-1.00(.908)	-1.85(.862)	-1.42(.773)	-.43(.431)
MCH, UUg	1.14	.40	-.06(.306)	-.40(.290)	-.23(.261)	-.17(.145)
MCHC, %	8.24**	.02	1.10(.282)**	.80(.267)*	.95(.240)**	-.15(.134)
WBC X 10^3	3.24*	.07	3.58(1.41)	1.59(1.34)	2.58(1.20)*	-.99(.668)
PMN, %	3.28*	.04	-3.25(2.07)	-5.00(1.96)	-4.13(1.76)*	-.88(.982)
BANDS, %	.93	.59	.75(.558)	.28(.529)	.51(.475)	-.24(.265)
LYMPH, %	2.95*	.23	2.63(2.62)	5.97(2.48)	4.30(2.23)	1.67(1.24)
MOND, %	3.14*	3.05	-.75(.589)	-1.40(.559)	-1.08(.501)*	-.32(.279)
EOSIN, %	1.06	4.80	.63(.452)	.15(.429)	.39(.385)	-.24(.214)

*P < .05

**P < .01

Table A-15

EFFECTS OF CHLOROBENZENE ON HEMATOLOGY OF RATS
AFTER 11 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITH CONTROL		OVERALL EFFECTS	
			DOSE= 75 PPM	DOSE= 250PPM	AVERAGE EFFECTS	LINEAR TREND
RBC X 10^6	.15	1.31	-.10(.200)	-.02(.200)	-.06(.177)	.04(.094)
HB, G %	1.25	.05	-.31(.276)	-.43(.276)	-.37(.243)	-.06(.130)
HCT, %	5.53**	.87	-2.14(.934)	-3.06(.934)*	-2.60(.824)**	-.46(.440)
MCV, U	6.34**	4.15	-1.67(.808)	-2.88(.808)**	-2.28(.712)**	-.60(.381)
MCH, UUg	.64	3.66	-.00(.278)	-.26(.278)	-.13(.245)	-.13(.131)
MCHC, %	24.17**	.17	1.04(.211)**	1.44(.211)**	1.24(.186)**	.20(.100)
WBC X 10^3	4.39*	1.45	-1.60(1.53)	-4.41(1.53)*	-3.01(1.35)*	-1.41(.721)
PMN, %	6.06**	1.59	2.88(2.48)	8.38(2.48)*	5.63(2.19)*	2.75(1.17)*
BANDS, %	1.79	0.00	.10(.164)	.30(.164)	.20(.145)	.10(.078)
LYMPH, %	3.73*	1.41	-1.52(2.52)	-6.43(2.52)	-3.97(2.22)	-2.45(1.19)
MONO, %	7.63**	6.60*	-.45(.300)	-1.15(.300)**	-.80(.265)**	-.35(.141)*
EOSIN, %	3.47*	5.36	-1.00(.454)	-1.10(.454)	-1.05(.400)*	-.05(.214)
BASO, %	-0.00					
PLATELETS, X 10^5	16.29**	4.45	5.80(1.18)**	5.85(1.18)**	5.82(1.02)**	.02(.589)
RETIC, %	8.85**	.22	-1.87(.516)**	-1.95(.516)**	-1.91(.455)**	-.04(.243)

*P < .05
**P < .01

Table A-16

EFFECTS OF CHLOROBENZENE ON HEMATOLOGY OF RATS
AFTER 24 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITH CONTROL		OVERALL EFFECTS	
			DOSE= 75 PPM	DOSE= 250 PPM	AVERAGE EFFECTS	LINEAR TREND
RBC x 10^6	1.55	7.38*	.25(.354)	-.38(.354)	-.06(.307)	-.31(.177)
HB, G %	1.49	11.71**	.60(.621)	-.47(.621)	.06(.538)	-.54(.310)
HCT, %	1.68	28.51**	1.76(1.84)	-1.61(1.84)	.08(1.59)	-1.69(*919)
MCV, U	1.55	2.86	.90(.806)	1.40(.806)	1.15(.698)	.25(.403)
MCH, UUg	.87	.09	.23(.251)	.32(.251)	.28(.217)	.04(.125)
MCHC, %	.11	3.23	-.02(.304)	.11(.304)	.04(.263)	.06(.152)
WBC x 10^3	2.09	6.38*	2.43(1.22)	1.68(1.22)	2.06(1.05)	-.38(.609)
PMN, %	1.31	2.22	-3.30(2.60)	-3.90(2.60)	-3.60(2.25)	-.30(1.30)
BANDS, %	3.46*	0.00	.00(.000)	.50(.219)	.25(.190)	.25(.110)*
LYMPH, %	1.55	3.69	2.50(2.40)	4.20(2.40)	3.35(2.08)	.85(1.20)
MONO, %	3.02*	6.88*	.30(.463)	-.80(.463)	-.25(.401)	-.55(.231)*
EOSIN, %	.66	1.57	.50(.503)	0.00(.503)	.25(.436)	-.25(.252)
BASO, %	-0.00					
PLATELETS, X 10^5	.98	14.02**	1.33(1.07)	1.26(1.07)	1.29(.925)	-.04(.534)
RETIC, %	6.82**	17.24**	.12(.237)	.81(.237)**	.46(.205)*	.35(.118)**

*P < .05
**P < .01

Table A-17

EFFECTS OF CHLOROBENZENE ON HEMATOLOGY OF RABBITS
AFTER 5 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITH CONTROL		OVERALL EFFECTS	
			DOSE= 75 PPM	DOSE= 250 PPM	AVERAGE EFFECTS	LINEAR TREND
RBC X 10^6	1.86	2.79	.13(.356)	.74(.394)	.44(.313)	.31(.207)
HB, G %	1.27	.72	.25(.806)	1.39(.892)	.82(.709)	.57(.468)
HCT, %	1.46	2.72	.85(2.01)	3.75(2.22)	2.30(1.77)	1.45(1.17)
MCV, U	.37	.57	-.14(1.31)	-1.20(1.45)	-.67(1.15)	-.53(.761)
MCH, UUg	.20	.16	-.09(.436)	-.30(.483)	-.20(.384)	-.10(.254)
MCHC, %	.20	.28	-.15(.514)	.23(.569)	.04(.452)	.19(.298)
WBC X 10^3	7.51**	1.83	-1.12(.813)	2.51(.900)*	.69(.716)	1.81(.472)**
PMN, %	-0.00					
BANDS, %	-0.00					
LYMPH, %	.33	.07	1.16(6.79)	-4.96(7.52)	-1.90(5.98)	-3.06(3.95)
MONO, %	5.14**	0.00	-.67(.238)*	-.67(.263)	-.67(.209)**	.00(.000)
EOSIN, %	.36	.08	-.38(6.83)	5.73(7.56)	2.68(6.02)	3.06(3.97)
BASO, %	.64	0.00	-.11(.112)	-.11(.124)	-.11(.099)	.00(.000)

*P < .05

**P < .01

Table A-18

EFFECTS OF CHLOROBENZENE ON HEMATOLOGY OF RABBITS
AFTER 11 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITH CONTROL		OVERALL EFFECTS	
			DOSE= 75 PPM	DOSE= 250 PPM	AVERAGE EFFECTS	LINEAR TREND
RBC X 10^6	1.96	10.36**	-.63(.400)	.11(.389)	-.26(.340)	.37(.200)
HB, G %	2.45	11.74**	-1.39(.940)	.66(.915)	-.36(.799)	1.02(.470)*
HCT, %	2.42	11.74**	-3.88(2.50)	1.48(2.44)	-1.20(2.13)	2.68(1.25)*
MCV, U	.50	3.90	-.44(1.49)	1.00(1.45)	.28(1.26)	.72(.743)
MCH, UU	1.13	3.98	-.27(.599)	.60(.583)	.16(.510)	.44(.300)
MCHC, %	1.86	4.64	-.33(.392)	.42(.381)	.04(.333)	.38(.196)
WBC X 10^3	.68	14.08**	-.86(2.56)	-2.84(2.49)	-1.85(2.18)	-.99(1.28)
PMN, %	.34	8.04*	-.12(1.22)	-.90(1.18)	-.51(1.04)	-.39(.609)
BANDS, %	-0.00					
LYMPH, %	1.44	1.04	-13.27(7.84)	-5.40(7.63)	-9.33(6.67)	3.93(3.92)
MOND, %	2.15	5.22	-.10(.653)	1.10(.636)	.50(.555)	.60(.326)
EOSIN, %	1.64	.37	13.59(7.59)	4.80(7.38)	9.19(6.45)	-4.39(3.79)
BASO, %	1.88	0.00	-.10(.276)	.40(.269)	.15(.235)	.25(.138)
PLATELETS, X 10^5	.14	1.99	.56(1.26)	.59(1.23)	.58(1.08)	.02(.614)
RETIC, %	.22	.33	.33(.735)	-.16(.715)	.08(.625)	-.24(.367)

*P < .05

**P < .01

Table A-19

EFFECTS OF CHLOROBENZENE ON HEMATOLOGY OF RABBITS
AFTER 24 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITH CONTROL		OVERALL EFFECTS	
			DOSE= 75 PPM	DOSE= 250 PPM	AVERAGE EFFECTS	LINEAR TREND
RBC X 10^6	.33	10.86**	-.10(.222)	.07(.202)	-.01(.185)	.08(.104)
HB, G %	2.33	5.51	-.14(.467)	.71(.424)	.28(.388)	.43(.219)
HCT, %	2.52	3.34	-.65(1.19)	1.70(1.08)	.52(*987)	1.17(.558)*
MCV, U	.73	7.97*	.13(1.72)	1.67(1.56)	.90(1.43)	.77(.808)
MCH, UUg	1.39	11.68**	.11(.584)	.81(.530)	.46(.486)	.35(.274)
MCHC, %	.55	.10	.09(.305)	.28(.277)	.19(.253)	.09(.143)
WBC X 10^3	.51	.91	.95(.948)	.51(.860)	.73(.788)	-.22(.445)
PMN, %	4.97**	10.88**	.25(.672)	1.75(.610)*	1.00(.559)	.75(.316)*
BANDS, %	.69	0.00	.00(.000)	.08(.083)	.04(.076)	.04(.043)
LYMPH, %	1.57	4.29	-.53(6.48)	8.64(5.88)	4.06(5.39)	4.58(3.04)
MONO, %	3.96*	1.18	1.72(.789)	-.28(.716)	.72(.656)	-1.00(.371)*
EOSIN, %	1.95	4.07	-1.69(6.46)	-10.61(5.86)	-6.15(5.37)	-4.46(3.03)
BASO, %	.81	0.00	.25(.362)	.42(.328)	.33(.301)	.08(.170)
PLATELETS, X 10^5	1.03	6.04*	-1.54(1.09)	-.57(1.02)	-1.05(*923)	.49(.509)
RETIC, %	.40	.73	-.30(.376)	-.03(.341)	-.16(.312)	.14(.176)

*P < .05
**P < .01

Table A-20

EFFECT OF CHLOROBENZENE ON CLINICAL CHEMISTRY OF RATS
AFTER 5 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITH CONTROL		OVERALL EFFECTS	
			DOSE= 75 PPM	DOSE= 250 PPM	AVERAGE EFFECTS	LINEAR TREND
GLUCOSE, MG %	1.38	15.75**	11.12(8.15)	11.80(7.93)	11.46(6.93)	.34(4.07)
BUN, MG %	.83	2.79	.89(1.13)	1.40(1.10)	1.14(.961)	.26(.565)
CREAT, MG %	12.52**	.47	.16(.038)**	0.00(.037)	.08(.032)*	-.08(.019)**
URIC ACID, MG %	2.13	.60	.11(.192)	-.27(.187)	-.08(.163)	-.19(.096)
NA, MEQ/L	35.33**	.57	-3.72(.527)**	-3.80(.513)**	-3.76(.448)**	-.04(.263)
K, MEQ/L	3.65*	.21	.65(.278)	.63(.270)	.64(.236)*	-.01(.139)
CO_2, MEQ/L	3.04*	2.43	-2.27(1.08)	.10(1.05)	-1.08(.915)	1.18(.538)*
CL, MEQ/L	3.65*	1.01	1.96(.733)*	1.20(.714)	1.58(.624)*	-.38(.367)
CA, MG %	1.66	3.36	-.03(.189)	.28(.184)	.13(.161)	.15(.095)
P, MG %	6.55**	2.92	-.70(.211)*	-.08(.206)	-.39(.180)*	.31(.106)**
NA-(CL+CO_2)	17.40**	1.28	-3.41(.904)**	-5.10(.880)**	-4.26(.769)**	-.84(.452)
CHOL, MG %	15.36**	1.19	-5.20(2.35)	-12.60(2.28)**	-8.90(2.00)**	-3.70(1.17)**
TRIG, MG %	5.67**	.27	-1.69(5.40)	-16.20(5.26)*	-8.94(4.59)	-7.26(2.70)*
BILI, MG %	.35	0.00	.01(.015)	-0.00(.015)	.01(.013)	-.01(.008)
SGOT, MU/ML	4.21*	23.93**	-24.74(29.1)	-80.30(28.3)*	-52.52(24.7)*	-27.78(14.5)
SGPT, MU/ML	1.03	23.13**	-15.91(12.5)	-14.70(12.2)	-15.31(10.6)	.61(6.26)
LDH, MU/ML	17.45**	.53	-362.94(185.)*	1048.50(180.)**	-705.72(157.)**	-342.78(92.5)**
ALK-P, MU/ML	1.44	.84	-54.62(33.0)	-36.50(32.2)	-45.56(28.1)	9.06(16.5)
IRON, MCG %	1.06	9.91**	-15.96(18.5)	11.00(18.0)	-2.48(15.8)	13.48(9.27)
PROTEIN, GM %	3.38*	.11	-.26(.126)	-.29(.123)	-.28(.107)*	-.01(.063)
ALBUMIN, GM %	1.38	.26	-.09(.115)	-.19(.112)	-.14(.099)	-.05(.056)
GLOBULIN, GM %	.99	.54	-.13(.095)	-.06(.092)	-.10(.081)	.04(.046)
A/G, RATIO	.73	.14	1.71(1.42)	.74(1.38)	1.23(1.22)	-.49(.690)

*P < .05
**P < .01

Table A-21

EFFECT OF CHLOROBENZENE ON CLINICAL CHEMISTRY OF RATS
AFTER 11 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITN CONTROL		OVERALL EFFECTS	
			DOSE= 75 PPM	DOSE= 250 PPM	AVERAGE EFFECTS	LINEAR TREND
GLUCOSE, MG %	8.31**	3.23	22.21(11.4)	-19.99(11.4)	1.11(10.2)	-21.10(5.18)**
BUN, MG %	3.42*	.55	2.97(1.26)	.57(1.26)	1.77(1.13)	-1.20(.574)*
CA, MG %	1.24	27.32**	.26(.553)	-.52(.553)	-.13(.492)	-.39(.251)
P, MG %	.25	.04	.16(.239)	.14(.239)	.15(.213)	-.01(.108)
CHOL, MG %	.45	3.79	-.26(3.77)	2.74(3.77)	1.24(3.36)	1.50(1.71)
BILI, MG %	1.89	0.00	.00(.000)	.02(.013)	.01(.011)	.01(.006)
SGOT, MU/ML	10.10**	7.32*	-41.24(12.5)*	-54.94(12.5)**	-48.09(11.1)**	-6.85(5.66)
LDH, MU/ML	.76	5.57	-251.20(299.)	-366.50(299.)	-308.85(266.)	-57.65(136.)
ALK-P, MU/ML	.54	1.55	17.16(23.0)	-3.44(23.0)	6.86(20.5)	-10.30(10.4)
PROTEIN, GM %	.37	2.04	-.00(.144)	-.10(.144)	-.05(.128)	-.05(.066)
ALBUMIN, GM %	.02	1.33	.00(.068)	-.01(.068)	-.00(.060)	-.01(.031)
GLOBULIN, GM %	.58	1.46	-.00(.105)	-.09(.105)	-.05(.093)	-.04(.048)
A/G, RATIO	.47	.29	.00(.031)	.02(.031)	.01(.027)	.01(.014)

*P < .05

**P < .01

Table A-22

EFFECT OF CHLOROBENZENE ON CLINICAL CHEMISTRY OF RATS
AFTER 24 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITH CONTROL		OVERALL EFFECTS	
			DOSE= 75 PPM	DOSE= 250 PPM	AVERAGE EFFECTS	LINEAR TREND
GLUCOSE, MG %	1.20	3.92	6.50(7.13)	11.00(7.13)	8.75(6.17)	2.25(3.56)
BUN, MG %	.25	4.47	.40(1.14)	-.40(1.14)	0.00(.989)	-.40(.571)
URIC ACID, MG %	1.84	5.24	.11(.233)	.43(.233)	.27(.202)	.16(.116)
CA, MG %	.14	1.81	-.07(.138)	-.02(.138)	-.04(.119)	.03(.069)
P, MG %	.09	2.97	.08(.255)	-.01(.255)	.03(.221)	-.04(.128)
CHOL, MG %	.14	11.49**	1.20(5.93)	3.10(5.93)	2.15(5.13)	.95(2.96)
BILI, MG %	-0.00					
SGOT, MU/ML	5.60**	2.50	-16.60(10.3)	-34.40(10.3)*	-25.50(8.90)**	-8.90(5.14)
LDH, MU/ML	1.62	11.95**	-242.00(220.)	-392.60(220.)	-317.30(191.)	-75.30(110.)
ALK-P, MU/ML	.42	.05	27.30(38.6)	33.10(38.6)	30.20(33.5)	2.90(19.3)
PROTEIN, GM %	.98	4.56	.02(.132)	-.15(.132)	-.06(.115)	-.08(.066)
ALBUMIN, GM %	3.28*	7.30*	.16(.063)	.07(.063)	.12(.054)*	-.04(.031)
GLOBULIN, GM %	1.05	15.71**	-.14(.154)	-.22(.154)	-.18(.133)	-.04(.077)
A/G, RATIO	1.53	13.55**	.07(.043)	.06(.043)	.06(.037)	-.00(.021)

*P < .05

**P < .01

Table A-23

EFFECT OF CHLOROBENZENE ON CLINICAL CHEMISTRY OF RABBITS AFTER 5 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITH CONTROL		OVERALL EFFECTS	
			DOSE= 75 PPM	DOSE= 250 PPM	AVERAGE EFFECTS	LINEAR TREND
GLUCOSE, MG %	1.32	2.78	-3.20(8.49)	10.00(8.49)	3.40(7.35)	6.60(4.24)
BUN, MG %	1.27	13.78**	-5.51(3.52)	-3.81(3.52)	-4.66(3.08)	.85(1.72)
URIC ACID, MG %	12.78**	9.49**	-1.13(.287)**	-1.07(.259)**	-1.10(.218)**	.03(.164)
CA, MG %	2.92*	2.42	1.04(.452)	.81(.452)	.93(.392)*	-.12(.226)
P, MG %	1.39	2.89	-.48(.288)	-.29(.288)	-.38(.252)	.10(.140)
CHOL, MG %	.96	4.09	-5.20(12.2)	11.40(12.2)	3.10(10.6)	8.30(6.11)
BILI, MG %	1.50	5.09	-.03(.024)	.01(.024)	-.01(.021)	.02(.012)
SGOT, MU/ML	2.73	18.10**	45.70(19.9)	15.70(19.9)	30.70(17.2)	-15.00(9.93)
LDH, MU/ML	6.99**	26.34**	224.90(62.6)**	56.40(62.6)	140.65(54.2)*	-84.25(31.3)*
ALK-P, MU/ML	1.60	2.15	21.40(19.8)	-13.60(19.8)	3.90(17.1)	-17.50(9.88)
PROTEIN, GM %	1.38	1.15	.07(.244)	.38(.244)	.22(.211)	.16(.122)
ALBUMIN, GM %	1.71	.66	.19(.211)	.39(.211)	.29(.183)	.10(.105)
GLOBULIN, GM %	.34	.15	-.12(.162)	-.01(.162)	-.06(.140)	.05(.081)
A/G, RATIO	.84	2.60	.16(.137)	.15(.137)	.15(.119)	-.00(.068)

*P < .05

**P < .01

Table A-24

EFFECT OF CHLOROBENZENE ON CLINICAL CHEMISTRY OF RABBITS
AFTER 11 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITH CONTROL		OVERALL EFFECTS	
			DOSE= 75 PPM	DOSE= 250 PPM	AVERAGE EFFECTS	LINEAR TREND
GLUCOSE, MG %	.03	5.78	-1.90(11.7)	1.00(11.7)	-.45(10.1)	1.45(5.86)
BUN, MG %	3.83*	5.01	4.00(2.06)	-1.50(2.06)	1.25(1.78)	-2.75(1.03)*
URIC ACID, MG %	42.25**	-38.00	-.63(.033)**	-.63(.033)**	-.63(.033)**	.00(.000)
CA, MG %	.85	6.79*	-.12(.678)	.70(.678)	.29(.587)	.41(.339)
P, MG %	3.68*	10.64**	-.72(.289)	-.09(.289)	-.40(.250)	.31(.145)*
CHOL, MG %	2.56	4.50	23.70(12.6)	-1.80(12.6)	10.95(10.9)	-12.75(6.29)
BILI, MG %	.74	8.33*	-.03(.025)	-.02(.025)	-.03(.022)	.01(.013)
SGOT, MU/ML	.07	2.70	2.60(35.2)	-10.10(35.2)	-3.75(30.4)	-6.35(17.6)
LDH, MU/ML	.56	43.67**	40.00(257.)	252.30(257.)	146.15(222.)	106.15(128.)
ALK-P, MU/ML	1.60	1.42	-30.20(20.6)	3.30(20.6)	-13.45(17.9)	16.75(10.3)
PROTEIN, GM %	1.52	4.89	.36(.212)	.25(.212)	.30(.183)	-.05(.106)
ALBUMIN, GM %	.60	4.34	.19(.196)	.18(.196)	.18(.169)	-.01(.098)
GLOBULIN, GM %	.31	10.42**	.17(.216)	.07(.216)	.12(.187)	-.05(.108)
A/G, RATIO	.16	9.98**	.05(.183)	.10(.183)	.08(.159)	.03(.091)

*P < .05

**P < .01

Table A-25

EFFECT OF CHLOROBENZENE ON CLINICAL CHEMISTRY OF RABBITS
AFTER 24 WEEKS OF INHALATION TREATMENT

DEPENDENT VARIABLE	ANOVA F RATIO	BARTLETTS CHI-SQUARE	DUNNETTS MULTIPLE COMPARISONS WITN CONTROL		OVERALL EFFECTS	
			DOSE= 75 PPM	DOSE= 250 PPM	AVERAGE EFFECTS	LINEAR TREND
GLUCOSE, MG %	2.52	4.40	23.78(11.1)	5.78(10.4)	14.78(9.45)	-9.00(5.21)
BUN, MG %	.06	2.28	.44(1.74)	.53(1.62)	.49(1.47)	.04(.811)
URIC ACID, MG %	.04	9.57**	.02(.095)	.03(.091)	.02(.081)	.00(.045)
CA, MG %	4.88**	5.26	-.48(.291)	.37(.272)	-.05(.247)	.43(.136)**
P, MG %	1.53	.91	-.30(.261)	.12(.244)	-.09(.221)	.21(.122)
CHOL, MG %	.72	.51	1.33(3.27)	3.58(3.06)	2.46(2.78)	1.13(1.53)
BILI, MG %	1.24	0.00	-.02(.014)	-.01(.013)	-.02(.012)	.01(.007)
SGOT, MU/ML	4.15*	10.14**	-9.22(10.3)	-26.92(9.63)*	-18.07(8.73)	-8.85(4.82)
LDH, MU/ML	6.37**	11.49**	-218.56(61.8)**	-133.19(57.8)	-175.87(52.4)**	42.68(28.9)
ALK-P, MU/ML	2.83	1.99	-8.33(8.77)	10.94(8.20)	1.31(7.43)	9.64(4.10)*
PROTEIN, GM %	2.35	33.19**	-.67(.440)	.21(.412)	-.23(.373)	.44(.206)*
ALBUMIN, GM %	4.56**	.77	-.18(.076)	.03(.071)	-.08(.064)	.10(.036)**
GLOBULIN, GM %	1.39	2.52	-.07(.167)	.18(.156)	.06(.142)	.12(.078)
A/G, RATIO	.86	.73	-.04(.028)	-.02(.026)	-.03(.024)	.01(.013)

*P < .05

**P < .01