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ORAL TOXICITY OF METHYL CHLORIDE WITH COVER LETTER

Chemical Name (300 per name) 25	CAS No. (10) 24
CHLOROMETHANE (METHYL CHLORIDE)	74-87-3

5/27 18

1i

THE DOW CHEMICAL COMPANY

MIDLAND, MICHIGAN 48640

December 9, 1982

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Dear Sir or Madam:

As required by 40 CFR 716, we herewith submit copies of reports which meet the requirements of the referenced rule as Health and Safety Studies. As noted in the statement enclosed with the reports, some contain confidential business information.

The reports are separated into three categories for your convenience.

Package 1. Reports which contain no Confidential Business Information.

Package 2. Reports which contain Confidential Business Information.

Package 3. Reports from which Confidential Business Information has been deleted. (Public File Copy of reports in Package 2).

Each report is marked with an identifying number at the top of the first page of the report, e.g., D-155. Use of this identification number in future correspondence regarding this submission will facilitate handling of questions.

In order to expedite the completion of our search and submission, no attempt was made to determine whether or not we manufactured or processed the chemicals which formed the subject of submitted reports. (40 CFR 716.6). Thus, submission of a report for any given material should not be construed as indicative of Dow's status as a manufacturer or processor of the material.

Many of the submitted reports contain information which is not relevant to Health or Safety Studies of listed chemicals, e.g., references to unlisted chemicals, marketing or process data, account numbers, internal document identification codes or distribution lists. Such information has been deleted from all copies submitted.

The index required by 40 CFR 716.6(b) is enclosed. It lists the Dow identification number and title of each report submitted in CAS number order. Please note that the index contains Dow Confidential Business Information.

We have also included a reprint of a recently published article dealing with methylene chloride.

Very truly yours,

Robert L. Magerman
Regulatory Specialist
Regulatory and Legislative Issues
Health and Environmental Sciences
1803 Building
(517)636-6855

rt

D-304
878210218

Biochemical Research Laboratory
THE DOW CHEMICAL COMPANY

Subject ORAL TOXICITY OF METHYL CHLORIDE
Chloromethane

Fil
Chg.
Rec'd. 3-1-39
Fin'd. 4-2-41
Work By H. J. Smith
V. K. Rowe

To File Report **Check** DWGrish 5-7-40 **Rept. By** V. K. Rowe

The methyl chloride used was a commercial product having the trade name "Artic." It has a melting point of -97° C. and a boiling point of -24° C. It is soluble to a certain extent in olive oil, the solubility increasing markedly with a decrease in temperature. If one maintains the oil at approximately 0° C. it is possible to make and maintain a 3% solution.

Analyses were made on the oil solution and it was found that the methyl chloride did not react with the olive oil and that it could be recovered from the oil.

Rabbits were fed this cold olive oil solution by means of a stomach tube each working day until 60 doses had been given. One animal received 60 doses at 0.04 g./kg. in 83 days and showed no signs of toxic effect. Another received 60 doses at 0.1 g./kg. in 85 days. This animal showed a very slight pathology of the spleen as evidenced by congestion, phagocytosis, and hemosiderosis; this may or may not be of significance.

It is not practical to feed larger doses because the volume of oil becomes too large and the rapid escape of the gas from the oil in the stomach causes considerable bloating.

rl

BIOCHEMICAL RESEARCH LABORATORY

Chronic Vapor Toxicity

Material: Methyl chloride T
Concentration [illegible] g./kg. **No. exposures** [illegible]
Date begun: 4-[illegible] **Date finished** 7-31-39 **No. days** [illegible]
Animal Rabbit **#** [illegible]
Initial weight [illegible] kg. **Final weight** [illegible] kg.

General Reactions:

Animal did not show any abnormalities and gained weight steadily throughout the course of the experiment.

Autopsy

Gross examination:

Entirely normal except for a walled off abscess on the back.

Microscopic examination:

Liver, kidney, spleen, adrenal, and pancreas were entirely normal.

878210218

BIOCHEMICAL RESEARCH LABORATORY

Chronic Vapor Toxicity

Material: Methyl chloride T
Concentration [illegible] No. exposures [illegible]
Date begun: [illegible] Date finished [illegible] No. days [illegible]
Animal Rabbit # [illegible]
Initial weight 1.[illegible] Final weight [illegible]

General Reactions:

Animal did not show any abnormalities and gained weight steadily throughout the experiment.

Autopsy

Gross examination:

Fat depots were only fair and the spleen was somewhat enlarged and dark-colored. Other organs all appeared normal.

Microscopic examination:

Liver, kidney, adrenal, and pancreas all appeared normal, but the spleen showed a moderate congestion, phagocytosis, and a slight hemosiderosis.

OFFICE OF TOXIC SUBSTANCES

REV. 7/27/82

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A NINETY DAY INHALATION TOXICOLOGY STUDY IN F-344 ALBINO RATS AND $B_6C_3F_1$ MICE EXPOSED TO ATMOSPHERIC METHYL CHLORIDE GAS

Chemical Name (300 per name)	25	CAS No. (10)	24
CHLOROMETHANE (METHYL CHLORIDE)		74-87-3	

87821021 9

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A NINETY DAY INHALATION TOXICOLOGY STUDY IN F-344 ALBINO RATS AND $B_6C_3F_1$ MICE EXPOSED TO ATMOSPHERIC METHYL CHLORIDE GAS

PERFORMED AT

BATTELLE COLUMBUS LABORATORIES
505 KING AVENUE
COLUMBUS, OH 43201

FOR THE

CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY
P. O. Box 12137
RESEARCH TRIANGLE PARK, NC 27709

June 15, 1979

Reviewed and Submitted by

E. J. Gralla

E. J. Gralla, VMD
Chief of Toxicology

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4.	OBJECTIVE	
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1. Introduction

Aided by a consensus of member companies, methyl chloride was selected by CIIT as a commodity chemical which required comprehensive investigation of possible toxic and carcinogenic effects during chronic inhalation exposure in mammals. Such an investigation was planned and began with a ninety-day pilot study. The design and results of this latter study are the subject of this report.

2. Protocol Design

Species

The Fischer-344 inbred rat and the $B_6C_3F_1$ hybrid mouse were selected as the species and strains of choice because of a long life span; moreover, the widespread acceptance and usage of these animals in long-term toxicology research has generated a considerable background of data on spontaneous changes. This data could be employed in the future to resolve questionable toxicities.

Route

Inhalation exposure for 6 hours a day, 5 days each week, was used to stimulate the conditions of occupational usage of this agent.

Dose Levels

Decisions regarding the exposure levels to be administered during the initial pilot study were based upon information obtained from the literature or outside sources on file at the CIIT library.

4. <u>Objective</u>

The objective of this study was to investigate the ability of male and female rats and mice to tolerate chronic inhalation exposure to 1,500-750 or 375 ppm of methyl chloride.

FINAL REPORT

on

A 90-DAY INHALATION TOXICOLOGY STUDY IN RATS AND MICE EXPOSED TO METHYL CHLORIDE

to

CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY

April 18, 1979

by

Ralph I. Mitchell, Kenneth Pavkov, Raymond M. Everett,
and Donald A. Holzworth

BATTELLE
Columbus Laboratories
505 King Avenue
Columbus, Ohio 43201

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FINAL REPORT

on

A 90-DAY INHALATION TOXICOLOGY STUDY IN RATS AND MICE EXPOSED TO METHYL CHLORIDE

to

CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY

by

Ralph I. Mitchell, Ph.D., Senior Scientist
Toxicology/Pharmacology Section

Kenneth L. Pavkov, B.S., Principal Research Scientist
Toxicology/Pharmacology Section

Raymond M. Everett, D.V.M., Ph.D., Principal Research Scientist
Pathology Section

Donald A. Holzworth, M.S.
Biostatistician/Toxicology Program Office

April 18, 1979

Principal Investigator

Co-Principal Investigator

Senior Pathologist

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Columbus Laboratories
505 King Avenue
Columbus, Ohio 43201

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April 18, 1979

Dr. Edward J. Gralla
Chief, Toxicology
Chemical Industry Institute of Toxicology
P.O. Box 12137
Research Triangle Park, North Carolina 27709

Dear Dr. Gralla:

Methyl Chloride

Enclosed are five copies of the revised final report on the methyl chloride pilot study. Again, we would like to apologize for the delay in the preparation of this report and any inconvenience which this delay might have caused CIIT.

Best regards,

Ralph I. Mitchell
Program Manager
Toxicology/Pharmacology Section

RIM:jlk

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FINAL REPORT

on

A 90-DAY INHALATION TOXICOLOGY STUDY IN RATS AND MICE EXPOSED TO METHYLE CHLORIDE

to

CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY

by

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Toxicology/Pharmacology Section

Kenneth L. Pavkov, B.S., Principal Research Scientist
Toxicology/Pharmacology Section

Raymond M. Everett, D.V.M., Ph.D., Principal Research Scientist
Pathology Section

Donald A. Holzworth, M.S.
Biostatistician/Toxicology Program Office

April 18, 1979

INTRODUCTION

The objective of this study was to evaluate the toxicologic effect of methyl chloride in rats and mice following inhalation exposure for 90 days. This pilot study was used to select appropriate exposure levels for a subsequent study to evaluate chronic toxicity. The pilot study was initiated on February 7, 1978, and the last exposure was conducted on May 11, 1978.

SUMMARY

A 90-day pilot study was conducted in which rats and mice were exposed to atmospheres containing 375, 750, or 1500 ppm of methyl chloride. Exposures were conducted approximately 6 hours per day on a 5 day per week basis for 13 weeks. An additional group of animals served as controls and were subjected to the same handling as the test animals. The control animals were exposed to clean, filtered air in the chamber environment. The following lists the target concentrations and the mean analytical chamber concentrations which were achieved.

Group	ppm- methyl chloride chamber concentration target	ppm-methyl chloride analytical (mean)
A04	0 (Control)	0
A01	375	368
A02	750	741
A03	1500	1473

Observations were made with respect to food consumption, body weight changes, mortality, and physical effects. Hematology and clinical chemistry analyses were conducted on the animals at 13 weeks (prior to exsanguinated and subjected to a complete gross pathological examination. Tissues from the control and highest test level were examined histopathologically. The organs listed on page 4 of Appendix A were taken from all animals and selected organs weighed; all tissues were fixed in 10 percent neutral buffered formalin.

Significant increases in SGPT activity were observed in male mice in the 1500 ppm dose group. These increases may be explained by the presence of histologic hepatic changes. One male mouse and one female rat at the 1500 ppm dose level each had evidence of hepatic infarction. All other changes in hematologic or hemochemical parameters were within the expected normal range and/or were changes for which a dose-response relationship could not be clearly established. Increased relative organ weights (liver) were observed in the 1500 ppm dose group.

Both male and female rats of the 1500 ppm group had significantly lower body weights when compared to controls from week 3 through week 13 and males and females of the 750 ppm group from week 6 through week 12.

Principal Investigator

Co-Principal Investigator

Senior Pathologist

Biostatistician

Department Manager

Materials and Methods

Experimental Animals

The groups of animals for this study consisted of eighty healthy Fischer 344 rats (6 weeks of age) and eighty $B_6C_3F_1$ mice (5 weeks of age) which were equally divided by sex. These animals were obtained from Charles River Breeding Laboratories, Inc.* and were observed for 14 days before exposure to insure that they were suitable for testing. During this quarantine period, they were weighed and their eyes examined for any possible lesions or abnormalities. Animals which had eye defects were eliminated. A systematized randomization procedure was followed using a computer-generated group assignment based on body weight. Group composition was structured such that mean body weights were statistically similar across groups and such that there was no between group heterogeneity of variance. All animals were ear notched for permanent identification. The housing and exposure cages used were constructed of stainless steel wire mesh. The rats were individually housed and the mice were group housed with no more than five animals per cage. Animals were offered a standard laboratory diet plus water ad libitum except during the inhalation exposure. All animals were transferred from housing rooms to the chambers on a daily basis.

Method of Exposure

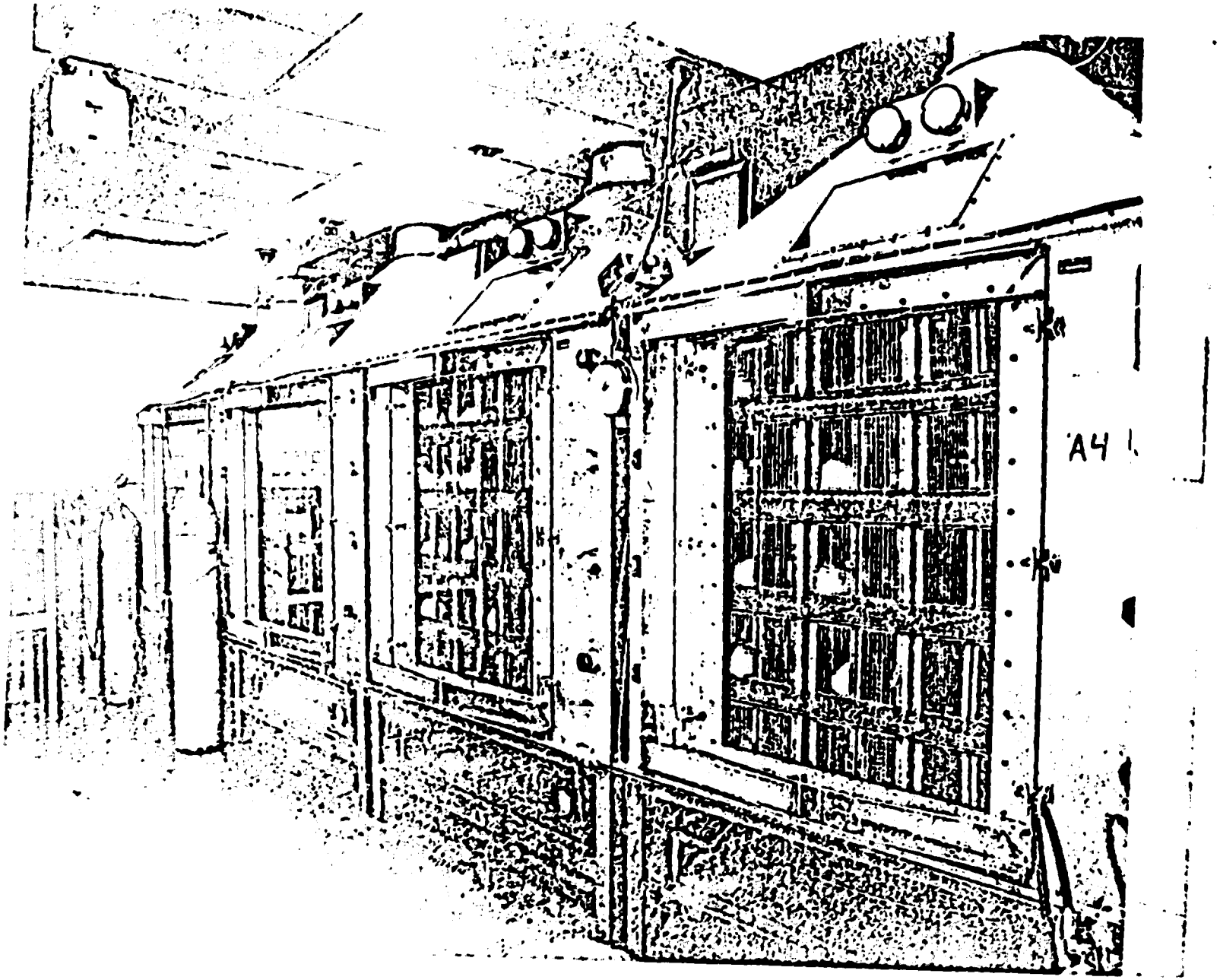
The animals were exposed for 6 hours per day, 5 days per week, for a period of 13 weeks. Each group of animals was exposed in a Hinners-type test chamber constructed of stainless steel and glass, having a normal volume of 5 cubic meters. The chambers as shown in Figure 1 are cuboidal in shape and are equipped with pyramidal tops and bottoms. The chambers are located in an air-conditioned room in which the temperature is maintained at 70 ± 2° F and a relative humidity of 45 ± 5 percent.

Air was pulled through the chambers by means of a large blower which is located on top of the building. Thus, the chambers were operated at a slightly negative pressure (approximately 1 inch of water). The conditioned air entering the chambers was passed through an absolute filter and then metered through an orifice to produce 12 air changes per hour.

---

*Rats from Portage, Michigan
Mice from Wilmington, Massachusetts

The test material was introduced into the chamber at the metering orifice so that it was well mixed with the incoming air by turbulence. The desired test concentration in each chamber (375, 750, and 1500 ppm) was regulated by passing the pure methyl chloride gas through precision rotameters mounted on each chamber. A pneumatic sensor was placed in the exhaust system so that in the event of malfunction, it would actuate an alarm system and a solenoid valve mounted on the outlet line of the methyl chloride supply.



PHOTOGRAPH OF ANIMAL EXPOSURE CHAMBERS FOR THE METHYL CHLORIDE INHALATION STUDY

Analysis of Chamber Atmosphere

1. Equipment: A Hewlett-Packard 5840A which contains a micro processor; Column 1/8" x 10' S. S. coiled; Porpak Q.

2. Conditions: Injection port at 88° C; Column Oven = 160°C; FID Temperature 200°C; Helium Flow - 28.5 cc/min.; H_2 Flow = 30.0 cc/min.; Air Flow = 300.0 cc/min. Under these conditions, the retention time for methyl chloride was 2.03 minutes.

Calibration

Standard concentrations of methyl chloride were made by injecting known volumes of pure methyl chloride* by means of a precision gas syringe into a Mylar mixing bag containing 10 liters of clean dry air. Gas mixtures covering the concentration of interest were sampled with the gas chromatograph to determine linearity. The area counts obtained were multipled by the response factor of the Hewlett-Packard 5840 data system to obtain ppm volumes. The calibration of the gas chromatograph was checked weekly by sampling a span gas of known concentration.

Chamber Sampling

The Hewlett-Packard 5840A gas chromatograph was equipped with a 12-port sampling valve system. Every fourth port of the valve was connected to the exhaust line of each chamber. After the sample was withdrawn through a port, the sampling system, by means of an automatic timer, advanced to the next sampling port. The sampling system was set so that a sample was taken approximately every 5 minutes. Because four chambers were monitored with the same chromatograph, gas concentration determinations for each chamber were determined every 20 minutes. A permanent record of each analysis included time and day, sampling port, concentration of methyl chloride in parts per million, and the resultant chromatograph.

Daily means were obtained by time averaging all results. Figure 2 shows a typical print out obtained during a run.

Observations

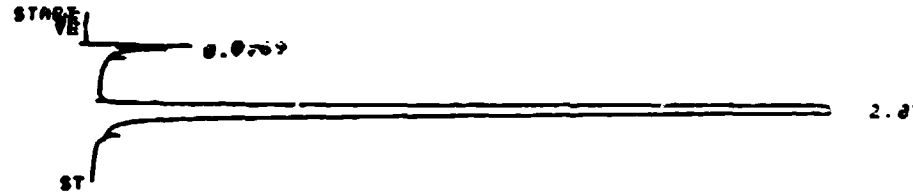
All animals were observed twice daily throughout the exposure period for abnormal reactions and mortalities. Several mice were accidentally killed during the initial stage of the study when their heads

*Purity - 99% min, Matheson Gas Products, Inc.

HP RUN # 139 APR/14/78 TIME 12:18:41
INPUT 8
NO PEAKS IN WDOS

RT	AREA	AREA %
0.69	623	39.732
0.77	945	60.268

DIL FACTOR: 1.0000 E+ 0



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INPUT 9
ESTD

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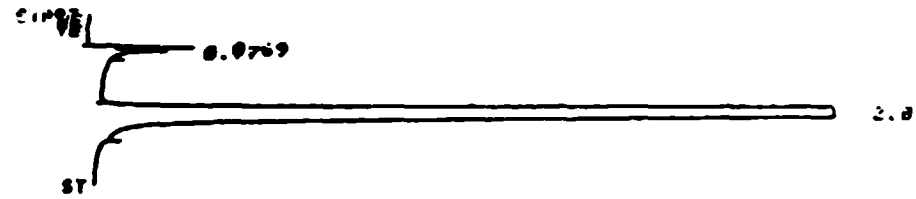
DIL FACTOR: 1.0000 E+ 0



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INPUT 10
ESTD

RT	EXP RT	AREA	CAL #	AMT
2.03	2.05	91700	(R) 1	756.100

DIL FACTOR: 1.0000 E+ 0

HP RUN # 142 APR/14/78 TIME 12:32:41
INPUT 11
ESTD

RT	EXP RT	AREA	CAL #	AMT
2.03	2.05	180200	(R) 1	1484.69

DIL FACTOR: 1.0000 E+ 0

FIGURE 2. TYPICAL GAS CHROMATOGRAPH OBTAINED FOR METHYL CHLORIDE

became entangled in the opening (1/2 inch mesh) of the exposure cage. These deaths were not related to the chemical exposure.

Ophthalmoscopic examinations, as well as general physical examinations of all animals were made before the animals were placed on study and just before the animals were necropsied.

Test Material

The test material for this study was high purity (99.5%) methyl chloride which was purchased from Matheson Gas Products Inc. by CIIT. It was filled from the same lot of material into (24) size 1J cylinders and was analyzed by Battelle upon receipt of the first partial shipment of the gas. Table 1 lists the trace impurities which were found. This analysis shows that the test material was extremely pure.

Food Consumption Data

All animals received a weighed fresh food* supply daily after the inhalation exposure was completed. The food was left in the cages until the next morning before exposure. The reduction in weight of the food can was a measure of the food consumed per cage per day. By following this procedure daily, weekly food consumption was estimated.

Body Weight Determinations

The weights of all animals were determined at the beginning of the study and weekly. The rats were weighed individually and the mice by cage groups (5 per cage). Weekly, as well as final body weights, and total weight changes were subjected to a standard analysis of variance (ANOVA).

Hematology Determinations

Blood samples were collected via periorbital sinus puncture from all rats and mice just prior to necropsy. The following hematology parameters were analyzed: HGB, HCT, WBC, RBC, MCV, reticulocytes, MCH, MCHC and a differential white cell count, and a bone marrow M:E ratio (see Appendix I for methods). These parameters were subjected to statistical analyses.

Clinical Chemistry Determinations

Fasted (16 hr.) blood samples were collected via cardiac puncture at the time of necropsy from all rats and mice and the sera analyzed for the

* Purina Lab Blocks 5001

TABLE 1. SUMMARY OF METHYL CHLORIDE SPECIFICATIONS AND ANALYSIS

Test Material - Methyl Chloride

Source - Matheson Gas Products, Inc.

Minimum Purity - 99.5%

Mass Spectrophotometer Analysis of Trace Impurities:

A, O_2, N_2, CH_4, CO, and CO_2 < 0.0025%

C_2H_2, C_2H_4, C_2H_6, C_3H_6, C_3H_8, or C_4H_{10} < 0.01%

Vinyl Chloride < 0.5 ppm

following clinical chemistry parameters: Glucose, BUN, AP, SGOT, SGPT, and CPK (see Appendix I for methods). These values were also subjected to statistical analyses.

Organ Weight Determinations

Individual weights for heart, adrenal glands, brain, testes/ovaries, spleen, liver, right and left kidneys, lungs and pancreas were taken at necropsy for all animals and subjected to statistical analysis.

Urinalysis Determinations

During week 13 of the study all animals were placed in metabolism cages for a 16-hour period for purposes of urine collection. During their time in the metabolism cages the rats were fasted but were given water ad libitum. These urine samples were then submitted to the clinical laboratory for the following determinations: Sp. gravity, pH, glucose, ketones, occult blood, protein, and urine sediment. These values were also subjected to statistical analyses.

Ophthalmoscopic Examination

Pretreatment and posttreatment eye examinations were performed on all mice and rats on the methyl chloride study. Prior to examination, pupils were dilated by instillation of one drop of Mydriacyl (Alcon Laboratories) into the conjunctival sac of each eye of each animal. Approximately 1/2 hour later, the eyes were examined using a Welch Allyn Direct Ophthalmoscope for fundoscopic examination and an American Optical Slit-Lamp Biomicroscope for examination of the iris, lens, cornea, and conjunctivae. All ophthalmoscopic examinations were done by a veterinarian trained and experienced in laboratory animal ophthalmology (Dr. H. Hugh Harroff, Jr.,.

Pathologic Examination

Pursuant to the study protocol (Appendix A), the tissues from the control group (A04) (Control) and the high-dose group (A03) (1500 ppm) were histologically evaluated first. Upon finding a compound-related lesion in the high-dose group (A03), an evaluation of the affected organ(s) in the next lower dose group was then required. This procedure was continued until the compound-related lesion was not found in any member of the next lower dose group (Tables 23, 24, 27 and 28).

Statistical Methods

Statistical analyses were performed separately for each sex and species on hematology, clinical chemistry, absolute organ weights, and organ weights relative to final body weight. In addition, analyses were performed on rat data only for weekly body weights and food consumption. Analysis of rat data, week 12 versus final body weight, was performed to define any fast-induced changes in mean body weight. To remove the possible effect of organ weight changes due to fasting, rat organ weight analyses were performed relative to the pre-fast body weights. For all the above comparisons a one-way analysis of variance (ANOVA) was used to test for overall differences in dose level including control. Where results of the ANOVA tests were found statistically significant, individual treatment versus control group mean comparisons were made using the least significant difference test (LSD) (Steel and Torrie, 1960). Prior to each ANOVA the Bartlett test was used to detect the presence of significant inter-group heterogeneity of variance (Bartlett, 1937). Where significant heterogeneity was exhibited, and for all differential white cell counts, the nonparametric Kruskal-Wallis (K-W) test was used in preference to the ANOVA (Kruskal and Wallis, 1952). Nonparametric equivalents to the LSD test as described by Dunn (1964) and Miller (1966) were used to make treatment versus control group comparisons when the K-W test results were statistically significant. Urinalysis variables were subjected to a Chi-Square contingency analysis as a test for homogeneity of response across all groups. Summary statistics including the mean, standard deviation, standard error, minimum, maximum and total number in each group were calculated and reported for all clinical and weight variables. All tests were performed on the Battelle-Columbus CDC 6500 and Cyber 73 computer systems using customized programming and a set of packaged statistical programs (Nie, et. al., 1975). All probability levels were deemed significantly below $\alpha = 0.5$

RESULTS

Exposure Conditions

Temperature and Relative Humidity

The temperature and relative humidity of the chambers during this study were determined at least three times a day by a dial thermometer (with a long probe) and a hair-type hygrometer located in each chamber. With the high air flow rate and small animal loading, the actual temperature and humidity for all the chambers was the same as the chamber room conditions.

Table 2 is a list of the temperature measurements which were made for each chamber during the inhalation study. The small differences measured between chambers is attributed to variations in the dial thermometers.

The relative humidity for this study was approximately 40 ± 5 percent. The actual humidity records are maintained by the Battelle Quality Assurance Unit of the Biological Ecological and Medical Sciences Department at Battelle to ensure compliance with G.L.P.

Exposure Concentrations

The methyl chloride concentration in each chamber was measured approximately every 20 minutes with a Hewlett Packard 5840A gas chromatograph. The actual concentrations were controlled with precision rotameters and the gas chromotograph served as a checking device and permanent record of the analysis.

Daily concentrations were time averaged. These and the overall study means are presented in Table 3.

To substantiate that the gas concentration was uniform throughout the chamber, samples were taken using a long-probe utilizing a 3 x 3 sampling matrix at the top, middle, and bottom of the chamber. A MIRAN Infrared Spectrophotometer was used to measure the gas concentration. Twenty-seven samples gave the same adsorption readings.

Table 2. DAILY AND MEAN CHAMBER TEMPERATURES (375 ppm METHYL CHLORIDE)

Exposure Day	1	2	3	4	5	6	7
	71	73	74	74	74	73	73
	71	73	74	74	75	73	73
$\bar{x}$, s	71 ± 0.0	73 ± 0.0	74 ± 0.0	74 ± 0.0	74.7 ± 0.6	73 ± 0.0	73 ± 0.0

Exposure Day	8	9	10	11	12	13	14
	74	74	74	74	74	72	74
	75	74	74	74	74	74	74
$\bar{x}$, s	74.7 ± 0.6	74 ± 0.0	74 ± 0.0	74 ± 0.0	74 ± 0.0	74 ± 1.2	74 ± 0.0

Exposure Day	15	16	17	18	19	20	21
	74	74	74	72	74	74	74
	74	75	74	74	74	74	74
$\bar{x}$, s	74 ± 0.0	74.7 ± 0.6	74 ± 0.0	73.3 ± 1.2	74 ± 0.0	74 ± 0.0	74 ± 0.0

Exposure Day	22	23	24	25	26	27	28
	75	74	75	74	76	76	76
	75	75	74	75	76	76	76
$\bar{x}$, s	74.7 ± 0.6	74.7 ± 0.6	74.3 ± 0.6	74.7 ± 0.6	76 ± 0.0	76 ± 0.0	76 ± 0.0

Exposure Day	29	30	31	32	33	34	35
	74	72	73	70	71	72	72
	73	73	74	72	72	72	73
$\bar{x}$, s	73.3 ± 0.6	73 ± 1.0	73.7 ± 0.6	71.7 ± 1.5	71.7 ± 0.6	72 ± 0.0	72.7 ± 0.6

000026

Table 2. (Continued)
(375 ppm METHYL CHLORIDE)

Exposure Day	36	37	38	39	40	41	42
	72	71	70	70	72	72	72
	73	71	73	70	72	73	73
	73	71	73	70	72	73	73
$\bar{x}$, s	72.7 ± 0.6	71 ± 0.0	71.3 ± 1.2	70 ± 0.0	72 ± 0.0	72.7 ± 0.6	72.7 ± 0.6

Exposure Day	43	44	45	46	47	48	49
	74	74	71	72	72	74	74
	73	75	71	72	72	73	73
	73	75	71	72	72	73	73
$\bar{x}$, s	73.3 ± 0.6	74.7 ± 0.6	71 ± 0.0	72 ± 0.0	72 ± 0.0	73.3 ± 0.6	73.3 ± 0.6

Exposure Day	50	51	52	53	54	55	56
	74	74	74	72	73	70	71
	74	74	74	74	74	72	72
	74	74	74	74	74	72	72
$\bar{x}$, s	74 ± 0.0	74 ± 0.0	74 ± 0.0	73.3 ± 1.2	73.7 ± 0.6	71.3 ± 1.2	71.7 ± 0.6

Exposure Day	57	58	59	60	61	62	63
	71	70	70	70	70	70	71
	72	72	70	72	72	72	72
	72	72	70	72	72	72	72
$\bar{x}$, s	71.7 ± 0.6	71.3 ± 1.2	70 ± 0.0	71.3 ± 1.2	71.3 ± 1.2	71.3 ± 1.2	71.7 ± 0.6

Exposure Day	64	65
	72	70
	--	72
	--	73
$\bar{x}$, s	72 ± 0.0	71.7 ± 1.5

Total $\bar{x}$, s 73.1 ± 0.6

000027

Table 2. DAILY AND MEAN CHAMBER TEMPERATURES (750 ppm METHYL CHLORIDE)

Exposure Day	1	2	3	4	5	6	7
	70	70	72	70	70	69	71
	70	70	72	71	70	70	71
$\bar{x}$, s	70 ± 0.0	70 ± 0.0	72 ± 0.0	70.7 ± 0.6	70 ± 0.0	69.7 ± 0.6	71 ± 0.0

Exposure Day	8	9	10	11	12	13	14
	71	72	70	70	69	70	70
	71	72	70	70	70	70	71
$\bar{x}$, s	71 ± 0.0	72 ± 0.0	70 ± 0.0	70 ± 0.0	69.7 ± 0.6	70 ± 0.0	70.7 ± 0.6

Exposure Day	15	16	17	18	19	20	21
	71	70	69	70	70	71	72
	72	71	70	70	70	70	72
$\bar{x}$, s	71.7 ± 0.6	70.7 ± 0.6	69.7 ± 0.6	70.7 ± 1.2	70 ± 0.0	70.3 ± 0.6	71.3 ± 1.2

Exposure Day	22	23	24	25	26	27	28
	72	71	72	73	72	72	68
	72	71	72	72	72	72	68
$\bar{x}$, s	72 ± 0.0	71 ± 0.0	72 ± 0.0	72.7 ± 0.6	72 ± 0.0	72 ± 0.0	68.7 ± 1.2

Exposure Day	29	30	31	32	33	34	35
	68	70	67	68	67	70	69
	69	70	68	67	67	70	69
$\bar{x}$, s	69 ± 1.0	70 ± 0.0	68 ± 1.0	67.3 ± 0.6	67.3 ± 0.6	70 ± 0.0	69 ± 0.0

000028

Table 2. (Continued)
(750 ppm METHYL CHLORIDE)

Exposure Day	36	37	38	39	40	41	42
	67	68	70	68	70	68	69
	67	69	70	68	69	69	69
$\bar{x}$, s	67 / 67 ± 0.0	69 / 68.7 ± 0.6	70 / 70 ± 0.0	68 / 68 ± 0.0	70 / 69.7 ± 0.6	69 / 68.7 ± 0.6	70 / 69.3 ± 0.6

Exposure Day	43	44	45	46	47	48	49
	70	68	70	69	69	69	69
	70	68	70	69	69	69	69
$\bar{x}$, s	70 / 70 ± 0.0	68 / 68 ± 0.0	70 / 70 ± 0.0	70 / 69.3 ± 0.6	69 / 69 ± 0.0	69 / 69 ± 0.0	69 / 69 ± 0.0

Exposure Day	50	51	52	53	54	55	56
	69	70	70	69	67	66	66
	70	70	70	70	67	66	66
$\bar{x}$, s	70 / 69.7 ± 0.6	70 / 70 ± 0.0	70 / 70 ± 0.0	70 / 69.7 ± 0.6	66 / 66.7 ± 0.6	66 / 66 ± 0.0	66 / 66 ± 0.0

Exposure Day	57	58	59	60	61	62	63
	65	65	66	65	65	66	66
	65	65	67	66	66	66	--
$\bar{x}$, s	65 / 65 ± 0.0	65 / 65 ± 0.0	67 / 66.7 ± 0.6	66 / 65.7 ± 0.6	66 / 65.7 ± 0.6	66 / 66 ± 0.0	-- / 66 ± 0.0

Exposure Day	64	65
	68	66
	67	67
$\bar{x}$, s	67 / 67.3 ± 0.6	67 / 66.7 ± 0.6

Total $\bar{x}$, s 69.2 ± 0.5

000029

Table 2. DAILY AND MEAN CHAMBER TEMPERATURES (1500 ppm METHYL CHLORIDE)

Exposure Day	1	2	3	4	5	6	7
	72	73	70	70	69	71	70
	72	73	70	70	70	71	71
$\bar{x}$, s	72 ± 0.0	72.7 ± 0.6	70 ± 0.0	70 ± 0.0	69.7 ± 0.6	71 ± 0.0	70.7 ± 0.6

Exposure Day	8	9	10	11	12	13	14
	70	70	70	70	70	70	70
	70	70	70	70	70	71	71
$\bar{x}$, s	70 ± 0.0	70 ± 0.0	70 ± 0.0	70 ± 0.0	70 ± 0.0	70.7 ± 0.6	70.7 ± 0.6

Exposure Day	15	16	17	18	19	20	21
	71	68	70	71	71	71	72
	71	70	70	71	70	71	72
$\bar{x}$, s	71 ± 0.0	69.3 ± 1.2	70 ± 0.0	71 ± 0.0	70.3 ± 0.6	70.7 ± 0.6	72 ± 0.0

Exposure Day	22	23	24	25	26	27	28
	71	72	72	73	72	69	68
	72	72	72	73	72	69	69
$\bar{x}$, s	71.7 ± 0.6	72 ± 0.0	72 ± 0.0	73 ± 0.0	72 ± 0.0	69 ± 0.0	69 ± 1.0

Exposure Day	29	30	31	32	33	34	35
	70	67	68	68	70	69	68
	70	69	68	68	70	70	68
$\bar{x}$, s	70 ± 0.0	68.3 ± 1.2	68 ± 0.0	68 ± 0.0	70 ± 0.0	69.7 ± 0.6	68 ± 0.0

000030

Table 2. (Continued)
(1500 ppm METHYL CHLORIDE)

Exposure Day	36	37	38	39	40	41	42
	69	68	68	69	69	70	71
	69	68	68	69	70	70	70
$\bar{x}$, s	69 / 69 ± 0.0	69 / 68.3 ± 0.6	68 / 68 ± 0.0	70 / 69.3 ± 0.6	70 / 69.7 ± 0.6	70 / 70 ± 0.0	70 / 70.3 ± 0.6

Exposure Day	43	44	45	46	47	48	49
	69	70	70	70	70	70	70
	69	70	70	70	70	70	70
$\bar{x}$, s	69 / 69 ± 0.0	70 / 70 ± 0.0	70 / 70 ± 0.0	70 / 70 ± 0.0	70 / 70 ± 0.0	70 / 70 ± 0.0	70 / 70 ± 0.0

Exposure Day	50	51	52	53	54	55	56
	70	70	69	67	67	66	66
	71	70	70	68	67	67	67
$\bar{x}$, s	70 / 70.3 ± 0.6	70 / 70 ± 0.0	70 / 69.7 ± 0.6	67 / 67.3 ± 0.6	67 / 67 ± 0.0	67 / 66.7 ± 0.6	67 / 66.7 ± 0.6

Exposure Day	57	58	59	60	61	62	63
	66	69	67	67	67	68	70
	66	66	67	67	66	--	68
$\bar{x}$, s	66 / 66 ± 0.0	68 / 67.7 ± 1.5	67 / 67 ± 0.0	67 / 67 ± 0.0	66 / 66.3 ± 0.6	-- / 68	67 / 68.3 ± 1.5

Exposure Day	64	65
	66	69
	67	69
$\bar{x}$, s	67 / 66.7 ± 0.6	67 / 68.3 ± 1.2

Total $\bar{x}$, s 69.5 ± 0.5

000031

Table 2. DAILY AND MEAN CHAMBER TEMPERATURES (CONTROL)

Exposure Day	1	2	3	4	5	6	7
	72	72	72	73	75	72	72
	71	72	72	73	75	73	73
$\bar{x}$, s	72 / 71.7 ± 0.6	72 / 72 ± 0.0	72 / 72 ± 0.0	73 / 73 ± 0.0	74 / 74.7 ± 0.6	73 / 72.7 ± 0.6	73 / 72.7 ± 0.6

Exposure Day	8	9	10	11	12	13	14
	72	73	73	72	72	72	72
	72	73	73	74	72	72	72
$\bar{x}$, s	72 / 72 ± 0.0	73 / 73 ± 0.0	73 / 73 ± 0.0	74 / 73.3 ± 1.2	-- / 72 ± 0.0	72 / 72 ± 0.0	72 / 72 ± 0.0

Exposure Day	15	16	17	18	19	20	21
	72	72	73	72	71	72	73
	72	73	73	73	72	72	73
$\bar{x}$, s	72 / 72 ± 0.0	73 / 72.7 ± 0.6	73 / 73 ± 0.0	73 / 72.7 ± 0.6	72 / 71.7 ± 0.6	72 / 72 ± 0.0	73 / 73 ± 0.0

Exposure Day	22	23	24	25	26	27	28
	72	73	74	72	73	74	74
	72	73	74	73	74	74	74
$\bar{x}$, s	72 / 72 ± 0.0	72 / 72.7 ± 0.6	74 / 74 ± 0.0	73 / 72.7 ± 0.6	74 / 73.7 ± 0.6	74 / 74 ± 0.0	74 / 74 ± 0.0

Exposure Day	29	30	31	32	33	34	35
	74	7'	70	72	70	70	70
	74	74	72	72	71	70	71
$\bar{x}$, s	74 / 74 ± 0.0	72 / 73.3 ± 1.2	72 / 71.3 ± 1.2	72 / 72 ± 0.0	72 / 71 ± 1.0	70 / 70 ± 0.0	71 / 70.7 ± 0.6

000032

Table 2. (Continued)
(CONTROL)

Exposure Day	36	37	38	39	40	41	42
	72	72	70	72	72	69	71
	72	72	70	72	72	69	71
	72	72	70	72	72	70	71
$\bar{x}$, s	72 ± 0.0	72 ± 0.0	70 ± 0.0	72 ± 0.0	72 ± 0.0	69.3 ± 0.6	71 ± 0.0

Exposure Day	43	44	45	46	47	48	49
	71	72	72	71	72	72	72
	71	72	72	71	72	72	72
	71	72	72	71	72	72	72
$\bar{x}$, s	71 ± 0.0	72 ± 0.0	72 ± 0.0	71 ± 0.0	72 ± 0.0	72 ± 0.0	72 ± 0.0

Exposure Day	50	51	52	53	54	55	56
	72	72	72	72	73	72	70
	72	72	73	73	73	72	70
	72	72	73	73	73	73	70
$\bar{x}$, s	72 ± 0.0	72 ± 0.0	72.7 ± 0.6	72.7 ± 0.6	73 ± 0.0	72.3 ± 0.6	70 ± 0.0

Exposure Day	57	58	59	60	61	62	63
	70	69	70	70	70	70	70
	71	70	70	70	70	70	70
	71	70	70	70	70	70	70
$\bar{x}$, s	70.7 ± 0.6	69.7 ± 0.6	70 ± 0.0	70 ± 0.0	70 ± 0.0	70 ± 0.0	70 ± 0.0

Exposure Day	64	65
	70	70
	70	70
	70	70
$\bar{x}$, s	70 ± 0.0	70 ± 0.0

Total $\bar{x}$, s 71.9 ± 0.4

000033

TABLE 3. CHAMBER CONCENTRATION OF METHYL CHLORIDE FOR 90-DAY PILOT STUDY

Chamber	A1	A2	A3	A4
Specified Concentration, ppm	375	750	1500	0
Test Day	Daily Mean Concentrations, ppm			
1	368 ± 39	743 ± 8	1488 ± 37	N
2	372 ± 6	744 ± 20	1508 ± 8	N
3	357 ± 29	755 ± 5	1532 ± 32	N
4	358 ± 6	770 ± 18	1495 ± 43	N
5	385 ± 11	759 ± 37	1478 ± 11	N
6	373 ± 7	742 ± 8	1400 ± 19	N
7	369 ± 5	752 ± 8	1361 ± 33	N
8	379 ± 14	746 ± 7	1385 ± 23	N
9	372 ± 7	746 ± 9	1447 ± 76	N
10	374 ± 4	749 ± 11	1364 ± 71	N
11	365 ± 4	744 ± 4	1466 ± 25	N
12	369 ± 6	743 ± 6	1432 ± 54	N
13	378 ± 32	748 ± 11	1445 ± 18	N
14	366 ± 8	745 ± 16	1543 ± 64	N
15	364 ± 14	727 ± 11	1461 ± 26	N
16	373 ± 3	726 ± 13	1470 ± 15	N
17	362 ± 6	731 ± 8	1495 ± 38	N
18	367 ± 13	737 ± 17	1430 ± 42	N
19	368 ± 10	711 ± 22	*1260 ±*433	N
20	360 ± 30	*618 ±*184	1543 ± 96	N
21	*303 ±*82	744 ± 3	1509 ± 10	N
22	373 ± 3	760 ± 3	1483 ± 7	N
23	380 ± 1	751 ± 5	1500 ± 31	N
24	373 ± 4	753 ± 7	1513 ± 11	N
25	368 ± 11	757 ± 13	1498 ± 11	N
26	352 ± 25	748 ± 6	1467 ± 54	N

TABLE 3. (CONT'D)

Chamber	A1	A2	A3	A4
Specified Concentration, ppm	375	750	1500	0
Test Day	Daily Mean Concentrations, ppm			
27	342 ± 61	732 ± 25	1401 ± 53	N
28	355 ± 22	718 ± 64	1437 ± 27	N
29	364 ± 36	730 ± 20	1469 ± 13	N
30	376 ± 16	738 ± 7	1467 ± 26	N
31	365 ± 19	731 ± 12	1482 ± 8	N
32	367 ± 21	737 ± 19	1455 ± 14	N
33	353 ± 62	730 ± 7	1473 ± 15	N
34	370 ± 8	733 ± 6	1493 ± 10	N
35	372 ± 3	743 ± 7	1497 ± 20	N
36	364 ± 7	745 ± 11	1465 ± 28	N
37	324 ± 29	725 ± 8	1508 ± 24	N
38	362 ± 8	734 ± 17	1458 ± 137	N
39	366 ± 7	742 ± 35	1466 ± 19	N
40	365 ± 22	745 ± 13	1465 ± 9	N
41	377 ± 16	751 ± 6	1468 ± 54	N
42	369 ± 4	759 ± 10	1480 ± 22	N
43	376 ± 5	753 ± 29	** **	N
44	362 ± 26	** **	** **	N
45	** **	** **	1412 ± 39	N
46	** **	723 ± 14	1453 ± 14	N
47	375 ± 2	733 ± 6	1456 ± 71	N
48	374 ± 7	748 ± 13	1452 ± 39	N
49	371 ± 5	736 ± 7	1480 ± 21	N
50	368 ± 4	742 ± 17	1509 ± 14	N
51	359 ± 63	749 ± 11	1504 ± 66	N
52	374 ± 11	733 ± 8	1505 ± 18	N
53	372 ± 8	735 ± 9	1539 ± 73	N

TABLE 3. (CONT'D)

Chamber	A1	A2	A3	A4
Specified Concentration, ppm	375	750	1500	0
Test Day	Daily Mean Concentrations, ppm			
54	363 ± 9	719 ± 37	1528 ± 22	N
55	344 ± 36	731 ± 10	*1414 ±*128	***0.1
56	366 ± 7	*704 ± *59	1477 ± 28	1.1
57	*346 ±*57	733 ± 17	1495 ± 4	1.6
58	367 ± 26	734 ± 4	1455 ± 13	N
59	378 ± 2	728 ± 15	1475 ± 5	N
60	372 ± 2	744 ± 2	1460 ± 72	N
61	374 ± 4	747 ± 3	1490 ± 17	N
62	376 ± 3	750 ± 3	1503 ± 17	N
63	376 ± 2	757 ± 14	1496 ± 10	N
64	386 ± 5	744 ± 6	1482 ± 25	N
65	379 ± 8	739 ± 10	1513 ± 98	N
66	367 ± 24	738 ± 29	1469 ± 70	N
Overall Mean and Std Deviation	368 ± 21.0	741 ± 16	1473 ± 42	

* It was necessary to change methyl chloride bottles during an exposure

** G. C. was out of operation

*** Small leak detected at regulator

Body Weight Data

Table 4 contains summary statistical analyses of body weights for the rats exposed to methyl chloride and Table 5 contains summary statistical analyses of body weight gains for these same rats. Starting at Week 5 of study and continuing to the end, the male rats in Groups 1, 2, and 3 showed significantly less total body weight, although their rate of body weight gain did not significantly differ from the controls. This is interpreted as a compound related effect that is gradual and subtle. The female rats in Groups 2 and 3 showed the same effect, but those in Group 1 did not. This may be indicative of a dose relationship.

Figure 3 and Figure 4 are time response curves for body weight gain in the rats. The average weight changes in the mice were too variable to make similar plots. However, Table 6 summarizes the statistical analyses of the final body weights for mice. There is no significant difference between treatment groups in final body weight for the male mice, although there is a significant depression in final body weight for females in Group 3.

Individual raw data and descriptive statistics for rat weekly body weights and mice final body weights are found in Appendix B.

Food Consumption Data

The food consumption data for the rats on study are summarized on Table 8. An examination of this data will show that there are no significant differences between treatment groups in the amount of feed consumed. Mouse food consumption data were too variable to be meaningful. Individual raw data and descriptive statistics for rat food consumption data are in Appendix C.

Hematology and Clinical Chemistry Data

Clinical chemistry and hematologic statistical analyses summaries are presented for rats in Tables 9 and 11 and for mice in Tables 10 and 12.

A statistically significant increase in SGPT activity occurred in male mice in the 1500 ppm dose group (Table 10). This increase was

TABLE 4. SUMMARY OF STATISTICAL ANALYSES† OF BODY WEIGHTS FOR FISCHER 344 RATS EXPOSED TO METHYL CHLORIDE (90-DAY PILOT STUDY)

Body Weight (g)	Sex	ANOVA[a]	B[b]	K-W[c]	LSD or[d] Equivalent
Initial	M	ns	ns		
	F	ns	ns		
Week 1	M	*	*	*	
	F	ns	ns		
Week 2	M	ns	ns		
	F	ns	ns		
Week 3	M	*	ns		3↓
	F	*	ns		3↓
Week 4	M	*	ns		3↓
	F	*	ns		3↓
Week 5	M	*	ns		1↓, 2↓, 3↓
	F	*	ns		3↓
Week 6	M	*	ns		1↓, 2↓, 3↓
	F	*	ns		2↓, 3↓
Week 7	M	*	ns		1↓, 2↓, 3↓
	F	*	ns		2↓, 3↓
Week 8	M	*	ns		1↓, 2↓, 3↓
	F	*	ns		2↓, 3↓
Week 9	M	*	ns		1↓, 2↓, 3↓
	F	*	ns		3↓
Week 10	M	*	ns		1↓, 2↓, 3↓
	F	*	ns		2↓, 3↓
Week 11	M	*	ns		1↓, 2↓, 3↓
	F	*	ns		2↓, 3↓
Week 12	M	*	ns		1↓, 2↓, 3↓
	F	*	ns		2↓, 3↓

TABLE 4. (Continued)

Body Weight (g)	Sex	ANOVA[a]	B[b]	K-W[c]	LSD or[d] Equivalent
Week 13	M	*	ns		2↓, 3↓
	F	*	*	*	3↓

[a] One-Way Analysis of Variance.

[b] Bartlett test for homogeneity of variance.

[c] Kruskal-Wallis test (nonparametric equivalent to ANOVA).

[d] Least significant difference or nonparametric equivalent treatment versus control group comparisons. Numbers given indicate which treatment group means were found significantly higher (↑) or lower (↓) than their corresponding control group. Group 1 = 375 ppm, 2 = 750 ppm, 3 = 1500 ppm, 4 = control.

ns = not significant
* = significant
† = Body Weight Statistical Data are located on pages B-1 through B-2

TABLE 5. SUMMARY OF STATISTICAL ANALYSES† OF BODY WEIGHT GAIN FOR FISCHER 344 RATS EXPOSED TO METHYL CHLORIDE (90-DAY PILOT STUDY)

Body Weight Gain (g)	Sex	ANOVA[a]	B[b]	K-W[c]	LSD or[d] Equivalent
Week 1	M	ns	ns		
	F	ns	ns		
Week 2	M	*	*	*	3↓
	F	ns	ns		
Week 3	M	*	ns		2↓, 3↓
	F	*	ns		3↓
Week 4	M	ns	ns		
	F	ns	ns		
Week 5	M	*	*	*	2↓, 3↓
	F	*	ns		3↓
Week 6	M	ns	ns		
	F	*	ns		2↓
Week 7	M	ns	ns		
	F	ns	ns		
Week 8	M	*	*	*	3↓
	F	ns	ns		
Week 9	M	ns	ns		
	F	ns	ns		
Week 10	M	ns	ns		
	F	ns	ns		
Week 11	M	ns	ns		
	F	ns	ns		
Week 12	M	ns	ns		
	F	ns	ns		

TABLE 5. (Continued)

Body Weight Gain (g)	Sex	ANOVA[a]	B[b]	K-W[c]	LSD or[d] Equivalent
Week 13	M	ns	ns		
	F	ns	ns		
Total	M	ns	ns		
	F	ns	ns		

[a] One-Way Analysis of Variance.

[b] Bartlett test for homogeneity of variance.

[c] Kruskal-Wallis test (nonparametric equivalent to ANOVA).

[d] Least significant difference or nonparametric equivalent treatment versus control group comparisons. Numbers given indicate which treatment group means were found significantly higher (↑) or lower (↓) than their corresponding control group. Group 1 = 375 ppm, 2 = 750 ppm, 3 = 1500 ppm, 4 = control.

ns = not significant
* = significant
† = Body Weight Gain Statistical Data are located on pages B-6 through B-13

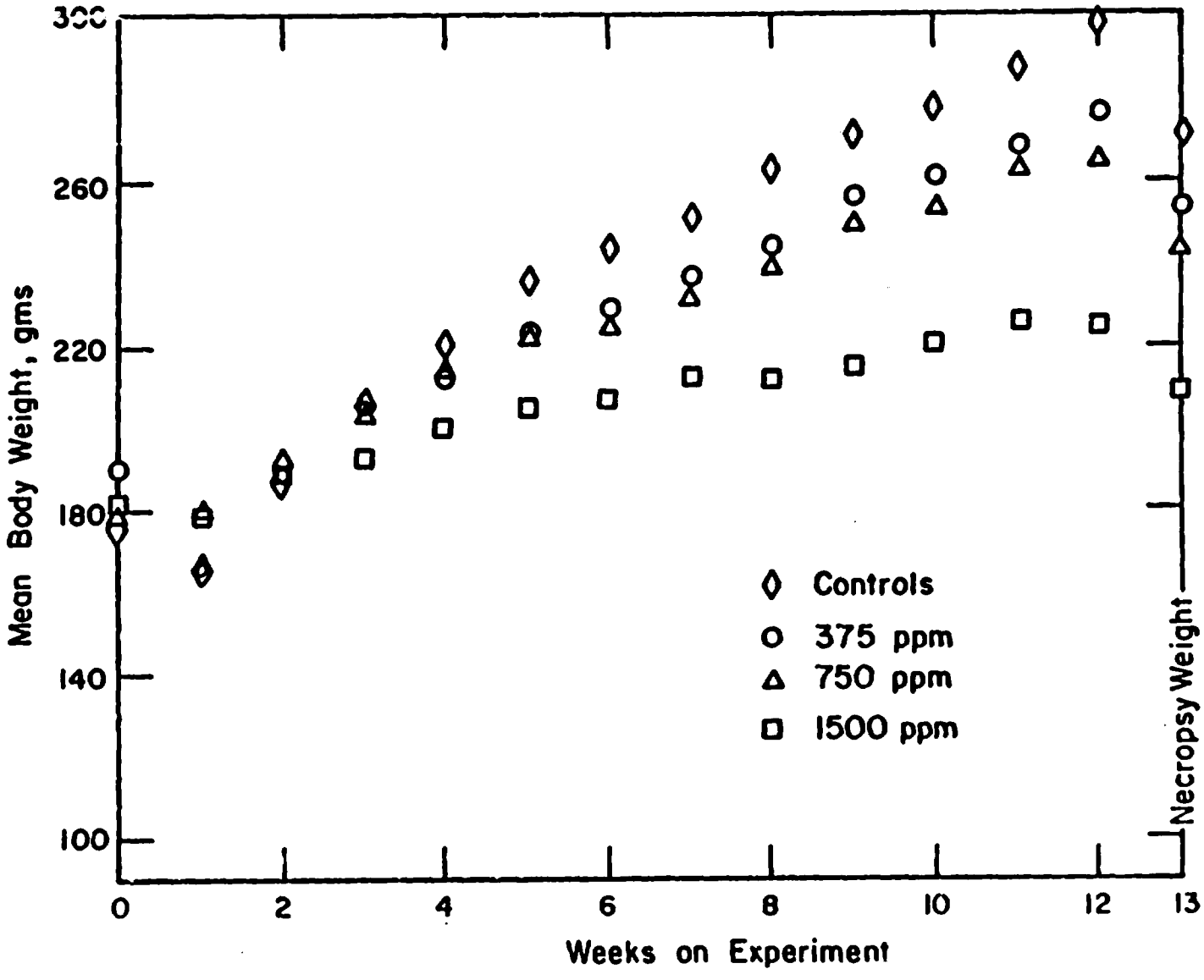

FIGURE 3. TIME-RESPONSE CURVES FOR BODY WEIGHT GAIN IN MALES, FISCHER 344 RATS EXPOSED TO 0 (CONTROLS), 375, 750 OR 1500 PPM METHYL CHLORIDE

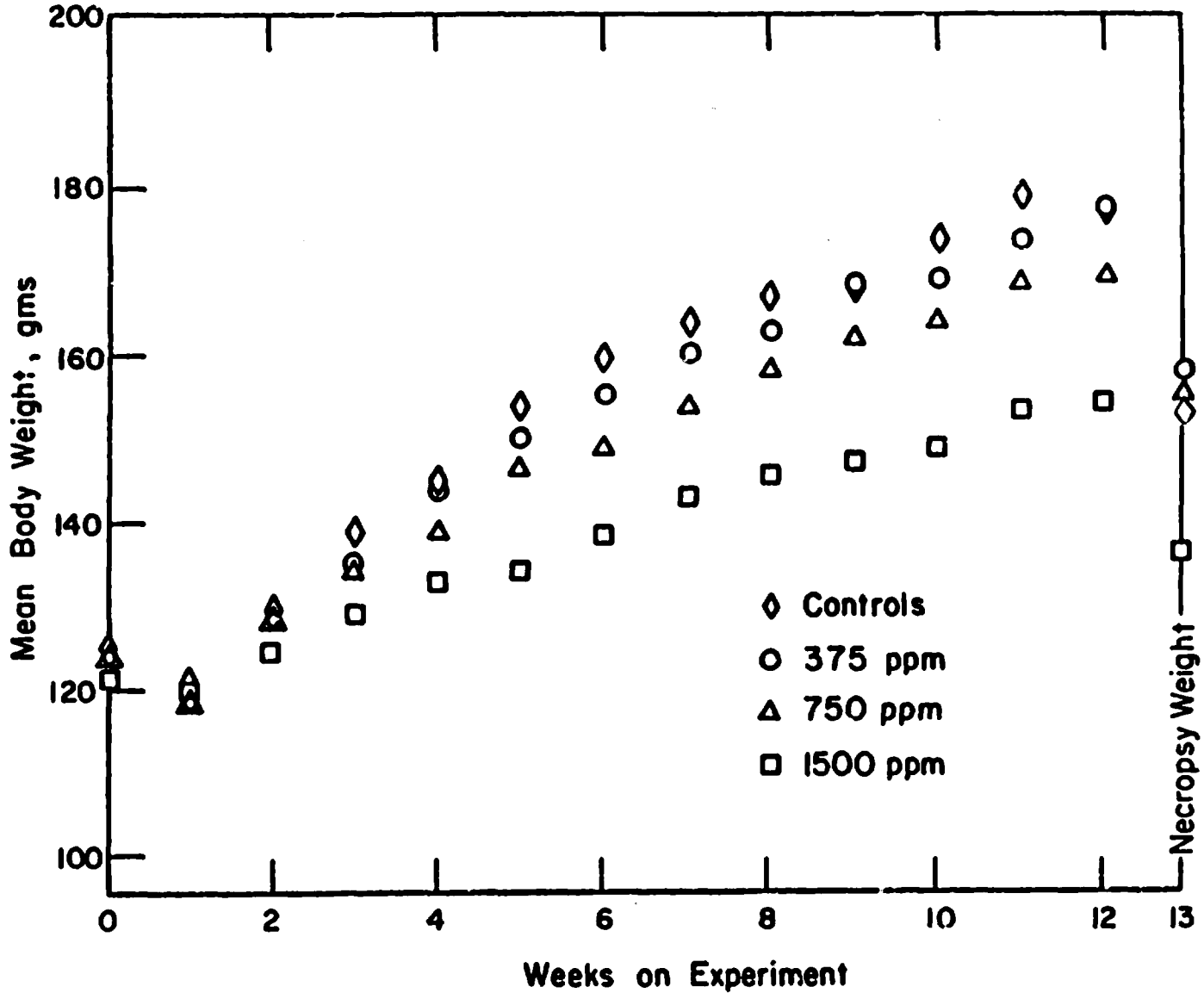

FIGURE 4. TIME- RESPONSE CURVES FOR BODY WEIGHT GAIN IN FEMALES, FISCHER 344 RATS EXPOSED TO 0 (CONTROLS), 375, 750 OR 1500 PPM METHYL CHLORIDE

TABLE 6. SUMMARY OF STATISTICAL ANALYSES OF FINAL BODY WEIGHT FOR $B_6C_3F_1$ MICE EXPOSED TO METHYL CHLORIDE (90-DAY PILOT STUDY)

Sex	ANOVA[a]	B[b]	LSD[c]
M	ns	ns	
F	*	ns	3↓

[a] One-Way Analysis of Variance.

[b] Bartlett test for homogeneity of variance.

[c] Least significant difference treatment versus control group comparisons. Numbers given indicate which treatment group means were found significantly higher (↑) or lower (↓) than their corresponding control group. Group 1 = 375 ppm, 2 = 750 ppm, 3 = 1500 ppm, 4 = control.

ns = not significant
* = significant

TABLE 7. AVERAGE FOOD CONSUMPTION FOR RATS EXPOSED TO METHYL CHLORIDE DURING 90-DAY PILOT STUDY

Level	GRAMS PER RAT PER WEEK	
	Male	Female
Control	120.0	89.2
375 ppm	119.5	92.1
750 ppm	119.6	87.2
1500 ppm	116.6	94.4

TABLE 8. SUMMARY OF STATISTICAL ANALYSES† OF FOOD CONSUMPTION FOR FISCHER 344 RATS EXPOSED TO METHYL CHLORIDE (90-DAY PILOT STUDY)

Food Consumption (g)	Sex	ANOVA[a]	B[b]	K-W[c]	LSD or[d] Equivalent
Week 1	M	*	ns		2↓, 3↓
	F	ns	ns		
Week 2	M	ns	ns		
	F	*	ns		1↓
Week 3	M	*	ns		3↓
	F	*	ns		3↓
Week 4	M	*	*	*	2↓
	F	*	ns		2↓,3↓
Week 5	M	*	ns		1↓, 2↓, 3↓
	F	*	ns		1↓, 2↓, 3↓
Week 6	M	*	ns		1↓, 2↓, 3↓
	F	*	*	*	2↓, 3↓
Week 7	M	ns	ns		
	F	ns	*	ns	
Week 8	M	ns	*	ns	
	F	ns	ns		
Week 9	M	ns	ns		
	F	ns	*	ns	
Week 10	M	ns	ns		
	F	ns	*	*	2↑, 3↑
Week 11	M	*	ns		
	F	ns	*	ns	
Week 12	M	ns	ns		
	F	*	*	*	1↓, 2↓, 3↓

TABLE 8. (Continued)

Food Consumption (g)	Sex	ANOVA[a]	B[b]	K-W[c]	LSD or[d] Equivalent
Week 13	M	*	ns		1†, 2†, 3†
	F	*	*	*	1†, 2†, 3†

[a] One-Way Analysis of Variance.

[b] Bartlett test for homogeneity of variance.

[c] Kruskal-Wallis test (nonparametric equivalent to ANOVA).

[d] Least significant difference or nonparametric equivalent treatment versus control group comparisons. Numbers given indicate which treatment group means were found significantly higher (↑) or lower (↓) than their corresponding control group. Group 1 = 375 ppm, 2 = 750 ppm, 3 = 1500 ppm, 4 = control.

ns = not significant
* = significant
† = Food Consumption Statistical Data are located on pages C-1 through C-7

TABLE 9. SUMMARY OF STATISTICAL ANALYSES† OF CLINICAL CHEMISTRY FOR FISCHER 344 RATS EXPOSED TO METHYL CHLORIDE (90-DAY PILOT STUDY)

Parameter	Sex	ANOVA[a]	B[b]	K-W[c]	LSD or[d] Equivalent
Glucose (mg/dl)	M	ns	ns		
	F	*	ns		1↓, 2↓, 3↓
BUN (mg/dl)	M	*	ns		1↓, 2↓, 3↓
	F	*	ns		1↓, 2↓, 3↓
AP (I.U./l)	M	*	ns		3↓
	F	*	ns		2↓
SGOT (I.U./l)	M	*	*	ns	
	F	*	*	*	
SGPT (I.U./l)	M	*	*	*	
	F	*	*	*	
CPK (I.U./l)	M	*	*	*	1↓
	F	ns	ns		

[a] One-Way Analysis of Variance.

[b] Bartlett test for homogeneity of variance.

[c] Kruskal-Wallis test (nonparametric equivalent to ANOVA).

[d] Least significant difference or nonparametric equivalent treatment versus control group comparisons. Numbers given indicate which treatment group means were found significantly higher (↑) or lower (↓) than their corresponding control group. Group 1 = 375 ppm, 2 = 750 ppm, 3 = 1500 ppm, 4 = control.

ns = not significant
* = significant
† = Clinical Chemistry Statistical Data are located on pages E-1 through E-10

TABLE 10. SUMMARY OF STATISTICAL ANALYSES† OF CLINICAL CHEMISTRY FOR $B_6C_3F_1$ MICE EXPOSED TO METHYL CHLORIDE (90-DAY PILOT STUDY)

Parameter	Sex	ANOVA[a]	B[b]	K-W[c]	LSD or[d] Equivalent
Glucose (mg/dl)	M	ns	ns		
	F	ns	ns		
BUN (mg/dl)	M	ns	ns		
	F	*	ns		1↑
AP (I.U. /l)	M	ns	ns		
	F	ns	ns		
SGOT (I.U./l)	M	*	ns		1↑
	F	ns	ns		
SGPT (I.U. /l)	M	*	ns		3↑
	F	ns	ns		
CPK (I.U./l)	M	ns	ns		
	F	ns	ns		

(a) One-Way Analysis of Variance.
(b) Bartlett test for homogeneity of variance.
(c) Kruskal-Wallis test (nonparametric equivalent to ANOVA).
(d) Least significant difference or nonparametric equivalent treatment versus control group comparisons. Numbers given indicate which treatment group means were found significantly higher (↑) or lower (↓) than their corresponding control group. Group 1 = 375 ppm, 2 = 750 ppm, 3 = 1500 ppm, 4 = control.

ns = not significant
* = significant
† = Clinical Chemistry Statistical Data are located on pages E-1 through E-10

TABLE 11. SUMMARY OF STATISTICAL ANALYSES* OF HEMATOLOGY FOR FISCHER 344 RATS EXPOSED TO METHYL CHLORIDE (90-DAY PILOT STUDY)

Parameter	Sex	ANOVA[a]	B[b]	K-W[c]	LSD or (d) Equivalent
HGB (g%)	M	ns	ns		
	F	ns	ns		
HCT (%)	M	ns	ns		
	F	ns	ns		
WBC ($10^3/mm^3$)	M	*	*	*	1+, 2+, 3+
	F	*	ns		1+, 2+, 3+
RBC ($10^6/mm^3$)	M	ns	ns		
	F	ns	ns		
MCV (μm^3)	M	ns	ns		
	F	ns	ns		
RETIC (%)	M	*	*	*	
	F	*	ns		3+
MCH (pg)	M	ns	ns		
	F	ns	ns		
MCHC (g%)	M	*	*	*	
	F	ns	ns		
SEGS (% WBC)	M			*	2+, 3+
	F			*	2+, 3+
SEGS ($10^3/mm^3$)	M	*	*	*	3+
	F	*	*	*	3+
EOS (% WBC)	M			ns	
	F			ns	
EOS ($10^3/mm^3$)	M	*	*	ns	
	F	ns	ns		
LYMPH (% WBC)	M			*	2+, 3+
	F			*	2+, 3+
LYMPH ($10^3/mm^3$)	M	*	*	*	1+, 2+, 3+
	F	*	ns		1+, 2+, 3+
M:E Ratio	M	ns	*	ns	
	F	*	ns		1+, 2+, 3+

[a] One-Way Analysis of Variance.

[b] Bartlett test for homogeneity of variance.

[c] Kruskal-Wallis test (nonparametric equivalent to ANOVA).

[d] Least significant difference or nonparametric equivalent treatment versus [illegible] group comparisons. Numbers given indicate which treatment group means were [illegible] significantly higher (+) or lower (-) than their corresponding control group. Group 1 = 375 ppm, 2 = 750 ppm, 3 = 1500 ppm, 4 = control.

ns = not significant
* = significant
+ = Hematology Statistical Data are located on pages D-1 through D-19

TABLE 12. SUMMARY OF STATISTICAL ANALYSES† OF HEMATOLOGY FOR $B_6C_3F_1$ MICE EXPOSED TO METHYL CHLORIDE (90-DAY PILOT STUDY)

Parameter	Sex	ANOVA(a)	B(b)	K-W(c)	LSD or(d) Equivalent
HGB (gX)	M	*	*	ns	
	F	*	ns		3↓
HCT (X)	M	ns	ns		
	F	*	ns		3↓
WBC ($10^3/mm^3$)	M	*	*	*	
	F	ns	ns		
RBC ($10^6/mm^3$)	M	*	*	ns	
	F	*	ns		3↓
MCV (μm^3)	M	*	ns		3↓
	F	ns	ns		
RETIC (X)	M	*	*	ns	
	F	*	ns		1↑
MCH (pg)	M	ns	ns		
	F	*	ns		
MCHC (gX)	M	*	ns		2↓, 3↓
	F	ns	ns		
SEGS(X WBC)	M			ns	
	F			*	
SEGS($10^3/mm^3$)	M	*	*	*	2↓
	F	*	*	*	2↓
EOS(X WBC)	M			ns	
	F			ns	
EOS($10^3/mm^3$)	M	ns	ns		
	F	ns	ns		
LYMPH(X WBC)	M			ns	
	F			*	
LYMPH($10^3/mm^3$)	M	ns	ns		
	F	ns	ns		
M:E Ratio	M	*	ns		
	F	ns	ns		2↑

(a) One-Way Analysis of Variance.
(b) Bartlett test for homogeneity of variance.
(c) Kruskal-Wallis test (nonparametric equivalent to ANOVA).
(d) Least significant difference or nonparametric equivalent treatment versus control group comparisons. Numbers given indicate which treatment group means were significantly higher (↑) or lower(↓) than their corresponding control group. Group 1 = 375 ppm, 2 = 750 ppm, 3 = 1500 ppm, 4 = control.

ns = not significant
* = significant
† = Hematology Statistical Data are located on pages D-1 through D-19

due to increases in serum activity of SGPT in two animals (Numbers 28 and 40). Microscopic evaluation of the liver from animal Number 40 revealed a single infarct (Table 23). The hepatic changes observed in animal 28 (Table 23) included moderate cytoplasmic vacuolar change and increased size of hepatic nuclei. The increased activity of SGPT in these two mice likely reflects increases in hepatocyte membrane permeability and the subsequent leakage of this enzyme into serum.

In the 375 ppm dose group, a statistically significant decrease was found in SGOT activity for male mice and in CPK activity for male rats. Decreases in the concentrations of leakage enzymes below published normal ranges for plasma or serum are not known to have clinical significance.

Similarly, statistically significant decreases in serum alkaline phosphatase activity were reported for female rats in the 750 ppm dose group and for male rats in the 1500 ppm dose group. A review of the individual animal data revealed these data to be within the expected range for clinically normal animals.

Statistically significant decreases in BUN and glucose were observed in all three compound-treated groups of male and female rats. Decreases in these substances have been associated with hepatic insufficiency; however, histologic evaluation of the livers from rats in the 750 and 1500 ppm dose groups did not reveal changes which would be compatible with this interpretation. Examination of the individual animal data revealed the changes to be due to unexplained low values in one or two animals in each of the affected groups. An increase in BUN for female mice in the 375 ppm dose group also were unexplained. Clinical evidence of renal disease was not apparent in these animals and pursuant to the study protocol, their cardiovascular and renal tissues were examined grossly but were not evaluated histologically.

Inspection of the individual animal data for the hematologic parameters shown to be statistically significant in Tables 11 and 12 revealed all values to be within the accepted ranges for clinically normal rats and mice. Within this range, statistically significant increases in WBC counts occurred in all treatment groups while decreases in neutrophils and increases in lymphocytes occurred in the 1500 ppm and 750 ppm treatment groups. While this appears to be a compound-related effect, these changes

are interpreted as being within the expected range for clinically normal animals; therefore, their significance is questionable.

Individual raw data and descriptive statistics for rats and mice are in Appendices D and E.

Urinalysis Data

Table 14 presents the summary of the statistical analyses of the urinalysis data for mice. As can be seen, nonsignificant differences were found, most likely due to the small number of observations at each dosage level. The statistical analyses summaries for rat urinalysis data are presented in Table 13. Significant decreases were found in both male and female rat urine specific gravity. Examination of the individual rat data revealed two high values in the male control group which accounted for the higher mean.

Individual raw data and descriptive statistics for rats and mice are in Appendix H.

Organ Weight Data and Organ to Body Weight Ratios

A review of the data on Table 15 and Table 16, shows some significant differences in absolute organ weights for both mice and rats. These differences occurred randomly and are not considered to be compound related. As shown in Table 18, the liver to body weight ratios were elevated in the two high dose mouse groups (male and female) and in the female rats at the highest dose (Table 17). The kidney to body weight ratios were elevated for the mice. These may be compound related effects. No other compound related effects were suggested.

Table 19 shows that for rats, Week 12 body weights were significantly different than the final body weights, due to fasting of the rats. Although a comparison of Tables 17 and 20 shows only one difference in the significances of these relative organ weights (male pancreas), an examination of the individual ratios shows that those ratios based on final body weights were, for the most part, larger than those based on Week 12 body weights.

Individual raw data and descriptive statistics for rats and mice for organ weights are in Appendices F and G.

TABLE 13. SUMMARY OF STATISTICAL ANALYSES† OF URINALYSIS DETERMINATIONS FOR FISCHER 344 RATS EXPOSED TO MENTHYL CHLORIDE (90-DAY PILOT STUDY)

Parameter	Sex	ANOVA[a]	B[b]	K-W[c]	LSD[d]	x^2[e]
Specific Gravity	M	ns	ns			
	F	ns	ns			
pH	M	ns	ns			
	F	ns	ns			
Protein	M					+
	F					+
Glucose	M					ns
	F					ns
Ketones	M					ns
	F					ns
Occult Blood	M					ns
	F					ns
WBC	M					+
	F					+
RBC	M					ns
	F					ns
Casts	M					ns
	F					ns
Epith	M					+
	F					+
Mucus	M					ns
	F					ns
Sperm	M					ns
	F					ns
Bacteria	M					ns
	F					ns
Yeast	M					+
	F					+
Amorph	M					+
	F					+
Crystals	M					ns
	F					+

(a) One-Way Analysis of Variance.
(b) Bartlett test for homogeneity of variance.
(c) Kruskal-Wallis test (nonparametric equivalent to ANOVA).
(d) Least significant difference or nonparametric equivalent treatment versus control group comparisons. Numbers given indicate which treatment group means were found significantly higher (↑) or lower (↓) than their corresponding control group. Group 1 = 375 ppm, 2 = 750 ppm, 3 = 1500 ppm, 4 = control.
(e) Chi-square test.

ns = not significant * = significant
+ = expected frequencies too small
† = Urinalysis Statistical Data are located on pages H-1 through H-20

TABLE 14. SUMMARY OF STATISTICAL ANALYSES† OF URINALYSIS DETERMINATIONS $B_6C_3F_1$ MICE EXPOSED TO METHYL CHLORIDE (90-DAY PILOT STUDY)

Parameter	Sex	ANOVA[a]	B[b]	K-W[c]	LSD[d]	x^2[e]
Specific Gravity	M	*	*	*	1+, 2+, 3+	
	F	*	ns		1+, 2+	
pH	M	ns	ns			
	F	ns	ns			
Protein	M					+
	F					+
Glucose	M					ns
	F					ns
Ketones	M					ns
	F					ns
Occult Blood	M					+
	F					ns
WBC	M					+
	F					+
RBC	M					+
	F					+
Casts	M					+
	F					ns
Epith	M					+
	F					+
Mucus	M					ns
	F					ns
Sperm	M					ns
	F					ns
Bacteria	M					+
	F					+
Yeast	M					+
	F					+
Amorph	M					ns
	F					+
Crystals	M					+
	F					ns

(a) One-Way Analysis of Variance.
(b) Bartlett test for homogeneity of variance.
(c) Kruskal-Wallis test (nonparametric equivalent to ANOVA).
(d) Least significant difference or nonparametric equivalent treatment versus control group comparisons. Numbers given indicate which treatment group means were found significantly higher (+) or lower (+) than their corresponding control group. Group 1 = 375 ppm, 2 = 750 ppm, 3 = 1500 ppm, 4 = control.
(e) Chi-square test.

ns = not significant * = significant
+ = expected frequencies too small
† = Urinalysis Statistical Data are located on pages H-1 through H-20

TABLE 15. SUMMARY OF STATISTICAL ANALYSES† OF ABSOLUTE ORGAN WEIGHTS FOR FISCHER 344 RATS EXPOSED TO METHYL CHLORIDE (90-DAY PILOT STUDY)

Organ (g)	Sex	ANOVA[a]	B[b]	K-W[c]	LSD or[d] Equivalent
Heart	M	*	*	ns	
	F	ns	ns		
Adrenal	M	ns	ns		
	F	ns	ns		
Brain	M	ns	ns		
	F	*	*	*	3↓
Testis/ Ovary	M	*	ns		3↓
	F	ns	ns		
Spleen	M	*	*	*	3↓
	F	ns	ns		
Liver	M	*	ns		3↓
	F	ns	ns		
R. Kidney	M	*	ns		
	F	ns	ns		
L. Kidney	M	ns	ns		
	F	ns	ns		
Lungs	M	ns	ns		
	F	ns	ns		
Pancreas	M	ns	ns		
	F	*	ns		1↓, 2↓

[a] One-Way Analysis of Variance.

[b] Bartlett test for homogeneity of variance.

[c] Kruskal-Wallis test (nonparametric equivalent to ANOVA).

[d] Least significant difference or nonparametric equivalent treatment versus control group comparisons. Numbers given indicate which treatment group means were found significantly higher (↑) or lower (↓) than their corresponding control group. Group 1 = 375 ppm, 2 = 750 ppm, 3 = 1500 ppm, 4 = control.

ns = not significant
* = significant
† = Absolute Organ Weight Statistical Data are located on pages F-1 through F-15

TABLE 16. SUMMARY OF STATISTICAL ANALYSES† OF ABSOLUTE ORGAN WEIGHTS FOR $B_6C_3F_1$ MICE EXPOSED TO METHYL CHLORIDE (90-DAY PILOT STUDY)

Organ (g)	Sex	ANOVA[a]	B[b]	K-W[c]	LSD or[d] Equivalent
Heart	M	ns	ns		
	F	*	ns		3↑
Adrenal	M	ns	ns		
	F	ns	ns		
Brain	M	ns	ns		
	F	*	ns		1↓, 3↓
Testis/	M	ns	ns		
Ovary	F	ns	ns		
Spleen	M	ns	ns		
	F	*	*	*	3↓
Liver	M	ns	ns		3↑
	F	*	*	*	
R. Kidney	M	ns	ns		
	F	ns	ns		
L. Kidney	M	ns	ns		
	F	ns	ns		
Lungs	M	ns	ns		
	F	*	*	*	
Pancreas	M	*	*	ns	
	F	ns	ns		

(a) One-Way Analysis of Variance.
(b) Bartlett test for homogeneity of variance.
(c) Kruskal-Wallis test (nonparametric equivalent to ANOVA).
(d) Least significant difference or nonparametric equivalent treatment versus control group comparisons. Numbers given indicate which treatment group means were found significantly higher (↑) or lower (↓) than their corresponding control group. Group 1 = 375 ppm, 2 = 750 ppm, 3 = 1500 ppm, 4 = control.

ns = not significant
* = significant
† = Absolute Organ Weight Statistical Data are located on pages F-1 through F-15

TABLE 17. SUMMARY OF STATISTICAL ANALYSES† OF ORGAN WEIGHTS RELATIVE TO FINAL BODY WEIGHT FOR FISCHER 344 RATS EXPOSED TO METHYL CHLORIDE (90-DAY PILOT STUDY)

Organ	Sex	ANOVA[a]	B[b]	K-W[c]	LSD or[d] Equivalent
Heart/	M	ns	ns		
Final Wt.	F	*	ns		3↑
Adrenal/	M	ns	ns		
Final Wt.	F	*	*	*	
Brain/	M	ns	ns		
Final Wt.	F	ns	ns		
Testis	M	ns	ns		
Ovary/	F	*	*	ns	
Final Wt.					
Spleen/	M	ns	ns		
Final Wt.	F	ns	ns		
Liver/	M	ns	ns		
Final Wt.	F	*	*	*	3↑
R. Kidney/	M	ns	ns		
Final Wt.	F	ns	ns		
L. Kidney/	M	*	*	*	3↑
Final Wt.	F	ns	ns		
Lungs/	M	ns	ns		
Final Wt.	F	ns	ns		
Pancreas/	M	ns	ns		
Final Wt.	F	*	ns		3↑

[a] One-Way Analysis of Variance.

[b] Bartlett test for homogeneity of variance.

[c] Kruskal-Wallis test (nonparametric equivalent to ANOVA).

[d] Least significant difference or nonparametric equivalent treatment versus control group comparisons. Numbers given indicate which treatment group means were found significantly higher (↑) or lower (↓) than their corresponding control group. Group 1 = 375 ppm, 2 = 750 ppm, 3 = 1500 ppm, 4 = control.

ns = not significant
* = significant

TABLE 18. SUMMARY OF STATISTICAL ANALYSES† OF ORGAN WEIGHTS RELATIVE TO FINAL BODY WEIGHTS FOR $B_6C_3F_1$ MICE EXPOSED TO METHYL CHLORIDE (90-DAY PILOT STUDY)

Organ	Sex	ANOVA[a]	B[b]	K-W[c]	LSD or[d] Equivalent
Heart/ Final Wt.	M	*	ns		3↑
	F	*	ns		3↑
Adrenal/ Final Wt.	M	ns	ns		
	F	ns	ns		
Brain/ Final Wt.	M	ns	ns		
	F	ns	ns		
Testis	M	ns	ns		
Ovary/ Final Wt.	F	ns	ns		
Spleen/ Final Wt.	M	ns	ns		
	F	ns	ns		
Liver/ Final Wt.	M	*	ns		2↑, 3↑
	F	*	ns		2↑, 3↑
R. Kidney/ Final Wt.	M	ns	ns		3↑
	F	*	ns		
L. Kidney/ Final Wt.	M	ns	ns		3↑
	F	*	ns		
Lungs/ Final Wt.	M	ns	ns		
	F	*	*	*	
Pancreas/ Final Wt.	M	*	*	*	
	F	ns	ns		

[a] One-Way Analysis of Variance.
[b] Bartlett test for homogeneity of variance.
[c] Kruskal-Wallis test (nonparametric equivalent to ANOVA).
[d] Least significant difference or nonparametric equivalent treatment versus control group comparisons. Numbers given indicate which treatment group means were found significantly higher (↑) or lower (↓) than their corresponding control group. Group 1 = 375 ppm, 2 = 750 ppm, 3 = 1500 ppm, 4 = control.

ns = not significant
* = significant

† = Relative Organ Weight Statistical Data are located on pages G-1 through G-21

TABLE 19. SUMMARY OF STATISTICAL ANALYSES† OF ORGAN WEIGHTS RELATIVE TO BODY WEIGHT AT WEEK 12 FOR FISCHER 344 RATS EXPOSED TO METHYL CHLORIDE (90-DAY PILOT STUDY)

Organ	Sex	ANOVA[a]	B[b]	K-W[c]	LSD or[d] Equivalent
Heart/	M	ns	ns		
Week 12 Wt.	F	*	ns		3↑
Adrenal/	M	ns	ns		
Week 12 Wt.	F	ns	ns		
Brain/	M	ns	ns		
Week 12 Wt.	F	*	*	*	3↑
Testis	M	ns	ns		
Ovary/	F	ns	ns		
Week 12 Wt.					
Spleen/	M	ns	ns		
Week 12 Wt.	F	ns	ns		
Liver/	M	ns	ns		
Week 12 Wt.	F	*	*	*	3↑
R. Kidney/	M	ns	ns		
Week 12 Wt.	F	ns	ns		
L. Kidney/	M	*	*	*	3↑
Week 12 Wt.	F	ns	ns		
Lungs/	M	ns	ns		
Week 12 Wt.	F	ns	ns		
Pancreas/	M	*	ns		2↑, 3↑
Week 12 Wt.	F	*	ns		3↑

[a] One-Way Analysis of Variance.

[b] Bartlett test for homogeneity of variance.

[c] Kruskal-Wallis test (nonparametric equivalent to ANOVA).

[d] Least significant difference or nonparametric equivalent treatment versus control group comparisons. Numbers given indicate which treatment group means were found significantly higher (↑) or lower (↓) than their corresponding control group. Group 1 = 375 ppm, 2 = 750 ppm, 3 = 1500 ppm, 4 = control.

ns = not significant
* = significant

† = Relative Organ Weight Statistical Data are located on pages G-1 through G-21

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TABLE 20. SUMMARY OF STATISTICAL ANALYSES OF WEEK 12 VERSUS FINAL BODY WEIGHT FOR FISCHER 344 RATS EXPOSED TO METHYL CHLORIDE (90-DAY PILOT STUDY)

Group	Sex	Difference in Week 12 vs Final Mean Body Weight (g)	t-test
375 ppm	M	22.9	*
	F	19.0	*
750 ppm	M	19.6	*
	F	14.0	ns
1500 ppm	M	15.9	ns
	F	18.2	*
Control	M	28.8	*
	F	21.6	*

ns = not significant
* = significant ($p<0.05$)

Ophthalmoscopic Examination Data

The type and severity of the eye lesions observed in the rats in this methyl chloride study were such that these lesions were considered not to be compound related. The mice, however, had a high incidence of an eye lesions that began as a mucopurulent conjunctivitis and progressed until the animals' eyes were totally destroyed. Lesions of a similar nature have been seen in other groups of mice, but it was believed that the high incidence might well be supported by chemical exposure.

Table 21 lists the results of the ophthalmic examination data for both rats and mice.

Mortality

At the beginning of this pilot study we had in use a caging system with which we had little experience in group-housing mice. Very early in the study we had numerous mice that were traumatically killed during the process of handling the cages while loading and unloading the exposure chambers. The incidence of mortality is shown on Table 21.

TABLE 21. OPHTHALMIC EXAMINATIONS
METHYL CHLORIDE 90-DAY STUDY

Animal Number	Pre-exposure Right Eye	Pre-exposure Left Eye	Post-exposure Right Eye	Post-exposure Left Eye
Group 1 375 ppm Male Mice				
M22	N	N	Dead	--
M24	N	N	N	N
M26	N	N	N	N
M31	N	N	N	N
M33	N	N	N	N
M34	N	N	Mucopurulent Conjunctivitis Eye is missing	N
M36	N	N	N	Mucopurulent Conjunctivitis Eye is missing
M37	N	N	N	N
M63	N	N	N	N
M76	N	N	Mucopurulent Conjunctivitis Eye is missing	N
Group 1 375 ppm Female Mice				
M10	N	N	N	N
M16	N	N	Mucopurulent Conjunctivitis Eye is missing	Mucopurulent Conjunctivitis Eye is missing
M43	N	N	N	Mucopurulent Conjunctivitis Eye is missing
M44	N	N	Corneal Opacity	N
M49	N	N	N	N
M56	N	N	Dead*	—
M57	N	N	Dead*	--
M58	N	N	Dead	—
M59	N	N	Mucopurulent Conjunctivitis Eye is missing	N
M60	N	N	Mucopurulent Conjunctivitis Eye is missing	N

M = Mouse, N = Normal

* = Dead due to trauma

TABLE 21. (Continued)

Animal Number	Pre-exposure Right Eye	Pre-exposure Left Eye	Post-exposure Right Eye	Post-exposure Left Eye
Group 2 750 ppm Male Mice				
M23	N	N	Mucopurulent Conjunctivitis Eye is missing	Corneal Opacity
M27	N	N	N	N
M39	N	N	N	Mucopurulent Conjunctivitis Eye is missing
M61	N	N	N	N
M62	N	N	N	N
M66	N	N	N	N
M69	N	N	Dead	--
M70	N	N	N	N
M74	N	N	Dead*	--
M79	N	N	N	N
Group 2 750 ppm Female Mice				
M4	N	N	Severe Purulent Conjunctivitis Globe is totally missing	N
M5	N	N	N	Mucopurulent Conjunctivitis Eye is missing
M8	N	N	N	N
M13	N	N	Dead	--
M14	N	N	N	N
M41	N	N	N	N
M45	N	N	Corneal Opacity	N
M47	N	N	N	N
M48	N	N	N	N
M50	N	N	N	N
Group 3 1500 ppm Male Mice				
M21	N	N	Dead*	--
M28	N	N	N	N

M = Mouse, N = Normal

* = Dead due to trauma

TABLE 21. (Continued)

Animal Number	Pre-exposure Right Eye	Pre-exposure Left Eye	Post-exposure Right Eye	Post-exposure Left Eye
M32	N	N	Dead*	—
M38	N	N	Dead*	—
M40	N	N	N	N
M67	N	N	Dead*	—
M68	N	N	Dead*	—
M71	N	N	N	N
M72	N	N	Dead*	—
M78	N	N	Dead*	—
Group 3 1500 ppm Female Mice				
M2	N	N	N	N
M11	N	N	N	N
M17	N	N	N	N
M18	N	N	N	N
M20	N	N	N	N
M42	N	N	N	N
M46	N	N	N	N
M52	N	N	N	N
M53	N	N	N	N
M55	N	N	N	N
Group 4 Control Male Mice				
M25	N	N	Lens is totally opaque	N
M29	N	N	N	N
M30	N	N	N	N
M35	N	N	N	N
M64	N	N	N	N
M65	N	N	Dead*	—
M73	N	N	Dead	—
M75	N	N	N	N
M77	N	N	Dead*	—
M80	N	N	N	N

M = Mouse, N = Normal
* = Dead due to trauma

TABLE 21. (Continued)

Animal Number	Pre-exposure Right Eye	Pre-exposure Left Eye	Post-exposure Right Eye	Post-exposure Left Eye
Group 4 Control Female Mice				
M1	N	N	N	N
M3	N	N	N	N
M6	N	N	Dead	--
M7	N	N	N	N
M9	N	N	N	N
M12	N	N	N	N
M15	N	N	N	N
M19	N	N	N	N
M51	N	N	Dead*	--
M54	N	N	N	N
Group 1 375 ppm Male Rats				
R22	N	N	N	N
R24	N	N	N	N
R26	N	N	N	N
R31	N	N	N	N
R33	N	N	N	N
R34	N	N	N	N
R36	N	N	N	N
R37	N	N	N	N
R63	N	N	N	N
R76	N	N	N	N
Group 1 375 ppm Female Rats				
R10	N	N	N	N
R16	N	N	N	N
R43	N	N	N	N
R44	N	N	N	N
R49	N	N	N	N
R56	N	N	N	N
R57	N	N	N	N
R58	N	N	N	N
R59	N	N	N	N
R60	N	N	N	N

M = Mouse, R = Rat, N = Normal
* = Dead due to trauma

TABLE 21. (Continued)

Animal Number	Pre-exposure Right Eye	Pre-exposure Left Eye	Post-exposure Right Eye	Post-exposure Left Eye
Group 2 750 ppm Male Rats				
R23	N	N	N	N
R27	N	N	N	N
R39	N	N	N	N
R61	N	N	N	N
R62	N	N	N	N
R66	N	N	N	N
R69	N	N	N	N
R70	N	N	N	N
R74	N	N	N	N
R79	N	N	N	N
Group 2 750 ppm Female Rats				
R4	N	N	N	N
R5	N	N	N	N
R8	N	N	N	N
R13	N	N	N	N
R14	N	N	N	N
R41	N	N	N	N
R45	N	N	N	N
R47	N	N	N	N
R48	N	N	N	N
R50	N	N	N	N
Group 3 1500 ppm Male Rats				
R21	N	N	N	N
R28	N	N	N	N
R32	N	N	N	N
R38	N	N	N	N
R40	N	N	N	N
R67	N	N	N	N
R68	N	N	N	N
R71	N	N	N	N
R72	N	N	N	N
R78	N	N	N	N

R = Rat, N = Normal

TABLE 21. (Continued)

Animal Number	Pre-exposure Right Eye	Pre-exposure Left Eye	Post-exposure Right Eye	Post-exposure Left Eye
Group 3 1500 ppm Female Rats				
R2	N	N	N	N
R11	N	N	N	N
R17	N	N	N	N
R18	N	N	N	N
R20	N	N	N	N
R42	N	N	N	Slight Corneal Opacity
R46	N	N	N	N
R52	N	N	N	N
R53	N	N	N	N
R55	N	N	N	N
Group 4 Control Male Rats				
R25	N	N	N	N
R29	N	N	N	N
R30	N	N	N	N
R35	N	N	N	N
R64	N	N	N	N
R65	N	N	N	N
R73	N	N	N	N
R75	N	N	N	N
R7	N	N	N	N
R80	N	N	N	N
Group 4 Control Female Rats				
R1	N	N	N	N
R3	N	N	N	N
R6	N	N	N	N
R77	N	N	N	N
R9	N	N	N	N
R12	N	N	N	N
R15	N	N	N	N
R19	N	N	N	N
R51	N	N	N	N
R54	N	N	N	N

R = Rat, N = Normal

Pathology Data

Mice. The microscopic lesions observed in mice from control and high-dose (1500 ppm) treatment groups are listed in Tables 22 and 23. The microscopic hepatic lesions observed in mice from the 750 ppm treatment group are listed in Tables 24 and 25.

Cytoplasmic vacuolar change of hepatocytes was observed in 37% of the control mice and 64% of the high-dose treated mice. The severity of this change was mild in six of the seven affected livers from the control group and was moderate in the remaining liver (Table 22). The livers of nine animals were affected in the high-dose group (Table 22); the change was mild in two animals, moderate in five animals, and marked in the remaining animal (Table 23). Cytoplasmic vacuolar change of hepatocytes occurred in 7 of 18 mice in the 750 ppm group. The change was similar in incidence and severity to that observed in the control group. The change occurred five times more frequently in females than males in the 750 ppm group. A similar sex predisposition was observed in the control and high-dose groups (Table 22 and 25).

An hepatic infarct was observed in one male in the high-dose (1500 ppm) treatment group. Hepatocytes adjacent to the infarcted area and in other paraportal areas throughout liver sections from this animal were hyperchromatic. The cytoplasm of the affected cells stained intensely eosinophilic and the nuclei were intensely basophilic.

The relative liver weights were increased for both males and females at both the 750 and 1500 ppm treatment groups.

Rats. The microscopic lesions observed in the rats from the control and high-dose (1500 ppm) treatment groups are listed in Tables 26 and 27. The microscopic hepatic lesions observed in rats from the 750 ppm treatment group are listed in Tables 28 and 29.

Massive infarction of the liver with a circumferential zone of congestion was observed in one rat in the high-dose treatment group (Table 27).

Discussion

Mice and Rats. The increased severity of the cytoplasmic vacuolar change in the hepatocytes from mice in the high-dose group

(1500 ppm) was considered to be a compound-related lesion. This conclusion was based on the increased severity and mild increased incidence of the change in the high-dose group when compared to the control group. The significance of the higher rate of occurrence of this change in female mice in all treatment groups was not determined.

The occurrence of hepatic infarction in one mouse was considered to be of questionable significance; however, hepatic infarction was also observed in a rat from the high-dose group (1500 ppm, Table 27). It was our opinion that the occurrence of a spontaneous lesion of this nature in two animals in the high-dose group, although of differing species, is highly unlikely and therefore was considered to be a compound-related lesion. All of the other lesions observed in rats and mice from the 1500 ppm treatment group and the changes observed in the livers of the animals in the 750 ppm treatment group were changes which were observed with similar frequency in the control group and/or are changes which are commonly found in untreated, laboratory-reared rats and mice and were interpreted as spontaneous changes.

Raw data for this study is stored in the BCL Biological, Ecological and Medical Sciences Department Archives.

TABLE 22. FREQUENCY OF LESIONS OCCURRING IN DIFFERENT TREATMENT GROUPS, MICE

Treatment Group	Control		1500 ppm	
Sex	M	F	M	F
Number/Sex Group	9	10	6	8
Adrenal glands, congestion, perimedullary		2		6
Bone marrow, myeloid hyperplasia		1		
Brain, multifocal hemorrhage		1		
Brain, congestion	1			
Eye, periorbital hemorrhage and inflammation	1	2		4
Heart, pigmentation of AV valves	4	3		2
Heart, myocardial degeneration			1	
Kidney, interstitial nephritis	3	1		
Liver, degeneration, focal mineralization		1		
Liver, cytoplasmic vacuolar change	1	6	2	7
Liver, subacute/chronic hepatitis	1	3		
Liver, congestion	1	2		
Liver, increased nuclear size, increased prominent nucleoli			2	1
Liver, infarct			1	
Lung, congestion	3	10	3	3
Lung, lymphoid hyperplasia	2	2		1
Lung, interstitial pneumonia		1		
Lung, bronchopneumonia	1	1		
Lymph node, congestion	2	3		
Pituitary, congestion			1	
Skeletal muscle, focal degeneration		1		
Skin, sebaceous gland hyperplasia		1		

TABLE 23. INCIDENCE AND SEVERITY* OF LESIONS OBSERVED, MICE**

Treatment Group	Control																				1500 ppm														
Animal No.	1	3	6	7	9	12	15	19	25	29	30	35	51	54	64	73	75	77	80		2	11	17	18	21	28	32	40	46	52	53	55	71	72	
Pathology No.	780983	780985	780988	780989	780991	780994	780997	781001	781007	781011	781012	781017	781033	781036	781046	781055	781057	781059	781062		780984	780993	780999	781000	781003	781010	781014	781022	781028	781034	781035	781037	781053	781054	
Sex	F	F	F	F	F	F	F	F	M	M	M	M	F	F	M	M	M	M	M		F	F	F	F	M	M	M	M	F	F	F	F	M	M	
Adrenal gland, congestion, perimedullary				2			2														2	2		2						2	1	1			
Bone marrow, myeloid hyperplasia			2																																
Brain, multifocal hemorrhage													1																						
Brain, congestion																		1																	
Eye, periorbital hemorrhage and/or inflammation		2							2					2							2	2									1	1			
Heart, pigmentation of AV valves				1		2		2	2			1				1		2						1						2					
Heart, myocardial degeneration																																	2		
Kidney, interstitial nephritis	1								1	1					2																				
Liver, mineralized degeneration	1																																		
Liver, cytoplasmic vacuolar change		1		1	1	1					2					1			1		2	2	2	1		3			2		2	1	2		
Liver, subacute hepatitis, chronic					2								1			2			2																
Liver, congestion							1						1					2																	
Liver, increased nuclear size, increased prominent nucleoli																										3					2		2		
Liver, infarct	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		-	-	-	-	-	-	-	+	-	-	-	-	-	-	
Lung, congestion	1	1	2	3		1	2	2			1	1	1	1			1		2			1		1	1	1		2				2			
Lung, lymphoid hyperplasia								1	1		1			1										1											
Lung, interstitial pneumonia													1																						
Lung, bronchopneumonia													2					1																	
Lymph node, congestion							1			1			1	2		1																			
Pituitary, congestion																									1										
Skeletal muscle, focal degeneration	1																																		
Skin, sebaceous gland hyperplasia	1																																		

* 0 = no involvement, 1 = mild, 2 = moderate, 3 = marked, 4 = severe; + = present, - = not present.

** Missing animals: 1500 ppm group-67M, 68M, 20F, 42F; control group-65M.

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TABLE 24. INCIDENCE AND SEVERITY OF HEPATIC LESIONS IN MICE, 750 ppm TREATMENT GROUP

	780986	780987	780990	780995	780996	781005	781009	781021	781023	781027	781029	781030	781032	781043	781044	781048	781052	781061
Animal Number	4	5	8	13	14	23	27	39	41	45	47	48	50	61	62	66	70	79
Sex	F	F	F	F	F	M	M	M	F	F	F	F	F	M	M	M	M	M
Liver, cytoplasmic vacuolar change	1*	1	1		1			1				1	1					
Liver, eosinophilic inflammation			1															
Liver, basophilia of centrilobular hepatocytes				1			1	1						1			1	
Liver, crystalline material in hepatocytes				1														
Subacute hepatitis								1	1									
Chronic hepatitis											1							

* 1 = mild.

000073

TABLE 25. FREQUENCY OF HEPATIC LESIONS OCCURRING IN MICE, 750 ppm TREATMENT GROUP

	Sex	M	F
	Number/Sex Group	8	10
Liver, cytoplasmic vacuolar change		1	6
Liver, eosinophilic inflammation			1
Liver, basophilia of centrilobular hepatocytes		4	1
Liver, crystalline material in hepatocytes			1
Subacute hepatitis		1	1
Chronic hepatitis			1

TABLE 26. FREQUENCY OF LESIONS OCCURRING IN DIFFERENT TREATMENT GROUPS, RATS

Treatment Group	Control		1500 ppm	
Sex	M	F	M	F
Number/Sex Group	10	10	10	10
Adrenal glands, congestion		1		
Bone marrow, hypoplasia, femur			1	
Eye, periorbital hemorrhage		1		
Heart, focal, chronic myocarditis	1	1	2	
Heart, chronic myocarditis	1			
Heart, focal myocardial hemorrhage			1	
Intestine, nematodiasis	2	1	2	3
Kidney, vacuolar cytoplasmic change, tubular	1			
Kidneys, interstitial nephritis	2		1	
Kidney, cystic				1
Kidney, tubular mineralization, degeneration				2
Kidney, tubular cast		1	4	
Liver, subacute, chronic hepatitis	2	3		
Liver, hepatic necrosis, acute inflammation		1		
Liver, hepatic necrosis, infarct				1
Liver, centrilobular degeneration				1
Liver, nuclear hyperchromism			1	
Lungs, peribronchiolar lymphoid hyperplasia	6	6	4	4
Lungs, mineralization of small arteries	1			
Lungs, interstitial pneumonia	4	1		
Lungs, congestion	3	3	2	1
Lymph nodes, congestion	3	5	3	4
Prostate, focal, acute prostatitis	1			
Seminal vesicles, acute inflammation			1	
Spinal cord, neuronal vacuolation		1	2	
Testes, testicular necrosis and mineralization	1			
Thymus, congestion			1	1

TABLE 27. INCIDENCE AND SEVERITY* OF LESIONS OBSERVED, RATS

Treatment Group	Control																					1500 ppm																				
Animal No.	1	3	6	7	9	12	15	19	25	29	30	35	51	54	64	65	73	77	80	75	2	11	17	18	20	21	28	32	38	40	42	46	52	53	55	67	68	71	72	78
Pathology No.	781143	781145	781148	781149	781151	781154	781157	781161	781167	781171	781172	781177	781193	781196	781206	781207	781215	781219	781222	781227	781144	781153	781159	781160	781162	781163	781170	781174	781180	781182	781184	781188	781194	781195	781197	781209	781210	781213	781214	781220
Sex	F	F	F	M	F	F	F	F	M	M	M	M	F	F	M	M	M	F	M	M	F	F	F	F	F	F	M	M	M	M	F	F	F	F	F	M	M	M	M	M
Adrenal glands, congestion														2																										
Bone marrow hypoplasia, femur																																							2	
Eye, periorbital hemorrhage								2																																
Heart, focal, chronic myocarditis		1														1													1	1										
Heart, chronic myocarditis											1																													
Heart, focal myocardial hemorrhage																																							2	
Intestines, nematodiasis	-	-	-	-	-	+	-	-	-	-	-	+	-	-	+	-	-	-	-	-	-	-	-	-	+	-	-	-	-	+	-	-	+	+	-	-	-	+	-	-
Kidney, vacuolar cytoplasmic change, tubular				2																																				
Kidney, interstitial nephritis										1	1																									1				
Kidney, cystic																							2																	
Kidney, tubular mineralization, degeneration																															1				2					
Kidney, tubular cast																	2											1	1	2								1		
Liver, subacute, chronic hepatitis	2				2				1							1	1																							
Liver, hepatic necrosis, acute inflammation																		2																						
Liver, hepatic necrosis, infarct																							2																	
Liver, centrilobular degeneration																									2															
Liver, nuclear hyperchromism																																								1
Lung, peribronchiolar lymphoid hyperplasia	1		2				2	1	1	1	1	2	1		1	1	1					1	1	1	1				1	1						1		1		

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TABLE 27. (Continued)

Treatment Group	Control																					1500 ppm																				
Animal No.	1	3	6	7	9	12	15	19	25	29	30	35	51	54	64	65	73	77	80	75	2	11	17	18	20	21	28	32	38	40	42	46	52	53	55	67	68	71	72	78
Pathology No.	781143	781145	781148	781149	781151	781154	781157	781161	781167	781171	781172	781177	781193	781196	781206	781207	781215	781219	781222	781227	781144	781153	781159	781160	781162	781163	781170	781174	781180	781182	781184	781188	781194	781195	781197	781209	781210	781213	781214	781220
Sex	F	F	F	M	F	F	F	F	M	M	M	M	F	F	M	M	M	F	M	M	F	F	F	F	F	F	M	M	M	M	F	F	F	F	F	M	M	M	M	M
Lung, mineralization of small arteries				1																																				
Lung, interstitial pneumonia				2		1				2					2	1																								
Lungs, congestion						2			2			2		1	1			1										1	2		2									
Lymph nodes, congestion and/or hemorrhage						2	1	1	1	1			2				1			1				1	2								1		1		2		1	2
Prostate, prostatitis, focal, acute															1																									
Seminal vesicles, acute inflammation																																						2		
Spinal cord, neuronal vacuolation																	1																					1		2
Testes, testicular necrosis and mineralization											2																													
Thymus, congestion																															1							1		

* 0 = no involvement, 1 = mild, 2 = moderate, 3 = marked, 4 = severe; + = present, - = not present.

000077

TABLE 28. INCIDENCE AND SEVERITY OF HEPATIC LESIONS IN RATS, 750 ppm TREATMENT GROUP

	781146	781147	781150	781155	781156	781163	781169	781181	781183	781187	781189	781190	781192	781203	781204	781208	781211	781212	781216	781221
Animal Number	4	5	8	13	14	23	27	39	41	45	47	48	50	61	62	66	69	70	74	79
Sex	F	F	F	F	F	M	M	M	F	F	F	F	F	M	M	M	M	M	M	M
Chronic hepatitis			1*					1				1		1		1	1		1	

* 1 = mild.

000078

TABLE 29. FREQUENCY OF HEPATIC LESIONS OCCURRING IN RATS, 750 ppm TREATMENT GROUP

	Sex Number/Sex Group	M 10	F 10
Chronic hepatitis		5	2

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APPENDIX A

TEST PROTOCOL FOR 90-DAY PILOT STUDY WITH METHYL CHLORIDE

A. OBJECTIVE

To establish the range of concentrations of atmospheric methyl chloride which cause exposure toxicity in rats and mice within a ninety day calendar period.

B. MATERIALS AND METHODS

1. Experimental Animals: Eighty healthy Fischer 344 rats and eightly $B_6C_3F_1$ mice, equally divided by sex, will be randomly assigned into four equal groups, 10/sex/group. Each group will be designated for high, intermediate or low level exposure, or control, and housed in stainless steel cages with wire bottoms, no more than 5 per cage. Animals are to be offered a standard laboratory diet plus water ad libitum except during inhalation exposure.

2. Method of Exposure: The animals will be exposed 6 hours per day, 5 days per week, excluding holidays, for a period of 13 weeks, in inhalation chambers of stainless steel and glass, each chamber having a nominal volume of about 8.0 cubic meters. The chambers will be rectangular in shape with pyramid-shaped tops and bottoms, and demonstrated to have a uniform distribution of the test atmosphere.

The chambers will be provided with clean, conditioned air at a rate of 10-15 air changes per hour, with the air drawn through the bottom of the chamber by an exhaust fan and scrubbed and diluted if necessary by a second fan before venting to the atmosphere. Chamber temperature and relative humidity will be maintained at $70^{o}F \pm 5^{o}$ and 40 to 50%, respectively, and verified by direct measurement at least three times daily. All chambers, except those housing untreated control animals are to be maintained at a slight negative pressure relative to the outside air.

Chambers containing untreated control animals are maintained at a slight positive pressure to prevent cross contamination.

The methyl chloride is introduced into the chamber air supply duct and mixes with the incoming air by turbulence. Target concentrations in each test chamber will be carefully regulated by adjusting the rate at which the compressed gas flows from a cylinder.

3. Chamber Monitoring: Continuous or semihourly analyses of test material concentrations and possible impurities or contaminants will be conducted on air samples collected from representative positions within each exposure chamber. Uniform distribution of the desired methyl chloride concentrations within the chambers will be verified prior to initiating the first animal exposure. Maximum allowed deviation in gas concentration will be ± 10 percent of the target concentration for any area in the chamber where animals are likely to be located.

(The investigating laboratory will propose the analytical methods and offer details of instrumentation, calibration and methodology for approval by CIIT before animal exposure begins.)

4. Animal Observations: All animals will be observed twice daily and a record kept of dead or moribund animals. Weekly records will be maintained of gross signs of systemic toxicity and/or pharmacologic effects. Direct ophthalmoscopic examination of all animals will be made before treatment and immediately before necropsy.

On the first day of test exposures, all animals are weighed individually or by cage groups. Body weights are then taken by the same system at 1-week intervals with the final body weight being recorded immediately prior to sacrifice. Weekly, as

well as final body weights, and total weight changes over the intervals are subjected to standard analysis of variance.

Fresh diets are offered daily and consumption measured as follows: Each rodent cage (5 animals per cage) is supplied with a fresh jar of food after the inhalation exposure is finished. The food is left in the cage overnight and removed before exposure begins the following day. By following this procedure daily, weekly food consumption data for rodents can be estimated.

5. Clinical Studies: The following hematology and clinical chemistry analyses will be conducted using blood samples collected after an overnight fast from all animals at 13 weeks (prior to sacrifice):

Glucose	Red Cell Count	Urinalysis (16 hr collection)
Blood Urea Nitrogen	White Cell Count	a) Glucose b) Ketones
SGOT/SGPT	Differential	c) Bile Pigments d) Volume
Alkaline Phosphatase	Hematocrit	e) Color f) Appearance of Microscopic Sediment
Creatine Phosphokinase	Hemoglobin	g) Specific Gravity
Reticulocyte Counts		h) Protein

6. Pathologic Studies: Arrangements should be made to subject any animal which might become moribund or die during the test to gross pathologic examination as soon as possible. Also, in those cases in which postmortem changes are judged to be not advanced, sections or representative tissues and organs will be taken and stored for possible histopathologic study.

Following the termination of exposures, each surviving animal will be anesthesized, immediately exsanguinated and subjected to a complete gross pathologic examination. The organs and tissues listed (Table I) will be taken from each animal, weighed and specimens fixed in 10% neutral buffered formalin. Tissues from the untreated control and high exposure groups will be trimmed, sectioned, stained and submitted to the

TABLE I

PATHOLOGIC EXAMINATION

TISSUE	OBSERVATIONS TO BE MADE: ORGAN WEIGHT	GROSS EXAM	MICROSCOPIC EXAM*
Brain (cerebellum, cerebrum, stem)	X	X	X**
Spinal cord		X	X**
Peripheral nerve (sciatic)		X	X**
Eyes	-	X	X
Pituitary		X	X
Thyroid		X	X
Parathyroid		X	X
Salivary glands (submaxillary)		X	X
Heart	X	X	X
Lungs	X	X	X
Spleen	X	X	X
Liver	X	X	X
Pancreas		X	X
Adrenals	X	X	X
Lymph nodes (mediastinal, cervical, laryngeal, bronchial)		X	X
Kidneys	X	X	X
Bladder		X	X
Prostate		X	X
Testes	X	X	X
Ovaries		X	X
Uterus		X	X
Fallopian tubes		X	X
Stomach		X	X
Small intestines - 3 levels		X	X
Large intestines - 3 levels		X	X
Skeletal muscle (thigh)		X	X
Skin (flank)		X	X
Mammary gland		X	X
Any gross lesion		X	X
Bone marrow		X	X
Adipose tissue		X	X
Aorta		X	X
Nasal turbinate		X	X
Trachea		X	X
Ear canal***		X	X
Tibial and plantal nerves***		X	X
Lumbar sacral and dorsal ganglia***		X	X**

* Control, high test level. Other levels if indicated
** Special stains to determine if neuropathological changes have occurred.
*** If clinical signs indicate.

pathologist for histopathologic examination. In the event that signifcant findings appear in the high dose group, the next lower dose group will also be examined histopathologically for similar or other effects.

7. Statistical Evaluation: Quantitative data should be statistically evaluated by analysis of variance and mean difference assessed by appropriate intra group comparisons (e.g., Tukey's Procedure). Comparisons will ordinarily be limited to within-sex analysis unless a scientific rationale supports a combination. The level of probability to be chosen shall be $p<0.05$. For evaluation of mean difference a "two tail" distribution should be used. Frequency data, such as incidences of mortality or micropathological conditions will be inter-compared by appropriate Chi-square analysis.

8. Reports: A draft report (5 copies) including histopathologic evaluation will be submitted to CIIT within 8 weeks of the terminal sacrifice. A final report (5 copies) including summary tables, mean body weights, laboratory data, mortality, gross and microscopic findings will be submitted to CIIT within 10 weeks of termination. Gross and histopathologic data, negative and positive, should be presented in a tabular form so that lesions can be traced to the animal in which they were observed. All copies will present individual body weights, hematology, clinical chemistry, urinalysis and organ weight data as an appendix.

APPENDIX B

BODY WEIGHT DATA

TABLE 1. BODY WEIGHT DATA FOR MALE RATS

Treatment Group	Animal ID	Initial	Weeks 1	2	3	4	5	6	7	8	9	10	11	12	13
1	22	195	196	212	228	208	234	242	238	258	249	278	280	289	248
1	24	161	157	179	196	205	215	216	223	241	249	252	259	278	246
1	28	177	164	181	208	229	225	218	244	238	260	268	272	281	249
1	31	181	167	197	213	227	237	248	256	258	271	277	285	291	244
1	33	172	167	186	218	225	231	244	252	259	275	273	283	291	278
1	34	181	165	197	212	218	225	245	243	260	271	248	284	288	244
1	36	167	171	185	194	208	221	222	238	231	247	257	263	272	249
1	37	162	162	195	203	193	209	216	225	239	242	244	253	262	248
1	43	168	168	176	195	208	220	232	227	245	241	261	244	277	247
1	78	171	165	188	195	201	208	210	218	223	232	232	258	249	224
2	23	149	142	198	216	228	244	245	253	263	278	273	285		246
2	27	176	177	201	218	224	237	243	258	256	244	258	278		243
2	30	152	174	149	202	216	225	226	233	243	249	252	268	265	268
2	61	197	188	195	205	212	223	226	225	233	243	250	257	254	242
2	62	157	166	176	185	206	209	205	213	217	227	233	248	246	224
2	66	183	172	191	195	208	214	218	226	231	244	247	252	258	228
2	69	196	193	202	208	218	214	221	236	244	253	268	269	273	244
2	70	188	198	186	198	207	208	219	223	228	238	244	252	252	233
2	76	158	141	197	203	196	225	226	235	239	258	257	278	272	246
2	79	181	172	195	201	217	221	227	238	250	268	264	269	278	248
3	21	185	192	203	206	214	221	225	225	232	238	248	239	241	228
3	29	164	174	184	191	199	203	201	206	205	212	211	217	211	195
3	32	179	176	198	199	214	217	214	224	238	237	241	258	253	228
3	38	142	148	185	192	195	201	192	198	197	202	209	269	215	185
3	44	171	174	142	187	196	208	208	205	204	207	206	212	214	195
3	67	179	173	182	187	205	207	212	219	218	224	231	238	236	248
3	68	183	172	188	183	191	193	203	207	207	208	218	216	222	241
3	71	201	191	208	218	214	218	219	228	227	235	233	244	244	208
3	72	188	198	189	177	198	189	196	206	185	194	216	222	241	184
3	78	183	168	177	183	198	196	197	208	204	198	207	212	215	195
4	25	172	178	184	208	206	222	238	240	247	281	278	274	385	246
4	29	167	122	175	199	216	248	242	254	257	282	272	284	384	
4	30	179	141	143	204	228	237	241	258	258	248	277	275	317	241
4	35	176	175	188	204	218	224	234	243	247	228	268	279	251	244
4	64	179	176	198	205	218	235	246	249	262	271	271	278	308	241
4	65	178	151	194	202	216	227	215	238	260	251	283	289	295	276
4	73	163	147	183	217	235	251	265	278	288	283	295	299	318	279
4	75	187	194	199	218	231	249	263	272	285	281	246	315	384	294
4	77	182	184	196	218	228	237	250	264	269	279	283	295	302	274
4	84	181	184	197	215	224	239	248	236	267	288	281	294	308	277

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TABLE 2. BODY WEIGHT DATA FOR FEMALE RATS

Treatment Group	Animal ID	Initial	Weeks 1	2	3	4	5	6	7	8	9	10	11	12	13
1	10	116	114	119	125	131	140	146	148	154	159	159	166	170	170
1	14	120	114	120	131	139	145	156	159	164	169	173	172	170	161
1	43	131	116	120	145	150	156	161	160	166	172	173	186	181	164
1	44	127	120	131	140	147	153	157	160	165	172	174	180	180	161
1	49	123	122	131	130	150	156	157	167	169	175	175	176	166	162
1	54	126	117	133	140	144	151	153	159	164	166	169	168	172	153
1	47	132	110	127	137	139	150	152	155	154	166	167	167	172	155
1	54	124	119	125	134	140	153	159	161	162	169	162	177	179	158
1	59	134	130	136	146	157	167	169	173	176	181	182	186	190	170
1	60	126	121	130	136	146	146	160	165	168	172	172	176	186	166
2	6	124	122	128	138	140	153	153	159	163	166	171	175		165
2	9	120	123	123	127	129	138	137	141	150	155	152	159	161	145
2	9	120	123	133	139	146	155	158	161	165	171	170	175	176	157
2	13	124	115	130	134	139	150	153	158	161	163	171	172	174	155
2	16	123	125	131	137	146	152	152	154	162	168	164	170	177	155
2	41	121	115	123	129	127	138	133	143	151	158	162	167	162	148
2	45	124	124	126	139	146	153	153	158	161	168	166	166	173	155
2	47	126	127	135	140	150	153	157	164	152	173	171	177	176	160
2	49	128	127	133	137	136	149	150	157	165	166	169	175	177	157
2	50	126	96	116	127	136	142	143	146	151	151	156	156	156	153
3	2	126	123	130	135	137	132	137	143	147	156	156	160	161	162
3	11	122	132	129	130	128	136	137	143	149	150	156	157	160	162
3	17	120	127	131	141	140	142	145	150	151	153	156	165	166	160
3	18	112	118	117	118	124	123	132	137	139	140	144	141	137	
3	20	121	116	125	126	137	138	139	141	146	148	144	156	155	137
3	42	131	120	132	135	142	140	151	153	160	164	164	168	170	166
3	46	117	125	123	127	129	136	140	144	148	159	152	155	157	148
3	52	124	116	124	126	134	131	132	144	146	145	148	155	153	148
3	53	125	123	125	136	141	141	143	147	149	146	149	158	156	136
3	55	116	113	120	123	125	126	131	134	137	131	136	140	144	124
4	1	123	98	127	133	140	144	155	158	158	165	164	171	175	159
4	3	126	135	134	146	151	157	166	170	169	165	177	181	178	
4	4	123	119	132	139	145	152	154	157	168	168	170	179	176	145
4	7	122	122	132	140	144	153	160	167	167	171	178	186	184	159
4	9	121	114	131	137	144	150	157	162	165	152	178	172	164	153
4	12	114	114	122	133	138	148	154	161	161	172	169	177	183	146
4	15	134	142	146	156	168	178	180	183	190	178	186	166	187	170
4	19	120	128	121	138	139	147	154	168	162	178	169	173	186	154
4	51	130	136	137	144	152	161	169	179	180	155	195	199	163	157
4	54	121	123	124	135	140	146	150	163	165	177	177	178	168	163

000090

TABLE 3. STATISTICAL ANALYSIS OF WEEKLY BODY WEIGHT DATA

Initial Body Weight

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	173.5000	10.3091	3.2600	161.0000	195.0000
750 ppm	10	178.1000	13.3621	4.2259	157.0000	197.0000
1500 ppm	10	180.7000	9.5579	3.0223	154.0000	201.0000
CONTROL	10	176.2000	7.2541	2.2940	163.0000	187.0000
TOTAL	40	177.1250			157.0000	201.0000
	UNGROUPED DATA		10.2906	1.6283		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	125.9000	5.5267	1.7477	116.0000	134.0000
750 ppm	10	123.6000	2.6750	.8459	120.0000	128.0000
1500 ppm	10	122.1000	6.2263	1.9689	112.0000	131.0000
CONTROL	10	123.5000	6.7074	2.1211	114.0000	139.0000
TOTAL	40	123.8750			112.0000	139.0000
	UNGROUPED DATA		5.4687	.8647		

Week 1

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	166.2000	7.4952	2.3702	157.0000	184.0000
750 ppm	10	178.6000	9.7091	3.0703	158.0000	193.0000
1500 ppm	10	178.9000	8.9001	2.8144	168.0000	192.0000
CONTROL	10	164.8000	23.4755	7.4249	122.0000	194.0000
TOTAL	40	172.1250			122.0000	194.0000
	UNGROUPED DATA		15.8166	2.3743		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	118.9000	5.0211	1.5878	112.0000	130.0000
750 ppm	10	119.1000	9.8933	3.1285	94.0000	127.0000
1500 ppm	10	120.7000	7.2119	2.2806	110.0000	132.0000
CONTROL	10	120.5000	14.8193	4.6863	90.0000	142.0000
TOTAL	40	119.8000			90.0000	142.0000
	UNGROUPED DATA		9.5788	1.5145		

Week 2

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	189.6000	10.6999	[illegible]	176.0000	212.0000
750 ppm	10	193.2000	7.6565	[illegible]	176.0000	202.0000
1500 ppm	10	187.2000	8.4956	2.6866	177.0000	203.0000
CONTROL	10	188.9000	7.6749	2.4333	175.0000	199.0000
TOTAL	40	189.4750			175.0000	212.0000
	UNGROUPED DATA		8.6853	1.3733		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	128.8000	[illegible].6619	1.4742	119.0000	136.0000
750 ppm	10	127.8000	5.3652	1.6967	114.0000	135.0000
1500 ppm	10	[illegible]	[illegible]	1.6452	117.0000	132.0000
CONTROL	10	130.[illegible]	[illegible]	2.4132	121.0000	146.0000
TOTAL	40	128.1250			116.0000	146.0000
	UNGROUPED DATA		6.0561	.0576		

000091

TABLE 3. STATISTICAL ANALYSIS OF WEEKLY BODY WEIGHT DATA

Week 3

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	205.4000	10.9565	3.4647	194.0000	228.0000
750 ppm	10	202.5000	7.5902	2.4000	189.0000	216.0000
1500 ppm	10	191.5000	10.5646	3.3408	177.0000	210.0000
CONTROL	10	207.4000	7.0899	2.2420	199.0000	218.0000
TOTAL	40	201.7000			177.0000	228.0000
	UNGROUPED DATA		10.8183	1.7105		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	136.4000	6.6533	2.1040	125.0000	146.0000
750 ppm	10	134.9000	5.1521	1.6292	127.0000	140.0000
1500 ppm	10	128.5000	8.6570	2.7376	110.0000	141.0000
CONTROL	10	139.3000	7.7179	2.4406	130.0000	156.0000
TOTAL	40	134.7750			110.0000	156.0000
	UNGROUPED DATA		7.9630	1.2591		

Week 4

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	212.2000	12.0074	3.7971	193.0000	229.0000
750 ppm	10	212.9000	9.3900	2.9719	196.0000	228.0000
1500 ppm	10	200.4000	9.6517	3.0521	190.0000	214.0000
CONTROL	10	220.4000	8.1404	2.5742	206.0000	235.0000
TOTAL	40	211.4750			190.0000	235.0000
	UNGROUPED DATA		11.9572	1.8906		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	145.1000	7.2703	2.3019	131.0000	157.0000
750 ppm	10	139.3000	7.7896	2.4633	127.0000	152.0000
1500 ppm	10	132.7000	6.5158	2.0605	124.0000	142.0000
CONTROL	10	140.1000	9.0489	2.8653	130.0000	154.0000
TOTAL	40	140.8000			124.0000	16[illegible].0000
	UNGROUPED DATA		9.1625	1.4519		

Week 5

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	222.5000	9.9135	3.1349	208.0000	237.0000
750 ppm	10	222.0000	11.0524	3.4948	208.0000	244.0000
1500 ppm	10	204.5000	11.0378	3.4905	189.0000	221.0000
CONTROL	10	236.1000	9.4774	3.0003	222.0000	251.0000
TOTAL	40	221.2750			189.0000	251.0000
	UNGROUPED DATA		19.2548	2.4123		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	151.7000	7.3944	2.3383	140.0000	167.0000
750 ppm	10	147.5000	8.1020	2.5874	130.0000	155.0000
1500 ppm	10	139.1000	7.5438	2.3919	123.0000	148.0000
CONTROL	10	153.4000	10.0133	3.1665	144.0000	178.0000
TOTAL	40	146.9750			123.0000	178.0000
	UNGROUPED DATA		10.0450	1.7148		

TABLE 3. STATISTICAL ANALYSIS OF WEEKLY BODY WEIGHT DATA

Week 6

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	228.9000	15.0292	4.7527	210.0000	240.0000
750 ppm	10	225.6000	11.6828	3.6944	205.0000	245.0000
1500 ppm	10	206.5000	11.1490	3.5253	192.0000	225.0000
CONTROL	10	243.6000	14.9755	4.7357	215.0000	265.0000
TOTAL	40	226.1500			192.0000	265.0000
		UNGROUPED DATA	18.5245	2.9290		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	157.0000	6.1101	1.9322	146.0000	169.0000
750 ppm	10	148.9000	8.4255	2.6644	133.0000	158.0000
1500 ppm	10	138.7000	6.3779	2.0169	131.0000	151.0000
CONTROL	10	159.9000	9.1827	2.9038	150.0000	168.0000
TOTAL	40	151.1250			131.0000	168.0000
		UNGROUPED DATA	11.1037	1.7556		

Week 7

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	235.6000	12.9203	4.0857	218.0000	256.0000
750 ppm	10	233.2000	12.2002	3.8580	213.0000	253.0000
1500 ppm	10	211.6000	10.7621	3.4033	198.0000	226.0000
CONTROL	10	250.8000	14.2813	4.5161	230.0000	272.0000
TOTAL	40	232.8000			198.0000	272.0000
		UNGROUPED DATA	18.6289	2.9455		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	161.5000	7.1220	2.2522	148.0000	173.0000
750 ppm	10	154.3000	7.9729	2.5212	141.0000	164.0000
1500 ppm	10	143.0000	5.2662	1.6653	136.0000	153.0000
CONTROL	10	166.0000	8.8569	2.8008	157.0000	183.0000
TOTAL	40	156.4000			136.0000	183.0000
		UNGROUPED DATA	11.0912	1.7537		

Week 8

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	244.4000	13.7937	4.3620	223.0000	260.0000
750 ppm	10	240.4000	13.7937	4.3620	217.0000	263.0000
1500 ppm	10	218.9000	15.3800	4.8636	185.0000	232.0000
CONTROL	10	263.2000	12.5060	3.9547	247.0000	285.0000
TOTAL	40	239.7250			185.0000	285.0000
		UNGROUPED DATA	23.2970	3.6693		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	164.4000	6.6366	2.0997	154.0000	176.0000
750 ppm	10	159.1000	5.9[illegible]	1.8941	15[illegible]	165.0000
1500 ppm	10	147.2000	6.3210	1.9989	1[illegible]	1[illegible]
CONTROL	10	167.7000	9.9783	3.1554	[illegible]	[illegible]
TOTAL	40	159.6000			137.0000	1[illegible]
		UNGROUPED DATA	10.6236	1.6797		

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TABLE 3. STATISTICAL ANALYSIS OF WEEKLY BODY WEIGHT DATA

Week 9

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	256.7000	14.5987	4.6165	232.0000	275.0000
750 ppm	10	249.8900	12.7523	4.0326	227.0000	270.0000
1500 ppm	10	214.9000	15.8146	5.0010	194.0000	237.0000
CONTROL	10	271.6000	18.0629	5.7120	228.0000	283.0000
TOTAL	40	246.2500			194.0000	283.0000
	UNGROUPED DATA		25.7610	4.0732		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	159.9000	6.0818	1.9232	159.0000	181.0000
750 ppm	10	163.1000	7.0824	2.2333	151.0000	173.0000
1500 ppm	10	147.6000	8.5461	2.7008	134.0000	164.0000
CONTROL	10	160.1000	9.1220	2.8846	152.0000	178.0000
TOTAL	40	162.1750			134.0000	181.0000
	UNGROUPED DATA		11.0264	1.0303		

Week 10

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	261.0000	14.9592	4.7305	232.0000	278.0000
750 ppm	10	253.0000	11.2131	3.5459	233.0000	273.0000
1500 ppm	10	220.4000	14.1908	4.4875	206.0000	241.0000
CONTROL	10	278.6000	8.5531	2.7047	268.0000	295.0000
TOTAL	40	253.4500			206.0000	295.0000
	UNGROUPED DATA		24.5137	[illegible]		

Rats- Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	170.0000	6.6533	2.1046	159.0000	182.0000
750 ppm	10	169.2000	6.7462	2.1333	152.0000	171.0000
1500 ppm	10	159.3000	7.8375	2.4907	[illegible]	[illegible]
CONTROL	10	175.3000	9.6683	2.8676	154.0000	195.0000
TOTAL	40	165.3500			136.0000	195.0000
	UNGROUPED DATA		12.0247	1.9013		

Week 11

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	270.3000	12.0743	3.8182	253.0000	285.0000
750 ppm	10	263.2000	11.3003	3.5908	246.0000	285.0000
1500 ppm	10	225.7000	15.0779	4.7681	204.0000	250.0000
CONTROL	10	288.4000	12.8426	4.0612	274.0000	315.0000
TOTAL	40	261.9000			209.0000	315.0000
	UNGROUPED DATA		26.2423	4.1493		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	175.0000	6.6332	2.0976	166.0000	184.0000
750 ppm	10	169.5000	7.0907	2.2423	156.0000	177.0000
1500 ppm	10	154.7000	9.0927	2.8754	140.0000	168.0000
CONTROL	10	180.0000	9.2832	2.9354	171.0000	199.0000
TOTAL	40	170.0000			140.0000	199.0000
	UNGROUPED DATA		12.5351	1.9820		

TABLE 3. STATISTICAL ANALYSIS OF WEEKLY BODY WEIGHT DATA

Week 12

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	277.0000	13.9682	4.4171	[illegible]	291.0000
750 ppm	8	262.2500	11.4736	4.0565	[illegible]	278.0000
1500 ppm	10	225.2000	17.0737	5.3992	201.0000	253.0000
CONTROL	10	298.6000	18.6202	5.8882	251.0000	317.0000
TOTAL	38	265.9474			201.0000	317.0000
	UNGROUPED DATA		31.6304	5.1311		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	179.0000	6.2903	1.9889	170.0000	190.0000
750 ppm	8	171.0000	7.9057	2.6352	159.0000	178.0000
1500 ppm	10	156.1000	9.9224	3.1378	137.0000	170.0000
CONTROL	10	178.4000	9.6992	3.0687	163.0000	188.0000
TOTAL	39	171.1282			137.0000	190.0000
	UNGROUPED DATA		12.5345	2.0071		

TABLE 3 . STATISTICAL ANALYSIS OF WEEKLY BODY WEIGHT DATA

Final Body Weight

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	254.1000	13.3171	4.2096	226.0000	275.0000
750 ppm	10	242.8000	12.2019	3.8039	220.0000	256.0000
1500 ppm	10	209.3000	26.0399	8.0670	184.0000	280.0000
CONTROL	5	269.7770	14.7460	4.9153	246.0000	296.0000
TOTAL	35	243.3333			184.0000	296.0000
		UNGROUPED DATA	28.4728	4.5593		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	160.0000	6.1101	1.9322	150.0000	170.0000
750 ppm	10	157.0000	14.4760	4.5777	133.0000	195.0000
1500 ppm	9	137.0889	6.6039	2.2013	124.0000	146.0000
CONTROL	9	156.7778	13.3583	4.4528	130.0000	182.0000
TOTAL	38	153.2105			124.0000	195.0000
		UNGROUPED DATA	13.5869	2.2041		

Mice - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	25.2500	1.4863	.5261	23.0000	23.0000
750 ppm	8	24.8750	1.2464	.4407	22.0000	26.0000
1500 ppm	3	22.6667	2.9166	1.4538	20.0000	25.0000
CONTROL	6	25.0000	.6733	.6831	24.0000	26.0000
TOTAL	25	24.7600			20.0000	26.0000
		UNGROUPED DATA	1.5982	.3380		

Mice - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	21.3750	.9161	.3239	20.0000	23.0000
750 ppm	13	21.6000	1.0753	.3399	20.0000	23.0000
1500 ppm	8	18.8750	1.6491	.6355	16.0000	22.0000
CONTROL	7	21.2857	1.3801	.5216	19.0000	23.0000
TOTAL	33	20.5102			16.6666	24.7000
		UNGROUPED DATA	1.7839	.2966		

TABLE 4. STATISTICAL ANALYSIS OF BODY WEIGHT GAIN DATA

Week 1

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	-7.3000	7.1655	2.2659	-18.0000	4.0000
750 ppm	10	.5000	10.5013	3.3204	-11.0000	22.0000
1500 ppm	10	-1.0000	9.0284	2.8550	-15.0000	10.0000
CONTROL	10	-11.4000	19.1439	6.0538	-45.0000	7.0000
TOTAL	40	-5.0000			-45.0000	22.0000
	UNGROUPED DATA		12.7641	2.0182		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	-7.0000	5.1206	1.6193	-15.0000	-1.0000
750 ppm	10	-4.5000	9.5714	3.0267	-30.0000	2.0000
1500 ppm	10	-1.4000	6.0406	1.9102	-8.0000	10.0000
CONTROL	10	-3.4000	11.9648	3.7836	-33.0000	9.0000
TOTAL	40	-4.0750			-33.0000	10.0000
	UNGROUPED DATA		8.5347	1.3494		

Week 2

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	22.4000	6.8508	2.1664	14.0000	34.0000
750 ppm	10	14.6000	6.9634	2.2020	2.0000	24.0000
1500 ppm	10	8.3000	4.0014	1.2654	-1.0000	14.0000
CONTROL	10	24.1000	17.4385	5.5145	5.0000	53.0000
TOTAL	40	17.3500			-1.0000	53.0000
	UNGROUPED DATA		11.7070	1.8510		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	9.9000	4.6296	1.4640	5.0000	21.0000
750 ppm	10	8.7000	6.3779	2.0169	0	22.0000
1500 ppm	10	4.5000	4.5765	1.4472	-3.0000	11.0000
CONTROL	10	10.2000	11.8303	3.7411	0	37.0000
TOTAL	40	8.3250			-3.0000	37.0000
	UNGROUPED DATA		7.5359	1.1915		

Week 3

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	16.8000	5.9963	1.8962	7.0000	27.0000
750 ppm	10	9.3000	4.4981	1.4224	5.0000	18.0000
1500 ppm	10	4.3000	6.1053	1.9496	-12.0000	10.0000
CONTROL	10	18.5000	6.9322	2.1922	8.0000	34.0000
TOTAL	40	12.2250			-12.0000	34.0000
	UNGROUPED DATA		8.1602	1.2902		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	7.6000	4.7656	1.5070	-1.0000	17.0000
750 ppm	10	7.1000	3.1073	.9826	4.0000	13.0000
1500 ppm	10	3.3000	4.6916	1.4834	-7.0000	10.0000
CONTROL	10	8.6000	2.0656	.6532	6.0000	11.0000
TOTAL	40	6.6500			-7.0000	17.0000
	UNGROUPED DATA		4.2035	.6646		

TABLE 4. STATISTICAL ANALYSIS OF BODY WEIGHT GAIN DATA

Week 4

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	6.8000	12.5503	3.9688	-20.0000	21.0000
750 ppm	10	10.4000	6.8678	2.1715	-7.0000	17.0000
1500 ppm	10	8.9000	4.3321	1.3699	3.0000	18.0000
CONTROL	10	13.0000	3.7417	1.1832	6.0000	18.0000
TOTAL	40	9.7750			-20.0000	21.0000
	UNGROUPED DATA		7.7476	1.2250		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	8.7000	5.3135	1.6803	2.0000	20.0000
750 ppm	10	4.4000	4.1687	1.3182	-2.0000	10.0000
1500 ppm	10	4.2000	5.5337	1.7499	-3.0000	14.0000
CONTROL	10	6.8000	2.3944	.7572	4.0000	12.0000
TOTAL	40	6.0250			-3.0000	20.0000
	UNGROUPED DATA		4.7366	.7489		

Week 5

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	10.3000	7.7035	2.4361	-4.0000	26.0000
750 ppm	10	9.1000	8.9499	2.8302	-2.0000	29.0000
1500 ppm	10	4.1000	2.5582	.8099	-1.0000	7.0000
CONTROL	10	15.7000	4.6679	1.4761	6.0000	24.0000
TOTAL	40	9.8000			-4.0000	29.0000
	UNGROUPED DATA		7.4943	1.1849		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	6.6000	3.0623	.9684	0	11.0000
750 ppm	10	8.2000	4.0497	1.2804	1.0000	13.0000
1500 ppm	10	2.4000	3.5653	1.1274	-3.0000	7.0000
CONTROL	10	7.5000	2.0138	.6368	4.0000	10.0000
TOTAL	40	6.1750			-3.0000	13.0000
	UNGROUPED DATA		3.0755	.6128		

Week 6

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	6.4000	8.4879	2.6841	-7.0000	20.0000
750 ppm	10	3.6000	4.1687	1.3182	-4.0000	11.0000
1500 ppm	10	2.0000	5.4772	1.7321	-9.0000	10.0000
CONTROL	10	7.5000	8.0035	2.5309	-12.0000	14.0000
TOTAL	40	4.8750			-12.0000	20.0000
	UNGROUPED DATA		6.8732	1.0867		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	5.3000	4.2439	1.3421	1.0000	14.0000
750 ppm	10	1.4000	3.1693	1.0022	-5.0000	7.0000
1500 ppm	10	3.6000	2.3664	.7483	1.0000	9.0000
CONTROL	10	6.3000	2.9078	.9195	2.0000	11.0000
TOTAL	40	4.1500			-5.0000	14.0000
	UNGROUPED DATA		3.6413	.5757		

TABLE 4. STATISTICAL ANALYSIS OF BODY WEIGHT GAIN DATA

Week 7

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	6.7000	9.1049	2.8792	-5.0000	26.0000
750 ppm	10	7.6000	4.1687	1.3182	-1.0000	15.0000
1500 ppm	10	5.1000	2.[illegible]310	.7371	0	8.0000
CONTROL	10	7.2000	7.[illegible]853	2.4535	-12.0000	[illegible]5.00[illegible]
TOTAL	40	6.6500			-12.0000	25.[illegible]
	UNGROUPED DATA		6.2984	.9959		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	4.5000	2.5495	.8062	2.0000	10.0000
750 ppm	10	5.4000	2.1705	.6864	3.0000	10.0000
1500 ppm	10	5.1000	2.8067	.8876	2.0000	12.0000
CONTROL	10	6.1000	3.3149	1.0483	3.0000	13.0000
TOTAL	40	5.2750			2.0000	13.0000
	UNGROUPED DATA		2.6984	.4267		

Week 8

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	8.0000	10.7164	3.3889	-14.0000	20.0000
750 ppm	10	7.2000	2.8204	.8919	4.0000	12.0000
1500 ppm	10	-.7000	7.7613	2.4542	-21.0000	7.0000
CONTROL	10	12.4000	10.1346	3.2049	3.0000	31.0000
TOTAL	40	6.9250			-21.0000	31.0000
	UNGROUPED DATA		9.4581	1.4955		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	2.9000	2.9609	.9363	-2.0000	7.0000
750 ppm	10	4.0000	3.2249	1.0198	-2.0000	9.0000
1500 ppm	10	3.4000	2.1187	.6700	1.0000	7.0000
CONTROL	10	1.7000	2.3118	.7311	-1.0000	7.0000
TOTAL	40	3.2000			-2.0000	9.0000
	UNGROUPED DATA		2.8212	.4461		

Week 9

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	12.3000	7.4543	2.3573	3.0000	30.0000
750 ppm	10	9.4000	2.0111	.6360	6.0000	13.0000
1500 ppm	10	4.0000	4.9666	1.5706	-6.0000	9.0000
CONTROL	10	8.4000	16.2494	5.1385	-19.0000	34.0000
TOTAL	40	8.5250			-19.0000	34.0000
	UNGROUPED DATA		9.4597	1.4957		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	5.5000	2.2730	.7184	2.0000	10.0000
750 ppm	10	4.0000	3.6818	1.1643	-1.0000	11.0000
1500 ppm	10	.4000	3.7771	1.1944	-6.0000	7.0000
CONTROL	10	.4000	13.3433	4.2195	-25.0000	16.0000
TOTAL	40	2.5750			-25.0000	16.0000
	UNGROUPED DATA		7.3376	1.1602		

TABLE 4. STATISTICAL ANALYSIS OF BODY WEIGHT GAIN DATA

Week 10

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	4.3000	4.9677	1.5709	-3.0000	10.0000
750 ppm	10	4.0000	3.9158	1.2383	-6.0000	7.0000
1500 ppm	10	5.5000	7.1066	2.2469	-2.0000	22.0000
CONTROL	10	7.0000	16.8325	5.3229	-11.0000	40.0000
TOTAL	40	5.2000			-11.0000	40.0000
	UNGROUPED DATA		9.3759	1.4825		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	.7000	3.0569	.9667	-7.0000	4.0000
750 ppm	10	2.1000	4.2202	1.3371	-4.0000	8.0000
1500 ppm	10	2.7000	1.8288	.5783	0	6.0000
CONTROL	10	7.2000	13.8628	4.3838	-9.0000	40.0000
TOTAL	40	3.1750			-9.0000	40.0000
	UNGROUPED DATA		7.5816	1.1988		

Week 11

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	9.3000	7.0087	2.2164	2.0000	26.0000
750 ppm	10	9.4000	3.4383	1.0873	5.0000	15.0000
1500 ppm	10	5.3000	3.5917	1.1358	-1.0000	11.0000
CONTROL	10	9.8000	8.3772	2.6491	-2.0000	29.0000
TOTAL	40	8.4500			-2.0000	29.0000
	UNGROUPED DATA		6.0551	.9574		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	4.4000	5.3790	1.7010	-1.0000	15.0000
750 ppm	10	4.3000	2.3118	.7311	0	7.0000
1500 ppm	10	4.4000	4.3256	1.3679	-3.0000	12.0000
CONTROL	10	5.5000	2.9907	.9458	1.0000	10.0000
TOTAL	40	4.6500			-3.0000	15.0000
	UNGROUPED DATA		3.8133	.6029		

Week 12

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	6.7000	5.9076	1.8684	-9.0000	11.0000
750 ppm	8	2.6250	4.1382	1.4631	-3.0000	9.0000
1500 ppm	10	-.5000	7.9757	2.5221	-21.0000	6.0000
CONTROL	10	10.2000	20.4928	6.4804	-20.0000	42.0000
TOTAL	38	4.8684			-20.0000	42.0000
	UNGROUPED DATA		12.1169	1.9656		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	4.0000	3.4960	1.1055	-3.0000	8.0000
750 ppm	9	2.1111	3.6209	1.2070	-5.0000	7.0000
1500 ppm	10	1.4000	2.9889	.9452	-4.0000	6.0000
CONTROL	10	-2.4000	14.0728	4.4502	-36.0000	13.0000
TOTAL	39	1.2564			-36.0000	13.0000
	UNGROUPED DATA		7.7068	1.2440		

TABLE 4. STATISTICAL ANALYSIS OF BODY WEIGHT GAIN DATA

Week 13

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	-22.9040	[illegible]	1.479[illegible]	-32.0000	-14.0000
750 ppm	8	-22.3750	[illegible]	2.9090	-38.0000	-12.0000
1500 ppm	10	-15.9040	1[illegible].314	6.0341	-36.0000	36.0000
CONTROL	9	-28.2222	21.9931	7.3310	-59.0000	7.0000
TOTAL	37	-22.1892			-59.0000	36.0000
	UNGROUPED DATA		15.4071	2.5329		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	-19.0040	1.7638	.5578	-22.0000	-17.0000
750 ppm	9	-18.2222	3.0322	1.0[illegible]07	-23.0000	-14.0000
1500 ppm	9	-20.3333	4.3509	1.4530	-2[illegible].0000	-13.0000
CONTROL	9	-22.5556	20.0132	6.6711	-57.0000	19.0000
TOTAL	37	-20.0000			-57.0000	19.0000
	UNGROUPED DATA		9.9387	1.6339		

Total Body Weight Gain

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	80.6000	11.6543	3.6854	55.0000	93.0000
750 ppm	10	64.7000	17.3016	5.4712	37.0000	87.0000
1500 ppm	10	28.6000	21.9048	6.9269	4.0000	79.0000
CONTROL	10	66.6000	83.0892	26.2751	-167.0000	116.0000
TOTAL	40	60.1250			-167.0000	116.0000
	UNGROUPED DATA		46.7202	7.3871		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	34.1000	5.6263	1.7792	23.0000	41.0000
750 ppm	10	33.4000	14.1122	4.4627	19.0000	71.0000
1500 ppm	10	2.0000	40.2934	12.7419	-112.0000	23.0000
CONTROL	10	17.2000	52.8095	16.6998	-126.0000	52.0000
TOTAL	40	21.6750			-126.0000	71.0000
	UNGROUPED DATA		35.3658	5.5918		

APPENDIX C

FOOD CONSUMPTION DATA

TABLE 1. FOOD CONSUMPTION DATA FOR MALE RATS

Treatment Group	Animal I.D.	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13
A01	22	111	122	140	129	139	128	133	133	153	144	140	155	167
A01	24	88	95	127	126	112	119	137	121	115	127	108	104	128
A01	26	109	78	142	148	125	125	140	143	139	151	153	154	156
A01	31	87	104	134	146	122	117	119	126	112	119	125	114	122
A01	33	94	88	122	131	98	114	119	111	118	112	114	119	127
A01	34	84	105	143	152	123	151	130	127	132	134	143	145	154
A01	36	111	79	116	136	133	106	112	63	119	116	114	109	127
A01	37	96	109	129	127	133	128	93	113	105	115	94	100	147
A01	63	96	82	135	138	130	107	81	130	114	112	118	106	121
A01	76	94	98	135	124	100	95	97	100	103	92	95	100	110
A02	23	100	115	149	123	121	139	141	165	154	164	142	142	153
A02	27	94	115	133	109	113	114	142	141	126	146	153	155	149
A02	39	86	108	134	96	131	107	118	106	112	135	143	118	156
A02	61	86	102	133	120	110	98	115	119	146	141	156	151	134
A02	62	108	92	133	110	116	93	98	104	94	95	124	97	116
A02	66	91	106	126	111	112	99	100	113	105	111	124	99	119
A02	69	131	103	125	113	121	105	125	125	123	121	118	100	124
A02	70	115	103	125	100	82	113	95	119	103	116	112	111	120
A02	74	104	96	134	132	111	105	139	147	104	146	156	133	140
A02	79	94	121	117	119	107	109	118	111	119	116	119	118	128
A03	21	104	120	106	109	122	123	122	110	122	115	111	134	144
A03	28	102	106	116	146	103	102	103	97	94	93	94	106	125
A03	32	103	102	106	141	120	120	115	117	116	107	119	111	132
A03	38	102	106	97	142	97	97	104	105	100	105	106	110	149
A03	40	102	102	97	151	130	130	102	98	95	87	97	89	103
A03	67	83	102	111	154	115	115	115	117	112	111	117	149	147
A03	68	99	87	129	166	105	105	88	116	110	109	107	109	121
A03	71	119	112	134	190	124	124	119	117	122	119	120	131	134
A03	72	122	106	89	181	123	124	161	109	130	126	128	164	134
A03	78	86	103	126	162	110	110	113	100	103	120	112	146	114
A04	25	90	107	1.6	126	141	128	99	112	134	102	116	140	88
A04	29	65	112	152	134	133	161	111	103	88	110	110	110	87
A04	30	63	111	141	137	136	135	120	113	120	107	101	146	73
A04	35	86	103	134	138	130	104	100	103	103	106	105	99	87
A04	64	103	94	124	141	124	151	129	144	130	119	136	103	160
A04	65	88	126	101	137	136	122	112	132	116	138	162	106	152
A04	73	55	76	165	156	149	142	125	110	122	142	113	124	92
A04	75	111	102	138	151	142	140	126	125	120	121	129	113	103
A04	77	103	115	136	133	143	140	122	111	110	105	110	117	92
A04	80	90	107	156	141	129	129	138	142	124	132	128	133	130

000103

Treatment Group	Animal I.D.	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13
A01	10	84	71	93	99	84	90	95	78	72	88	97	97	119
A01	16	85	76	104	110	59	103	95	102	85	109	92	121	101
A01	43	72	73	120	113	92	85	95	83	95	134	98	125	142
A01	44	75	78	124	118	120	76	86	87	76	79	84	84	97
A01	49	93	74	99	110	71	103	74	84	83	79	78	75	100
A01	56	85	73	102	107	85	108	81	80	88	95	83	88	95
A01	57	111	70	103	116	105	89	84	96	79	82	160	78	90
A01	58	91	54	111	120	81	120	81	84	86	72	81	81	123
A01	59	90	64	105	128	90	85	90	92	90	82	87	91	104
A01	60	54	68	104	125	101	62	83	85	86	88	82	89	104
A02	4	91	70	109	84	92	77	81	110	88	92	90	86	95
A02	5	77	79	101	78	88	76	76	83	83	85	79	82	96
A02	8	94	85	102	96	45	87	88	88	88	82	87	82	95
A02	13	67	78	105	63	92	82	85	95	83	86	88	91	120
A02	14	71	81	116	81	70	79	89	96	83	89	103	93	128
A02	41	87	81	107	66	105	57	94	94	93	89	88	84	100
A02	45	88	71	111	79	92	84	95	78	81	96	81	85	135
A02	47	85	79	106	95	85	89	100	85	89	81	84	84	90
A02	48	86	74	107	77	94	83	88	87	79	83	87	88	100
A02	50	83	63	116	84	98	73	87	85	74	81	71	82	93
A03	2	94	82	88	132	103	103	84	84	98	87	91	95	107
A03	11	89	78	76	104	98	98	93	112	119	92	99	105	114
A03	17	74	81	85	125	101	101	89	62	77	88	98	89	105
A03	18	69	76	77	120	62	63	132	107	81	108	107	127	136
A03	20	72	94	97	133	98	98	85	89	68	73	77	83	102
A03	42	76	88	83	125	94	94	97	99	99	98	96	91	101
A03	46	86	78	104	130	88	88	83	91	84	101	98	123	110
A03	52	68	79	105	147	83	84	93	109	130	126	123	164	134
A03	53	77	73	108	145	78	78	88	76	71	88	74	83	86
A03	55	68	88	103	129	101	101	82	88	75	74	76	79	84
A04	1	51	94	107	108	102	111	106	77	78	73	67	76	60
A04	3	88	81	104	106	104	115	77	72	78	78	97	72	63
A04	6	67	81	105	108	121	97	178	72	124	69	73	72	71
A04	7	69	82	124	108	136	104	59	75	76	79	79	77	62
A04	9	82	83	99	95	104	102	98	77	78	71	75	72	65
A04	12	67	78	103	109	112	108	110	86	95	87	84	82	76
A04	15	96	81	116	125	125	103	89	89	87	66	84	84	68
A04	19	86	74	101	101	104	97	77	77	74	76	77	74	68
A04	57	89	78	108	104	105	103	112	103	101	91	100	71	53
A04	54	84	76	118	113	114	99	88	86	115	81	80	82	66

TABLE 3. STATISTICAL ANALYSIS OF FOOD CONSUMPTION DATA

Week 1

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	97.0000	10.8333	3.1728	84.0000	111.0000
750 ppm	10	100.1000	13.9320	4.4057	86.0000	131.0000
1500 ppm	10	102.2000	12.1063	3.8291	83.0000	122.0000
CONTROL	10	84.6000	10.0043	5.9464	55.0000	111.0000
TOTAL	40	95.9750			55.0000	111.0000
		UNGROUPED DATA	15.2654	2.4042		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	84.0000	14.9839	4.7399	54.0000	111.0000
750 ppm	10	82.1000	8.5042	2.6053	67.0000	94.0000
1500 ppm	10	76.5000	10.4376	3.3007	68.0000	94.0000
CONTROL	10	77.9000	13.7957	4.3626	51.0000	98.0000
TOTAL	40	86.1250			51.0000	111.0000
		UNGROUPED DATA	12.1279	1.9176		

Week 2

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	96.2000	14.5434	4.5990	78.0000	122.0000
750 ppm	10	106.1000	8.9499	2.8302	92.0000	121.0000
1500 ppm	10	104.6000	8.3693	2.6466	87.0000	120.0000
CONTROL	10	105.3000	13.3670	4.2270	76.0000	126.0000
TOTAL	40	103.0500			76.0000	126.0000
		UNGROUPED DATA	11.8753	1.8777		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	69.3000	7.6155	2.4335	54.0000	78.0000
750 ppm	10	76.1000	6.5556	2.0734	63.0000	85.0000
1500 ppm	10	80.1000	5.9267	1.7477	73.0000	94.0000
CONTROL	10	80.4000	5.4324	1.7179	74.0000	94.0000
TOTAL	40	76.5750			54.0000	94.0000
		UNGROUPED DATA	7.6923	1.2099		

Week 3

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	132.3000	8.7946	2.7811	116.0000	143.0000
750 ppm	10	130.9000	8.4731	2.6810	117.0000	149.0000
1500 ppm	10	111.1000	15.0144	4.7480	89.0000	134.0000
CONTROL	10	130.3000	17.7530	5.6239	101.0000	165.0000
TOTAL	40	128.1500			89.0000	165.0000
		UNGROUPED DATA	16.3324	2.5824		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	107.3000	10.8959	3.4458	93.0000	128.0000
750 ppm	10	108.8000	9.1424	1.6262	101.0000	115.0000
1500 ppm	10	91.6000	12.7765	4.0409	76.0000	103.0000
CONTROL	10	107.7000	7.4851	2.3667	99.0000	124.0000
TOTAL	40	103.7000			76.0000	128.0000
		UNGROUPED DATA	11.5141	1.8205		

TABLE 3. STATISTICAL ANALYSIS OF FOOD CONSUMPTION DATA

Week 4

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	135.7000	10.0117	3.1660	124.0000	152.0000
750 ppm	10	113.3000	10.7888	3.3864	96.0000	132.0000
1500 ppm	10	154.2000	22.7147	7.1836	109.0000	198.0000
CONTROL	10	139.4000	8.6020	2.7459	126.0000	156.0000
TOTAL	40	135.6500			96.0000	198.0000
	UNGROUPED DATA		20.1489	3.1856		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	113.0000	7.5962	2.4026	99.0000	125.0000
750 ppm	10	79.5000	11.2668	3.5963	63.0000	96.0000
1500 ppm	10	129.0000	12.2232	3.8644	104.3000	147.0000
CONTROL	10	137.4000	7.9478	2.5131	95.0000	125.0000
TOTAL	40	107.4250			63.0000	147.0000
	UNGROUPED DATA		20.9050	3.2421		

Week 5

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	121.9000	13.9948	4.4253	96.0000	139.0000
750 ppm	10	112.4000	12.7712	4.0393	82.0000	131.0000
1500 ppm	10	115.7000	12.1042	3.8278	97.0000	138.0000
CONTROL	10	137.1000	7.2458	2.2923	124.0000	149.0000
TOTAL	40	121.6750			82.0000	149.0000
	UNGROUPED DATA		14.6614	2.3538		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	88.8000	17.3192	5.4764	59.0000	122.0000
750 ppm	10	84.5000	16.6683	5.2718	45.0000	107.0000
1500 ppm	10	89.8000	13.4644	4.2578	67.0000	103.0000
CONTROL	10	112.7000	11.3627	3.5935	102.0000	136.0000
TOTAL	40	93.9500			45.0000	136.0000
	UNGROUPED DATA		18.1475	2.8694		

Week 6

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	119.0000	15.4209	4.8762	95.0000	151.0000
750 ppm	10	108.2000	12.6024	4.0105	93.3000	139.0000
1500 ppm	10	115.0000	12.4347	3.9322	97.0000	138.0000
CONTROL	10	139.2000	15.7959	4.9951	104.0000	161.0000
TOTAL	40	119.5500			93.0000	161.0000
	UNGROUPED DATA		16.8750	2.6682		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	92.9000	18.4177	5.8242	69.0000	129.0000
750 ppm	10	70.7500	9.1849	2.9052	57.0000	89.0000
1500 ppm	10	90.0000	13.1629	4.1607	63.0000	133.0000
CONTROL	10	103.1000	9.8395	3.1466	97.0000	115.0000
TOTAL	40	91.1750			57.0000	128.0000
	UNGROUPED DATA		14.9287	2.3604		

TABLE 3. STATISTICAL ANALYSIS OF FOOD CONSUMPTION DATA

Week 7

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	116.1000	20.1439	6.3591	81.0000	140.0000
750 ppm	10	115.1000	17.7732	5.6223	95.0000	142.0000
1500 ppm	10	114.6000	15.0741	6.0318	[illegible]	[illegible]
CONTROL	10	118.2000	12.5769	3.9772	[illegible]	[illegible]
TOTAL	40	117.6000			81.0000	161.0000
		UNGROUPED DATA	17.0354	2.6935		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	86.4000	7.1833	2.2716	74.0000	95.0000
750 ppm	10	88.3000	6.9230	2.1911	76.0000	100.0000
1500 ppm	10	91.8000	15.1739	4.8000	80.0000	132.0000
CONTROL	10	98.6000	30.1264	9.5268	59.0000	170.0000
TOTAL	40	91.2750			59.0000	170.0000
		UNGROUPED DATA	17.5441	2.7740		

Week 8

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	116.7000	22.4947	7.1134	63.0000	143.0000
750 ppm	10	125.8000	19.8718	6.2840	104.0000	165.0000
1500 ppm	10	118.2000	8.0939	2.5595	97.0000	118.0000
CONTROL	10	119.5000	15.2698	4.8267	103.0000	144.0000
TOTAL	40	117.8500			63.0000	165.0000
		UNGROUPED DATA	17.4922	2.7658		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	87.1000	7.4454	2.3544	78.0000	102.0000
750 ppm	10	89.3000	9.5690	3.0260	78.0000	110.0000
1500 ppm	10	92.9000	13.0337	4.1216	76.0000	112.0000
CONTROL	10	81.4000	9.6747	3.0594	72.0000	103.0000
TOTAL	40	87.6750			72.0000	112.0000
		UNGROUPED DATA	10.6106	1.6777		

Week 9

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	121.0000	15.7339	4.9755	103.0000	151.0000
750 ppm	10	118.6000	19.3460	6.1177	94.0000	154.0000
1500 ppm	10	118.4000	12.2754	3.8822	94.0000	130.0000
CONTROL	10	116.7000	13.4825	4.2637	88.0000	134.0000
TOTAL	40	116.6750			88.0000	154.0000
		UNGROUPED DATA	15.3646	2.4294		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	83.2000	6.7462	2.1333	72.0000	95.0000
750 ppm	10	84.1000	5.5257	1.7477	74.0000	93.0000
1500 ppm	10	89.4000	20.7402	6.5612	68.0000	139.0000
CONTROL	10	98.6000	17.6899	5.5940	74.0000	124.0000
TOTAL	40	86.8250			68.0000	130.0000
		UNGROUPED DATA	14.1329	2.2344		

TABLE 3. STATISTICAL ANALYSIS OF FOOD CONSUMPTION DATA

Week 10

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	122.2000	17.2807	5.4646	92.0000	151.0000
750 ppm	10	127.1000	20.7226	6.5531	95.0000	164.0000
1500 ppm	10	109.2000	12.0620	3.8146	87.0000	126.0000
CONTROL	10	119.0000	14.3836	4.5485	102.0000	142.0000
TOTAL	40	119.0750			87.0000	164.0000
	UNGROUPED DATA		17.3769	2.7475		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	83.2000	18.0644	5.9718	72.0000	134.0000
750 ppm	10	86.4000	5.0376	1.5939	81.0000	96.0000
1500 ppm	10	91.9000	16.2169	5.1282	73.0000	126.0000
CONTROL	10	77.1000	7.0521	2.4031	66.0000	91.0000
TOTAL	40	88.1000			66.0000	134.0000
	UNGROUPED DATA		13.9625	2.2077		

Week 11

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	119.6000	20.1016	6.3756	94.0000	[illegible]
750 ppm	10	134.7000	17.1278	5.4180	112.0000	[illegible]
1500 ppm	10	111.9000	11.5271	3.6[illegible]	[illegible]	[illegible]
CONTROL	10	121.0000	18.2757	5.7733	[illegible]	[illegible]
TOTAL	40	121.8000			94.0000	[illegible]
	UNGROUPED DATA		18.3934	2.9083		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	99.0000	26.5286	8.3891	74.0000	163.0000
750 ppm	10	89.8000	[illegible].2839	2.6196	71.0000	[illegible]
1500 ppm	10	92.3000	[illegible].2441	4.7[illegible]	74.[illegible]	[illegible]
CONTROL	10	88.6000	[illegible].0006	2.8489	67.0000	[illegible]
TOTAL	40	88.4250			67.0000	[illegible]
	UNGROUPED DATA		16.8618	2.6566		

Week 12

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	128.6000	22.1420	7.0019	100.0000	155.0000
750 ppm	10	123.2000	20.9221	6.6161	97.0000	155.0000
1500 ppm	10	125.7000	23.1139	7.3091	89.0000	164.0000
CONTROL	10	119.1000	16.1138	5.0996	99.0000	146.0000
TOTAL	40	122.1500			89.0000	164.0000
	UNGROUPED DATA		20.0966	3.1776		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	92.1000	17.5718	5.5567	75.0000	[illegible]
750 ppm	10	89.7000	3.8602	1.2207	82.0000	93.0000
1500 ppm	10	103.9000	26.8101	8.4806	79.0000	164.0000
CONTROL	10	76.2000	4.8717	1.5406	71.0000	84.0000
TOTAL	40	89.4750			71.0000	164.0000
	UNGROUPED DATA		18.7110	2.9585		

TABLE 3. STATISTICAL ANALYSIS OF FOOD CONSUMPTION DATA

Week 13

Rats - Male

LEVEL	[illegible]	MEAN	[illegible]	[illegible]	[illegible]	[illegible]
375 ppm	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
750 ppm	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
1500 ppm	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
CONTROL	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
TOTAL	[illegible]	[illegible]			[illegible]	[illegible]
	UNGROUPED DATA		[illegible]	[illegible]		

Rats - Female

LEVEL	[illegible]	MEAN	[illegible]	[illegible]	[illegible]	[illegible]
375 ppm	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
750 ppm	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
1500 ppm	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
CONTROL	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
TOTAL	[illegible]	[illegible]			[illegible]	[illegible]
	UNGROUPED DATA		[illegible]	[illegible]		

APPENDIX D

HEMATOLOGY DATA

TABLE 1. CIIT METHYL CHLORIDE PILOT
MALE RAT HEMATOLOGY

Treatment Group	Animal ID	HGB gm %	HCT %	WBC $10^3/mm^3$	RBC $10^6/mm^3$	MCV	SEGS %	EOS %	LYMPH %	RETIC %
A01	22	18.4	48	6.6	10.19	49	27		73	0.4
A01	36	17.2	47	7.6	9.41	50	52		48	0.1
A01	24	17.1	47	5.8	9.47	50	31	1	68	0.3
A01	37	17.8	48	7.4	9.79	50	21		79	0.9
A01	26	18.9	49	6.3	10.27	51	23	1	76	0.5
A01	63	16.5	45	5.2	9.15	50	27	2	70	0.5
A01	31	17.2	48	7.1	9.60	50	34	2	64	0.5
A01	76	17.4	49	6.1	9.12	54	39	2	59	0.3
A01	33	18.0	48	6.8	10.22	50	44		56	1.0
A01	34	17.6	48	6.9	9.60	51	29	2	69	0.2
A02	23	15.8	47	6.7	9.23	51	10		90	0.6
A02	69	17.3	49	5.6	9.93	50	16	1	83	0.3
A02	27	15.6	45	8.1	8.85	51	26	1	73	0.7
A02	70	17.3	49	5.5	9.84	51	18		82	0.2
A02	39	18.3	50	7.4	10.40	51	32		68	1.5
A02	74	17.5	50	4.7	9.92	52	22		78	1.2
A02	61	17.8	48	4.7	10.10	50	20	1	79	0.1
A02	79	14.1	46	5.1	9.10	50	18		82	2.0
A02	62	15.8	45	6.0	8.95	50	21		79	0.5
A02	66	16.5	47	5.1	8.82	54	17		83	2.0
A03	21	17.6	49	6.9	10.26	50	10		90	1.1
A03	68	16.6	48	6.0	9.52	50	10		90	1.6
A03	28	17.2	48	8.7	9.66	50	6		94	2.5
A03	71	16.5	41	5.6	8.08	51	12		88	0.7
A03	32	17.6	50	5.9	10.07	51	14		86	0.7
A03	72	16.8	48	4.4	9.48	51	15		83	0.6
A03	38	16.9	52	5.3	9.47	55	12		88	1.0
A03	78	17.0	50	5.3	9.82	51	18	1	[illegible]	1.5
A03	40	15.8	45	4.2	8.93	51	6		94	2.1
A03	67	17.8	50	5.8	10.22	52	16	1	[illegible]	1.3
A04	25	17.5	49	3.7	9.66	50	46		54	1.0
A04	73	15.7	47	3.8	8.23	55	40		59	1.4
A04	29	17.1	48	3.5	9.26	51	54	2	44	0.3
A04	85	17.1	49	3.4	9.60	51	49	2	49	0.7
A04	30	17.2	49	3.3	9.42	52	34	2	59	1.0
A04	77	17.5	50	4.6	9.27	54	28	1	71	1.0
A04	35	17.1	49	4.0	9.4[illegible]	5[illegible]	42		58	1.1
A04	80	15.5	45	3.6	8.58	51	52		48	0.4
A04	64	16.8	48	3.9	9.30	51	46		54	1.3
A04	65	17.1	49	4.2	9.51	51	51	2	47	0.6

TABLE 2. CIIT METHYL CHLORIDE PILOT
FEMALE RAT HEMATOLOGY

Treatment Group	Animal ID	HGB gm %	HCT %	WBC $10^3/mm^3$	RBC $10^6/mm^3$	MCV	SEGS %	EOS %	LYMPH %	RETIC %
A01	10	17.1	47	5.2	9.02	53	27	2	71	0.4
A01	54	16.3	46	6.7	8.10	57	33	1	66	0.3
A01	16	15.7	43	6.5	8.19	53	35	1	64	2.0
A01	58	17.1	47	4.6	8.11	58	41	1	58	2.5
A01	43	17.2	47	5.6	9.02	52	31		69	0.5
A01	59	17.2	47	4.3	8.78	54	21		79	0.4
A01	44	17.3	48	4.3	9.15	53	35		64	0.1
A01	60	17.6	48	5.4	9.11	53	24		76	2.0
A01	49	17.3	46	6.8	8.91	52	19	1	80	1.1
A01	56	16.7	47	4.1	8.75	54	21		79	3.2
A02	4	17.1	49	4.9	9.27	54	16		84	0.1
A02	45	17.0	48	4.8	9.03	53	16	2	82	0.3
A02	5	17.4	50	4.2	9.37	53	12	1	87	0.8
A02	47	16.3	46	4.3	8.67	54	18		81	1.9
A02	8	16.9	47	4.9	9.14	52	16		84	1.6
A02	48	17.6	49	5.1	9.51	52	14		86	0.1
A02	13	16.5	46	3.7	8.91	52	17	1	82	0.4
A02	50	16.8	46	4.1	9.03	51	15		85	0.1
A02	14	17.3	48	5.2	9.30	52	13	2	85	0.4
A02	41	17.9	51	4.4	9.63	53	11		89	0.1
A03	2	16.4	47	5.8	8.99	53	14		86	1.9
A03	46	17.5	49	5.8	9.44	52	17	2	81	2.1
A03	11	14.7	51	4.3	9.42	55	13		87	1.1
A03	52	16.1	47	4.0	8.84	53	8		92	2.3
A03	17	16.7	48	5.0	8.96	54	5		95	2.0
A03	53	17.0	48	4.0	9.30	52	8		92	1.2
A03	18	16.4	49	3.3	8.55	57	10		90	1.1
A03	55	16.5	48	3.9	9.15	53	12		88	0.4
A03	20	15.7	37	4.5	6.21	59	7		93	3.2
A03	43	17.9	51	4.3	9.48	54	14		86	1.8
A04	1	15.7	49	3.0	9.29	53	10		90	0.9
A04	15	14.9	44	4.6	6.98	62	41	3	56	1.9
A04	3	18.0	51	2.6	9.44	54	21	1	78	0.2
A04	19	17.4	50	3.5	9.17	54	30		70	1.3
A04	6	17.6	49	4.1	9.12	53	46	1	23	0.6
A04	51	16.6	47	3.7	8.73	54	54	1	45	1.7
A04	7	17.9	49	4.0	9.96	50	23		77	0.8
A04	54	17.5	50	3.8	9.26	53	45	1	54	0.8
A04	9	16.7	48	3.2	8.93	53	37		63	0.2
A04	12	17.8	50	3.5	9.33	54	45		55	0.5

TABLE 3. CIIT METHYL CHLORIDE PILOT
MALE MOUSE HEMATOLOGY

Treatment Group	Animal ID	MCH pg %	HCT %	WBC $10^3/mm^3$	RBC $10^6/mm^3$	MCV	SEGS %	EOS %	LYMPH %	RETIC %
A01	36	17.9	50	3.4	10.43	52	40		60	1.9
A01	33	17.5	49	7.0	10.92	49	40		60	4.0
A01	76	19.2	49	5.3	11.44	50	27		73	3.5
A01	24	17.2	48	5.4	10.27	50	11		89	2.6
A01	36	16.6	49	2.4	9.89	50	37		63	
A01	37	17.3	48	2.8	10.43	50	49		51	1.8
A02	61	17.0	48	3.9	10.27	50	26		74	0.6
A02	62	17.2	50	2.2	10.36	51	34		64	1.4
A02	66	16.5	48	1.7	10.04	50	28		72	0.6
A02	79	17.4	48	2.2	10.60	51	39		61	1.0
A02	23	17.9	47	2.7	10.67	49	16		84	0.3
A02	27	16.9	49	1.4	10.04	52	37		63	1.3
A02	39	16.3	48	3.4	10.02	50	19		81	0.4
A02	70	17.4	50	4.8	10.35	51	31		69	1.0
A03	28	16.9	52	4.5	10.02	53	20		60	0.2
A03	40	16.9	51	3.5	10.12	52	28		72	1.1
A03	71	13.0	40	4.5	7.67	52	59		41	0.2
A04	35	16.2	46	5.9	9.89	47	26		74	0.3
A04	75	17.2	49	6.3	10.04	51	63		37	0.5
A04	80	16.3	48	3.9	9.84	50	35		65	1.6
A04	25	17.8	48	8.1	10.51	48	71		29	0.3
A04	29	17.8	49	4.4	10.61	50	39		61	0.9
A04	30	18.1	48	12.5	10.61	49	45		55	0.7
A04	64	17.6	49	4.1	10.40	51	36		64	1.5
A04	73	17.7	47	4.4	10.74	49	62		38	0.7

TABLE 4. CIIT METHYL CHLORIDE PILOT
FEMALE MOUSE HEMATOLOGY

Treatment Group	Animal ID	HGB gm %	HCT %	WBC $10^3/mm^3$	RBC $10^6/mm^3$	MCV	SEGS %	EOS %	LYMPH %	RETIC %
A01	16	18.2	48	2.4	10.50	50	20		79	1.1
A01	43	18.0	49	2.8	10.61	50	23		77	2.7
A01	59	18.6	48	3.0	10.87	49	37		63	2.3
A01	60	17.2	47	3.0	10.45	48				1.5
A01	10	17.7	48	3.9	10.37	59	55		45	2.7
A01	44	17.3	47	4.4	10.07	48	43		57	0.9
A01	49	18.5	47	7.5	10.76	48	48		52	2.2
A01	58	17.8	48	6.5	10.24	49	53		47	1.3
A02	41	17.7	48	2.5	10.49	50	21		79	0.7
A02	45	18.6	49	3.2	10.87	50	11		89	1.2
A02	47	16.9	47	3.0	10.06	49	16		84	1.1
A02	48	17.3	48	2.1	10.33	49	17	1	82	0.7
A02	50	16.6	48	1.6	9.80	49	18		82	0.6
A02	4	17.0	48	2.8	10.16	50	18		82	0.4
A02	5	16.9	48	4.8	10.43	49	12		88	2.3
A02	8	17.9	48	5.4	10.79	49	13	1	86	1.6
A02	14	17.6	48	4.3	10.74	49	14		86	0.7
A03	2	16.2	49	3.9	9.67	51	24		36	0.4
A03	11	16.1	48	3.8	9.82	49	36		64	0.6
A03	17	17.0	49	3.0	10.24	50	44		56	0.3
A03	20									
A03	46	16.6	49	6.3	9.90	50	16		84	0.9
A03	18	16.7	49	5.6	10.05	51	20		80	1.1
A03	52	17.1	50	4.3	10.39	51	54		46	0.8
A03	53	17.0	47	5.4	10.14	49	19		80	1.3
A03	55	17.3	49	5.5	10.40	51	29		70	1.1
A04	9	17.5	48	3.8	10.49	49	44		56	1.2
A04	19	17.6	48	2.7	10.54	49	34		66	0.8
A04	54	17.9	48	3.0	10.60	50	24		76	1.3
A04	1	17.7	49	7.0	10.47	50	16	1	82	0.6
A04	3	18.3	47	3.8	10.77	49	19		81	0.8
A04	7	18.2	48	4.1	10.86	49	38		62	
A04	12	17.3	48	4.8	10.17	49	32		68	1.3

TABLE 5 . STATISTICAL ANALYSIS OF HEMATOLOGY DATA - HGB

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible] ppm	10	17.6100	.6951	.2198	16.5000	18.9000
[illegible] ppm	10	16.8000	.9580	.3029	15.6000	18.3000
[illegible] ppm	10	16.9000	.6052	.1914	15.8000	17.4000
CONTROL	10	16.8000	.6963	.2202	15.5000	17.5000
	40	17.0625			15.5000	18.9000
	UNGROUPED DATA		.7915	.1252		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible] ppm	10	16.9500	.5662	.1790	15.7000	17.6000
[illegible] ppm	10	17.0800	.4894	.1548	16.3000	17.9000
[illegible] ppm	10	16.6900	.6454	.2041	15.7000	17.9000
CONTROL	10	17.0200	1.0311	.3261	14.9000	18.3000
TOTAL	40	16.9325			14.9000	18.0000
	UNGROUPED DATA		.7022	.1110		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible] ppm	4	17.6033	.8884	.3628	16.6000	19.2000
[illegible] ppm	8	17.0750	.5175	.1830	16.3000	17.9000
[illegible] ppm	3	15.6000	2.2517	1.3000	13.0000	16.9000
CONTROL	8	17.3375	.7170	.2535	16.2000	18.1000
TOTAL	23	17.1200			13.0000	19.2000
	UNGROUPED DATA		1.0953	.2191		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible] ppm	8	17.9125	.5139	.1817	17.2000	18.4000
[illegible] ppm	9	17.3889	.4254	.2589	16.6000	18.6000
[illegible] ppm	8	16.7500	.4339	.1524	16.1000	17.3000
CONTROL	7	17.7857	.3671	.1394	17.3000	18.3000
TOTAL	32	17.4469			16.1000	18.6000
	UNGROUPED DATA		.6009	.1148		

TABLE 5. STATISTICAL ANALYSIS OF HEMATOLOGY DATA - HCT

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	10	47.7000	1.1595	.3667	43.0000	49.0000
[illegible]	10	47.6000	1.8974	.6000	45.0000	50.0000
[illegible]	10	48.1000	3.1073	.9826	41.0000	52.0000
[illegible]	10	48.3000	1.4181	.4485	47.0000	50.0000
TOTAL	40	47.9250			4[illegible].0000	52.0000
	UNGROUPED DATA		1.9792	.3129		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	10	46.6000	1.4298	.4522	43.0000	49.0000
[illegible]	10	48.0000	1.7638	.5578	44.0000	51.0000
[illegible]	10	47.5000	3.9511	1.2494	37.0000	51.0000
[illegible]	10	48.7000	2.0028	.6333	44.0000	51.0000
TOTAL	40	47.7000			37.0000	51.0000
	UNGROUPED DATA		2.5136	.3974		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	6	48.8333	.7528	.3073	48.0000	50.0000
[illegible]	4	48.5000	1.0693	.3748	47.0000	50.0000
[illegible]	3	47.6667	6.6583	3.8442	40.0000	52.0000
[illegible]	4	48.3000	1.0000	.3780	46.0000	49.0000
TOTAL	24	48.3200			40.0000	52.0000
	UNGROUPED DATA		2.1548	.4319		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	8	47.7500	.7071	.2500	47.0000	49.0000
[illegible]	8	48.0000	.5000	.1667	47.0000	49.0000
[illegible]	9	48.7500	.9064	.3134	47.0000	50.0000
[illegible]	7	48.0000	.5774	.2182	47.0000	49.0000
TOTAL	32	48.1250			47.0000	50.0000
	UNGROUPED DATA		.7513	.1329		

TABLE 5 . STATISTICAL ANALYSIS OF HEMATOLOGY DATA - WBC

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	10	6.5800	.7621	.2347	5.2000	7.6000
[illegible]	10	6.0900	1.1050	.3494	4.7300	8.1000
[illegible]	10	5.8100	1.2793	.4045	4.2000	8.7300
[illegible]	10	3.8300	.3944	.1247	3.3000	4.0000
TOTAL	40	5.5700			3.3000	8.7000
	UNGROUPED DATA		1.4041	.2220		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	5.3500	1.0363	.3277	4.1000	6.8000
750 ppm	10	4.5600	.4904	.1551	3.7000	5.2000
1500 ppm	10	4.4900	.8171	.2584	3.3000	5.8000
CONTROL	10	3.6000	.5774	.1826	3.6000	4.6000
TOTAL	40	4.5000			3.6000	6.8000
	UNGROUPED DATA		.9634	.1523		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	6	4.3833	1.7960	.7332	2.4000	7.4000
750 ppm	8	2.7875	1.1630	.4112	1.0000	4.8000
1500 ppm	3	4.1667	.5774	.3333	3.5000	4.5000
CONTROL	8	4.2800	2.9174	1.0315	3.6000	12.5000
TOTAL	25	4.4260			1.0000	12.5000
	UNGROUPED DATA		2.3515	.4703		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	8	4.1875	1.8646	.6590	2.4000	7.5000
[illegible]	4	3.3500	1.2738	.4244	1.0000	5.4000
[illegible]	8	4.7250	1.1336	.4008	3.0000	6.3000
[illegible]	7	4.1714	1.4268	.5393	2.7000	7.0000
TOTAL	32	4.0687			1.0000	7.5000
	UNGROUPED DATA		1.4759	.2609		

TABLE 5. STATISTICAL ANALYSIS OF HEMATOLOGY DATA - RBC

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	10	9.6820	.4264	.1348	9.1200	10.2700
[illegible]	10	9.5300	.6196	.1959	8.8200	10.6000
[illegible]	10	9.5530	.6565	.2076	8.0600	10.2600
[illegible]	10	9.2270	.4607	.1457	8.2300	9.6600
TOTAL	40	9.4990			8.0800	10.6000
	UNGROUPED DATA		.5546	.0877		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	8.7140	.4289	.1331	8.1000	9.1500
[illegible]	10	9.1860	.2885	.0912	8.6700	9.6300
1500 ppm	10	8.8360	.9691	.3064	6.2100	9.4800
CONTROL	10	9.0210	.7869	.2488	[illegible].9800	9.9600
TOTAL	40	8.9393			[illegible].2100	9.9600
	UNGROUPED DATA		.6729	.1064		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	6	10.5633	.5424	.2214	9.3900	11.4400
[illegible]	6	10.2937	.2528	.0894	10.0200	10.6700
[illegible]	3	9.2700	1.3865	.8005	7.6700	10.1200
[illegible]	8	10.3300	.3546	.1254	9.8400	10.7400
TOTAL	25	10.2472			7.6700	11.4400
	UNGROUPED DATA		.6513	.1303		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	8	10.4838	.2636	.0932	10.0700	10.4700
[illegible]	9	10.4478	.3507	.1169	9.8000	10.8700
[illegible]	8	10.0743	.2563	.0942	9.6700	10.4000
[illegible]	7	10.5571	.2240	.0847	10.1700	10.8000
TOTAL	32	10.3746			9.6700	10.8700
	UNGROUPED DATA		.3297	.0583		

TABLE 5. STATISTICAL ANALYSIS OF HEMATOLOGY DATA - MCV

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	10	50.5000	1.3540	.4282	45.0000	54.0000
[illegible]	10	51.0000	1.2472	.3944	50.0000	54.0000
[illegible]	10	51.2000	1.4757	.4667	50.0000	55.0000
[illegible]	10	51.7000	1.5670	.4955	50.0000	55.0000
TOTAL	40	51.1000			45.0000	55.0000
	UNGROUPED DATA		1.4286	.2259		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	53.9000	2.0248	.6403	52.0000	58.0000
750 ppm	10	52.6000	.9661	.3055	51.0000	54.0000
1500 ppm	10	54.2000	2.2509	.7118	52.0000	59.0000
CONTROL	10	54.8000	3.0551	.9661	50.0000	62.0000
TOTAL	40	53.6750			50.0000	62.0000
	UNGROUPED DATA		2.2117	.3497		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	4	50.1667	.9032	.4514	49.0000	52.0000
[illegible]	4	50.5000	.9258	.3273	49.0000	52.0000
[illegible]	3	52.3333	.5774	.3333	52.0000	53.0000
CONTROL	8	49.3750	1.4079	.4978	47.0000	51.0000
TOTAL	29	50.2000			47.0000	53.0000
	UNGROUPED DATA		1.3699	.2748		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	4	50.1250	3.6815	1.3314	48.0000	59.0000
[illegible]	6	49.3333	.5030	.1027	49.0000	50.0000
[illegible]	4	50.2500	.8864	.3134	49.0000	51.0000
[illegible]	7	49.2857	.4880	.1844	49.0000	50.0000
TOTAL	32	49.7500			48.0000	59.0000
	UNGROUPED DATA		1.8837	.3330		

TABLE 5. STATISTICAL ANALYSIS OF HEMATOLOGY DATA - MCH

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	18.1952	.3847	.1217	17.6125	19.0789
750 ppm	10	17.6331	.4226	.1336	17.1181	18.7075
1500 ppm	10	17.8248	.9397	.2972	17.1540	20.4208
CONTROL	10	18.2834	.4058	.1283	17.6125	19.0765
TOTAL	40	17.9841			17.1181	20.4208
	UNGROUPED DATA		.6242	.0987		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	19.4723	.6711	.2122	18.9071	21.0651
750 ppm	10	18.5953	.1261	.0399	18.4486	18.8261
1500 ppm	10	19.3976	2.2133	.6999	17.7282	25.2818
CONTROL	10	18.9292	1.1115	.3515	16.8999	21.3467
TOTAL	40	19.0226			16.8999	25.2818
	UNGROUPED DATA		1.2750	.2016		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	6	16.7427	.2956	.1843	16.3918	17.1428
[illegible]	9	16.5844	.2083	.0735	16.2675	16.8327
[illegible]	3	16.8383	.1271	.0734	16.6996	16.9492
[illegible]	9	16.7816	.2783	.0984	16.3602	17.1315
TOTAL	28	16.7167			16.2675	17.1428
	UNGROUPED DATA		.2034	.0487		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	17.0367	.2473	.1619	16.6593	17.3828
750 ppm	9	16.7641	.2796	.0932	16.2913	17.1113
1500 ppm	8	16.6240	.1403	.0494	16.3951	16.7677
CONTROL	7	16.8478	.1352	.0511	16.6826	17.0108
TOTAL	32	16.8126			16.2833	17.3828
	UNGROUPED DATA		.2336	.0446		

TABLE 5. STATISTICAL ANALYSIS OF HEMATOLOGY DATA - MCHC

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	34.0373	.5085	.1583	33.2250	36.8509
750 ppm	10	34.5834	.6410	.2027	33.5449	35.3844
1500 ppm	10	34.8360	2.0196	.6387	32.4470	40.8408
CONTROL	10	35.3743	.5150	.1629	34.6844	36.2319
TOTAL	40	35.2670			32.4470	40.8408
	UNGROUPED DATA		1.2145	.1920		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	36.1354	.6297	.1991	35.3043	37.3192
750 ppm	10	35.3619	.6262	.1980	34.1604	36.4797
1500 ppm	10	35.1758	2.8534	.9023	32.2332	42.8505
CONTROL	10	35.8407	1.2315	.3894	31.8864	36.4118
TOTAL	40	35.4333			31.8864	42.8505
	UNGROUPED DATA		1.6098	.2545		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	6	33.2776	.2338	.0954	33.0829	33.5493
750 ppm	9	32.8923	.6391	.2260	32.1865	34.2367
1500 ppm	3	32.1774	.3895	.2249	31.8231	32.5945
CONTROL	9	34.6051	.8421	.2977	33.1301	35.2839
TOTAL	29	33.2462			31.8231	35.2839
	UNGROUPED DATA		.8484	.1721		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	5	34.2279	2.2078	.7947	28.9296	35.8194
[illegible]	4	33.8703	.4653	.1618	33.8679	34.5649
[illegible]	8	33.6914	.6351	.2246	32.2708	34.2149
[illegible]	7	34.1861	.3795	.1434	33.7736	34.7108
TOTAL	32	33.8341			28.9296	35.8194
	UNGROUPED DATA		1.2375	.2184		

TABLE 5. STATISTICAL ANALYSIS OF HEMATOLOGY DATA - SEGS (% WBC)

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	10	29.7000	7.4989	2.3714	21.0000	[illegible]
[illegible]	10	20.0000	5.9442	1.8797	10.0000	32.0000
[illegible]	10	11.9000	4.0125	1.2689	6.0000	18.0000
[illegible]	10	44.7000	7.7610	2.4542	28.0000	54.0000
TOTAL	40	26.5750			6.0000	54.0000
	UNGROUPED DATA		13.8488	2.1897		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	10	28.7000	7.3944	2.3383	19.0000	41.0000
[illegible]	10	14.8000	2.2509	.7118	11.0000	18.0000
[illegible]	10	13.8000	3.7947	1.2000	5.0000	17.0000
[illegible]	10	35.2000	13.7985	4.3669	8.0000	54.0000
TOTAL	40	22.3750			5.0000	54.0000
	UNGROUPED DATA		12.7474	2.0155		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	4	34.3000	13.2944	6.6243	11.0000	49.0000
[illegible]	8	28.7500	8.2371	2.9117	15.0000	39.0000
[illegible]	3	35.0667	23.5994	11.8000	23.0000	59.0000
[illegible]	8	47.1250	16.1726	5.7179	25.0000	71.0000
TOTAL	25	36.7200			11.0000	71.0000
	UNGROUPED DATA		15.0700	3.0150		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	4	34.0750	19.1365	6.7645	0	55.0000
[illegible]	9	15.5956	3.2039	1.0673	11.0000	21.0000
[illegible]	9	24.4889	16.1047	5.3682	0	54.0000
[illegible]	7	29.5714	10.2605	3.8782	16.0000	44.0000
TOTAL	33	26.3330			0	55.0000
	UNGROUPED DATA		14.6461	2.5044		

TABLE 5. STATISTICAL ANALYSIS OF HEMATOLOGY DATA - SEGS ($10^3/mm^3$)

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	194.4500	50.7931	16.0622	148.4000	299.2030
750 ppm	10	124.4900	56.0188	17.7122	67.2000	236.0000
1500 ppm	10	67.4000	20.4011	6.4514	25.2000	95.4000
CONTROL	10	160.4100	26.7006	8.4435	120.7000	214.2090
TOTAL	40	130.6075			25.2000	299.2030
	UNGROUPED DATA		62.9163	9.9479		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	153.6900	48.9492	15.4770	86.1000	227.5000
750 ppm	10	67.3200	11.3107	3.5760	48.4000	78.4300
1500 ppm	10	49.6200	24.4661	7.7368	25.0000	90.6000
CONTROL	10	130.5900	59.6071	18.8747	30.0000	199.0030
TOTAL	40	100.2950			25.0000	227.5000
	UNGROUPED DATA		58.6994	9.2812		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	6	140.7500	75.0268	30.6956	59.4000	280.0033
750 ppm	8	77.2500	35.1000	12.4125	43.2000	144.3000
1500 ppm	3	151.1667	99.0963	57.2133	90.0000	265.5000
CONTROL	8	302.8500	186.1713	65.8215	136.5000	575.1300
TOTAL	25	173.2960			43.2000	575.1300
	UNGROUPED DATA		146.3270	29.2654		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	7	190.2286	126.1958	47.6972	48.0000	360.0000
750 ppm	9	48.7333	13.4187	4.4702	20.0000	70.2000
1500 ppm	8	133.6875	45.5269	16.0962	93.6000	232.2000
CONTROL	7	117.0000	40.9321	15.4709	72.0000	167.2000
TOTAL	31	110.2032			20.0000	360.0000
	UNGROUPED DATA		82.3041	14.7822		

TABLE 5 . STATISTICAL ANALYSIS OF HEMATOLOGY DATA - EOS (% WBC)

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	1.0000	.9428	.2981	0	2.0000
750 ppm	10	.3000	.4830	.1528	0	1.0000
1500 ppm	10	.2000	.4216	.1333	0	1.0000
CONTROL	10	.9000	.9944	.3145	0	2.0000
TOTAL	40	.6800			0	2.0000
	UNGROUPED DATA		.8102	.1281		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	.6300	.6992	.2211	0	2.0000
750 ppm	10	.6000	.8433	.2667	0	2.0000
1500 ppm	10	.2000	.6325	.2000	0	2.0000
CONTROL	10	.7000	.9487	.3000	0	3.0000
TOTAL	40	.5250			0	3.0000
	UNGROUPED DATA		.7841	.1240		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	6	0	0	0	0	0
750 ppm	4	0	0	0	0	0
1500 ppm	3	0	0	0	0	0
CONTROL	2	0	0	0	0	0
TOTAL	25	0			0	0
	UNGROUPED DATA		0	0		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	0	0	0	0	0
750 ppm	9	.2222	.4410	.1470	0	1.0000
1500 ppm	9	0	0	0	0	0
CONTROL	7	.1429	.3780	.1429	0	1.0000
TOTAL	33	.0909			0	1.0000
	UNGROUPED DATA		.2919	.0509		

TABLE 5. STATISTICAL ANALYSIS OF HEMATOLOGY DATA - EOS ($10^3/mm^3$)

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	6.2700	6.0467	1.9120	0	14.2000
750 ppm	10	2.0400	3.3374	1.0554	0	8.1000
1500 ppm	10	1.1100	2.3431	.7409	0	5.8000
CONTROL	10	3.3400	3.6357	1.1497	0	8.4000
TOTAL	40	3.1900			0	14.2000
	UNGROUPED DATA		4.3838	.6931		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	3.5000	3.9469	1.2481	0	10.4000
750 ppm	16	2.7900	4.1340	1.3973	0	10.4000
1500 ppm	10	1.1400	3.6682	1.1600	0	11.6000
CONTROL	10	2.6000	4.2654	1.3488	0	13.0000
TOTAL	40	2.5625			0	13.0000
	UNGROUPED DATA		3.9437	.6249		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	6	0	0	0	0	0
750 ppm	8	0	0	0	0	0
1500 ppm	3	0	0	0	0	0
CONTROL	8	0	0	0	0	0
TOTAL	25	0			0	0
	UNGROUPED DATA		0	0		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	7	0	0	0	0	0
750 ppm	9	.0333	1.0000	.0160	0	5.4000
1500 ppm	8	0	0	0	0	0
CONTROL	7	1.0000	2.6450	1.0000	0	7.0000
TOTAL	31	.4677			0	7.0000
	UNGROUPED DATA		1.5894	.2855		

TABLE 5. STATISTICAL ANALYSIS OF HEMATOLOGY DATA - LYMPH (% WBC)

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	66.2000	9.5661	3.0251	48.0000	79.0000
750 ppm	10	79.7000	6.3009	1.8977	68.0000	90.0000
1500 ppm	10	87.7000	4.4981	1.4224	81.0000	94.0000
CONTROL	10	54.3000	7.9169	2.5036	45.0000	71.0000
TOTAL	40	71.9750			45.0000	94.0000
	UNGROUPED DATA		14.6943	2.3234		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	70.6000	7.6623	2.4230	58.0000	80.0000
750 ppm	10	84.5000	2.4608	.7782	81.0000	89.0000
1500 ppm	10	89.0000	4.1899	1.3250	81.0000	95.0000
CONTROL	10	61.1000	19.0930	6.0378	21.0000	90.0000
TOTAL	40	76.3000			21.0000	95.0000
	UNGROUPED DATA		15.1424	2.3942		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	6	66.0000	13.2966	5.4283	51.0000	89.0000
750 ppm	8	71.2500	8.2071	2.9017	61.0000	84.0000
1500 ppm	3	57.6667	15.6312	9.0247	41.0000	72.0000
CONTROL	8	52.0750	16.1726	5.7179	39.0000	74.0000
TOTAL	25	62.4800			29.0000	89.0000
	UNGROUPED DATA		14.6803	2.9361		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	4	52.5000	24.7155	8.7383	0	79.0000
750 ppm	9	84.2222	3.2702	1.0901	79.0000	89.0000
1500 ppm	9	57.3333	26.9629	8.9876	3	84.0000
CONTROL	7	70.1429	9.8392	3.7189	56.0000	82.0000
TOTAL	33	66.2121			0	89.0000
	UNGROUPED DATA		22.3003	3.8924		

TABLE 5. STATISTICAL ANALYSIS OF HEMATOLOGY DATA - LYMPH ($10^3/mm^3$)

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	433.9500	73.5894	23.2710	359.9000	584.6000
750 ppm	10	432.4700	73.5911	23.7040	366.6000	603.0000
1500 ppm	10	511.6100	129.8324	41.0566	365.2000	817.8000
CONTROL	10	237.8700	48.4613	15.3248	154.0000	326.6000
TOTAL	40	488.9775			154.0000	817.8000
	UNGROUPED DATA		147.8251	23.2467		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	377.3000	82.7597	26.1709	266.0000	544.0000
750 ppm	10	385.4600	43.9373	13.8942	303.4000	442.0000
1500 ppm	10	398.2200	65.0057	20.5575	297.3000	494.0000
CONTROL	10	214.3500	59.6479	18.9256	94.3000	308.0000
TOTAL	40	343.8525			94.3000	544.0000
	UNGROUPED DATA		98.8722	15.5066		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	6	297.5033	148.7294	60.7185	142.6000	488.6000
750 ppm	6	281.9000	98.4769	31.9804	88.2000	331.2000
1500 ppm	3	235.5000	45.8749	26.0240	184.5000	278.0000
CONTROL	6	317.9500	167.8274	59.3359	167.2000	687.5000
TOTAL	25	265.9040			88.2000	687.5000
	UNGROUPED DATA		134.2849	26.8970		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	7	245.1429	78.1223	29.5274	175.5000	398.0000
750 ppm	9	280.4333	115.2493	38.4164	131.2000	494.4000
1500 ppm	8	317.4500	147.8700	52.2628	140.4000	529.2000
CONTROL	7	297.1429	132.6654	50.1281	178.2000	574.0000
TOTAL	31	285.9645			131.2000	574.0000
	UNGROUPED DATA		118.6717	21.3141		

TABLE 5. STATISTICAL ANALYSIS OF HEMATOLOGY DATA - RETIC

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	.4700	.2869	.0907	.1000	1.0000
750 ppm	10	.9100	.7187	.2273	.1000	2.0000
1500 ppm	10	1.3100	.6286	.1986	.6000	2.5000
CONTROL	10	.8800	.3676	.1162	.3000	1.4000
TOTAL	40	.8925			.1000	2.5000
	UNGROUPED DATA		.5924	.0937		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	1.2500	1.0927	.3455	.1000	3.2000
750 ppm	10	.5900	.6579	.2081	.1000	1.9000
1500 ppm	10	1.7100	.7866	.2488	.4000	3.2000
CONTROL	10	.8900	.5820	.1841	.2000	1.8000
TOTAL	40	1.[illegible]375			.1000	3.2000
	UNGROUPED DATA		.8821	.1395		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	6	2.3000	1.4227	.5808	0	4.3000
750 ppm	8	.8250	.4097	.1449	.3000	1.4300
1500 ppm	3	.5000	.5196	.3000	.2000	1.1000
CONTROL	8	.8125	.4998	.1767	.3000	1.6000
TOTAL	25	1.1360			0	4.3000
	UNGROUPED DATA		1.0111	.2022		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	1.6375	.7230	.2556	.5000	2.7000
750 ppm	9	1.5333	.6300	.2000	.4000	2.3000
1500 ppm	9	.7222	.6295	.1432	0	1.3000
CONTROL	7	.8571	.4685	.1771	0	1.3000
TOTAL	33	1.1061			0	2.7000
	UNGROUPED DATA		.6941	.1208		

TABLE 5. STATISTICAL ANALYSIS OF HEMATOLOGY DATA - M:E RATIO

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	9	1.8833	.6358	.2119	.8700	2.6300
750 ppm	9	1.4767	.2211	.0737	1.1000	1.9400
1500 ppm	6	1.3412	.3411	.1206	1.0733	1.9400
CONTROL	5	1.4469	.3293	.1473	1.1100	1.9930
TOTAL	31	1.5316			.8700	2.6300
	UNGROUPED DATA		.4431	.0796		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	7	1.4871	.3933	.1487	.9500	2.6700
750 ppm	7	1.5729	.3850	.1455	1.0300	2.6100
1500 ppm	10	1.3790	.2977	.0941	1.0000	1.9900
CONTROL	6	2.1650	.5171	.2111	1.5900	2.9100
TOTAL	30	1.5888			.8900	2.9100
	UNGROUPED DATA		.4777	.0872		

Mice - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	6	2.0367	.5061	.2066	1.3400	2.9100
750 ppm	7	3.0343	.6584	.2488	1.8400	3.9500
1500 ppm	3	1.6967	.3201	.1846	1.3300	1.9200
CONTROL	9	2.3867	.5431	.1827	1.6200	3.2000
TOTAL	25	2.3724			1.3300	3.9500
	UNGROUPED DATA		.6946	.1389		

Mice - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	7	1.8243	.2781	.1051	1.3700	2.2100
750 ppm	7	2.3614	.7483	.2828	1.4000	3.7200
1500 ppm	7	1.7200	.4008	.1515	1.2400	2.2600
CONTROL	8	1.7625	.6146	.2173	.7200	2.7900
TOTAL	29	1.9117			.7200	3.7200
	UNGROUPED DATA		.5774	.1072		

APPENDIX E

CLINICAL CHEMISTRY DATA

TABLE 1. CLINICAL CHEMISTRY DATA FOR MALE RATS

Treatment Group	Animal ID	Glucose	BUN	AP	SGOT	SGPT	CPK
1	22	165	11	78	103	30	227
1	24	151	15	77	114	29	237
1	28	176	16	67	122	35	317
1	31	170	16	64	125	53	302
1	33	151	13	72	95	26	298
1	34	154	15	60	100	34	239
1	36	177	13	77	174	35	244
1	37	185	16	79	139	37	287
1	63	132	14	82	116	38	362
1	76	137	13	74	104	29	232
2	23	138	12	68	127	32	372
2	27	195	15	67	116	27	343
2	39	139	16	80	138	50	407
2	61	158	10	67	116	40	443
2	66	136	13	76	156	31	627
2	69	154	12	74	159	80	278
2	70	155	12	66	140	29	366
2	74	140	13	75	96	33	176
2	79	124	15	74	102	28	264
3	21	159	17	65	115	41	377
3	28	147	16	68	113	40	369
3	32	159	18	70	120	44	432
3	38	168	15	64	294	138	1798
3	40	179	21	63	241	77	897
3	67	188	14	67	99	32	237
3	68	140	20	64	505	84	1845
3	71	138	14	65	445	53	1962
3	72	130	13	64	124	25	478
3	78	184	16	52	376	89	989
4	25	125	18	73	94	25	268
4	29	139	20	82	164	77	1111
4	30	149	17	59	116	38	475
4	35	202	21	74	410	50	1623
4	64	150	17	80	198	87	973
4	65	191	21	86	199	59	821
4	73	167	20	63	115	38	433
4	77	154	19	82	143	48	690
4	80	183	20	71	162	66	620
4	85	143	16	66	167	83	1098

TABLE 2. CLINICAL CHEMISTRY DATA FOR FEMALE RATS

Treatment Group	Animal ID	Glucose	BUN	AP	SGOT	SGPT	CPK
1	10	154	15	58	108	28	269
1	16	155	15	75	150	31	716
1	43	158	17	81	87	25	175
1	44	135	16	58	107	23	221
1	49	128	18	69	94	22	289
1	56	145	18	77	104	30	465
1	57	130	15	77	95	25	142
1	58	93	16	79	120	30	253
1	59	110	16	65	88	24	217
1	60	110	13	50	121	24	615
2	4	109	13	49	125	26	437
2	5	104	14	64	1[illegible]1	31	376
2	8	140	14	70	114	26	305
2	13	114	16	56	156	30	795
2	14	148	18	60	122	30	374
2	41	88	14	67	111	28	224
2	45	111	15	58	129	29	698
2	47	120	21	67	160	52	690
2	48	144	13	46	122	38	278
2	50	116	16	49	164	31	451
3	2	123	16	62	312	60	1871
3	11	147	16	61	97	27	195
3	17	163	16	64	139	64	317
3	18	143	15	67	133	30	210
3	20	132	16	45	278	112	261
3	43	115	19	53	220	53	470
3	46	152	17	58	147	70	251
3	52	112	10	54	408	84	1933
3	53	106	19	82	150	41	443
3	55	130	21	63.	465	72	2099
4	1	158	18	57	96	25	461
4	3	144	19	73	90	25	246
4	6	154	21	64	120	29	564
4	7	182	24	72	145	58	434
4	9	169	23	65	122	32	557
4	12	124	18	81	154	40	504
4	15	176	18	60	94	26	366
4	19	138	18	67	153	40	321
4	51	116	20	70	154	40	813
4	54	141	21	72	201	40	1051

TABLE 3. CLINICAL CHEMISTRY DATA FOR MALE MICE

Treatment Group	Animal ID	Glucose	BUN	AP	SGOT	SGPT	CPK
1	22						
1	24	102	32	72	322	82	996
1	31						
1	33	196	38	88	434	162	1628
1	34						
1	34						
1	36						
1	36						
1	37	156	32	68	550	120	1590
1	63						
1	76	138	28	52	446	86	3638
2	23	130	28	56	842	102	1148
2	27	128	20	54	470	98	3366
2	39	98	20	50	244	52	5864
2	61						
2	62						
2	66						
2	69						
2	70	130	30	66	434	98	2038
2	74						
2	79						
3	28	148	20	62	1238	254	1826
3	32						
3	34						
3	40	102	26	78	848	336	2496
3	67						
3	68						
3	71						
3	72						
3	78						
4	25	144	30	58	978	74	6158
4	29	176	42	52	560	74	4216
4	30	160	34	58	642	60	
4	35	162	28	68	466	106	4060
4	64	168	28	66	942	106	
4	65						
4	75	148	26	68	1262	122	
4	77						
4	80						

TABLE 4. CLINICAL CHEMISTRY DATA FOR FEMALE MICE

Treatment Group	Animal ID	Glucose	BUN	AP	SGOT	SGPT	CPK
1	10						
1	16	134	24	74	924	126	4352
1	43	122	38	112	354	64	1462
1	44	144	28	90	500	154	1804
1	49	130	38	68	792	100	2542
1	56						
1	57						
1	58	94	38	106	896	190	
1	59	118	34	130	802	180	3192
1	60						
2	4						
2	5	112	22	78	372	54	442
2	8	144	22	58	820	90	798
2	13						
2	14						
2	41						
2	45						
2	47						
2	48						
2	50						
3	2	78	20	70	1234	464	1968
3	11						
3	17						
3	18						
3	20						
3	42						
3	46	138	18	66	652	96	474
3	52	160	18	68		440	4002
3	53						
3	55	126	20	50	1346	126	3240
4	1	132	22	72	346	60	2446
4	3	184	22	68	598	86	4268
4	4						
4	9	124	22	76	1326	100	5982
4	12	118	30	118	14	212	4
4	15						
4	19						
4	51						
4	54	182	34	54	654	72	2104

TABLE 5. STATISTICAL ANALYSIS OF CLINICAL CHEMISTRY DATA

GLUCOSE

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	159.8000	17.6568	5.5833	132.0000	185.0000
750 ppm	9	148.7778	20.4742	6.8247	124.0000	195.0000
1500 ppm	10	159.2000	20.3677	6.4438	130.0000	188.0000
CONTROL	10	168.3000	24.7523	7.8274	125.0000	202.0000
TOTAL	39	157.2308			124.0000	202.0000
	UNGROUPED DATA		20.6786	3.3112		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	131.8000	22.8494	6.9728	93.0000	158.0000
750 ppm	10	119.4000	19.1287	6.0465	88.0000	148.0000
1500 ppm	10	132.3000	18.7264	5.9218	106.0000	163.0000
CONTROL	10	151.4000	22.6823	7.1728	116.0000	182.0000
TOTAL	40	133.7250			88.0000	182.0000
	UNGROUPED DATA		23.0306	3.6415		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	4	148.0000	39.0896	19.5448	102.0000	196.0000
750 ppm	4	121.5000	15.0958	7.8475	98.0000	130.0000
1500 ppm	2	125.0000	32.5269	23.0000	102.0000	148.0000
CONTROL	6	159.6667	12.0277	4.9103	144.0000	176.0000
TOTAL	16	142.8750			98.0000	196.0000
	UNGROUPED DATA		27.5291	6.6823		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	6	123.6667	17.1778	7.0127	94.0000	144.0000
750 ppm	2	128.0000	22.6274	16.0000	112.0000	144.0000
1500 ppm	4	125.5000	34.6554	17.3277	78.0000	160.0000
CONTROL	5	148.0000	12.3419	14.4637	118.0000	164.0000
TOTAL	17	131.7647			78.0000	184.0000
	UNGROUPED DATA		27.0082	6.5504		

TABLE 5. STATISTICAL ANALYSIS OF CLINICAL CHEMISTRY DATA

BLOOD UREA NITROGEN

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	14.2000	1.6865	.5333	11.0000	16.0000
750 ppm	9	13.1111	1.9003	.6334	10.0000	16.0000
1500 ppm	10	16.4000	2.6331	.8327	13.0000	21.0000
CONTROL	10	18.9000	1.7920	.5667	16.0000	21.0000
TOTAL	39	15.7179			10.0000	21.0000
	UNGROUPED DATA		2.9731	.4761		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	15.9000	1.5239	.4819	13.0000	18.0000
750 ppm	10	15.4000	2.5333	.7916	13.0000	21.0000
1500 ppm	10	16.5000	2.9533	.9339	10.0000	21.0000
CONTROL	10	20.0000	2.2111	.6992	18.0000	24.0000
TOTAL	40	16.9500			10.0000	24.0000
	UNGROUPED DATA		2.9084	.4599		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	4	32.5000	4.1231	2.0616	28.0000	38.0000
750 ppm	4	24.5000	5.2599	2.6300	20.0000	30.0000
1500 ppm	2	23.0000	4.2426	3.0000	20.0000	26.0000
CONTROL	6	31.3333	5.8878	2.4037	26.0000	42.0000
TOTAL	16	28.8750			20.0000	42.0000
	UNGROUPED DATA		6.1087	1.5272		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	6	33.3333	6.0222	2.4585	24.0000	38.0000
750 ppm	2	22.0000	0	0	22.0000	22.0000
1500 ppm	4	19.0000	1.1547	.5774	18.0000	20.0000
CONTROL	5	26.0000	5.6569	2.5298	22.0000	34.0000
TOTAL	17	26.4706			18.0000	38.0000
	UNGROUPED DATA		7.3324	1.7784		

TABLE 5. STATISTICAL ANALYSIS OF CLINICAL CHEMISTRY DATA

ALKALINE PHOSPHATASE

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	73.0000	7.1447	2.2657	60.0000	82.0000
750 ppm	9	71.6667	5.3151	1.7717	64.0000	80.0000
1500 ppm	10	64.2000	4.8028	1.5188	52.0000	70.0000
CONTROL	10	73.6000	8.9839	2.8410	59.0000	86.0000
TOTAL	39	70.5897			52.0000	86.0000
	UNGROUPED DATA		7.5966	1.2155		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	68.9000	10.6810	3.3779	50.0000	81.0000
750 ppm	10	58.6000	8.5140	2.6924	46.0000	70.0000
1500 ppm	10	66.9000	9.8257	3.1072	45.0000	82.0000
CONTROL	10	68.1000	6.9992	2.2133	57.0000	81.0000
TOTAL	40	64.1250			45.0000	82.0000
	UNGROUPED DATA		9.0566	1.5575		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	4	70.0000	14.7874	7.3937	52.0000	88.0000
750 ppm	4	56.5000	6.8069	3.4034	50.0000	66.0000
1500 ppm	2	70.0000	11.3137	8.0000	62.0000	78.0000
CONTROL	6	61.6667	6.6232	2.7039	52.0000	68.0000
TOTAL	16	63.5000			50.0000	88.0000
	UNGROUPED DATA		10.3466	2.5917		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	6	96.6667	23.7284	9.6839	66.0000	130.0000
750 ppm	2	68.0000	14.1421	10.0000	58.0000	78.0000
1500 ppm	4	63.5000	9.1469	4.5735	50.0000	76.0000
CONTROL	5	77.6000	24.0583	10.7592	54.0000	110.0000
TOTAL	17	79.0824			50.0000	130.0000
	UNGROUPED DATA		23.2537	5.6399		

TABLE 5. STATISTICAL ANALYSIS OF CLINICAL CHEMISTRY DATA

SGOT

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	119.2000	23.3847	7.3949	95.0000	174.0000
750 ppm	9	127.7778	22.2979	7.4326	96.0000	159.0000
1500 ppm	10	244.2000	156.5594	49.5084	99.0000	505.0000
CONTROL	10	175.8000	88.7966	28.0800	94.0000	410.0000
TOTAL	39	167.7436			94.0000	505.0000
	UNGROUPED DATA		102.2774	16.3775		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	107.4000	19.1381	6.0520	87.0000	150.0000
750 ppm	10	131.4000	20.6677	6.5357	111.0000	164.0000
1500 ppm	10	274.3000	126.6951	40.0845	97.0000	465.0000
CONTROL	10	122.9000	35.0855	11.0950	90.0000	201.0000
TOTAL	40	151.6500			87.0000	465.0000
	UNGROUPED DATA		81.5219	12.8897		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	4	443.0000	94.3398	47.1699	322.0000	550.0000
750 ppm	4	497.5000	250.1540	125.0770	244.0000	842.0000
1500 ppm	2	1343.0000	275.7716	195.0000	848.0000	1238.0000
CONTROL	6	808.3333	302.9036	123.6925	464.0000	1262.0000
TOTAL	16	640.6250			244.0000	1262.0000
	UNGROUPED DATA		312.8004	78.2001		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	6	711.3333	230.8269	94.2347	350.0000	924.0000
750 ppm	2	596.0000	316.7038	224.0000	372.0000	820.0000
1500 ppm	3	1077.3333	372.5020	215.1103	652.0000	1346.0000
CONTROL	5	587.6000	484.8290	216.4647	14.0000	1326.0000
TOTAL	16	726.8750			14.0000	1346.0000
	UNGROUPED DATA		372.6202	93.1551		

TABLE 5. STATISTICAL ANALYSIS OF CLINICAL CHEMISTRY DATA

SGPT

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	34.6000	7.5601	2.3907	26.0000	53.0000
750 ppm	9	39.8889	17.0180	5.6727	27.0000	80.0000
1500 ppm	10	62.3000	34.6604	10.9606	25.0000	138.0000
CONTROL	10	57.1000	20.9149	6.6139	25.0000	87.0000
TOTAL	39	48.4615			25.0000	138.0000
	UNGROUPED DATA		24.5955	3.9384		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	26.2000	3.2592	1.0306	22.0000	31.0000
750 ppm	10	32.1000	7.7067	2.4361	26.0000	52.0000
1500 ppm	10	61.3000	25.6517	8.1118	27.0000	112.0000
CONTROL	10	35.5000	10.2875	3.2532	25.0000	58.0000
TOTAL	40	38.7750			22.0000	112.0000
	UNGROUPED DATA		19.4284	3.0719		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	4	112.5000	37.1439	18.5719	82.0000	162.0000
750 ppm	4	87.5000	23.7417	11.8708	52.0000	102.0000
1500 ppm	2	295.0000	57.9828	41.0000	254.0000	336.0000
CONTROL	6	90.3333	24.2789	9.9118	60.0000	122.0000
TOTAL	16	120.7500			52.0000	336.0000
	UNGROUPED DATA		74.4361	18.6090		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	6	135.6667	48.4878	19.7951	64.0000	190.0000
750 ppm	2	72.0000	25.4558	18.0000	54.0000	90.0000
1500 ppm	4	281.5000	197.5002	98.7501	94.0000	464.0000
CONTROL	5	164.0000	61.1228	27.3350	60.0000	212.0000
TOTAL	17	153.7647			54.0000	464.0000
	UNGROUPED DATA		121.5460	29.4792		

TABLE 5. STATISTICAL ANALYSIS OF CLINICAL CHEMISTRY DATA

CREATINE PHOSPHOKINASE

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	274.5000	45.6441	14.3707	227.0000	362.0000
750 ppm	9	364.0000	127.7243	42.5748	176.0000	627.0000
1500 ppm	10	940.4000	682.3333	215.7727	237.0000	1962.0000
CONTROL	10	811.2000	402.7417	127.3581	240.0000	1623.0000
TOTAL	39	603.5128			176.0000	1962.0000
		UNGROUPED DATA	485.6946	77.7734		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	336.2000	195.3370	61.7712	142.0000	716.0000
750 ppm	10	442.8000	197.0893	62.3251	224.0000	795.0000
1500 ppm	10	807.0000	807.7917	255.4335	195.0000	2099.0000
CONTROL	10	531.7000	240.2018	75.9585	246.0000	1051.0000
TOTAL	40	534.4250			142.0000	2099.0000
		UNGROUPED DATA	460.5303	72.8175		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	4	1963.0000	1153.5551	576.7775	996.0000	3638.0000
750 ppm	4	3184.0000	2053.3325	1026.6664	1148.0000	5864.0000
1500 ppm	2	2161.0000	473.7615	335.0000	1826.0000	2496.0000
CONTROL	3	4811.3333	1168.8530	674.8376	4060.0000	6158.0000
TOTAL	13	3001.8462			996.0000	6158.0000
		UNGROUPED DATA	1712.5220	474.9684		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	5	2670.4000	1184.0376	516.1013	1462.0000	4352.0000
750 ppm	2	420.0000	251.7200	178.0000	442.0000	798.0000
1500 ppm	4	2426.0000	1543.6450	771.8225	474.0000	4002.0000
CONTROL	5	2960.8000	2268.1688	1014.2523	4.0000	5982.0000
TOTAL	16	2443.7500			4.0000	5982.0000
		UNGROUPED DATA	1660.6074	415.1519		

APPENDIX F

ABSOLUTE ORGAN WEIGHT DATA

TABLE 1. ORGAN WEIGHT DATA FOR MALE RATS

Treatment Group	Animal ID	Heart	Adrenal	Brain	Testes	Spleen	Liver	Right Kidney	Left Kidney	Lungs	Pancreas	Week 12 Body Weight	Final Body Weight
A01	22	1.018	.051	1.868	4.267	.505	8.471	1.092	1.140	1.202	.619	289	268
A01	24	.947	.062	1.894	4.288	.468	6.988	.988	.968	1.043	.777	270	246
A01	26	.918	.066	1.894	4.287	.438	6.763	1.048	1.012	1.288	.432	281	249
A01	31	1.062	.086	1.844	4.782	.518	7.836	1.059	1.042	1.233	.525	291	264
A01	33	1.118	.064	1.960	4.391	.536	8.542	1.129	1.078	1.191	.648	291	270
A01	34	.977	.045	1.930	4.355	.519	8.129	1.095	1.067	1.182	.570	288	264
A01	36	.983	.088	1.828	4.384	.507	7.757	1.098	1.049	1.360	.582	272	249
A01	37	.908	.061	1.762	4.123	.456	7.124	1.043	1.081	1.053	.491	262	248
A01	63	.964	.068	1.925	5.882	.475	7.124	.978	.955	1.048	.232	277	257
A01	76	.960	.119	1.984	4.209	.455	6.792	1.151	1.034	1.277	.313	249	226
A02	23	1.143	.072	1.942	4.265	.492	7.564	1.060	1.064	1.277	.537		256
A02	27	1.034	.071	1.898	4.913	.478	7.549	.971	1.004	1.271	1.243		253
A02	39	1.102	.062	1.846	4.255	.433	7.177	1.051	1.086	1.517	.446	265	240
A02	61	.964	.055	1.846	4.151	.454	6.981	1.053	1.083	1.216	.648	254	242
A02	62	1.011	.099	1.788	3.775	.528	6.461	.953	.983	1.201	.686	246	229
A02	66	.963	.078	1.965	4.461	.472	7.386	.989	1.069	1.267	1.186	258	220
A02	69	.922	.067	1.841	4.080	.500	8.098	1.098	1.076	1.355	.614	273	249
A02	70	.886	.045	1.859	5.411	.481	7.139	.943	1.020	1.250	.305	252	233
A02	74	1.011	.074	1.879	4.598	.511	7.906	1.094	1.071	1.408	.585	272	256
A02	79	.996	.078	1.886	3.981	.516	8.068	1.039	1.132	1.172	.557	278	250
A03	21	.970	.063	1.820	2.620	.410	7.130	1.010	1.990	1.660	1.310	241	220
A03	28	.790	.076	1.850	4.935	.430	6.880	1.040	.972	.998	.857	211	195
A03	32	.966	.050	1.790	2.740	.400	7.390	.948	1.039	1.110	.891	253	228
A03	38	.870	.073	1.860	2.870	.414	6.860	.963	1.080	1.350	.450	215	195
A03	40	.817	.072	1.630	2.590	.425	6.301	.921	.951	1.200	.521	214	195
A03	67	.948	.029	1.730	3.150	.489	7.040	.981	1.010	1.140	.535	236	200
A03	68	.957	.085	1.870	2.847	.302	6.520	.959	.969	1.254	1.086	222	201
A03	71	1.034	.067	2.000	3.210	.468	7.490	1.083	1.189	1.220	.786	244	280
A03	72	.729	.171	1.786	2.007	.372	6.090	.897	.879	1.171	.579	201	184
A03	78	.221	.081	1.865	3.841	.372	6.310	.935	.915	.898	.279	215	195
A04	7	1.036	.083	2.047	4.435	.509	8.080	1.144	1.100	1.150	.880	188	159
A04	25	.877	.069	4.246	1.956	.467	6.795	1.000	.986	.989	.786	305	246
A04	29	.908	.078	1.926	4.654	.500	7.751	1.043	1.027	1.016	.433	304	
A04	30	.860	.087	1.950	5.030	.540	7.300	1.000	1.000	2.650	.383	317	261
A04	35	.923	.051	1.937	4.178	.432	7.384	1.146	1.016	1.143	.433	251	258
A04	64	.960	.061	1.935	5.511	.547	7.965	1.068	1.077	1.177	.300	300	261
A04	65	.892	.088	1.851	4.633	.490	8.268	1.053	1.098	1.245	.511	285	276
A04	73	1.145	.065	2.085	4.349	.680	7.947	1.103	1.105	1.055	.884	310	279
A04	80	1.172	.087	1.948	4.550	.442	7.521	1.045	1.109	1.209	.515	308	277
A04	75	1.060	.070	1.890	4.600	.470	8.060	1.050	1.070	1.230	.390	304	296

TABLE 2. ORGAN WEIGHT DATA FOR FEMALE RATS

Treatment Group	Animal ID	Heart	Adrenal	Brain	Ovaries	Spleen	Liver	Right Kidney	Left Kidney	Lungs	Pancreas	Week 12 Body Weight	Final Body Weight
A01	10	.678	.065	1.754	.116	.392	4.344	.688	.658	.980	.465	170	150
A01	16	.891	.098	1.811	.131	.466	5.131	.663	.676	1.030	.434	178	161
A01	43	.679	.089	1.760	.146	.417	5.629	.773	.715	.895	.448	181	164
A01	44	.671	.077	1.722	.122	.371	4.437	.642	.677	.931	.479	180	161
A01	49	.615	.091	1.820	.145	.487	4.921	.649	.691	1.101	.260	184	162
A01	56	.602	.073	1.789	.208	.416	4.735	.633	.672	.755	.229	172	153
A01	57	.581	.084	1.763	.186	.290	4.371	.677	.616	.817	.139	172	155
A01	58	.689	.074	1.852	.085	.354	4.775	.660	.668	1.019	.345	179	158
A01	59	.665	.061	1.771	.118	.488	5.293	.644	.652	1.012	.414	190	170
A01	60	.685	.059	1.748	.117	.324	4.696	.635	.646	.974	.607	184	166
A02	4	.547	.075	1.791	.099	3.750	4.556	.627	.669	.729	.348		195
A02	5	.624	.058	1.711	.108	.359	4.470	.616	.629	.782	.379	161	145
A02	8	.658	.068	1.798	.095	.337	4.614	.626	.615	.845	.272	176	157
A02	13	.624	.068	1.776	.082	.352	4.504	.631	.660	.848	.257	178	155
A02	14		.067	1.743	.128	.367	4.598	.642	.659	1.000	.010	177	155
A02	41	.633	.089	1.736	.140	.298	4.069	.643	.781	2.360	.229	162	148
A02	45	.644	.061	1.626	.114	.387	4.602	.647	.659	.993	.303	173	155
A02	47	.761	.069	1.894	.140	.457	5.031	.811	.761	1.126	.664	176	160
A02	48	.632	.076	1.718	.167	.377	4.830	.685	.787	.795	.363	177	157
A02	50	.630	.072	1.884	.143	.378	4.386	.651	.644	1.034	.406	159	143
A03	2	.659	.0[illegible]4	1.770	.110	.378	4.928	.790	.734	1.010	.994	161	142
A03	11	.656	.248	1.630	.126	.357	5.098	.688	.660	.954	.310	168	142
A03	17	.607	.077	1.720	.553	.318	5.020	.789	.724	.977	.590	168	140
A03	18	.618	.054	1.522	.098	.247	3.865	.530	.548	.767	.298	137	
A03	20	.617	.093	1.715	.168	.351	4.680	.711	.672	.853	.915	155	132
A03	42	.785	.096	1.698	.117	.473	5.218	.744	.762	1.130	.448	170	146
A03	46	.606	.067	1.718	.098	.321	4.966	.660	.659	1.063	.569	157	148
A03	52	.592	.077	1.781	.312	.317	4.466	.688	.616	1.288	.375	153	140
A03	53	.898	.073	1.740	.287	.348	4.750	.698	.698	.970	.430	156	135
A03	55	.537	.066	1.598	.087	.282	3.863	.567	.602	1.031	.510	144	124
A04	1	.622	.098	1.511	.086	.413	4.478	.657	.671	1.426	.292	175	159
A04	3	.661	.084	1.887	.125	.359	4.829	.669	.647	1.367	.329	170	
A04	6	.610	.078	1.870	.040	1.620	4.478	1.498	.998	.738	.570	178	155
A04	9	.638	.039	1.798	.187	.354	4.470	.654	.638	.871	.511	166	153
A04	12	.608	.093	1.749	.187	.348	4.967	.654	.647	.921	.311	183	156
A04	15	.648	.075	1.866	.094	.445	5.151	.682	.775	.898	.290	187	138
A04	19	.617	.067	1.676	.133	.387	4.538	.614	.641	.760	.535	186	154
A04	51	.684	.072	1.899	.153	.439	5.878	.811	.726	.982	.56[illegible]	163	182
A04	54	.646	.081	1.766	.104	.338	4.529	.648	.654	.802	.333	188	163
A04	77	.670	.110	1.888	.186	.398	5.080	.420	.640	.850	.350	302	274

TABLE 3. ORGAN WEIGHT DATA FOR MALE MICE

Treatment Group	Animal ID	Heart	Adrenal	Brain	Testes	Spleen	Liver	Right Kidney	Left Kidney	Lungs	Pancreas	Final Body Weight
A01	24	.170	.026	.416	.367	.102	1.325	.213	.214	.204	.131	25
A01	26	.232	.013	.468	.386	.069	1.511	.282	.287	.202	.145	28
A01	31	.143	.013	.435	.406	.084	1.444	.238	.225	.220	.177	26
A01	33	.137	.013	.419	.342	.066	1.091	.224	.222	.179	.124	25
A01	34	.147	.007	.431	.366	.051	.927	.184	.188	.161	.084	23
A01	36	.170	.006	.430	.354	.067	1.250	.228	.196	.187	.125	25
A01	37	.179	.002	.445	.443	.075	1.301	.235	.215	.205	.137	26
A01	76	.151	.008	.431	.341	.056	1.088	.217	.195	.197	.167	24
A02	23	.131	.006	.391	.434	.038	1.013	.206	.192	.193	.104	25
A02	27	.183	.009	.441	.471	.072	1.460	.253	.242	.128	.181	25
A02	39	.139	.012	.425	.425	.058	1.465	.253	.219	.135	.171	26
A02	61	.138	.011	.400	.233	.070	1.226	.210	.212	.302	.254	26
A02	62	.195	.026	.473	.372	.067	1.414	.224	.276	.236	.312	25
A02	66	.148	.005	.421	.403	.072	1.316	.200	.186	.112	.174	25
A02	78	.160	.019	.495	.218	.069	1.387	.228	.232	.207	.374	25
A02	79	.170	.018	.430	.290	.060	1.220	.190	.180	.160	.200	22
A03	28	.195	.009	.390	.330	.053	1.493	.238	.242	.167	.113	25
A03	40	.205	.008	.430	.485	.073	1.280	.243	.237	.228	.127	23
A03	71	.157	.011	.401	.363	.044	1.299	.192	.202	.144	.131	20
A04	25	.179	.014	.435	.399	.133	1.325	.215	.201	.212	.224	26
A04	35	.150	.010	.428	.395	.060	1.039	.188	.181	.152	.146	24
A04	54	.150	.010	.446	.310	.082	1.137	.205	.219	.188	.174	24
A04	64	.147	.012	.4[illegible]	.371	.085	1.163	.209	.228	.166	.129	24
A04	73	.173	.007	.504	.478	.087	1.269	.265	.259	.270	.260	28
A04	75	.116	.017	.429	.405	.072	1.132	.216	.212	.189	.090	24

TABLE 4. ORGAN WEIGHT DATA FOR FEMALE MICE

Treatment Group	Animal ID	Heart	Adrenal	Brain	Ovaries	Spleen	Liver	Right Kidney	Left Kidney	Lungs	Pancreas	Final Body Weight
A01	10	.115	.013	.441	.043	.059	1.067	.162	.168	.169	.087	20
A01	16	.125	.011	.455	.034	.093	1.088	.171	.171	.188	.204	22
A01	43	.136	.010	.481	.036	.066	1.075	.179	.163	.204	.167	21
A01	44	.126	.013	.433	.012	.074	1.134	.169	.170	.154	.117	22
A01	49	.123	.004	.476	.035	.069	1.093	.195	.165	.212	.105	21
A01	58	.107	.023	.455	.039	.061	1.026	.144	.185	.145	.140	21
A01	59	.110	.022	.384	.071	.077	1.011	.207	.187	.154	.148	21
A01	60	.118	.008	.418	.034	.085	1.058	.160	.166	.188	.120	23
A02	4	.127	.010	.436	.058	.073	1.521	.195	.190	.225	.161	24
A02	5	.132	.014	.432	.044	.065	1.194	.166	.150	.191	.111	22
A02	8	.102	.012	.449	.035	.078	1.282	.215	.120	.211	.103	21
A02	13	.161	.012	.415	.042	.063	1.354	.213	.198	.279	.076	22
A02	14	.126	.009	.418	.012	.055	1.311	.179	.175	.090	.177	22
A02	41	.116	.002	.475	.130	.072	1.212	.171	.177	.217	.184	21
A02	45	.110	.009	.454	.020	.067	1.203	.177	.167	.176	.122	21
A02	47	.120	.013	.450	.034	.0508	1.112	.150	.134	.187	.161	22
A02	48	.102	.010	.429	.024	.062	1.092	.126	.152	.191	.103	21
A02	50	.106	.017	.479	.041	.078	1.148	.176	.175	.213	.129	20
A03	2	.104	.023	.448	.051	.063	1.532	.221	.236	.405	.195	22
A03	11	.131	.012	.481	.069	.044	1.368	.175	.175	.206	.086	18
A03	17		.012	.432	.049	.072	1.273	.197	.192	.235	.113	21
A03	18	.105	.023	.408	.048	.046	1.230	.181	.154	.233	.129	18
A03	46	.150	.015	.473	.036	.061	1.443	.186	.193	.168	.112	19
A03	52	.146	.013	.471	.030	.046	1.200	.190	.160	.236	.169	16
A03	53	.150	.009	.400	.031	.063	1.426	.195	.195	.419	.103	19
A03	55	.127	.011	.395	.059	.064	1.320	.189	.173	.218	.086	18
A04	3	.127	.008	.516	.027	.138	1.33	.204	.199	.240	.151	
A04	12	.112	.012	.438	.047	.067	.980	.155	.146	.208	.124	20
A04	15	.119	.009	.454	.021	.070	1.010	.176	.173	.262	.031	19
A04	19		.010	.474	.043	.074	.944	.183	.172	.204	.143	22
A04	1	.110	.010	.470	.030	.060	1.020	.170	.160	.180	.150	22
A04	7	.118	.011	.463	.070	.080	1.221	.188	.191	.186	.117	22
A04	9	.130	.010	.500	.050	.080	1.180	.180	.180	.210	.180	23
A04	40	.105	.009	.465	.045	.093	1.052	.156	.154	.208		21

TABLE 5 . STATISTICAL ANALYSIS OF ORGAN WEIGHT DATA

HEART

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible] ppm	10	.9845	.0647	.0205	.9030	1.1180
[illegible]	10	1.0032	.0774	.0245	.8860	1.1430
[illegible] ppm	10	.8302	.2343	.0741	.2210	1.0340
CONTROL	10	.9933	.1131	.0358	.8500	1.1720
TOTAL	40	.9505			.2210	1.1720
	UNGROUPED DATA		.1516	.0240		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible] ppm	10	.6756	.0849	.0268	.5810	.8910
[illegible] ppm	9	.6383	.0549	.0183	.5470	.7610
[illegible] ppm	10	.6481	.0959	.0303	.5370	.8930
CONTROL	10	.6396	.0274	.0086	.6080	.6840
TOTAL	39	.6507			.5370	.8910
	UNGROUPED DATA		.0702	.0112		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	.1736	.0279	.0099	.1370	.2320
750 ppm	8	.1500	.0231	.0082	.1310	.1950
1500 ppm	3	.1857	.0253	.0146	.1570	.2050
CONTROL	6	.1525	.0223	.0091	.1160	.1790
TOTAL	25	.1650			.1160	.2320
	UNGROUPED DATA		.0260	.0052		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	.1200	.0094	.0033	.1070	.1360
750 ppm	10	.1202	.0179	.0056	.1020	.1610
1500 ppm	7	.1533	.0231	.0087	.1270	.1850
CONTROL	7	.1173	.0091	.0034	.1050	.1300
TOTAL	32	.1267			.1020	.1850
	UNGROUPED DATA		.0209	.0037		

TABLE 5 . STATISTICAL ANALYSIS OF ORGAN WEIGHT DATA

ADRENAL

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	.0730	.0221	.0070	.0450	.1190
750 ppm	10	.0693	.0143	.0045	.0450	.0993
1500 ppm	10	.0747	.0369	.0117	.0290	.1710
CONTROL	10	.0739	.0127	.0040	.0510	.0860
TOTAL	40	.0732			.0290	.1710
	UNGROUPED DATA		.0220	.0034		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	.0771	.0132	.0042	.0590	.0960
750 ppm	10	.0715	.0118	.0037	.0500	.0890
1500 ppm	10	.0937	.0528	.0167	.0540	.2400
CONTROL	10	.0709	.0195	.0062	.0390	.1160
TOTAL	40	.0803			.0390	.2400
	UNGROUPED DATA		.0296	.0047		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	.0110	.0073	.0026	.0020	.0240
750 ppm	8	.0200	.0209	.0074	.0050	.0690
1500 ppm	3	.0093	.0015	.0009	.0080	.0110
CONTROL	6	.0117	.0035	.0014	.0070	.0170
TOTAL	25	.0138			.0020	.0690
	UNGROUPED DATA		.0128	.0026		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	.0130	.0065	.0023	.0040	.0230
750 ppm	10	.0108	.0040	.0013	.0020	.0170
1500 ppm	8	.0147	.0054	.0019	.0090	.0230
CONTROL	8	.0099	.0012	.0004	.0080	.0120
TOTAL	34	.0120			.0020	.0230
	UNGROUPED DATA		.0048	.0008		

TABLE 5. STATISTICAL ANALYSIS OF ORGAN WEIGHT DATA

BRAIN

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	1.8839	.0577	.0182	1.7620	1.9620
750 ppm	10	1.8742	.0512	.0162	1.7350	1.9050
1500 ppm	10	1.8209	.0981	.0310	1.6300	2.0300
CONTROL	10	2.1315	.7286	.2304	1.8512	4.2463
TOTAL	40	1.9364			1.6300	4.2463
	UNGROUPED DATA		.3830	.0606		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	1.7730	.0389	.0123	1.7223	1.8523
750 ppm	10	1.7597	.0711	.0225	1.6204	1.8940
1500 ppm	10	1.6784	.0757	.0239	1.5226	1.7780
CONTROL	10	1.7734	.1129	.0357	1.5110	1.8993
	40	1.7077			1.5110	1.8990
	UNGROUPED DATA		.0864	.0137		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	.4344	.0163	.0058	.4160	.4680
750 ppm	8	.4345	.0350	.0124	.3910	.4950
1500 ppm	3	.4070	.0207	.0119	.3900	.4300
CONTROL	6	.4460	.0291	.0119	.4280	.5040
TOTAL	25	.4339			.3900	.5040
	UNGROUPED DATA		.0278	.0056		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	.4429	.0317	.0112	.3840	.4810
750 ppm	10	.4477	.0262	.0083	.4150	.4890
1500 ppm	8	.4275	.0331	.0117	.3950	.4730
CONTROL	8	.4725	.0269	.0088	.4380	.5160
TOTAL	34	.4476			.3840	.5160
	UNGROUPED DATA		.0319	.0055		

TABLE 5 . STATISTICAL ANALYSIS OF ORGAN WEIGHT DATA

TESTICLE - OVARY

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	10	4.4726	.5213	.1649	4.1733	5.8023
[illegible]	10	4.3643	.4827	.1526	3.7753	5.4113
[illegible]	10	3.6410	.8040	.2551	2.3173	4.9350
[illegible]	10	4.4496	1.3241	.3238	1.9560	5.8300
TOTAL	40	4.1029			1.9563	5.8823
	UNGROUPED DATA		.9311	.1472		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible] ppm	10	.1376	.0364	.0115	.0853	.2030
750 ppm	10	.1208	.0270	.0085	.0420	.1473
[illegible] ppm	10	.1945	.1083	.0469	.0670	.5433
CONTROL	10	.1215	.0457	.0144	.0400	.1070
TOTAL	40	.1436			.0400	.5500
	UNGROUPED DATA		.0834	.0132		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	.3756	.0349	.0123	.3410	.4430
750 ppm	8	.3958	.0964	.0341	.2160	.4710
1500 ppm	3	.3927	.0816	.0471	.3300	.4850
CONTROL	6	.3930	.0544	.0222	.3100	.4780
TOTAL	25	.3756			.2100	.4850
	UNGROUPED DATA		.0469	.0134		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	.0300	.0162	.0057	.0120	.0710
750 ppm	10	.0432	.0327	.0103	.0120	.1300
1500 ppm	6	.0466	.0137	.0048	.0300	.0690
CONTROL	8	.0416	.0155	.0055	.0210	.0700
TOTAL	34	.0424			.0120	.1300
	UNGROUPED DATA		.0212	.0036		

TABLE 5 . STATISTICAL ANALYSIS OF ORGAN WEIGHT DATA

SPLEEN

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	.4977	.0628	.0199	.4380	.5750
750 ppm	10	.4697	.0279	.0088	.4330	.5200
1500 ppm	10	.4162	.0389	.0123	.3720	.4490
CONTROL	10	.5077	.0713	.0226	.4220	.6800
TOTAL	40	.4768			.3720	.6800
	UNGROUPED DATA		.0587	.0093		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	.3037	.0508	.0161	.2930	.4040
750 ppm	10	.7026	1.0715	.3389	.2960	3.7500
1500 ppm	10	.3369	.0403	.0191	.2470	.4730
CONTROL	10	.5105	.3916	.1238	.3300	1.6200
TOTAL	40	.4034			.2470	3.7500
	UNGROUPED DATA		.5670	.0898		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	.0713	.0161	.0057	.0510	.1020
750 ppm	8	.0633	.0115	.0041	.0380	.0720
1500 ppm	3	.0547	.0148	.0086	.0440	.0730
CONTROL	6	.0865	.0249	.0102	.0600	.1330
TOTAL	25	.0706			.0380	.1330
	UNGROUPED DATA		.0192	.0038		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	.0730	.0117	.0042	.0590	.0930
750 ppm	10	.0671	.0080	.0025	.0550	.0780
1500 ppm	8	.0574	.0105	.0037	.0440	.0720
CONTROL	8	.0827	.0244	.0086	.0600	.1380
TOTAL	34	.0699			.0440	.1380
	UNGROUPED DATA		.0167	.0029		

TABLE 5. STATISTICAL ANALYSIS OF ORGAN WEIGHT DATA

LIVER

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	7.5526	.6603	.2151	6.7630	8.5420
750 ppm	10	7.4321	.5156	.1630	6.4610	8.0900
1500 ppm	10	6.8801	.4815	.1523	6.0650	7.4900
CONTROL	10	7.7063	.4512	.1427	6.7950	8.2600
TOTAL	40	7.3708			6.0860	8.5420
	UNGROUPED DATA		.6248	.0988		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	4.8332	.4194	.1324	4.3440	5.6290
750 ppm	10	4.5563	.2620	.0828	4.0690	5.0310
1500 ppm	10	4.6830	.4815	.1523	3.8630	5.2160
CONTROL	10	4.8310	.4482	.1417	4.4700	5.8780
TOTAL	40	4.7263			3.8630	5.8780
	UNGROUPED DATA		.4120	.0651		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	1.2431	.1962	.0694	.9270	1.5110
750 ppm	8	1.3126	.1543	.0545	1.0130	1.4650
1500 ppm	3	1.3573	.1179	.0681	1.2800	1.4930
CONTROL	6	1.1775	.1032	.0421	1.0390	1.3250
TOTAL	25	1.2633			.9270	1.5110
	UNGROUPED DATA		.1595	.0319		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	1.0690	.0388	.0137	1.0110	1.1340
750 ppm	10	1.2429	.1290	.0408	1.0920	1.5210
1500 ppm	8	1.3490	.1144	.0404	1.2900	1.5320
CONTROL	8	1.0921	.1357	.0400	.9440	1.5300
TOTAL	34	1.1915			.9440	1.5320
	UNGROUPED DATA		.1562	.0268		

TABLE 5. STATISTICAL ANALYSIS OF ORGAN WEIGHT DATA

RIGHT KIDNEY

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	1.0073	.0577	.0182	.9700	1.1500
750 ppm	10	1.0243	.0556	.0176	.9420	1.0940
1500 ppm	10	.9767	.0563	.0178	.8970	1.0830
CONTROL	10	1.0652	.0516	.0163	1.0000	1.1400
TOTAL	40	1.0339			.8970	1.1510
	UNGROUPED DATA		.0646	.0102		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	.6584	.0445	.0141	.6020	.7730
750 ppm	10	.6579	.0570	.0180	.6160	.8110
1500 ppm	10	.6769	.0773	.0244	.5330	.7930
CONTROL	10	.7291	.2038	.0897	.4200	1.4900
TOTAL	40	.6805			.4200	1.4900
	UNGROUPED DATA		.1484	.0235		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	.2276	.0277	.0098	.1840	.2820
750 ppm	8	.2205	.0235	.0083	.1900	.2530
1500 ppm	3	.2243	.0281	.0162	.1920	.2430
CONTROL	6	.2163	.0259	.0106	.1880	.2650
TOTAL	25	.2222			.1840	.2820
	UNGROUPED DATA		.0247	.0049		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	.1734	.0201	.0071	.1440	.2070
750 ppm	10	.1760	.0270	.0085	.1260	.2150
1500 ppm	8	.1917	.0138	.0049	.1750	.2210
CONTROL	8	.1765	.0163	.0058	.1550	.2040
TOTAL	34	.1794			.1260	.2210
	UNGROUPED DATA		.0208	.0036		

TABLE 5. STATISTICAL ANALYSIS OF ORGAN WEIGHT DATA

LEFT KIDNEY

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	1.0346	.0545	.0172	.9550	1.1400
750 ppm	10	1.0508	.0459	.0145	.9830	1.1320
1500 ppm	10	1.0634	.3249	.1027	.8790	1.9900
CONTROL	10	1.0588	.0471	.0149	.9860	1.1090
TOTAL	40	1.0569			.8790	1.9900
	UNGROUPED DATA		.1624	.0257		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	.6663	.0268	.0085	.6160	.7150
750 ppm	10	.6495	.0430	.0136	.6150	.7610
1500 ppm	10	.6667	.0653	.0207	.5480	.7620
CONTROL	10	.7021	.1110	.0351	.6300	.9400
TOTAL	40	.6761			.5480	.9900
	UNGROUPED DATA		.0682	.0108		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	.2178	.0311	.0110	.1880	.2870
750 ppm	8	.2174	.0323	.0114	.1880	.2760
1500 ppm	3	.2270	.0218	.0126	.2020	.2420
CONTROL	6	.2167	.0263	.0107	.1810	.2590
TOTAL	25	.2185			.1800	.2870
	UNGROUPED DATA		.0279	.0056		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	.1719	.0091	.0032	.1630	.1870
750 ppm	10	.1638	.0246	.0078	.1200	.1980
1500 ppm	8	.1848	.0258	.0091	.1540	.2360
CONTROL	8	.1719	.0181	.0064	.1460	.1990
TOTAL	34	.1725			.1200	.2360
	UNGROUPED DATA		.0213	.0036		

TABLE 5. STATISTICAL ANALYSIS OF ORGAN WEIGHT DATA

LUNGS

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	10	1.1099	.1110	.0351	1.0400	[illegible]
[illegible]	10	1.2534	.1092	.0339	1.1720	[illegible]
[illegible]	10	1.2099	.2058	.0651	.8966	[illegible]
CONTROL	10	1.2864	.4472	.1541	[illegible]	2.6500
TOTAL	40	1.2419			.8960	2.6500
	UNGROUPED DATA		.2690	.0425		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	.9914	.1945	.0331	.7550	1.1070
750 ppm	10	1.0564	.4777	.1511	.7290	2.3600
1500 ppm	10	1.0035	.1413	.0447	.7570	1.2830
CONTROL	10	.9600	.2413	.0765	.7330	1.4260
TOTAL	40	.9915			.7290	2.3600
	UNGROUPED DATA		.2736	.0433		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	.1954	.0200	.0071	.1610	.2200
750 ppm	8	.1941	.0870	.0308	.1120	.3820
1500 ppm	3	.1797	.0434	.0251	.1440	.2280
CONTROL	6	.1962	.0417	.0170	.1520	.2700
TOTAL	25	.1933			.1120	.3820
	UNGROUPED DATA		.0534	.0107		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	.1768	.0249	.0088	.1450	.2120
750 ppm	10	.1900	.0476	.0151	.0900	.2790
1500 ppm	8	.2082	.0933	.0330	.1680	.4190
CONTROL	8	.2123	.0269	.0095	.1800	.2620
TOTAL	34	.2122			.0900	.4190
	UNGROUPED DATA		.0616	.0106		

TABLE 1. RELATIVE ORGAN WEIGHT DATA FOR MALE RATS
BASED ON FINAL BODY WEIGHTS

Treatment Group	Animal I.D.	Heart	Adrenal	Brain	Testes	Spleen	Liver	Right Kidney	Left Kidney	Lungs	Pancreas
A01	22	3.88	.19	6.97	15.92	1.88	31.61	4.87	4.25	4.49	2.31
A01	24	3.85	.25	7.70	17.87	1.98	28.41	4.02	3.93	4.24	3.16
A01	26	3.69	.27	7.61	16.98	1.76	27.16	4.21	4.06	5.17	1.73
A01	31	4.02	.33	6.98	17.81	1.96	29.68	4.01	3.95	4.67	1.99
A01	33	4.14	.24	7.26	16.26	1.99	31.64	4.19	3.99	4.41	2.48
A01	34	3.70	.17	7.31	16.58	1.97	30.79	4.15	4.04	4.48	2.16
A01	36	3.95	.35	7.34	17.61	2.04	31.19	4.41	4.21	5.46	2.34
A01	37	3.66	.25	7.18	16.62	1.64	28.73	4.21	4.04	4.25	1.98
A01	63	3.75	.34	7.49	22.89	2.24	27.72	3.77	3.72	4.05	.98
A01	76	4.25	.53	8.42	18.62	2.01	30.05	5.09	4.58	5.65	1.38
A02	23	4.46	.28	7.59	16.66	1.92	29.55	4.14	4.16	4.99	2.18
A02	27	4.09	.24	7.47	19.42	1.89	29.84	3.84	3.97	5.02	4.91
A02	39	4.59	.26	7.69	17.73	1.68	29.98	4.38	4.19	6.32	1.86
A02	61	3.98	.23	7.63	17.15	1.88	28.85	4.35	4.48	5.82	2.68
A02	62	4.41	.43	7.81	16.44	2.27	28.21	4.16	4.29	5.24	3.88
A02	66	4.38	.32	8.93	20.28	2.15	33.57	4.58	4.86	5.76	5.39
A02	69	3.78	.27	7.39	16.39	2.01	32.49	4.38	4.32	5.44	2.47
A02	78	3.88	.19	7.98	23.22	2.06	38.64	4.05	4.38	5.36	1.31
A02	74	3.95	.29	7.34	17.96	2.08	38.88	4.27	4.18	5.58	2.29
A02	79	3.98	.31	7.54	15.92	2.06	32.27	4.16	4.53	4.69	2.23
A03	21	4.41	.29	8.27	11.91	1.86	32.41	4.59	9.05	7.55	5.95
A03	26	4.05	.39	9.49	25.31	2.21	35.28	5.33	4.98	5.12	4.39
A03	32	4.24	.22	7.85	12.82	1.75	32.41	4.38	4.56	4.87	3.91
A03	38	4.46	.37	9.54	14.72	2.12	35.18	4.94	5.13	6.92	2.31
A03	48	4.19	.37	8.36	13.28	2.18	32.31	4.72	4.88	6.15	2.67
A03	67	4.74	.14	8.65	15.75	2.44	35.28	4.90	5.85	5.74	2.67
A03	68	4.76	.42	9.34	14.16	1.98	32.44	4.77	4.82	6.24	5.48
A03	71	3.63	.24	7.14	11.46	1.67	26.75	3.87	3.96	4.36	2.41
A03	72	3.96	.93	9.71	18.91	2.82	33.84	4.87	4.78	6.36	3.15
A03	78	1.13	.42	9.56	19.78	1.91	32.36	4.79	4.69	4.61	1.43
A04	7	6.52	.52	12.47	27.89	3.28	50.82	7.19	6.92	7.23	5.53
A04	25	3.57	.26	17.26	7.95	1.98	27.62	4.07	4.01	4.82	3.28
A04	29										
A04	38	3.38	.33	7.47	22.34	2.07	27.97	3.83	3.83	10.15	1.47
A04	35	3.58	.28	7.51	16.19	1.67	28.62	4.44	3.94	4.43	1.68
A04	64	3.68	.23	7.41	21.11	2.18	38.52	4.09	4.13	4.51	1.15
A04	65	3.23	.32	6.71	16.79	1.78	29.93	3.82	3.98	4.51	1.65
A04	73	4.18	.23	7.47	15.59	2.44	28.48	3.95	3.96	3.78	3.17
A04	80	4.23	.31	7.83	16.43	1.68	27.15	3.77	4.08	4.36	1.86
A04	75	3.56	.24	6.39	15.54	1.59	27.23	3.55	3.61	4.16	1.32

TABLE 4. RELATIVE ORGAN WEIGHTS FOR FEMALE MICE BASED ON FINAL BODY WEIGHTS

Treatment Group	Animal I.D.	Heart	Adrenal	Brain	Ovaries	Spleen	Liver	Right Kidney	Left Kidney	Lungs	Pancreas
A01	10	5.75	.65	22.89	2.15	2.95	53.35	8.10	8.40	8.45	4.35
A01	16	5.60	.58	20.68	1.55	4.23	49.45	7.77	7.77	8.55	9.27
A01	43	6.48	.48	22.98	1.71	3.14	51.19	8.52	7.76	9.71	7.95
A01	44	5.73	.59	19.68	.55	3.36	51.55	7.68	7.73	7.88	5.32
A01	49	5.86	.19	22.67	1.67	3.29	52.85	9.29	7.86	10.18	5.88
A01	58	5.18	1.18	21.67	1.86	2.98	48.86	6.86	8.81	8.98	6.67
A01	59	5.24	1.85	18.29	3.38	3.67	48.14	9.86	6.98	7.33	7.85
A01	68	5.13	.35	18.17	1.48	3.70	46.88	6.96	7.22	8.17	5.22
A02	4	5.29	.42	18.17	2.88	3.84	63.37	8.13	7.92	9.37	6.71
A02	5	6.88	.64	19.64	2.88	2.95	54.27	7.55	6.82	8.68	5.85
A02	8	4.86	.57	23.29	1.67	3.71	61.85	10.24	5.71	10.85	4.98
A02	13	7.32	.55	18.86	1.91	2.86	61.55	9.68	9.88	12.68	3.45
A02	14	5.73	.41	19.88	.55	2.58	59.59	8.14	7.95	4.89	8.85
A02	41	5.52	.18	22.62	6.19	3.43	57.71	8.14	8.43	10.33	4.55
A02	45	5.24	.43	21.62	.95	3.19	57.29	8.43	7.95	8.38	5.81
A02	47	5.45	.59	20.45	1.55	2.64	58.55	6.82	6.89	8.50	7.32
A02	48	4.86	.48	20.43	1.14	2.95	52.08	6.88	7.24	9.10	4.98
A02	50	5.38	.85	23.95	2.85	3.98	57.48	8.88	8.75	10.65	6.45
A03	2	8.36	1.85	20.36	2.32	2.86	69.64	10.85	10.73	10.41	8.86
A03	11	7.28	.67	22.28	3.83	2.44	76.88	9.72	9.72	11.56	4.78
A03	17		.57	20.57	2.33	3.43	60.62	9.38	9.14	11.19	5.38
A03	18	10.28	1.28	22.22	2.67	2.56	68.33	10.86	8.56	12.94	7.17
A03	46	7.89	.79	24.89	1.89	3.21	75.95	9.79	10.16	8.84	5.89
A03	52	9.13	.81	29.44	1.88	2.88	75.88	11.88	10.88	14.75	10.56
A03	53	7.89	.47	21.85	1.63	3.32	75.85	10.26	10.26	22.85	5.42
A03	55	7.86	.61	21.94	3.28	3.56	73.33	10.50	9.61	12.11	4.78
A04	3										
A04	12	5.68	.68	21.98	2.35	3.35	49.88	7.75	7.38	10.48	6.28
A04	15	6.26	.47	23.89	1.11	3.68	53.16	9.26	9.11	13.79	1.63
A04	19		.45	21.55	1.95	3.36	42.91	9.32	7.82	9.27	6.50
A04	1	5.88	.45	21.36	1.36	2.73	46.36	7.73	7.27	8.18	6.82
A04	7	5.36	.58	21.85	3.18	3.64	55.58	8.55	8.68	8.45	5.32
A04	9	5.65	.43	21.74	2.17	3.48	51.38	7.83	7.83	9.13	7.83
A04	80	5.08	.43	22.14	2.14	4.43	50.18	7.43	7.33	9.98	0

TABLE 5. RELATIVE ORGAN WEIGHTS FOR MALE RATS
BASED ON WEEK 12 BODY WEIGHTS

Treatment Group	Animal I.D.	Heart	Adrenal	Brain	Testes	Spleen	Liver	Right Kidney	Left Kidney	Lungs	Pancreas
A01	22	3.52	.18	6.46	14.76	1.75	29.31	3.78	3.94	4.16	2.14
A01	24	3.51	.23	7.01	15.56	1.73	25.88	3.66	3.59	3.86	2.88
A01	26	3.27	.23	6.74	14.97	1.56	24.87	3.73	3.60	4.58	1.54
A01	31	3.65	.38	6.34	16.16	1.78	26.93	3.64	3.58	4.24	1.88
A01	33	3.84	.22	6.74	15.89	1.84	29.35	3.88	3.78	4.89	2.23
A01	34	3.39	.16	6.78	15.12	1.88	28.23	3.80	3.70	4.10	1.98
A01	36	3.61	.3[illegible]	6.72	16.12	1.86	28.52	4.04	3.86	5.08	2.14
A01	37	3.47	.23	6.73	15.74	1.74	27.19	3.98	3.82	4.02	1.87
A01	63	3.48	.32	6.95	21.23	2.08	25.72	3.50	3.45	3.75	.84
A01	76	3.86	.48	7.65	16.98	1.83	27.28	4.62	4.15	5.13	1.26
A02	23										
A02	27										
A02	39	4.16	.23	6.97	16.06	1.63	27.88	3.97	3.80	5.72	1.68
A02	61	3.88	.22	7.27	16.34	1.79	27.48	4.15	4.26	4.79	2.55
A02	62	4.11	.40	7.27	15.35	2.11	26.26	3.87	4.08	4.82	2.79
A02	66	3.73	.27	7.62	17.29	1.83	28.63	3.83	4.14	4.91	4.60
A02	69	3.38	.25	6.74	14.95	1.83	29.63	3.99	3.94	4.56	2.25
A02	70	3.52	.18	7.38	21.47	1.91	28.33	3.74	4.05	4.96	1.21
A02	74	3.72	.27	6.91	16.90	1.80	29.07	4.02	3.94	5.10	2.15
A02	79	3.58	.28	6.78	14.32	1.86	29.02	3.74	4.07	4.22	2.00
A03	21	4.02	.26	7.55	10.37	1.78	29.59	4.19	8.26	6.89	5.44
A03	28	3.74	.36	8.77	23.39	2.04	32.61	4.93	4.61	4.73	4.06
A03	32	3.82	.20	7.08	10.83	1.58	29.21	3.94	4.11	4.39	3.52
A03	38	4.05	.34	8.65	13.35	1.93	31.91	4.48	4.65	6.28	2.09
A03	40	3.82	.34	7.62	12.18	1.99	29.44	4.30	4.44	5.61	2.43
A03	67	4.02	.12	7.33	13.35	2.07	29.83	4.16	4.28	4.86	2.27
A03	68	4.31	.38	8.46	12.82	1.72	29.37	4.32	4.36	5.65	4.89
A03	71	4.24	.27	8.28	13.14	1.92	30.78	4.44	4.55	5.88	3.22
A03	72	3.63	.[illegible]	8.89	9.99	1.85	30.25	4.46	4.37	5.83	2.88
A03	78	1.83	.[illegible]	8.67	17.87	1.73	29.35	4.35	4.26	4.18	1.38
A04	7	5.51	.44	18.89	23.59	2.71	42.98	6.09	5.85	6.12	4.68
A04	25	2.88	.23	13.92	6.41	1.53	22.28	3.28	3.23	3.24	2.58
A04	29	2.99	.26	6.34	15.31	1.64	25.58	3.43	3.38	3.34	1.42
A04	30	2.71	.27	6.15	18.39	1.70	23.83	3.15	3.15	8.36	1.21
A04	35	3.68	.28	7.72	16.65	1.72	29.42	4.57	4.85	4.55	1.73
A04	64	3.20	.20	6.45	18.37	1.82	26.55	3.56	3.59	3.92	1.08
A04	65	3.13	.31	6.49	16.26	1.72	28.98	3.69	3.85	4.37	1.79
A04	73	3.69	.21	6.73	14.03	2.19	25.64	3.56	3.56	3.40	2.85
A04	80	3.81	.28	6.32	14.77	1.44	24.42	3.39	3.60	3.93	1.67
A04	75	3.49	.23	6.22	15.13	1.55	26.51	3.45	3.52	4.05	1.28

TABLE 7. STATISTICAL ANALYSIS OF RELATIVE ORGAN WEIGHT DATA

ADRENAL TO FINAL BODY WEIGHT

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	10	.2909	.1028	.0325	.1765	.5265
[illegible]	10	.2461	.0635	.0201	.1931	.4323
[illegible]	10	.3791	.2147	.3679	.1450	.9293
[illegible]	9	.2944	.0966	.0322	.1977	.5220
TOTAL	39	.3136			.1450	.9293
	UNGROUPED DATA		.1337	.0214		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	10	.4826	.0848	.0244	.3554	.6087
[illegible]	10	.4572	.0795	.0252	.3448	.6614
[illegible]	9	.7946	.3763	.1254	.4766	1.6981
[illegible]	9	.4694	.1159	.0386	.2549	.6164
TOTAL	38	.5255			.2549	1.6981
	UNGROUPED DATA		.2188	.0354		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	.6369	.2859	.1011	.0769	1.0438
750 ppm	9	.8824	.8338	.2948	.2888	2.7888
1500 ppm	7	.4193	.1134	.0455	.3478	.5500
CONTROL	6	.4717	.1526	.0623	.2500	.7083
TOTAL	25	.5594			.0769	2.7888
	UNGROUPED DATA		.5116	.1023		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	.6123	.3170	.1121	.1905	1.0952
750 ppm	10	.5020	.1947	.0616	.0952	.8500
1500 ppm	8	.7810	.2667	.0943	.4737	1.2778
CONTROL	7	.4700	.0589	.0223	.4286	.6000
TOTAL	33	.5913			.0952	1.2778
	UNGROUPED DATA		.2515	.0438		

TABLE 7. STATISTICAL ANALYSIS OF RELATIVE ORGAN WEIGHT DATA

BRAIN TO FINAL BODY WEIGHT

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	10	7.4142	.4298	.1359	6.9761	8.4243
[illegible]	10	7.7372	.4509	.1457	7.3593	8.9316
[illegible]	10	8.7915	.8730	.2761	7.1429	9.7055
[illegible]	9	8.9027	3.6933	1.2278	6.3851	17.2632
TOTAL	39	8.1949			6.3851	17.2632
	UNGROUPED DATA		1.8859	.3020		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	10	11.1340	.5037	.1593	10.4176	11.7215
[illegible]	10	11.2756	.9254	.2936	9.1846	12.6134
[illegible]	9	12.3192	.5423	.1808	11.4769	12.9424
[illegible]	9	10.8393	2.0891	.6964	6.5693	14.3538
TOTAL	38	11.3322			6.5693	14.3538
	UNGROUPED DATA		1.2584	.2041		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	17.2322	.7470	.2641	16.6400	18.7391
750 ppm	8	17.5245	1.7407	.6154	15.3846	19.8000
1500 ppm	3	18.1152	2.2811	1.3170	15.6030	20.0500
CONTROL	6	17.8510	.6113	.2496	16.7308	18.5833
TOTAL	25	17.5770			15.3846	20.0500
	UNGROUPED DATA		1.2860	.2572		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	20.7639	1.8784	.6641	18.1739	22.9048
750 ppm	10	20.8024	1.9893	.6291	18.1667	23.9500
1500 ppm	8	22.0455	3.0171	1.0667	20.3636	29.4375
CONTROL	7	21.9473	.9302	.3516	21.0455	23.8947
TOTAL	33	21.5312			18.1667	29.4375
	UNGROUPED DATA		2.1958	.3822		

TABLE 7. STATISTICAL ANALYSIS OF RELATIVE ORGAN WEIGHT DATA

TESTICLES OR OVARIES TO FINAL BODY WEIGHT

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	10	17.5203	2.0163	.6376	15.4216	22.6272
[illegible]	10	18.1217	2.2660	.7160	15.4260	23.2232
[illegible]	10	1[illegible].4218	4.4752	1.4152	10.[illegible]076	2[illegible]
[illegible]	9	17.7596	5.5[illegible]	1.8481	7.4512	27.4931
TOTAL	39	17.6889			7.4512	27.4931
	UNGROUPED DATA		3.8465	.6228		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	10	.8039	.2475	.0783	.5380	1.3545
[illegible]	10	.7777	.1959	.0619	.5077	1.0637
[illegible]	9	1.0445	1.0938	.3645	.7886	3.9266
[illegible]	9	.7164	.2004	.0668	.2581	1.2222
TOTAL	38	.9534			.2581	3.9266
	UNGROUPED DATA		.6247	.1013		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	14.8851	1.1901	.4208	13.6880	17.0385
750 ppm	8	14.3012	3.7549	1.3276	8.7200	18.8488
1500 ppm	3	17.4790	3.9861	2.3014	13.2889	21.0870
CONTROL	6	16.6877	1.5340	.6263	12.9167	17.0714
TOTAL	25	15.2021			8.7200	21.0870
	UNGROUPED DATA		2.7112	.5422		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	1.7923	.7921	.2801	.5455	3.3816
750 ppm	10	2.0804	1.5579	.4926	.5455	6.1905
1500 ppm	8	2.4788	.7539	.2666	1.6316	3.8333
CONTROL	7	2.0389	.6791	.2567	1.1053	3.1818
TOTAL	33	2.0746			.5455	6.1905
	UNGROUPED DATA		1.0455	.1826		

TABLE 7. STATISTICAL ANALYSIS OF RELATIVE ORGAN WEIGHT DATA
SPLEEN TO FINAL BODY WEIGHT

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	10	1.9545	.1292	.0409	1.7590	2.2374
[illegible]	10	2.0040	.1393	.0441	1.8042	2.2707
[illegible]	10	2.0372	.2340	.0740	1.6714	2.4459
CONTROL	9	2.0372	.5167	.1722	1.5878	3.2013
TOTAL	39	2.0038			1.5878	3.2013
	UNGROUPED DATA		.2802	.0449		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	10	2.4042	.3236	.1023	1.8710	2.8944
[illegible]	10	4.0664	5.3337	1.6867	1.9593	19.2306
[illegible]	9	2.5092	.3191	.1064	2.2143	3.2397
[illegible]	9	3.2798	2.7401	.9134	1.4234	10.4516
TOTAL	38	3.0728			1.4234	19.2308
	UNGROUPED DATA		3.0112	.4885		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	2.8163	.6022	.2129	2.2174	4.0800
750 ppm	8	2.5463	.4619	.1633	1.5200	2.8880
1500 ppm	3	2.4980	.5867	.3388	2.1200	3.1739
CONTROL	6	3.4468	.8950	.3654	2.5000	5.1154
TOTAL	25	2.8430			1.5200	5.1154
	UNGROUPED DATA		.7065	.1413		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	3.4046	.4426	.1565	2.9048	4.2273
750 ppm	10	3.1182	.4481	.1417	2.5000	3.9000
1500 ppm	8	3.0311	.4087	.1445	2.4444	3.5556
CONTROL	7	3.5240	.5082	.1921	2.7273	4.4286
TOTAL	33	3.2526			2.4444	4.4286
	UNGROUPED DATA		.4734	.0824		

TABLE 7. STATISTICAL ANALYSIS OF RELATIVE ORGAN WEIGHT DATA

LIVER TO FINAL BODY WEIGHT

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	10	29.6937	1.6256	.5144	27.1606	31.4370
[illegible]	13	30.6207	1.7369	.5394	28.2140	33.5727
[illegible]	10	32.7336	2.4737	.7823	26.7500	35.2621
[illegible]	9	30.9246	7.5473	2.5158	27.1516	50.8176
TOTAL	39	30.9467			26.7500	50.8176
	UNGROUPED DATA		4.0852	.6413		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	10	30.1882	2.0359	.6449	27.5590	34.3232
[illegible]	13	29.1904	2.3200	.7334	28.3541	31.4434
[illegible]	9	34.5777	1.7786	.5929	31.1532	35.8571
[illegible]	9	29.4974	5.5635	1.8545	18.2482	39.6231
TOTAL	38	30.7991			18.2482	39.6231
	UNGROUPED DATA		3.7935	.6154		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	49.0174	5.3984	1.9086	40.3043	55.5385
750 ppm	8	52.8193	6.0356	2.1339	40.5200	58.4000
1500 ppm	3	60.1074	4.6010	2.6910	55.6522	64.9500
CONTROL	6	47.0958	2.6269	1.0724	43.2917	50.9615
TOTAL	25	51.1036			40.3043	64.9500
	UNGROUPED DATA		6.2414	1.2483		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm.	8	50.0735	2.3973	.8476	46.0000	53.3500
750 ppm	10	57.4777	4.1762	1.3206	50.5455	63.3750
1500 ppm	8	71.7403	5.3412	1.8884	60.6190	76.0000
CONTROL	7	49.7615	4.2039	1.5889	42.9091	55.5000
TOTAL	33	57.5036			42.9091	76.0000
	UNGROUPED DATA		9.6592	1.6815		

TABLE 7. STATISTICAL ANALYSIS OF RELATIVE ORGAN WEIGHT DATA

RIGHT KIDNEY TO FINAL BODY WEIGHT

Rats - Males

[illegible]	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	10	4.2122	.3511	.1110	3.7742	5.0929
[illegible]	10	4.2223	.1931	.0611	3.8373	4.4955
[illegible]	10	4.7177	.3874	.1225	3.8679	5.3333
[illegible]	9	4.3915	1.1135	.3712	3.5473	7.1950
TOTAL	39	4.3650			3.5473	7.1950
	UNGROUPED DATA		.6163	.0987		

Rats - Females

[illegible]	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	10	4.1174	.2085	.0649	3.7002	4.7134
[illegible]	10	4.2167	.4468	.1476	3.2154	5.0687
[illegible]	9	5.0234	.3170	.1057	4.5726	5.5634
[illegible]	9	4.5956	2.1300	.7100	1.5328	9.6129
TOTAL	38	4.4714			1.5328	9.6129
	UNGROUPED DATA		1.0966	.1779		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	8.9882	.5880	.2079	8.0000	10.0714
750 ppm	8	8.8605	.7756	.2742	8.0000	10.1200
1500 ppm	3	9.8951	.5817	.3359	9.5200	10.5652
CONTROL	6	8.6361	.5677	.2318	7.8333	9.4643
TOTAL	25	8.9717			7.8333	10.5652
	UNGROUPED DATA		.7145	.1429		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	8.1294	1.0556	.3732	6.8571	9.8571
750 ppm	10	8.1516	1.2451	.3937	6.0000	10.2381
1500 ppm	8	10.2048	.7571	.2677	9.3810	11.8750
CONTROL	7	8.1227	.6302	.2382	7.4286	9.2632
TOTAL	33	8.6498			6.0000	11.8750
	UNGROUPED DATA		1.2952	.2255		

TABLE 7. STATISTICAL ANALYSIS OF RELATIVE ORGAN WEIGHT DATA

LEFT KIDNEY TO FINAL BODY WEIGHT

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	4.3774	.2299	.0727	3.7160	4.5752
750 ppm	13	4.3354	.2461	.0774	3.9664	4.8591
1500 ppm	10	5.1493	1.3942	.4409	3.9637	9.0455
CONTROL	9	4.2844	1.0053	.3351	3.6149	6.9182
TOTAL	39	4.4718			3.6149	9.0455
	UNGROUPED DATA		.9442	.1512		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	4.1096	.2031	.0642	3.6353	4.3922
750 ppm	10	4.2446	.3943	.1247	3.6304	4.7562
1500 ppm	9	4.9332	.2902	.0967	4.6033	5.2192
CONTROL	9	4.3764	1.1028	.3943	2.3358	6.3871
TOTAL	38	4.4244			2.3358	6.3871
	UNGROUPED DATA		.6739	.1093		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	8.5948	.7464	.2639	7.8400	10.2500
750 ppm	8	8.7348	1.1973	.4233	7.4400	11.0400
1500 ppm	3	10.0281	.3183	.1838	9.6800	10.3043
CONTROL	6	8.4435	.8263	.3373	7.5417	9.5000
TOTAL	25	8.8278			7.4400	11.0400
	UNGROUPED DATA		.9491	.1938		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	8.0563	.5885	.2081	7.2174	8.9048
750 ppm	10	7.5864	1.1001	.3479	5.7143	9.0000
1500 ppm	8	9.7725	.6823	.2412	8.5556	10.7273
CONTROL	7	7.9053	.7244	.2739	7.2727	9.1053
TOTAL	33	8.2979			5.7143	10.7273
	UNGROUPED DATA		1.1690	.2035		

TABLE 7. STATISTICAL ANALYSIS OF RELATIVE ORGAN WEIGHT DATA

LUNGS TO FINAL BODY WEIGHT

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	[illegible]	[illegible]	.5518	.1742	4.0467	[illegible]
[illegible]	[illegible]	[illegible]	.4632	.1465	[illegible]	[illegible]
[illegible]	[illegible]	5.7914	1.0429	.3294	[illegible]	7.5455
[illegible]	[illegible]	[illegible]	2.1033	.7311	3.7814	10.1533
TOTAL	39	5.2538			3.7814	10.1533
	UNGROUPED DATA		1.2141	.1944		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	14	[illegible]	.6633	.1988	[illegible]	6.7983
[illegible]	13	[illegible]	3.3739	1.0649	3.7395	15.4453
[illegible]	[illegible]	[illegible]	.6349	.2734	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	1.0253	.5017	3.1022	[illegible]
TOTAL	39	6.4553			3.1022	15.4459
	UNGROUPED DATA		2.0267	.3249		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	7.7346	.6215	.2197	7.0000	8.7692
750 ppm	8	7.7747	3.2887	1.1627	4.4000	14.6923
1500 ppm	3	7.9310	1.7361	1.0023	6.6000	9.9130
CONTROL	6	7.7925	1.1344	.4440	6.3333	9.6429
TOTAL	25	7.7849			4.4000	14.6923
	UNGROUPED DATA		1.9471	.3894		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	8.2771	1.1886	.4202	6.9048	10.0952
750 ppm	10	9.1037	2.2060	.6974	6.0909	12.6818
1500 ppm	8	13.9819	4.3095	1.5236	8.8421	22.0526
CONTROL	7	9.8763	1.8886	.7138	8.1818	13.7895
TOTAL	33	10.2740			6.0909	22.0526
	UNGROUPED DATA		3.3540	.5839		

TABLE 7. STATISTICAL ANALYSIS OF RELATIVE ORGAN WEIGHT DATA

PANCREAS TO FINAL BODY WEIGHT

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	10	2.0354	.6126	.1937	.9027	3.1565
[illegible]	10	2.8221	1.3137	.4154	1.3090	5.3909
[illegible]	10	3.4434	1.4251	.4507	1.0338	5.0545
[illegible]	9	2.3579	1.4032	.4677	1.1494	5.5245
TOTAL	39	2.6794			.9027	5.9545
	UNGROUPED DATA		1.3025	.2046		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
[illegible]	10	2.3751	.8397	.2655	.8958	3.6556
[illegible]	10	2.6616	1.3525	.3324	.8645	4.1503
[illegible]	9	4.1958	1.7323	.5774	2.1831	7.9303
[illegible]	4	2.5536	.8558	.2853	1.2774	3.6774
TOTAL	38	2.7584			.8645	7.9858
	UNGROUPED DATA		1.3907	.2248		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	5.3833	1.0629	.3758	3.6522	6.9583
750 ppm	8	8.9044	3.4788	1.2299	4.1600	14.9600
1500 ppm	3	5.5366	1.0158	.5866	4.5200	6.5500
CONTROL	6	6.7266	2.0732	.8464	3.7500	9.2857
TOTAL	29	6.8502			3.6522	14.9600
	UNGROUPED DATA		2.6807	.5341		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	8	6.3531	1.6467	.5956	4.3500	9.2727
750 ppm	10	5.7903	1.3732	.4342	3.6545	8.8455
1500 ppm	8	6.6056	2.1099	.7459	4.7778	10.5625
CONTROL	6	5.7157	2.1613	.8824	1.6316	7.8261
TOTAL	32	6.1112			1.6316	10.5625
	UNGROUPED DATA		1.7594	.3110		

TABLE 8. STATISTICAL ANALYSIS OF RELATIVE ORGAN WEIGHT DATA

ADRENAL TO WEEK 12 BODY WEIGHT

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	18	.2655	.0927	.0293	.1562	.4779
750 ppm	8	.2625	.0658	.0233	.1786	.4824
1500 ppm	10	.3501	.1947	.0616	.1229	.8507
CONTROL	10	.2636	.0722	.0228	.2032	.4415
TOTAL	39	.2973			.1229	.8507
	UNGROUPED DATA		.1220	.0198		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	.4315	.0762	.0241	.3287	.5586
750 ppm	9	.4164	.0758	.0253	.3166	.5494
1500 ppm	10	.5972	.3249	.1027	.3942	1.5380
CONTROL	10	.4189	.0916	.0290	.2349	.5606
TOTAL	39	.4673			.2349	1.5880
	UNGROUPED DATA		.1886	.0302		

BRAIN TO WEEK 12 BODY WEIGHT

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	6.8934	.3562	.1127	6.3768	7.6466
750 ppm	8	7.1164	.3115	.1101	6.7436	7.6153
1500 ppm	10	8.1239	.6473	.2118	7.0751	8.8856
CONTROL	18	7.7226	2.6072	.8245	6.1514	13.9213
TOTAL	36	7.4573			6.1514	13.9213
	UNGROUPED DATA		1.4456	.2345		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	9.9492	.3994	.1263	9.3211	10.4812
750 ppm	9	10.2995	.6191	.2064	9.3968	11.3459
1500 ppm	10	10.7733	.4616	.1460	9.9412	11.1538
CONTROL	10	9.6183	1.5705	.4966	5.3603	11.6503
TOTAL	39	10.1521			9.3603	11.6503
	UNGROUPED DATA		.9733	.1559		

TABLE 8. STATISTICAL ANALYSIS OF RELATIVE ORGAN WEIGHT DATA

TESTICLES OR OVARIES TO WEEK 12 BODY WEIGHT

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	16.1193	1.8984	.6003	14.7647	21.2347
750 ppm	8	16.5446	2.2397	.7812	14.3201	21.4722
1500 ppm	17	13.7719	5.0149	1.2696	9.9451	23.2556
CONTROL	10	15.8933	4.3165	1.3656	6.4131	23.5334
TOTAL	38	15.5515			6.4131	23.5334
		UNGROUPED DATA	3.3879	.5496		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	.7725	.2214	.0702	.4749	1.2293
750 ppm	9	.7223	.1665	.0555	.4687	.9435
1500 ppm	10	1.2265	.6654	.2088	.6842	3.2738
CONTROL	10	.6488	.2984	.0792	.2247	1.1265
TOTAL	39	.8463			.2247	3.2738
		UNGROUPED DATA	.5224	.0835		

SPLEEN TO WEEK 12 BODY WEIGHT

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	1.7974	.1299	.0411	1.5597	2.0754
750 ppm	8	1.8593	.1337	.0473	1.6340	2.1138
1500 ppm	10	1.9524	.1679	.0515	1.5910	2.0723
CONTROL	10	1.8025	.3793	.1200	1.4351	2.7074
TOTAL	38	1.8252			1.4351	2.7074
		UNGROUPED DATA	.2229	.0362		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	2.1449	.2809	.0912	1.6843	2.6193
750 ppm	9	2.1293	.2396	.0795	1.7381	2.5366
1500 ppm	10	2.1479	.2888	.0886	1.8323	2.7024
CONTROL	10	2.7917	2.2487	.7111	1.2914	9.1011
TOTAL	39	2.3979			1.2914	9.1011
		UNGROUPED DATA	1.1537	.1847		

TABLE 8. STATISTICAL ANALYSIS OF RELATIVE ORGAN WEIGHT DATA

LIVER TO WEEK 12 BODY WEIGHT

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	27.2473	1.6895	.5343	24.8676	29.3540
750 ppm	8	28.1885	1.1456	.4050	26.2642	29.6337
1500 ppm	10	30.2246	1.1752	.3716	29.2095	32.6066
CONTROL	10	27.5331	5.8838	1.8606	22.2787	42.9787
TOTAL	38	29.3934			22.2787	42.9787
	UNGROUPED DATA		3.3411	.5420		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	26.9878	1.9335	.6114	24.6588	31.8994
750 ppm	9	26.6546	1.1393	.3798	25.1173	28.5052
1500 ppm	10	29.9400	1.9203	.6018	26.8264	33.8125
CONTROL	10	26.1928	4.8027	1.5187	16.5563	36.8613
TOTAL	39	27.4624			16.5563	36.8613
	UNGROUPED DATA		3.8785	.6917		

RIGHT KIDNEY TO WEEK 12 BODY WEIGHT

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	3.8638	.3113	.0984	3.5818	4.6225
750 ppm	8	3.9142	.1438	.0508	3.7374	4.1497
1500 ppm	10	4.3574	.2584	.0818	3.9447	4.9293
CONTROL	10	3.8179	.8846	.2797	3.1546	6.0951
TOTAL	38	3.9919			3.1546	6.0951
	UNGROUPED DATA		.5331	.0865		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	3.6818	.2583	.0817	3.3895	4.2787
750 ppm	9	3.8787	.3329	.1110	3.5449	4.6068
1500 ppm	10	4.3270	.3953	.1969	3.6686	4.9362
CONTROL	10	4.8232	1.7661	.5585	1.3937	8.3708
TOTAL	39	3.9797			1.3967	8.3708
	UNGROUPED DATA		.9266	.1484		

[illegible]

[illegible]

[illegible]

TABLE 8. STATISTICAL ANALYSIS OF RELATIVE ORGAN WEIGHT DATA

PANCREAS TO WEEK 12 BODY WEIGHT

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	1.8673	.5435	.1782	.8375	2.8776
750 ppm	8	2.4062	1.8122	.3579	1.2183	4.5359
1500 ppm	10	3.2185	1.2957	.4097	1.2977	5.6357
CONTROL	10	2.3215	1.1025	.3486	1.3808	4.6609
TOTAL	38	2.3744			.8375	5.6357
	UNGROUPED DATA		1.1257	.1826		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	2.1273	.7979	.2397	.3081	3.2989
750 ppm	9	1.8826	1.0394	.3365	.8565	3.7727
1500 ppm	10	3.4652	1.4798	.4677	1.9379	6.1739
CONTROL	10	2.2414	.8251	.2609	1.1589	3.4724
TOTAL	39	2.4431			.8965	6.1739
	UNGROUPED DATA		1.1908	.1906		

HEART TO WEEK 12 BODY WEIGHT

Rats - Male

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	3.5595	.1459	.0580	3.2669	3.8554
750 ppm	8	3.7456	.2729	.0965	3.3773	4.1585
1500 ppm	10	3.6872	.9519	.3010	1.0279	4.5138
CONTROL	10	3.5873	.7961	.2518	2.7129	5.5136
TOTAL	38	3.6141			1.0279	5.5136
	UNGROUPED DATA		.6365	.1033		

Rats - Female

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	3.7765	.4792	.1515	3.3424	5.0855
750 ppm	8	3.8282	.2595	.0918	3.5956	4.3239
1500 ppm	10	4.1571	.5978	.1493	3.6131	5.7651
CONTROL	10	3.4623	.5247	.1659	2.2185	4.1963
TOTAL	38	3.5032			2.2185	5.7851
	UNGROUPED DATA		.5766	.0871		

APPENDIX H

URINALYSIS DATA

Treatment Group	Animal I.D.	Specific Gravity	pH	Protein	Glucose	Ketones	Occult Blood	WBC	RBC	Casts	Epith	Mucus	Sperm	Bacteria	Yeast	Amorph	Crystals	Volume
A01	22	1.032	6.0	1	0	0	1	3	0	0	5	0	2	1	1	1	0	5.0
A01	24	1.044	6.0	1	0	0	1	4	0	0	3	0	2	1	1	1	1	3.5
A01	26	1.064	5.5	3	0	0	0	1	0	0	2	0	0	1	1	1	0	1.5
A01	31																	
A01	33	1.025	6.0	0	0	0	0	1	0	0	2	1	0	1	1	1	1	4.5
A01	34	1.040	6.0	3	0	0	1	1	1	0	3	1	0	1	1	1	0	.2
A01	36	1.023	7.0	0	0	0	2	0	0	0	1	0	0	1	1	0	1	4.5
A01	37	1.033	6.0	0	0	0	1	3	0	0	4	0	0	1	1	1	1	6.5
A01	63	1.044	6.0	2	0	0	0	2	0	0	1	1	0	1	1	0	1	2.5
A01	76	1.015	7.0	0	0	0	0	6	0	0	2	0	1	1	1	0	1	10.5
A02	23	1.032	6.5	1	0	0	0	4	0	0	5	0	0	1	1	2	1	5.5
A02	37	1.052	6.0	2	0	0	2	1	0	0	0	0	0	1	1	2	0	3.0
A02	39	1.054	6.0	1	0	0	1	0	0	1	1	0	1	1	1	2	1	4.0
A02	61	1.026	6.5	0	0	0	0	1	0	0	2	0	2	1	2	0	1	5.5
A02	62	1.064	6.0	2	0	0	0	0	0	0	2	0	0	1	1	1	0	.5
A02	66	1.068	5.5	2	0	0	0	0	0	0	1	1	0	1	1	0	1	1.0
A02	69	1.033	6.0	1	0	0	0	2	0	0	1	0	0	1	1	1	1	5.0
A02	70	1.021	6.0	1	0	0	1	1	0	0	3	0	0	1	1	1	0	7.5
A02	74	1.008	5.0	0	0	0	0	0	0	0	1	0	0	1	1	0	0	1.0
A02	79	1.064	6.0	2	0	0	0	1	0	0	3	0	1	1	1	0	0	1.5
A03	21	1.060	6.0	2	0	0	0	2	0	0	2	0	0	1	1	1	1	3.0
A03	28	1.023	6.0	1	0	0	1	3	2	0	4	1	0	1	1	1	0	6.0
A03	32	1.050	6.0	2	0	0	0	1	0	0	2	0	0	2	1	1	1	3.0
A03	38	1.028	6.0	0	0	0	0	2	1	0	4	0	0	1	1	2	0	5.0
A03	40	1.035	6.0	1	0	0	0	2	0	0	3	1	0	1	1	1	0	4.5
A03	67	1.027	6.0	1	0	0	1	2	0	0	2	0	0	1	1	2	0	5.5
A03	68	1.056	6.0	2	0	0	1	0	0	0	1	0	0	1	1	1	0	2.5
A03	71	1.015	6.0	1	0	0	1	1	0	0	4	0	0	2	2	1	0	14.5
A03	72	1.021	6.0	0	0	0	0	1	0	0	1	0	0	1	1	0	0	5.0
A03	78	1.024	6.0	1	0	0	0	2	0	0	1	1	0	2	1	0	0	2.5
A04	25	1.004	6.0	3	0	0	0	2	0	0	1	0	2	1	1	0	0	.1
A04	29	1.140	6.0	4	0	0	0	0	0	0	2	0	2	0	1	0	1	2.0
A04	30	1.140	6.0	3	0	0	0	1	1	0	1	0	1	1	2	0	0	2.0
A04	35	1.068	6.0	2	0	0	0	1	0	0	1	0	1	1	1	0	2	3.5
A04	64	1.072	6.0	2	0	0	0	3	0	0	0	0	0	1	1	2	0	3.0
A04	65	1.136	5.5	3	0	0	0	1	0	0	2	0	0	1	1	1	0	[illegible]
A04	73	1.048	6.0	2	0	0	0	1	0	0	1	1	0	1	1	2	1	4.0
A04	77	1.036	6.5	1	0	0	0	1	0	0	3	0	0	2	1	0	1	7.0
A04	80	1.046	6.0	2	0	0	1	1	0	0	1	0	1	2	1	1	1	6.0
A04	85	1.028	7.0	1	0	0	0	1	0	0	0	0	2	[illegible]	1	0	1	13.5

Treatment Group	Animal I.D.	Specific Gravity	pH	Protein	Glucose	Ketones	Occult Blood	WBC	RBC	Casts	Epith	Mucus	Sperm	Bacteria	Yeast	Amorph	Crystals	Volume
A01	18	1.016	6.5	0	0	0	0	2	0	0	0	0	0	1	1	0	1	10.0
A01	16	1.017	6.5	0	0	0	0	2	2	0	1	0	0	1	1	0	2	5.5
A01	43	1.038	6.0	0	0	0	0	0	0	0	2	0	0	1	1	0	1	4.5
A01	44	1.046	5.5	1	0	0	2	3	0	0	1	1	0	1	1	0	0	2.0
A01	49	1.018	6.0	0	0	0	0	1	0	0	2	0	0	1	1	0	0	3.5
A01	56	1.022	6.0	0	0	0	0	1	0	0	2	0	0	1	1	0	0	3.5
A01	57	1.017	6.0	0	0	0	0	2	1	0	1	0	0	1	1	1	0	8.5
A01	58	1.017	5.5	0	0	0	2	4	0	0	1	0	0	1	1	0	1	9.0
A01	59	1.024	6.0	0	0	0	0	2	0	0	1	0	0	1	1	0	0	5.5
A01	60	1.035	6.0	0	0	0	1	1	0	0	1	0	0	1	1	0	0	3.0
A02	4	1.028	6.0	0	0	0	0	1	0	0	1	0	0	1	1	0	0	6.0
A02	5	1.054	6.0	1	0	0	0	1	0	0	1	0	0	1	1	0	0	1.5
A02	8	1.024	6.0	0	0	0	1	0	0	0	1	0	0	2	1	0	1	5.0
A02	13	1.018	6.5	0	0	0	0	10	0	0	5	0	0	2	1	0	1	14.0
A02	14	1.034	6.0	0	0	0	0	1	0	0	3	0	0	1	1	0	0	3.0
A02	41	1.046	6.0	0	0	0	2	2	0	0	2	1	0	1	1	0	0	1.5
A02	45	1.016	6.0	0	0	0	0	2	0	0	1	0	0	1	1	0	1	8.5
A02	47	1.017	6.5	0	0	0	0	1	0	0	2	0	0	2	1	0	1	6.0
A02	48	1.013	6.5	0	0	0	0	2	0	0	4	1	0	2	1	0	1	9.5
A02	50	1.005	6.0	0	0	0	0	1	0	0	0	0	0	1	1	0	0	23.0
A03	2	1.014	7.5	0	0	0	0	1	0	0	2	0	0	2	1	0	1	9.0
A03	11	1.028	6.0	0	0	0	0	1	0	0	0	0	0	1	1	0	0	6.0
A03	17	1.027	6.0	0	0	0	0	0	0	0	1	0	0	1	1	0	0	5.0
A03	18	1.013	6.5	0	0	0	0	1	0	0	1	0	0	1	1	0	1	10.5
A03	20	1.025	6.0	0	0	0	0	1	0	0	2	1	0	2	1	0	0	5.0
A03	42	1.076	6.0	2	0	0	0	2	0	0	3	0	0	1	1	0	1	1.0
A03	46	1.027	6.0	0	0	0	1	0	0	0	1	0	0	1	1	0	0	5.0
A03	52	1.024	8.0	1	0	0	2	3	0	0	2	0	0	3	1	2	1	5.0
A03	53	1.032	6.0	0	0	0	0	1	0	0	0	0	0	1	1	0	0	2.0
A03	55	1.056	6.0	1	0	0	0	0	0	0	1	0	0	1	1	0	0	.3
A04	1	1.044	6.5	1	0	0	0	1	0	0	1	0	0	0	1	1	2	4.5
A04	3	1.040	6.5	0	0	0	0	1	1	0	0	0	0	1	0	1	1	5.0
A04	6	1.056	6.0	0	0	0	0	2	0	0	0	1	0	1	1	0	0	3.0
A04	7	1.078	6.0	0	0	0	0	0	0	0	2	0	0	1	1	1	2	2.5
A04	9	1.044	9.0	0	0	0	1	3	0	0	1	0	0	2	1	2	0	1.0
A04	12	1.038	7.0	0	0	0	1	1	0	0	0	0	0	2	1	2	1	4.0
A04	15	1.032	6.0	1	0	0	0	2	0	0	0	0	0	1	1	3	0	3.0
A04	19	1.044	6.0	2	0	0	0	1	0	0	2	0	0	1	1	2	1	5.5
A04	51	1.029	6.5	0	0	0	0	1	0	0	3	0	0	1	1	0	1	9.0
A04	54	1.048	6.5	1	0	0	0	0	1	0	2	0	0	1	0	1	2	5.0

TABLE 3. URINALYSIS DATA FOR MALE MICE

Treatment Group	Subgroup	Animal I.D.	Specific Gravity	pH	Protein	Glucose	Ketones	Occult Blood	WBC	RBC	Casts	Epith	Mucus	Sperm	Bacteria	Yeast	Amorph	Crystals	Volume
A02	1	23	1.078	6.0	2	0	0	0	1	0	0	0	0	0	1	1	0	0	.5
A02	1	27																	
A02	1	69																	
A02	1	78																	
A02	2	61	1.035	6.0	1	0	0	0	20	0	0	5	0	0	1	1	0	0	1.5
A02	2	62																	
A02	2	66																	
A02	2	79																	
A03	1	28	1.028	6.0	0	0	0	0	2	0	0	1	0	0	1	1	0	0	2.5
A03	1	78																	
A03	1	40																	
A03	2	71																	.1
A04	1	25	1.012	6.0	1	0	0	0	2	0	0	2	0	0	1	0	1	0	20.0
A04	1	29																	
A04	1	38																	
A04	1	73																	
A04	2	35	1.010	6.0	0	0	0	0	4	0	0	1	0	0	1	1	0	0	20.0
A04	2	64																	
A04	2	75																	
A04	2	88																	

000175

TABLE 4. URINALYSIS DATA FOR FEMALE MICE

Treatment Group	Subgroup	Animal I.D.	Specific Gravity	pH	Protein	Glucose	Ketones	Occult Blood	WBC	RBC	Casts	Epith	Mucus	Sperm	Bacteria	Yeast	Amorph	Crystals	Volume
A02	1	4																	.1
A02	1	5																	
A02	1	8																	
A02	1	14																	
A02	2	41	1.028	6.0	0	0	0	0	3	0	0	2	0	0	1	1	0	0	2.5
A02	2	45																	
A02	2	47																	
A02	2	48																	
A02	2	50																	
A03	1	2	1.028	6.0	1	0	0	0	1	0	0	0	0	0	1	1	0	1	1.0
A03	1	11																	
A03	1	17																	
A03	1	20																	
A03	1	46																	
A03	2	18	1.019	6.0	0	0	0	0	0	0	0	1	0	0	1	1	0	0	1.0
A03	2	52																	
A03	2	53																	
A03	2	55																	
A04	1	1	1.012	6.0	0	0	0	0	2	0	0	1	0	0	1	0	0	0	20.0
A04	1	3																	
A04	1	7																	
A04	1	12																	
A04	2	9	1.011	6.0	0	0	0	0	2	0	0	1	0	0	1	1	1	0	14.0
A04	2	15																	
A04	2	19																	
A04	2	54																	

000176

TABLE 5. STATISTICAL ANALYSIS OF URINALYSIS DATA

Specific Gravity

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	9	1.0356	.0145	.0048	1.0150	1.0649
750 ppm	10	1.0414	.0224	.0071	1.0000	1.0600
1500 ppm	10	1.0339	.0158	.0050	1.0150	1.0600
CONTROL	10	1.0798	.0439	.0139	1.0200	1.1400
TOTAL	39	1.0488			1.0000	1.1400
	UNGROUPED DATA		.0324	.0052		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	1.0242	.0100	.0031	1.0169	1.0469
750 ppm	9	1.0214	.0148	.0049	1.0050	1.0549
1500 ppm	10	1.0314	.0197	.0062	1.0135	1.0760
CONTROL	10	1.0437	.0125	.0040	1.0290	1.0793
TOTAL	39	1.0304			1.0050	1.0760
	UNGROUPED DATA		.0166	.0027		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	2	1.0525	.0247	.0175	1.0350	1.0700
1500 ppm	1	1.0200				
CONTROL	2	1.0110	.0014	.0010	1.0100	1.0120
TOTAL	5	1.0310			1.0100	1.0700
	UNGROUPED DATA		.0242	.0108		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	1	1.0200				
1500 ppm	2	1.0235	.0064	.0045	1.0190	1.0240
CONTROL	2	1.0115	.0007	.0005	1.0110	1.0120
TOTAL	5	1.0196			1.0110	1.0290
	UNGROUPED DATA		.0083	.0037		

TABLE 5. STATISTICAL ANALYSIS OF URINALYSIS DATA

pH

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	9	6.1667	.5000	.1667	5.5000	7.0000
750 ppm	10	5.9500	.4370	.1384	5.0000	6.5000
1500 ppm	10	6.0000	0	0	6.0000	6.0000
CONTROL	10	6.1000	.3944	.1247	5.5000	7.0000
TOTAL	39	6.0513			5.0000	7.0000
	UNGROUPED DATA		.3769	.0603		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	6.0000	.3333	.1054	5.5000	6.5000
750 ppm	9	6.1667	.2500	.0833	6.0000	6.5000
1500 ppm	10	6.4000	.7379	.2333	6.0000	8.0000
CONTROL	10	6.6000	.9068	.2867	6.0000	9.0000
TOTAL	39	6.2949			5.5000	9.0000
	UNGROUPED DATA		.6450	.1034		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	2	6.0000	0	0	6.0000	6.0000
1500 ppm	1	6.0000				
CONTROL	2	6.0000	0	0	6.0000	6.0000
TOTAL	5	6.0000			6.0000	6.0000
	UNGROUPED DATA		0	0		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	1	6.0000				
1500 ppm	2	6.0000	0	0	6.0000	6.0000
CONTROL	2	6.0000	0	0	6.0000	6.0000
TOTAL	5	6.0000			6.0000	6.0000
	UNGROUPED DATA		0	0		

TABLE 5. STATISTICAL ANALYSIS OF URINALYSIS DATA

Protein

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	9	1.1111	1.2693	.4231	0	3.0000
750 ppm	10	1.2000	.7856	.2484	0	2.0000
1500 ppm	10	1.1000	.7379	.2333	0	2.0000
CONTROL	10	2.3000	.9487	.3000	1.0000	4.0000
TOTAL	39	1.4359			0	4.0000
	UNGROUPED DATA		1.0462	.1675		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	.1000	.3162	.1000	0	1.0000
750 ppm	9	.1111	.3333	.1111	0	1.0000
1500 ppm	10	.4000	.6992	.2211	0	2.0000
CONTROL	10	.5000	.7071	.2236	0	2.0000
TOTAL	39	.2821			0	2.0000
	UNGROUPED DATA		.5995	.0896		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	2	1.5000	.7071	.5000	1.0000	2.0000
1500 ppm	1	0				
CONTROL	2	.5000	.7071	.5000	0	1.0000
TOTAL	5	.8000			0	2.0000
	UNGROUPED DATA		.6367	.3742		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	1	0				
1500 ppm	2	.5000	.7071	.5000	0	1.0000
CONTROL	2	0	0	0	0	0
TOTAL	5	.2000			0	1.0000
	UNGROUPED DATA		.4472	.2000		

TABLE 5. STATISTICAL ANALYSIS OF URINALYSIS DATA

Glucose

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	9	0	0	0	0	0
750 ppm	10	0	0	0	0	0
1500 ppm	10	0	0	0	0	0
CONTROL	10	0	0	0	0	0
TOTAL	39	0			0	0
	UNGROUPED DATA		0	0		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	0	0	0	0	0
750 ppm	9	0	0	0	0	0
1500 ppm	10	0	0	0	0	0
CONTROL	10	0	0	0	0	0
TOTAL	39	0			0	0
	UNGROUPED DATA		0	0		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	2	0	0	0	0	0
1500 ppm	1	0				
CONTROL	2	0	0	0	0	0
TOTAL	5	0			0	0
	UNGROUPED DATA		0	0		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	1	0				
1500 ppm	2	0	0	0	0	0
CONTROL	2	0	0	0	0	0
TOTAL	5	0			0	0
	UNGROUPED DATA		0	0		

TABLE 5. STATISTICAL ANALYSIS OF URINALYSIS DATA

Ketones

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	9	0	0	0	0	0
750 ppm	10	0	0	0	0	0
1500 ppm	10	0	0	0	0	0
CONTROL	10	0	0	0	0	0
TOTAL	39	0			0	0
	UNGROUPED DATA		0	0		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	0	0	0	0	0
750 ppm	9	0	0	0	0	0
1500 ppm	10	0	0	0	0	0
CONTROL	10	0	0	0	0	0
TOTAL	39	0			0	0
	UNGROUPED DATA		0	0		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	2	0	0	0	0	0
1500 ppm	1	0				
CONTROL	2	0	0	0	0	0
TOTAL	5	0			0	0
	UNGROUPED DATA		0	0		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	1	0				
1500 ppm	2	0	0	0	0	0
CONTROL	2	0	0	0	0	0
TOTAL	5	0			0	0
	UNGROUPED DATA		0	0		

TABLE 5. STATISTICAL ANALYSIS OF URINALYSIS DATA

WBC

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	9	3.2222	2.4351	.8127	1.0000	8.0000
750 ppm	10	1.0000	1.2472	.3944	0	4.0000
1500 ppm	10	1.6000	.8433	.2667	0	3.0000
CONTROL	10	1.2000	.7888	.2494	0	3.0000
TOTAL	39	1.7179			0	8.0000
	UNGROUPED DATA		1.6375	.2622		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	1.0000	1.1353	.3590	0	4.0000
750 ppm	9	2.1111	3.0165	1.0062	0	10.0000
1500 ppm	10	1.0000	.9428	.2981	0	3.0000
CONTROL	10	1.2000	.5189	.2944	0	3.0000
TOTAL	39	1.5128			0	10.0000
	UNGROUPED DATA		1.6039	.2615		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	2	10.5000	13.4350	9.5000	1.0000	20.0000
1500 ppm	1	2.0000				
CONTROL	2	3.0000	1.4142	1.0000	2.0000	4.0000
TOTAL	5	5.0000			1.0000	20.0000
	UNGROUPED DATA		8.0125	3.5833		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	1	3.0000				
1500 ppm	2	.5000	.7071	.5000	0	1.0000
CONTROL	2	2.0000	0	0	2.0000	2.0000
TOTAL	5	1.0000			0	3.0000
	UNGROUPED DATA		1.1402	.5099		

TABLE 5. STATISTICAL ANALYSIS OF URINALYSIS DATA

RBC

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	9	.1111	.3333	.1111	0	1.0000
750 ppm	10	0	0	0	0	0
1500 ppm	10	.3000	.6749	.2134	0	2.0000
CONTROL	10	.1000	.3162	.1000	0	1.0000
TOTAL	39	.1282			0	2.0000
	UNGROUPED DATA		.4091	.0655		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	.3000	.6749	.2134	0	2.0000
750 ppm	9	0	0	0	0	0
1500 ppm	10	0	0	0	0	0
CONTROL	10	.2000	.4216	.1333	0	1.0000
TOTAL	39	.1282			0	2.0000
	UNGROUPED DATA		.4091	.0655		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	2	0	0	0	0	0
1500 ppm	1	0				
CONTROL	2	0	0	0	0	0
TOTAL	5	0			0	0
	UNGROUPED DATA		0	0		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	1	0				
1500 ppm	2	0	0	0	0	0
CONTROL	2	0	0	0	0	0
TOTAL	5	0			0	0
	UNGROUPED DATA		0	0		

TABLE 5. STATISTICAL ANALYSIS OF URINALYSIS DATA

Casts

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	9	0	0	0	0	0
750 ppm	10	.1000	.3162	.1000	0	1.0000
1500 ppm	10	0	0	0	0	0
CONTROL	10	0	0	0	0	0
TOTAL	39	.0256			0	1.0000
	UNGROUPED DATA		.1681	.3256		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	0	0	0	0	0
750 ppm	9	0	0	0	0	0
1500 ppm	10	0	0	0	0	0
CONTROL	10	0	0	0	0	0
TOTAL	39	0			0	0
	UNGROUPED DATA		0	0		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	2	0	0	0	0	0
1500 ppm	1	0				
CONTROL	2	0	0	0	0	0
TOTAL	5	0			0	0
	UNGROUPED DATA		0	0		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	1	0				
1500 ppm	2	0	0	0	0	0
CONTROL	2	0	0	0	0	0
TOTAL	5	0			0	0
	UNGROUPED DATA		0	0		

TABLE 5. STATISTICAL ANALYSIS OF URINALYSIS DATA

Epith

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	9	2.5556	1.3333	.4444	1.0000	5.0000
750 ppm	10	2.7000	2.2632	.7157	1.0000	6.0000
1500 ppm	10	2.4000	1.2649	.4000	1.0000	4.0000
CONTROL	10	1.2000	.9189	.2906	0	3.0000
TOTAL	39	2.2051			0	6.0000
	UNGROUPED DATA		1.5924	.2550		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	1.2000	.6325	.2000	0	2.0000
750 ppm	9	2.2222	1.9221	.6407	0	5.0000
1500 ppm	10	1.3000	.9487	.3000	0	3.0000
CONTROL	10	1.1000	1.1005	.3480	0	3.0000
TOTAL	39	1.4359			0	5.0000
	UNGROUPED DATA		1.2523	.2005		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	2	2.5000	3.5355	2.5000	0	5.0000
1500 ppm	1	1.0000				
CONTROL	2	1.5000	.7071	.5000	1.0000	2.0000
TOTAL	5	1.8000			0	5.0000
	UNGROUPED DATA		1.9235	.8602		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	1	2.0000				
1500 ppm	2	.5000	.7071	.5000	0	1.0000
CONTROL	2	1.0000	0	0	1.0000	1.0000
TOTAL	5	1.0000			0	2.0000
	UNGROUPED DATA		.7071	.3162		

TABLE 5. STATISTICAL ANALYSIS OF URINALYSIS DATA

Mucus

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	9	.3333	.5000	.1667	0	1.0000
750 ppm	10	.1000	.3162	.1000	0	1.0000
1500 ppm	10	.3000	.4830	.1528	0	1.0000
CONTROL	10	.1000	.3162	.1000	0	1.0000
TOTAL	39	.205[illegible]			0	1.0000
	UNGROUPED DATA		.4091	.0655		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	.1000	.3162	.1000	0	1.0000
750 ppm	9	.1111	.3333	.1111	0	1.0000
1500 ppm	10	.1000	.3162	.1000	0	1.0000
CONTROL	10	.1000	.3162	.1000	0	1.0000
TOTAL	39	.1026			0	1.0000
	UNGROUPED DATA		.3374	.0492		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	2	0	0	0	0	0
1500 ppm	1	0				
CONTROL	2	0	0	0	0	0
TOTAL	5	0			0	0
	UNGROUPED DATA		0	0		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	1	0				
1500 ppm	2	0	0	0	0	0
CONTROL	2	0	0	0	0	0
TOTAL	5	0			0	0
	UNGROUPED DATA		0	0		

TABLE 5. STATISTICAL ANALYSIS OF URINALYSIS DATA

Sperm

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	9	.5556	.8819	.2940	0	2.0000
750 ppm	10	.4000	.6992	.2211	0	2.0000
1500 ppm	10	0	0	0	0	0
CONTROL	10	.9000	.8756	.2769	0	2.0000
TOTAL	39	.4615			0	2.0000
	UNGROUPED DATA		.7595	.1216		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	0	0	0	0	0
750 ppm	9	0	0	0	0	0
1500 ppm	10	0	0	0	0	0
CONTROL	10	0	0	0	0	0
TOTAL	39	0			0	0
	UNGROUPED DATA		0	0		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	2	0	0	0	0	0
1500 ppm	1	0				
CONTROL	2	0	0	0	0	0
TOTAL	5	0			0	0
	UNGROUPED DATA		0	0		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	1	0				
1500 ppm	2	0	0	0	0	0
CONTROL	2	0	0	0	0	0
TOTAL	5	0			0	0
	UNGROUPED DATA		0	0		

TABLE 5. STATISTICAL ANALYSIS OF URINALYSIS DATA

Bacteria

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	9	1.0000	0	0	1.0000	1.0000
750 ppm	10	1.0000	0	0	1.0000	1.0000
1500 ppm	10	1.3000	.4830	.1526	1.0000	2.0000
CONTROL	10	1.3333	.8233	.2603	0	3.0000
TOTAL	39	1.1538			0	3.0000
	UNGROUPED DATA		.4887	.0783		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	1.0000	0	0	1.0000	1.0000
750 ppm	9	1.4444	.5278	.1757	1.0000	2.0000
1500 ppm	10	1.4000	.6992	.2211	1.0000	3.0000
CONTROL	10	1.1000	.5676	.1795	0	2.0000
TOTAL	39	1.2308			0	3.0000
	UNGROUPED DATA		.5361	.0859		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	2	1.0000	0	0	1.0000	1.0000
1500 ppm	1	1.0000				
CONTROL	2	1.0000	0	0	1.0000	1.0000
TOTAL	5	1.0000			1.0000	1.0000
	UNGROUPED DATA		0	0		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	1	1.0000				
1500 ppm	2	1.0000	0	0	1.0000	1.0000
CONTROL	2	1.0000	0	0	1.0000	1.0000
TOTAL	5	1.0000			1.0000	1.0000
	UNGROUPED DATA		0	0		

TABLE 5. STATISTICAL ANALYSIS OF URINALYSIS DATA

Yeast

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	9	1.0000	0	0	1.0000	1.0000
750 ppm	10	1.1000	.3162	.1000	1.0000	2.0000
1500 ppm	10	1.1000	.3162	.1000	1.0000	2.0000
CONTROL	10	1.1000	.3162	.1000	1.0000	2.0000
TOTAL	39	1.0769			1.0000	2.0000
	UNGROUPED DATA		.2700	.0432		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	1.0000	0	0	1.0000	1.0000
750 ppm	9	1.0000	0	0	1.0000	1.0000
1500 ppm	10	1.0000	0	0	1.0000	1.0000
CONTROL	10	.6000	.4216	.1333	0	1.0000
TOTAL	39	.5487			0	1.0000
	UNGROUPED DATA		.2239	.0358		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	2	1.0000	0	0	1.0000	1.0000
1500 ppm	1	1.0000				
CONTROL	2	.5000	.7071	.5000	0	1.0000
TOTAL	5	.8000			0	1.0000
	UNGROUPED DATA		.4472	.2000		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	1	1.0000				
1500 ppm	2	1.0000	0	0	1.0000	1.0000
CONTROL	2	.5000	.7071	.5000	0	1.0000
TOTAL	5	.8000			0	1.0000
	UNGROUPED DATA		.4472	.2000		

TABLE 5. STATISTICAL ANALYSIS OF URINALYSIS DATA

Crystals

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	9	.6667	.5000	.1667	0	1.0000
750 ppm	10	.5000	.5270	.1667	0	1.0000
1500 ppm	10	.2000	.4216	.1333	0	1.0000
CONTROL	10	.7000	.6749	.2134	0	2.0000
TOTAL	39	.5128			0	2.0000
	UNGROUPED DATA		.5559	.0890		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	.5000	.7071	.2236	0	2.0000
750 ppm	9	.5556	.5270	.1757	0	1.0000
1500 ppm	10	.4000	.5164	.1633	0	1.0000
CONTROL	10	1.0000	.8165	.2582	0	2.0000
TOTAL	39	.6154			0	2.0000
	UNGROUPED DATA		.6734	.1078		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	2	0	0	0	0	0
1500 ppm	1	0				
CONTROL	2	0	0	0	0	0
TOTAL	5	0			0	0
	UNGROUPED DATA		0	0		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	1	0				
1500 ppm	2	.5000	.7071	.5000	0	1.0000
CONTROL	2	0	0	0	0	0
TOTAL	5	.2000			0	1.0000
	UNGROUPED DATA		.4472	.2000		

TABLE 5. STATISTICAL ANALYSIS OF URINALYSIS DATA

Occult Blood

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	6	.6667	.7071	.2357	0	2.0000
750 ppm	10	.4000	.6992	.2211	0	2.0000
1500 ppm	10	.4000	.5164	.1633	0	1.0000
CONTROL	10	.1000	.3162	.1000	0	1.0000
TOTAL	39	.3846			0	2.0000
	UNGROUPED DATA		.5461	.0945		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	.5000	.8498	.2687	0	2.0000
750 ppm	9	.1111	.3333	.1111	0	1.0000
1500 ppm	10	.3000	.6749	.2134	0	2.0000
CONTROL	10	.2000	.4216	.1333	0	1.0000
TOTAL	39	.2921			0	2.0000
	UNGROUPED DATA		.6047	.0968		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	2	0	0	0	0	0
1500 ppm	1	0				
CONTROL	2	0	0	0	0	0
TOTAL	5	0			0	0
	UNGROUPED DATA		0	0		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	1	0				
1500 ppm	2	0	0	0	0	0
CONTROL	2	0	0	0	0	0
TOTAL	5	0			0	0
	UNGROUPED DATA		0	0		

TABLE 5. STATISTICAL ANALYSIS OF URINALYSIS DATA

Amorph

Rats - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	9	.6667	.5000	.1667	0	1.0000
750 ppm	10	.9000	.4796	.2769	0	2.0000
1500 ppm	10	1.0000	.6667	.2108	0	2.0000
CONTROL	10	.6000	.8433	.2667	0	2.0000
TOTAL	39	.7949			0	2.0000
	UNGROUPED DATA		.7323	.1172		

Rats - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
375 ppm	10	.1000	.3162	.1000	0	1.0000
750 ppm	9	0	0	0	0	0
1500 ppm	10	.2000	.6325	.2000	0	2.0000
CONTROL	10	1.3000	.9487	.3000	0	3.0000
TOTAL	39	.4103			0	3.0000
	UNGROUPED DATA		.7853	.1258		

Mice - Males

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	2	0	0	0	0	0
1500 ppm	1	0				
CONTROL	2	.5000	.7071	.5000	0	1.0000
TOTAL	5	.2000			0	1.0000
	UNGROUPED DATA		.4472	.2000		

Mice - Females

LEVEL	COUNT	MEAN	STANDARD DEVIATION	STANDARD ERROR	MINIMUM	MAXIMUM
750 ppm	1	0				
1500 ppm	2	0	0	0	0	0
CONTROL	2	.5000	.7071	.5000	0	1.0000
TOTAL	5	.2000			0	1.0000
	UNGROUPED DATA		.4472	.2000		

APPENDIX I

CLINICAL LABORATORY PROCEDURE

CLINICAL LABORATORY PROCEDURES

Methods used for hematology and clinical chemistry determinations are below. Detailed procedures are on file with the Quality Assurance Unit, Battelle's Columbus Laboratories, Columbus, Ohio.

Hematologic and Clinical Chemistry Determinations

HCT	Hematocrit (percent) determination with the Coulter flat pack accessory.
HGB	Hemoglobin (g percent) determined by the Coulter Hemoglobinometer.
RBC	Red blood cells ($10^6/mm^3$) determined with the Coulter counter, Model FN.
MCV	Mean Cell Volume (cubic microns) determined with the Coulter System.
MCH	Mean Corpuscular Hemoglobin calculated as MCH = HGB x 10/RBC.
MCHC	Mean Corpuscular Hemoglobin Concentration calculated as MCHC = MCH x 100/MCV.
WBC	White blood cells ($10^3/mm^3$) determined with the Coulter counter, Model FN.
WBC Differential	Differential percent determined after staining with May-Grunwald and Giemsa stains.
Reticulocytes	Reticulocytes (percent of RBC) stained with New Methylene Blue.
BUN	Blood urea nitrogen (mg percent serum) determined by the Spin Chem® kinetic procedure, a modification of the Talke and Schubert[4] method, using Smith Kline Instruments reagents.
AP	Alkaline phosphatase (International Units) hydrolysis of magnesium thymolphthalein monophosphate to thymolphthalein. Coleman, C. M.[2]

8782102219

SGPT — Serum glutamic-pyruvic transaminase (I.U./l). Kinetic assays based on an oxidation of NADH by LDH. Modified and optimized by Henry, etal.[3]

Glucose — Glucose (mg percent serum) determined by the Spin Chem® enzymatic procedure using coupling of hexokinase and glucose-6-phosphate dehydrogenase (G-6-PDH) as developed by Barthelmai and Czok[2]. Modified by Smith Kline Instruments.

CPK — Serum Creatinine Phosphokinase (I.U./l) kinetic assays based on the reduction of NAD to NADH. Worthington/Gilford Diagnostis - Done on a Gemsaec Autoanalyzer.

Urinalysis Determinations

Sp. Gr.	Specific gravity determined by the American Optical Refractometer.
pH, Sugar, Ketones, Blood Protein	Determined with Labstix Reagent Strips (Ames Company).
Urine Sediment	Evaluated microscopically.

Urinalysis Codes:

Sugar, Ketones, blood and mucus (0-3)	0 = none, 1 = few, 2 = moderate, 3 = many.
Protein (0-5)	0 = negative, 1 = $\leq$ 30 mg/100 ml, 2 = 31-100 mg/100 ml, 3 = 101-300 mg/100 ml, 4 = 301-1000 mg/100 ml, 5 = $\geq$ 1000 mg/100 ml.

Bone Marrow Analysis

M:E Ratios	Determined after staining with May-Grunwald and Giemsa stains.

OFFICE OF TOXIC SUBSTANCES REV. 7/27/82

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METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

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SUMMARY

Male cats and male beagle dogs (3/group) were exposed to 0, 200 or 500 ppm methyl chloride (MeCl) for approximately 23-1/2 hours/day for three days. The animals were subsequently observed for 2 (cats) or 4 (dogs) weeks and then necropsied. Parameters monitored included clinical observations; neurological exams; routine clinical chemistry, hematology and urinalysis; body weights and selected organ weights obtained at necropsy. Gross and microscopic pathology exams were performed on all animals.

Male cats showed no effects attributable to methyl chloride exposure. Male beagle dogs exposed to 500 ppm MeCl exhibited neurological effects ranging from near normal presentation to severe upper motor neuron disease characterized by ataxia, paralysis and tremors. Pathological examination of these dogs revealed lesions in the brain stem and spinal cord consistent with the clinical neurological findings. The effects noted were observed immediately following exposure and even the most severely affected animal exhibited signs of reversibility of symptoms during the ensuing 4-week observation period.

Dogs exposed to 200 ppm MeCl showed no effects attributable to exposure. Under the conditions of this study no-observable-effect-levels (NOEL) were judged to be 200 ppm for dogs and 500 ppm for cats.

INTRODUCTION

Studies currently underway in the Dow Toxicology Research Laboratory (Burek et al., 1981) were designed to evaluate the inhalation toxicity of methyl chloride (MeCl) to rats upon continuous exposure for 48 or 72 hours. Little is known of the inhalation toxicity of MeCl in other species under similar conditions (i.e. continuous exposure). Smith and von Oettingen (1947a, b) found that dogs and cats were more sensitive than rats to the effects of MeCl upon repeated daily exposures. They reported no adverse effect levels for dogs and rats for 300 ppm and 500 ppm MeCl, respectively.

The purpose of this study was to provide information on the inhalation toxicity of MeCl in dogs and cats following continuous exposure to MeCl and to evaluate possible species differences in reponse to MeCl under this exposure regimen.

MATERIALS AND METHODS

Test Material

General Physical Properties:

Physical State	Colorless, odorless & tasteless gas
Molecular Formula	CH_3Cl
Molecular Weight	50.49 g/mole
Boiling Point	-24.22°C at 760 mmHg
Vapor Density (Air = 1)	1.785
Flash Point (TOC)	<32°F
Synonyms	Chloromethane

The test material was obtained from Matheson Gas Products, Joliet, Illinois in three gas cylinders with the following numbers (filling dates): J262 (5/6/76), J888 (8/10/76), and J2001 (9/23/76). Each was analyzed by the Dow Chemical Analytical Laboratory, Midland, Michigan and was determined to be 99.9% pure by mass spectrometry.

Exposure Chamber, Vapor Generation and Analysis

Exposures were conducted in 4.1 cubic meter stainless steel chambers (Dow design) under dynamic airflow conditions. Control animals were placed in an identical chamber. Temperature and humidity in the chambers were controlled by a system designed to maintain temperature at approximately 72°F and relative humidity at approximately 50%. Temperature and relative humidity in the exposure chambers were recorded 4-6 times per 24 hour period.

The MeCl gas was metered at a controlled rate into the air inlet of the exposure chamber through a calibrated flowmeter. Upon entry into the air inlet the gas was further diluted to the desired concentration. Total airflow through the chamber was approximately 700 liters/minute.

The analytical concentration of MeCl in the exposure chamber was determined by an infrared spectrometer equipped with a variable pathlength gas cell (Miran I, Foxboro-Wilks, Norwalk, CT). The wavelength used for the analysis was 13.4 microns. The analysis was performed 2 times per hour for each exposure chamber. Standards for the analysis were prepared by injecting a known volume of MeCl gas into a 100 liter Saran gas sampling bag filled with a known volume of air. The concentration of MeCl in the exposure chamber was determined by interpolation from a standard curve derived from vapor standards of known concentrations. Standard curves were run prior to each 72-hour exposure period. A standard bag was run at each 24-hour period and at the end of each 72-hour exposure to check the analytical system.

The nominal concentration of MeCl gas in the exposure chamber was the ratio of the rate at which the test material was dispensed to the rate of total airflow through the chamber.

Animal Exposures

Three groups of 3 male Beagle dogs (Hazelton Research Animals, Cumberland, Virginia) and 3 adult male cats (Liberty Laboratories, Liberty Corner, New Jersey) were exposed to analytical concentrations of 0, 200, or 500 ppm MeCl. The dogs and cats were assigned to exposure groups to provide the most uniform distribution of body weight and to avoid exposure of litter mates in the same exposure group. All dogs were housed in 4 x 9 ft kennels (3 dogs/kennel) and all except one dog were acclimated for more than 2 months prior to exposure. The sudden illness and death of one dog (cause of death was peracute pneumonia) postponed the scheduled start of the dog study. A replacement dog was obtained and was assigned to the control group since he was acclimated for 19 days instead of the preferred one month acclimation period. Each cat was housed in a 24 in. x 24 in. x 25-1/2 in. stainless steel cage and was acclimated for more than 1-1/2 months prior to exposure. All animals were housed in rooms designed to maintain a temperature of 72°F and a relative humidity of 40-60%, and a light cycle of 12 hours light and dark. The dogs were 7-8 months old and the cats were 8-9 months

old at the initiation of exposure. Each animal was uniquely identified by a tatoo on the inside of its ear. A standard diet (Purina Laboratory Chow, Ralston Purina Co., St. Louis, Missouri) and water were available ad libitum at all times including during exposure. EXCEPTION: During the acclimation period cat #IK-5(78-8105, 200 ppm group) was given Nutri-cal (a dietary supplement) during an approximately 24-hour illness.

Exposures were conducted on separate days for each species. Animals were housed in approximately 2 ft x 1-1/2 ft x 2 ft stainless steel exposure cages with food and water available ad libitum. They were exposed for approximately 23-1/2 hours per 24 hour period for a total treatment duration of 72 hours. At approximately 23-1/2 and 47-1/2 hours after exposure was first initiated, the chambers were rapidly exhausted of MeCl until the infrared spectrophotometer showed less than 50 ppm MeCl in the exposure chambers. Personnel wearing respirators and gloves then entered the exposure chambers to remove and clean the exposure cages and to change the food and water. At this time the animals were removed from their cages, observed for signs of toxicity, and then replaced into the chambers so that exposures could be resumed. Following termination of exposure the animals were returned to their original holding cages or kennels (EXCEPTION: The 500 ppm dogs were housed individually) and were held for observation during a recovery period of 4 weeks for the dogs and 2 weeks for the cats.

Criteria of Response

During the acclimation period the animals were observed and were handled frequently to become familiar with them and their personalities. During and after exposure, the animals were observed each work day for possible signs of toxicity. On post-exposure days 4, 12, 19 and 26 video tapes were taken of 0 ppm dog #HQLAR-1(78-8111), of 200 ppm dog #HUUAF-1(78-8112), and of 500 ppm dogs #HTBBX-2(78-8115), #HQRBF-1 (78-8117) and #RCSBK-1 (78-8109). These video tapes were taken to help describe the effects observed in representative animals from each treatment group.

The eyes of all animals were examined using an indirect opthalmoscope before and after exposure. The dogs' eyes were examined 1 month prior to exposure except for 1 dog which was examined 15 days prior to exposure. All dogs were examined on post-exposure day 4. The cats' eyes were examined 1 month prior to exposure and on post-exposure day 13. Body weights of all

animals were obtained weekly for 3-10 weeks prior to exposure, just before exposure, right after exposure, and weekly thereafter.

Hematology, clinical chemistry, and urinalysis parameters were obtained as outlined in Table 1. (NOTE: Urinalysis was performed on cats only at necropsy.) Blood for hematological and clinical chemistry parameters was obtained from all animals by jugular vein puncture. Urine was collected from the dogs by catherization and from the cats by aspiration directly from the bladder at necropsy. Hematology parameters included red blood cell (RBC), white blood cell (WBC) and differential blood cell counts, hemoglobin (Hgb) concentration and packed cell volume (PCV)[a]. Clinical chemistry studies included determination of blood urea nitrogen (BUN), serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), serum alkaline phosphatase (AP), bilirubin, and glucose[b].

Urinalysis included pH, glucose, ketones, protein, bilirubin, occult blood, and urobilinogen (Multistix, Ames Co., Elkhart, IN), specific gravity[c], visual examination of color and appearance, and light microscopic examination of white and red blood cells under high power field (HPF), casts under low power field (LPF), crystals, bacteria, mucous, epithelial cells and others.

Statistical Evaluation

For comparison of control versus methyl chloride exposed animals, organ weights and organ to body weight data were evaluated using a one-way analysis of variance (ANOVA) and Dunnett's test (Steel and Torrie, 1960). The level of significance in all cases was $p < 0.05$ (two sided).

In order to increase the sensitivity of the analysis for the body weight, hematology, clinical chemistry and urinalysis data, a two-way repeated measures ANOVA (time and exposure concentration) was used to compare the exposure groups and the control population. This method of analysis makes some restrictive assumptions about the data (Winer, 1971) however the validity of these assumptions cannot be tested with only three animals per exposure group. The result of violating the statistical assumption is that that too many statistically significant effects will be found. Since the data consists of pre-exposure and post-exposure

[a]PCV: Microhematocrit Centrifuge®, Clay Adams Co., New York; RBC, WBC counts: Coulter Counter Model ZBI; and Hgb: Hemoglobinometer, Coulter Electronics, Hialeah, FL.

[b]Centrifi Chem® System 400, Methods File, Union Carbide Corp., Rye, NY.

[c]T. S. Meter, American Optical Co., Buffalo, NY.

measurements, only the dose by time interaction is of interest as a measure of possible exposure related differences across time.

Statistical significance for a particular parameter is indicated in the first post-exposure table (Post-Exposure I) in all cases.

This two-way repeated measures ANOVA was performed on body weights, hematology parameters, clinical chemistry determinations and urinalysis data (specific gravity, pH, and protein for dogs only). (NOTE: Cat urinalysis data was not analyzed by this method since it was collected only once, at necropsy.) As a measure of pre-exposure baseline levels the average of the last two pre-exposure measurements was used. In the case of dog urine analyses, only one pre-exposure determination was made.

Clinical Neurology

A neurologic examination was performed by a veterinarian on all control and exposed dogs on post-exposure day 4. The dogs were brought individually and randomly to a quiet examination room for evaluation. The examination consisted of observing each dog's gait, posture, demeanor, and general appearance. The cranial nerves, spinal reflexes, pain sensation, attitudinal and postural reactions were evaluated. On post-exposure day 26 only those dogs exposed to 500 ppm MeCl were given an additional neurologic examination.

Pathology

A gross necropsy examination was performed on all dogs and cats at the end of the study. The animals were presented alive after having been deprived of food overnight. They were anesthetized using intravenous pentobarbital and were killed by ensanguination following the severing of the cervical blood vessels.

A complete gross pathologic examination was performed by a veterinary pathologist. All animals were examined externally and internally and any observations were recorded. The tissues that were routinely collected at the time of gross necropsy are summarized in Table 2. Prior to fixation, weights of the liver, kidneys, heart and testicles were recorded. The eyes from all animals were fixed in Zenker's fixative while all other tissues were fixed in phosphate-buffered 10% formalin. In addition, the lungs and trachea were removed from each animal as a unit and expanded with phosphate-buffered 10% formalin.

Representative sections were made through the major tissues. These sections were processed using conventional methods, embedded in paraffin,

sectioned (5-6μ) and stained with hematoxylin and eosin. A complete list of the organs and tissues examined microscopically is presented in Table 3. In general, complete sets of tissues were examined from all animals, however, organs such as mammary tissue and parathyroid glands were evaluated only to the extent that they were present in the routine sections of the skin or thyroid tissue respectively.

RESULTS

MeCl Vapor Concentration

A summary of exposure chamber temperature, relative humidity, and analytical data for MeCl vapor is shown in Table 4. The exposure concentrations were satisfactorily within 4% of the target concentrations.

Clinical Observations

Dogs: During the first 24 hr of exposure no difference in demeanor could be distinguished between control and methyl chloride exposed dogs. After 48 hours of exposure, the dogs exposed to 500 ppm MeCl were observed to be more tranquil; one dog (#HTBBX-2, 78-8115) had intermittant tremors and slight excessive salivation but all were alert and responsive. Right after the 72-hour exposure (post-exposure day 0) the dogs of the 0 and 200 ppm exposure group were comparable in appearance and demeanor which continued throughout the recovery period. Only one dog of the 200 ppm group showed a possible hind limb stiffness which was not apparent a day later and was probably the result of confinement in the exposure cage. The 500 ppm exposure group showed a range of adverse effects from the MeCl exposure. Dog #HTBBX-2 (78-8115) was most severely affected. His front and rear limbs were stiff so that he could not sit up or walk but lay on his side or abdomen. He showed tremors in all limbs and salivated excessively. Initially dog #RCSBK-1(78-8109) was classified as "moderately affected" for he showed stiffness in his rear legs and would not stand on his own even when helped. Later the same day when returned to his kennel he stood up and cautiously walked about with his rear legs occasionally slipping out from under him, causing him to fall. Dog #HQRBD-1 (78-8117) was able to walk about the kennel but demonstrated sufficient hind limb incoordination as to cause loss of balance frequently while walking. All the 500 ppm dogs appeared weak, but alert and responsive.

On post-exposure day 1 or 24 hours after exposure there was no visible change in the condition of the 500 ppm dogs. However, it was observed that dog #HTBBX-2(78-8115) was not eating. He was given two tablespoons of Nutri-cal (dietary supplement). After the observation of this dog's decreased appetite and continued weakness (apparently he could no longer obtain food), his food and water consumption was monitored and he was given canned dog food (Alpo) to provide approximately the same caloric intake as the other dogs on study. This dog's decreased food consumption may have been the result of his inability to sit up and chew the solid food because of his awkward postion of lying on his side; he readily consumed the soft, moist canned food. He was given canned food and then gradually returned to a normal diet by post-exposure day 14. By post-exposure day 10 improvement was observed in the condition of all the 500 ppm dogs. The hind limb stiffness of dogs #RCSBK-1(78-8109) and #HQRBF-1 (78-8117) was reduced. By post-exposure day 11 dog #HTBBX-2 (78-8115) had improved sufficiently to be able to stand and walk a few steps. However, he had not approached the condition of the other two dogs nor had his tremors ceased. On post-exposure day 17 it was noted that the front legs of dogs #RCSBK-1 and #HQRBF-1 were positioned slightly further apart than the controls with their paws angled away from their bodies. This may have been a result of a compensation for the incoordination and loss of stability in the rear limbs. By termination of this study, dog #HTBBX-2 was frequently on his feet and walking albeit with numerous falls because of his front and rear limb stiffness. Also, the tremors continued but this dog was always in apparent good spirits and alert as were the other 500 ppm dogs.

Cats: During the first 48 hours of exposure the cats of the 200 and 500 ppm exposure groups appeared to have eaten less but their appetites appeared to be normal thereafter. After 24 hours of exposure the 200 and 500 ppm exposure groups were observed to be less active than the controls. However, they were always alert and showed no signs of inactivity or sluggishness after their removal from the exposure chamber. The 200 and 500 ppm exposure groups were comparable to the controls throughout the recovery period.

Neurological Examination

Table 44 lists the results of the neurologic examination performed on each dog on Post-Exposure Day 4 and on the dogs in the 500 ppm exposure group on Post-Exposure Day 26.

No exposure-related neurological abnormalities were observed in the control dogs or those exposed to 200 ppm of MeCl. The few observations recorded represented expected or normal responses and could not be attributed to the MeCl exposure.

All three dogs exposed to 500 ppm of MeCl exhibited clinical neurological deficiencies that appeared to be related to the exposure. The most severely affected dog #HTBBX-2 (78-8115) was unable to walk and remained in lateral recumbency during the initial examination. It was alert and good-natured throughout the examination. Cranial nerve impairment was not observed. Voluntary movement of all four limbs was observed. The dog was able to position itself in sternal recumbency by "thrashing about" with its forelimbs and torso. Posterior paresis and extensor tonus of all four limbs were also observed. Opisthotonus and "intention" tremors were observed when the dog became excited or attempted to relocate. Twenty-six days after exposure to 500 ppm of MeCl this dog was walking with intermittent ataxia and was able to maintain its balance normally when challenged. Spinal reflexes and postural reactions were all normal. Therefore, most of the neurological abnormalities that were present on post-exposure day 4 had completely or partially recovered by post-exposure day 26.

The second dog #HQRBF-1 (78-8117) in the 500 ppm exposure level had a nervous, apprehensive demeanor when examined on post-exposure day 4. The dog protested being handled during the examination by whining and fidgeting. He could walk and run but rear limb ataxia and poor placement of the rear limbs were observed. When walking or running a stiff "hopping" gait with, what appeared to be, ventriflexion of the rear limb digits was also observed. There was a failure to reposition the hind feet after proprioceptive positioning. Only the torso was used by this dog for righting itself after being placed on its back. Tremors occurred over the left thoracic, cervical and forelimb region during the examination. Balance was not maintained when challenged. On Post-Exposure Day 26 this dog had a significant improvement in demeanor, gait and posture. The dog was alert, inquisitive and did not protest being handled. There was a slight rigidity and ataxia still present involving the rear limbs. No other abnormal observations were noted indicating nearly complete reversibility of the observations present on post-exposure day 4.

The third dog in the 500 ppm exposure group #RCSBK-1 (78-8109) was also examined on post-exposure day 4 and showed an alert and active demeanor in

the examination room. A "hopping" gait was observed with a "walking on toes" appearance involving the rear limbs. The dog could be pushed off-balance easily. There was a positive response to proprioceptive positioning but the reaction was slow. There was a slight exaggeration of the patellar reflex. The dog made no attempt to right itself when dropped on its back. Interpretation of this observation's significance is equivocal because of the dog's very submissive attitude during this test. On post-exposure day 26 this dog was examined and there were no gait, postural or neurological abnormalities observed, indicating that any exposure-related observation present on post-exposure day 4 were no longer present on post-exposure day 26.

NOTE: At the request of the authors Dr. Charles T. Lowrie, D.V.M., Clinical Neurology Center of Michigan State University visited the Toxicology Research Laboratory to examine and to evaluate all the data from the dog study. His report (See Appendix 1) substantiates the findings of the neurological examination stated above.

Opthalmoscopic Examination

Dogs: Opthalmoscopic examination of all dogs revealed no visible lesions or abnormalities before or after exposure.

Cats: No abnormalities or lesions were observed in the cats' eyes prior to exposure. However, on post-exposure day 13 opthalmoscopic examination revealed focal opacity of the cornea consistent with a temporal persistent papillary membrane in the left eyes of two cats; a control group cat #JR-3(78-8100) and a 200 ppm cat #IV-2(78-8103). These lesions were not considered to be treatment-related. No other lesions or abnormalities were observed in any of the other cats.

Body Weights

Dogs: Individual and mean body weights of dogs are given in Table 5 . The ANOVA indicated significant differences in body weights. Examination of the data shows decreased body weights immediately following exposure to methyl chloride. This weight loss of the 200 ppm group was a temporary response probably caused by prolonged residence time in the exposure chambers and these dogs quickly regained weight to their pre-exposure weights. The 500 ppm exposure group showed a decreasing body weight trend for several days after exposure; then they slowly gained weight until they reached their pre-exposure weights a few days prior to their termination. (The decreasing weight trend of the 500 ppm group is

primarily a result of 1 dog, #HTBBX-2(78-8115) who continued to lose weight on post-exposure day 3 at which time the other two dogs' weights stabilized.) Thus, the 500 ppm group weight pattern shows a definite exposure-related response.

Cats: Individual and mean body weights of cats are presented in Table 6. The body weights of the 200 and 500 ppm MeCl groups were not statistically significantly different from their controls. Only the 500 ppm exposure group had a slight decrease in body weight right after exposure. However, they quickly regained the lost weight and resumed their pre-exposure weight gain. This initial weight loss was not statistically significant but may be treatment-related.

Organ Weights

Dogs: Values for terminal (fasted) body weight, organ weights, and organ to body weight ratios are given in Table 7. There were no statistically significant deviations from the control group for any of these values.

Cats: The individual terminal fasted body weights, organ weights, and organ to body weight ratios are presented in Table 8. The statistically significant decrease of the mean relative heart weights of the cats was not interpreted to be of toxicological significance as a result of its lack of a dose response relationship and the high degree of variability encountered with such small group sizes.

Clinical Laboratory Parameters

Routine hematology clinical chemistry and urinalysis parameters were evaluated for each animal on test at several times prior to and after the MeCl exposures. These data were evaluated statistically by a two way repeated measures analysis of variance to determine alterations in these parameters with respect to both time and methyl chloride exposure concentration. To facilitate pre- vs. post-exposure comparisons for each animal the pre-exposure data were averaged. Statistically significantly altered parameters are indicated only at the bottom of the table for Post-Exposure I samples in all cases. The significance of these findings are discussed below.

Hematology

Dogs: Hematology parameters for dogs are summarized in Tables 9-16. Statistically significant differences in packed cell volume (PCV) were observed as a result of decreased pre-exposure PCV values in the dogs of the

500 ppm exposure group and decreased PCV values in control dogs for post-exposure samples III and IV. This is not interpreted as an exposure-related effect.

White blood cell counts (WBC) were not significantly different at $p < 0.05$ although a possible trend ($p < .10$) towards lower WBC values for the 500 ppm dogs was observed in samples taken just prior to necropsy (Table 16).

Alterations in differential white blood cell counts were observed in dogs of the 500 ppm exposure group at the first sampling time following MeCl exposure (Table 12). A statistically significant increase in segmented neutrophils and a corresponding decrease in the percentage of lymphocytes was observed in the blood samples from these animals. This effect was apparently secondary to the treatment and differential WBC evaluations were again unremarkable at the next sampling interval (Table 13).

All other hematologic parameters for dogs of the 500 ppm group did not deviate significantly with time or exposure concentration and were judged as unaffected by treatment. There were no significant alterations observed in data from dogs of the 200 ppm MeCl exposure group.

Cats: Tables 17-22 present the individual and mean hematologic parameters of the cats. The PCV values for the cats of the 500 ppm group showed statistically significant differences. The differences are not dose-related and are not consistent across post-exposure days. In fact, the 500 ppm group contains both the largest and smallest mean PCV. These differences are not interpreted to be treatment-related. This large variability with this data including the controls was considered to be of no toxicological significance. All other hematologic parameters showed no significant deviation from the controls for either the 200 ppm or 500 ppm exposure groups.

Clinical Chemistry

Dogs: The individual values and group means for clinical chemistry parameters are shown in Tables 23-30. SGPT and SGOT values show significant differences between treatment groups, but the data are difficult to interpret.

SGPT values show a large increase at post-exposure I (Table 26) in one animal in the 500 ppm exposure group, and subsequent decreases in all three 500 ppm animals. The SGPT values for the 200 ppm group were all consistently low including pre-exposures whereas the control values

were inconsistent.

SGOT values were approximately the same for all post-exposure measurements in all groups but were elevated in the pre-exposure determination of the 500 ppm exposure group (Tables 23-25). Thus the apparent decrease pre- to post-exposure in the 500 ppm group is not judged to be treatment-related.

Total bilirubin values showed apparent statistical differences post-exposure but examination of the data indicate no consistent patterns with respect to doses or times. The 200 ppm group contains both the largest and smallest means while the high dose group is the most consistent. There were no other statistically significant differences in any remaining clinical chemistry parameters.

Cats: The individual and mean clinical chemistry determinations are shown in Tables 31-36. None of the parameters revealed statistically significant differences when evaluated by ANOVA.

Urinalysis

Dogs: Individual and mean urinalysis data of the dogs are presented in Tables 37-42. No statistically significant effects were found.

Cats: The urinalysis data collected from the cats at necropsy is shown in Table 43. There were no statistically significant differences observed.

Gross Pathology and Histopathology

Dogs: The gross and histopathologic findings from the control dogs as well as those exposed to 200 or 500 ppm of MeCl are summarized in Table 45. There were a number of observations made on control and MeCl exposed dogs, however, most were spontaneously occurring nonspecific lesions that are commonly observed. For example, most dogs had gross and histopathologic lesions in the lungs which were suggestive for infection and migration by the nematode parasite Filaroides hirthi. This parasite is commonly found in commerically reared beagles (Hirth, 1977). Therefore, none of the gr sly observed alterations and only a few of the histologically observed lesions were considered to be treatment-related.

Lesions considered to be the result of MeCl exposure were confined to the brain, spinal cord or both of dogs exposed to 500 ppm MeCl for 72 hours and sacrificed following a 4-week recovery period. In order to evaluate these lesions, 15 hematoxylin and eosin stained sections of brain were prepared for histopathology. They represented step-sections through the entire brain including the cerebrum, cerebellum

and midbrain. In addition, selected sections were stained with Luxol Fast Blue-Periodic Acid-Schiff-Hematoxylin Stain, Bodian's Nerve Fiber Stain or both to better characterize the alterations.

All 3 dogs in the 500 ppm exposure group had lesions in the brain and spinal cord consisting of vacuolization, swollen eosinophilic axons, loss of axons, demyelinization and gitter cells. In general, the changes were very slight and multifocal in the brain stem (medulla, pons or both) and were slight and multifocal in the lateral and ventral funiculi of the spinal cord. Lesions were not recognized in the cerebrum or cerebellum of the brain nor were they observed in the dorsal funiculi or grey matter of the spinal cord. Even though lesions were recognized in the brain stem and spinal cord from all 3 dogs exposed to 500 ppm, none had lesions in the peripheral nerves.

No treatment-related alterations were recognized in any dog exposed to 200 ppm of methyl chloride.

Cats: The gross and histopathologic findings from the control cats and those exposed to 200 or 500 ppm of MeCl are summarized in Table 46. The histopathologic examination of the nervous tissue from the cats was similar in degree of thoroughness to the examination of the dogs and included multiple sections (9 or more through the cerebrum, cerebellum and midbrain) stained with hematoxylin and eosin as well as numerous sections stained with Luxol Fast Blue-Periodic Acid-Schiff-Hematoxylin Stain and Bodian's Nerve Fiber Stain. There were some observations made at gross necropsy and histopathological evaluation of the tissues of both the control and MeCl exposed cats; however, most of these observations were typical of spontaneously occurring nonspecific lesions.

Histopathologic examination of the central nervous system revealed lesions in the brain and/or spinal cord in 1 of 3 of the control cats, 1 of 3 cats exposed to 200 ppm and 3 of 3 cats exposed to 500 ppm. These lesions in the brain occurred in a multifocal or random pattern in the white matter of the cerebrum, cerebellum and midbrain. In the spinal cord they occurred primarily in the lateral and ventral funiculi. These lesions consisted of degeneration, demyelinization, focal or multifocal gliosis and perivascular aggregates of mononuclear lymphoid and plasma cells.

Although lesions were observed in the brain and spinal cord of both the cats and dogs, several features of the lesions in the cats were

different than those observed in dogs, suggesting a different etiologic cause. First, perivascular aggregates of mononuclear cells occurred in the cats but not the dogs. Second, lesions occurred in the cerebrum, cerebellum and midbrain of the cats but only in the midbrain of the dogs. Third, focal or multifocal gliosis occurred in some of the cats, but not in the dogs. Finally, even though lesions were present in 3 of 3 cats exposed to 500 ppm, similar lesions were present in 1 of 3 controls and 1 of 3 exposed to 200 ppm. This was clearly different than the dogs where 3 of 3 dogs exposed to 500 ppm had lesions attributed to treatment, but none of the control or 200 ppm exposed dogs had brain or spinal cord lesions.

The lesions in the nervous system of the cats were most consistent with an infection or post-vaccinal reaction. A similar spectrum and distribution of lesions in adult cats has been reported by Csiza et al. (1972) following vaccination for panleukopenia. The cats used in this study had been vaccinated for panleukopenia by the supplier. Furthermore, an outbreak of panleukopenia was confirmed in the breeding facility of the supplier (Wortley, 1979; Scott, 1979). Also, Mesfin et al. (1980) has discussed viral induced nervous system lesions in cats. Others (Lehrich et al., 1976) have shown similar lesions in mice following experimental infection by a virus. Therefore, it is likely that the brain lesions in control and MeCl exposed cats were the result of either a postvaccinal reaction or an infection by a virus such as panleukopenia virus or both. On the other hand, it is also possible that the exposure to 500 ppm of MeCl may have exacerbated the tissue lesions since only 1 of the 3 cats exposed to 0 or 200 ppm had lesions as contrasted to 3 of 3 cats exposed to 500 ppm.

Therefore, there were no definite treatment-related gross or histopathologic alterations recognized in male cats exposed to 200 or 500 ppm of MeCl for 72 hours. The possibility exists that the exposure to 500 ppm resulted in an exacerbation of a viral induced spontaneously occurring disease process in the central nervous system of the cats, but this cannot be resolved based on this study alone.

DISCUSSION AND CONCLUSIONS

Continuous inhalation exposure of male Beagle dogs to 200 ppm methyl chloride did not result in definitive adverse effects which could be judged to be related to exposure to the test chemical. Some transient alterations in body weight gain and demeanor were observed in these animals however they would reasonably be judged as secondary effects which arose due to the prolonged inactivity and confinement imposed as a condition of the treatment regimen. All dogs of the 200 ppm exposure group were devoid of neurological symptoms and no treatment-related histopathology was observed in any organ system. Therefore 200 ppm MeCl was judged to represent a no-observable-effect-level (NOEL) under the conditions of this study.

The primary effects observed in dogs exposed to 500 ppm MeCl were neurological in character. A spectrum of clinically observable effects were seen in these three dogs ranging from apparently normal to severe upper motor neuron disease. In all three cases mental status of these animals was alert and responsive throughout the experimental period. In two of the three dogs neurological deficits were observed and the onset of symptoms was judged to be during the last 24 hours of exposure. The less severely affected dog (#HQRBF-1) was ambulatory post-exposure but gait abnormalities characterized by ataxia, posterior paresis and increased extensive tonus were present. These symptoms initially observed immediately post-exposure were nearly completely reversible by 26 days following treatment. The most severely affected dog (#HTBBX-2) exhibited lateral recumbancy with tetraparesis and extensive tonus involving all four limbs. Opisthotonus and "intention" tremors could be initiated by moving this dog. Twenty-six days after exposure this dog was ambulatory but with intermittant ataxia; tremors and paresis were absent.

Despite the wide spectrum of clinical neurology observed in the 3 dogs of the 500 ppm group all animals showed similar histopathological lesions in the brain stem and spinal cord. Multifocal vacuolization, axonal swelling and degeneration in the brain stem (medulla and pons) and the lateral and ventral funiculi of the spinal cord were observed in all three animals. Peripheral nerve changes were absent.

Other parameters monitored during the course of the study included basic hematology, clinical chemistry, urinalysis and organ weights. None of these parameters revealed changes which would suggest a primary effect of MeCl. Alterations noted in clinical laboratory parameters with time could reasonably be interpreted as secondary to the clinical status of these animals and most likely represent sequelae of long term confinement and diminished food and water intake. Body weights of the dogs of the 500 ppm exposure group were affected by the treatment regimen and recovery to pre-exposure weights was prolonged in this group.

Male cats continuously exposed to either 200 or 500 ppm MeCl on an identical treatment regimen did not show any significant alterations in any of the parameters evaluated which were judged to be treatment-related.

The clinical symptoms observed in dogs exposed to 500 ppm MeCl in this study are similar to those reported by Smith and Von Oettingen (1947b). These investigators exposed dogs (sex and strain not specified) to concentrations of MeCl ranging from 300 to 3,000 ppm for six hours a day, six days per week until death. At concentrations of 1,000 to 3,000 ppm death usually occurred after 2-6 daily exposures and was preceded by neurological signs of spasticity, opisthotonus, and tremor as well as dyspnea and gastrointestinal disorders. Pathology revealed that the liver, kidneys and lungs were target organs but histological examination of the brain and spinal cord was confounded by the presence of "lesions which appeared to be of an infectious nature and from which possible toxic morphologic changes could not be disassociated" (Dunn and Smith, 1947). Three of four dogs exposed to 500 ppm MeCl in this experiment showed spasticity and tremors following the first week of treatment. None of these animals survived more than four weeks of treatment (Smith and von Oettingen, 1947b). In contrast to these observations, male beagle dogs exposed to 400 ppm MeCl, 6 hr/day 5 days/week for 13 weeks showed no evidence of treatment-related changes (McKenna et al., 1981). Although the symptomatology in dogs appears consistent between continuous and repeated intermittant exposure regimens, there is no doubt that continuous exposure of dogs to MeCl results in a markedly greater challenge to the animal than intermittant exposure at comparable concentrations. Furthermore slight changes in exposure schedules (5 vs. 6 days/week) or in MeCl concentration (400 vs. 500 ppm) apparently alter the response of dogs to MeCl significantly, and may indicate a very steep dose-response relationship for the production

of neurological effects by MeCl in this test species.

Smith and von Oettingen (1947b) also studied cats in their experiments and found ataxia, and tremors after one week of exposure to 2000 ppm MeCl. Respiratory function was also compromised in these animals and subsequent pathological findings revealed moderate pulmonary congestion and hepatic fatty infiltration. Cats exposed to 2000 ppm survived three to four weeks of MeCl exposure. In the present study continuous exposure of cats to 500 ppm MeCl for approximately 72 hr was not sufficient to produce adverse effects in any organ system.

The marked species differences observed in laboratory animals exposed to methyl chloride are poorly understood. Landry et al (1981a, b) have investigated the pharmacokinetics of inhaled methyl chloride in dogs and rats, however these experiments show little evidence for differences in the uptake or elimination of the gas between the two species which might account for the differences in target organ toxicity. Studies targeted at possible biochemical mechanisms of MeCl toxicity (Bus, 1980) may serve to provide indications of critical organ or tissue susceptibility to MeCl and hopefully some explanation of the influence of treatment regimen and species sensitivity in response to MeCl exposure.

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METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS
HET-K-2525-(7)

QUALITY ASSURANCE STATEMENT

This report represents data generated prior to the enactment of the FDA Good Laboratory Practice Regulations. The study was conducted according to standards used in this laboratory at that time. The report accurately reflects all of the data generated. All data and reports are located at the submitting laboratory.

Study Started: 16 January 1979 Report Issued: 20 February 1981

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TABLE 1

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Schedules of Samples Collected for Hematology, Clinical Chemistry and Urinalysis Determinations

Sample Designation	Pre-Exposure Day or Post-Exposure Day	Hematology	Clinical Chemistry	Urinalysis
Dogs:				
Pre-Exposure III[a]	Pre-Day 5	X	X	X
Pre-Exposure IV	Pre-Day 1	X	X	X[b]
72-Hour Exposure	-	-	-	-
Post-Exposure I	Post-Day 0[c]	X	X	X
Post-Exposure II	Post-Day 6	X	X	X
Post-Exposure III	Post-Day 12	X	X	X
Post-Exposure IV	Post-Day 19	X	X	X
Post-Exposure V	Post-Day 25	X	X	X
Post-Exposure V	Post-Day 26	-	-	X
Terminal Kill or day of Necropsy	Post-Day 27	-	-	-
Cats:				
Pre-Exposure I	Pre-Day 4	X	X	-
Pre-Exposure II	Pre-Day 1	X	X	-
72-Hr Exposure	-	-	-	-
Post-Exposure I	Post-Day 0[c]	X	X	-
Post-Exposure II	Post-Day 6	X	X	-
Post-Exposure III	Post-Day 13	X	X	-
Terminal Kill or day of Necropsy	Post-Day 14	-	-	X

X = Samples were collected and analyzed for the specified determination.

[a]Pre-Exposure I and II were samples collected prior to initial planned start of exposure which was postponed due to the sudden illness and death of dog #HOEBC-2(78-8116).

[b]A second analysis was done only on dog #HUVAF-1(78-8110) because of the blood found in his urine at Pre-Exposure III. Blood was not found in the sample of Pre-Exposure IV. Therefore, the blood in the sample of Pre-Exposure III was probably traumatically induced by catherization.

[c]Samples were collected right after the exposure on post-exposure day 0.

TABLE 2

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Representative Tissue Specimens Obtained at Necropsy From Dogs and Cats

Adipose Tissue	Pancreas
Adrenal Glands	Parathyroid
Accessory Sex Glands	Peripheral Nerve (Sciatic)
Aorta	Pituitary
Brain { Cerebrum, Cerebellum, Brain Stem }	Salivary Glands
	Skeletal Muscle
	Skin
Epididymides	Small Intestine
Esophagus	Spinal Cord
Eyes	Spleen
Heart	Sternum and Sternal Bone Marrow
Kidneys	Stomach
Large Intestine	Testes
Liver	
Lungs (bronchi)	Thymus
Lymph Nodes (Thoracic, mesenteric)	Thyroid
Mammary Tissue	Trachea
Nasal Turbinates	Urinary Bladder
Gall Bladder	Any gross lesion or mass

TABLE 3

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1 ? HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Number of Organs and Tissues Examined Histologically in Dogs and Cats

Species	Dogs			Cats		
Exposure Concentration (ppm)	0	200	500	0	200	500
Number of Animals	3	3	3	3	3	3
Liver	3	3	3	3	3	3
Gallbladder	3	3	2	3	3	3
Heart	3	3	3	3	3	3
Spleen	3	3	3	3	3	3
Pancreas	3	3	3	3	3	3
Brain	3	3	3	3	3	3
Spinal Cord	3	3	3	3	3	3
Pituitary	3	3	3	3	3	3
Peripheral Nerve (Sciatic)	3	3	3	3	3	3
Peripheral Nerve (Femoral)	3	3	3	0	0	0
Adrenal Glands	3	3	3	3	3	3
Aorta	2	3	3	3	3	3
Kidneys	3	3	3	3	3	3
Stomach	3	3	3	3	3	2
Small Intestine	3	3	3	3	3	3
Large Intestine	3	3	3	3	3	3
Testicles	3	2	3	3	3	3
Epididymides	3	3	3	3	3	3
Prostate	3	3	3	0	0	0
Urinary Bladder	3	3	3	3	3	3
Mesenteric Lymph Nodes	3	3	3	3	3	3
Mesenteric Fat	3	3	3	3	3	3
Mesenteric Blood Vessels	3	3	3	3	2	3
Lungs	3	3	3	3	3	3
Esophagus	3	3	3	3	3	3
Trachea	3	3	3	3	2	3
Thyroid	3	3	3	3	3	3
Parathyroid	2	2	3	1	0	2
Thymus	3	3	3	3	3	3
Salivary Glands	2	3	3	0	0	0
Tonsils	3	3	2	0	0	0
Skeletal Muscle	3	3	3	3	3	3
Skin	3	3	2	3	2	3
Eyes	3	3	3	3	3	3
Tongue	3	3	3	2	3	3
Bone	3	3	3	3	3	3
Bone Marrow	3	3	3	3	3	3
Nasal Turbinates	3	3	2	3	3	3
Subcutaneous Lymph Nodes	0	0	0	0	0	1
Lymph Nodes (origin undetermined)	1	0	0	0	0	0

TABLE 4

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Analysis of Chamber Atmospheres

	Cat Exposures			Dog Exposures		
Target Concentration (ppm)	0	200	500	0	200	500
Analytical Concentration[a] (ppm) $\bar{X}$±S.D.[b]	-	192±10	501±9	-	197±11	496±9
Range of Analytical Concentration (ppm)	-	170-225	475-527	-	173-217	473-515
Average Temperature (°F) $\bar{X}$±S.D.	69±1	75±1	70±1	70±1	76±1	70±1
Average Relative Humidity (%) $\bar{X}$±S.D.	43±1	42±1	39±2	44±4	50±2	47±3

[a]Data is mean and standard deviation of the 72 hour exposure duration (~23-1/2 hr/day).

[b]Mean ($\bar{X}$) ± Standard Deviation (S.D.)

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TABLE 5

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Individual and Mean Body Weights of Dogs (kg)

Exposure Conc. (ppm)	Animal Number: Ear Tatoo	Animal Number: Pathology No.		Pre-Exposure Days: 19	11	7	1	Post-Exposure Days: 0[a]	3	6	12	19	25
0	HUVAF-1	78-8110		13.8	13.6	13.6	13.8	14.6	13.3	13.2	14.3	13.8	14.2
	HQLAR-1	78-8111		13.6	13.4	13.3	13.2	13.7	13.1	13.6	13.3	13.2	14.0
	HTBBX-1	79-447		10.3	11.1	11.1	11.1	12.1	11.1	11.2	11.4	11.5	12.0
			Mean	12.6	12.7	12.7	12.7	13.4	12.5	12.7	13.0	12.8	13.4
			±S.D.	2.0	1.4	1.4	1.4	1.2	1.2	1.3	1.5	1.2	1.2
200	HUUAF-1	78-8112		14.2	14.4	14.4	14.3	13.8	14.2	13.9	14.0	14.0	14.8
	HTOBV-3	78-8113		13.5	13.8	14.2	13.8	13.4	13.9	13.9	14.0	14.4	15.0
	HWOBX-2	78-8114		13.2	13.3	13.4	13.5	12.7	13.1	13.2	13.5	13.4	13.4
			Mean	13.6	13.8	14.0	13.9	13.3	13.7	13.7	13.8	13.9	14.4
			±S.D.	0.5	0.6	0.5	0.4	0.6	0.6	0.4	0.3	0.5	0.9
500	RCSBK-1	78-8109		13.3	13.8	13.7	13.8	13.1	13.2	13.3	13.4	13.9	14.4
	HTBBX-2	78-8115		14.3	14.5	14.2	13.9	12.9	11.9	11.8	12.4	12.5	13.0
	HQRBF-1	78-8117		12.8	12.6	12.2	12.6	11.6	12.1	11.8	12.4	12.6	12.9
			Mean	13.5	13.6	13.4	13.4	12.5	12.4	12.3	12.7	13.0	13.4
			±S.D.	0.8	1.0	1.0	0.7	0.8	0.7	0.9	0.6	0.8	0.8

[a]Dogs were weighed right after the 72-hour exposure on post-exposure day 0.

Data were analyzed by a repeated measures ANOVA. See text for discussion.

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TABLE 6

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Individual and Mean Body Weights of Cats (kg)

Exposure Conc. (ppm)	Animal Number: Ear Tatoo	Animal Number: Pathology No.		Pre-Exposure Days: 20	Pre-Exposure Days: 13	Pre-Exposure Days: 6	Pre-Exposure Days: 1	Post-Exposure Days: 0[a]	Post-Exposure Days: 3	Post-Exposure Days: 11
0	JR-3	78-8100		3.83	3.88	4.01	4.05	4.17	4.47	4.58
	IZ-5	78-8101		3.33	3.50	3.60	3.60	3.72	3.78	3.92
	JC-1	78-8102		2.32	2.42	2.55	2.52	2.56	2.74	2.79
			Mean	3.16	3.27	3.39	3.39	3.48	3.66	3.76
			±S.D.	0.77	0.76	0.76	0.79	0.83	0.87	0.90
200	IV-2	78-8103		3.76	3.84	4.06	3.93	4.10	4.18	4.21
	JI-3	78-8104		3.19	3.30	3.32	3.47	3.50	3.58	3.70
	IK-5	78-8105		2.78	2.85	2.98	2.96	3.05	3.15	3.27
			Mean	3.24	3.33	3.45	3.45	3.55	3.64	3.73
			±S.D.	0.49	0.50	0.55	0.48	0.53	0.52	0.47
500	JR-4	78-8106		3.39	3.58	3.73	3.72	3.61	3.86	4.09
	IS-2	78-8107		3.11	3.25	3.36	3.38	3.34	3.32	3.45
	JC-4	78-8108		2.82	2.86	3.02	3.08	3.05	3.17	3.15
			Mean	3.11	3.23	3.37	3.39	3.33	3.45	3.56
			±S.D.	0.28	0.36	0.36	0.32	0.28	0.36	0.48

[a]Cats were weighed right after the 72-hour exposure on post-exposure day 0.

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TABLE 7

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Individual and Mean Body Weights, Organ Weights and Organ to Body Weight Ratios of Dogs

Exposure Conc. (ppm)	Animal Number	Body Wt[a] g	Brain g	Brain g/100	Heart g	Heart g/100	Liver g	Liver g/100	Kidney g	Kidney g/100	Testes g	Testes g/100
0	78-8110	13700	78.30	0.57	92.50	0.68	354.00	2.58	82.00	0.60	17.80	0.13
	78-8111	13300	80.50	0.61	112.50	0.85	416.30	3.13	65.10	0.49	15.80	0.12
	79-447	11400	82.70	0.73	09.20	0.78	372.40	3.27	66.60	0.58	16.00	0.14
	Mean	12800	80.50	0.63	98.07	0.77	380.90	2.99	71.20	0.56	16.53	0.13
	±S.D.	1229	2.20	0.08	12.61	0.09	32.01	0.36	9.38	0.06	1.10	0.01
200	78-8112	13800	82.70	0.60	94.70	0.69	365.10	2.65	89.90	0.65	20.40	0.15
	78-8113	14500	76.80	0.53	102.50	0.71	429.20	2.96	86.80	0.60	19.60	0.14
	78-8114	13000	80.90	0.62	95.30	0.73	310.60	2.39	66.00	0.51	15.20	0.12
	Mean	13767	80.13	0.58	97.50	0.71	368.30	2.66	80.90	0.59	18.40	0.13
	±S.D.	751	3.02	0.05	4.34	0.02	59.36	0.29	13.00	0.07	2.80	0.02
500	78-8109	14000	86.50	0.62	102.30	0.73	375.10	2.68	59.50	0.43	15.00	0.11
	78-8115	12600	84.90	0.67	83.60	0.66	333.50	2.65	65.00	0.52	9.70	0.08
	78-8117	12200	84.10	0.69	84.50	0.69	353.30	2.90	60.20	0.49	13.90	0.11
	Mean	12933	85.17	0.66	90.13	0.70	353.97	2.74	61.57	0.48	12.87	0.10
	±S.D.	945	1.22	0.04	10.55	0.03	20.81	0.14	2.99	0.05	2.80	0.02

There were no statistically significant deviations from the control mean using Dunnett's test, $p < 0.05$.

[a]Values represent fasted body weights.

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TABLE 8

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Individual and Mean Body Weights, Organ Weights and Organ to Body Weight Ratios of Cats

Exposure Conc. (ppm)	Animal Number	Body Wt[a] g	Brain g	Brain g/100	Heart g	Heart g/100	Liver g	Liver g/100	Kidney g	Kidney g/100	Testes g	Testes g/100
0	78-8100	4420	25.46	0.58	17.46	0.40	116.06	2.63	30.06	0.68	1.49	0.03
	78-8101	3800	28.91	0.76	16.58	0.44	95.65	2.52	27.29	0.72	2.15	0.06
	78-8102	2700	23.60	0.87	12.48	0.46	71.83	2.66	20.48	0.76	1.68	0.06
	Mean	3640	25.99	0.74	15.51	0.43	94.51	2.60	25.94	0.72	1.77	0.05
	±S.D.	871	2.69	0.15	2.66	0.03	22.14	0.07	4.93	0.04	0.34	0.02
200	78-8103	4050	25.03	0.62	14.75	0.36	98.80	2.44	35.16	0.87	2.77	0.07
	78-8104	3620	25.80	0.71	12.18	0.34	75.24	2.08	24.30	0.67	1.51	0.04
	78-8105	3280	24.03	0.73	11.60	0.35	89.69	2.73	22.49	0.69	2.27	0.07
	Mean	3650	24.95	0.69	12.84	0.35*	87.91	2.42	27.32	0.74	2.18	0.06
	±S.D.	386	0.89	0.06	1.68	0.01	11.88	0.33	6.85	0.11	0.63	0.02
500	78-8106	4040	24.23	0.60	14.81	0.37	107.63	2.66	29.99	0.74	2.03	0.05
	78-8107	3450	25.22	0.73	14.01	0.41	83.60	2.42	26.50	0.77	2.37	0.07
	78-8108	3250	23.96	0.74	13.30	0.41	82.14	2.53	25.35	0.78	2.39	0.07
	Mean	3580	24.47	0.69	14.04	0.39	91.12	2.54	27.28	0.76	2.26	0.06
	±S.D.	411	0.66	0.08	0.76	0.02	14.31	0.12	2.42	0.02	0.20	0.01

*Statistically significant deviation from control mean using Dunnett's test, $p < 0.05$.

[a]Values represent fasted body weights.

000033

TABLE 9

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Pre-Exposure III: Individual and Mean Hematologic Values of Dogs

Exposure Conc. (ppm)	Animal Number	PCV %	RBC $x10^6/mm^3$	Hgb gm/100ml	WBC $x10^3/mm^3$	WBC Differential Count (%) Neut Seg.	Neut B J	Lym.	Mon.	Eos.	Bas.
0	78-8110	42.0	6.02	14.6	11.4	56	3/0	32	4	5	0
	78-8111	48.0	6.83	16.5	12.1	59	4/0	29	6	2	0
	79-447	47.5	7.28	16.8	12.5	48	5/0	39	5	3	0
	Mean	45.8	6.71	16.0	12.0	54	4/0	33	5	4	0
	±S.D.	3.3	0.64	1.2	0.6						
200	78-8112	40.0	5.77	14.3	11.4	53	5/0	32	4	6	0
	78-8113	47.0	6.91	16.4	12.0	65	4/0	26	3	2	0
	78-8114	43.0	7.60	19.5	12.2	51	4/0	37	8	0	0
	Mean	43.3	6.76	16.7	11.8	56	4/0	32	5	3	0
	±S.D.	3.5	0.92	2.6	0.4						
500	78-8109	44.0	6.54	15.9	20.9	69	7/0	17	3	4	0
	78-8115	45.0	7.27	15.9	13.8	67	7/0	19	4	3	0
	78-8117	40.5	6.07	14.4	16.4	67	4/0	19	4	6	0
	Mean	43.2	6.63	15.4	17.0	68	6/0	18	4	4	0
	±S.D.	2.4	0.60	0.9	3.6						

000034

TABLE 10

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Pre-Exposure IV: Individual and Mean Hematologic Values of Dogs

Exposure Conc. (ppm)	Animal Number	PCV %	RBC $x10^6/mm^3$	Hgb gm/100ml	WBC $x10^3/mm^3$	WBC Differential Count (%) Neut Seg.	Neut B/J	Lym.	Mon.	Eos.	Bas.
0	78-8110	44.5	5.97	14.5	12.5	51	1/0	37	4	7	0
	78-8111	47.0	6.64	16.0	12.9	54	4/0	36	5	1	0
	79-447	47.0	6.72	16.3	11.8	53	1/0	35	7	4	0
	Mean	46.2	6.44	15.6	12.4	53	2/0	36	5	4	0
	±S.D.	1.4	0.41	1.0	0.6						
200	78-8112	44.0	6.06	15.3	12.8	51	3/0	34	3	9	0
	78-8113	44.5	6.71	15.8	11.1	88	2/0	33	5	2	0
	78-8114	52.0	7.24	18.6	13.1	54	3/0	36	5	2	0
	Mean	46.8	6.67	16.6	12.3	54	3/0	34	5	4	0
	±S.D.	4.5	0.59	1.8	1.1						
500	78-8109	44.5	6.53	15.6	14.0	57	4/0	35	4	0	0
	78-8115	44.0	7.07	15.7	13.4	73	3/0	20	2	2	0
	78-8117	37.0	5.60	13.4	14.1	62	6/0	27	3	2	0
	Mean	41.8	6.40	14.9	13.8	64	5/0	27	3	1	0
	±S.D.	4.2	0.74	1.3	0.4						

000035

TABLE 11

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Pre-Exposures III & IV: Average of Individual Hematologic Values for Dogs

Exposure Conc. (ppm)	Animal Number	PCV %	RBC $x10^6/mm^3$	Hgb gm/100ml	WBC $x10^3/mm^3$	WBC Differential Count (%) Neut Seg.	Neut B/J	Lym.	Mon.	Eos.	Bas.[a]
0	78-8110	43.25	5.995	14.55	11.95	53.5	2.0	34.5	4.0	6.0	0
	78-8111	47.50	6.735	16.25	12.50	56.5	4.0	32.5	5.5	1.5	0
	79-447	47.25	7.000	16.55	12.15	50.5	3.0	37.0	6.0	3.5	0
	Mean	46.00	6.577	15.78	12.20	53.5	3.0	34.7	5.2	3.7	0
	±S.D.	2.38	0.521	1.08	0.28	3.0	1.0	2.3	1.0	2.3	
200	78-8112	42.00	5.915	14.80	12.10	52.0	4.0	33.0	3.5	7.5	0
	78-8113	45.75	6.810	16.10	11.55	61.5	3.0	29.5	4.0	2.0	0
	78-8114	47.50	7.420	19.05	12.65	52.5	3.5	36.5	6.5	1.0	0
	Mean	45.08	6.715	16.65	12.10	55.3	3.5	33.0	4.7	3.5	0
	±S.D.	2.81	0.757	2.18	0.55	5.3	0.5	3.5	1.6	3.5	
500	78-8109	44.25	6.535	15.75	17.45	63.0	5.5	26.0	3.5	2.0	0
	78-8115	44.50	7.170	15.80	13.60	70.0	5.0	19.5	3.0	2.5	0
	78-8117	38.75	5.835	13.90	15.25	64.5	5.0	23.0	3.5	4.0	0
	Mean	42.50	6.513	15.15	15.43	65.8	5.2	22.8	3.3	2.8	0
	±S.D.	3.25	0.668	1.08	1.93	3.7	0.3	3.3	0.3	1.0	

NOTE: The Pre-Exposure III and IV hematologic data was averaged for use in the statistical analysis of pre- and post-exposure data by two way (time and exposure concentration) repeated measures ANOVA.

[a]Not evaluated statistically.

000036

TABLE 12

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Post-Exposure I: Individual and Mean Hematologic Values of Dogs

Exposure Conc. (ppm)	Animal Number	PCV %	RBC $x10^6/mm^3$	Hgb gm/100ml	WBC $x10^3/mm^3$	WBC Differential Count (%) Neut Seg.	Neut B/J	Lym.	Mon.	Eos.	Bas.
0	78-8110	42.0	5.41	13.3	18.0	68	3/0	21	5	3	0
	78-8111	46.5	7.03	16.5	13.4	55	5/0	34	5	1	0
	79-447	45.0	6.73	15.9	12.2	57	4/0	32	5	2	0
	Mean	44.5	6.39	15.2	14.5	60	4/0	29	5	2	0
	±S.D.	2.3	0.86	1.7	3.1						
200	78-8112	38.0	5.49	13.7	10.2	62	4/0	28	2	4	0
	78-8113	42.0	6.35	15.1	10.4	64	3/0	27	3	3	0
	78-8114	52.0	7.11	18.5	10.6	58	4/0	33	4	1	0
	Mean	44.0	6.32	15.8	10.4	61	4/0	29	3	3	0
	±S.D.	7.2	0.81	2.5	0.2						
500	78-8109	46.5	6.54	15.9	9.8	89	1/0	7	0	3	0
	78-8115	50.0	8.04	17.7	14.3	83	5/0	10	1	1	0
	78-8117	40.5	5.97	14.4	10.3	83	3/0	11	1	2	0
	Mean	45.7	6.85	16.0	11.5	85	3/0	9	1	2	0
	±S.D.	4.8	1.07	1.7	2.5						

Parameters found to be significantly altered from pre-exposure values by a two-way repeated measures ANOVA were: PCV, total WBC, segmented neutrophil and lymphocyte counts. A discussion of these findings and their interpretation may be found in the text.

000037

TABLE 13

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Post-Exposure II: Individual and Mean Hematologic Values of Dogs

Exposure Conc. (ppm)	Animal Number	PCV %	RBC $x10^6/mm^3$	Hgb gm/100ml	WBC $x10^3/mm^3$	WBC Differential Count (%) Neut Seg.	Neut B/J	Lym.	Mon.	Eos.	Bas.
0	78-8110	43.0	5.97	14.2	10.1	52	1/0	35	5	7	0
	78-8111	47.0	7.04	16.7	11.8	50	5/0	38	3	4	0
	79-447	48.0	7.35	17.3	15.4	64	4/0	26	4	2	0
	Mean	46.0	6.79	16.1	12.4	55	3/0	33	5	4	0
	±S.D.	2.6	0.72	1.6	2.7						
200	78-8112	42.0	6.27	15.0	10.4	41	4/0	41	5	9	0
	78-8113	41.5	6.42	15.0	15.1	62	7/0	23	4	4	0
	78-8114	51.0	7.64	19.2	11.5	54	7/0	32	6	1	0
	Mean	44.8	6.78	16.4	12.3	52	6/0	32	5	5	0
	±S.D.	5.3	0.75	2.4	2.5						
500	78-8109	42.0	6.66	15.9	9.3	60	2/0	30	5	3	0
	78-8115	48.5	7.76	17.1	7.7	60	4/0	34	2	10	0
	78-8117	42.0	5.95	14.4	12.7	48	7/0	31	6	8	0
	Mean	45.8	6.79	15.8	9.9	53	4/0	32	4	7	0
	±S.D.	3.4	0.91	1.4	2.6						

000038

TABLE 14

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Post-Exposure III: Individual and Mean Hematologic Values of Dogs

Exposure Conc. (ppm)	Animal Number	PCV %	RBC $x10^6/mm^3$	Hgb gm/100ml	WBC $x10^3/mm^3$	WBC Differential Count (%) Neut Seg.	Neut B/J	Lym.	Mon.	Eos.	Bas.
0	78-8110	41.0	6.18	14.5	10.0	67	1/0	29	8	5	0
	78-8111	47.0	6.92	16.6	15.8	55	4/0	31	7	3	0
	79-447	43.0	7.67	15.1	11.5	57	2/0	32	3	6	0
	Mean	43.7	6.92	15.4	12.4	56	2/0	31	6	5	0
	±S.D.	3.1	0.75	1.1	3.0						
200	78-8112	44.0	6.27	16.0	10.6	44	3/0	41	3	9	0
	78-8113	44.0	6.73	16.0	10.6	57	3/0	35	3	2	0
	78-8114	51.5	9.26	18.6	12.2	50	7/0	34	5	4	0
	Mean	46.5	7.42	16.9	11.1	50	4/0	37	4	5	0
	±S.D.	4.3	1.61	1.5	0.9						
500	78-8109	44.5	6.45	15.8	9.3	60	5/0	25	6	4	0
	78-8115	50.0	7.63	17.7	11.0	62	4/0	25	6	3	0
	78-8117	40.5	6.03	15.0	9.9	55	5/0	25	4	11	0
	Mean	45.0	6.70	16.2	10.1	59	5/0	25	5	6	0
	±S.D.	4.8	0.83	1.4	0.9						

000039

TABLE 15

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Post-Exposure IV; Individual and Mean Hematologic Values of Dogs

Exposure Conc. (ppm)	Animal Number	PCV %	RBC $x10^6/mm^3$	Hgb gm/100ml	WBC $x10^3/mm^3$	WBC Differential Count (%) Neut Seg.	Neut B/U	Lym.	Mon.	Eos.	Bas.
0	78-8110	42.0	6.27	14.8	11.6	50	2/0	35	6	7	0
	78-8111	48.5	7.12	17.2	13.0	51	2/0	31	9	7	0
	79-447	44.0	6.47	15.7	11.5	51	6/0	37	5	1	0
	Mean	44.8	6.62	15.9	12.0	51	3/0	34	7	5	0
	±S.D.	3.3	0.44	1.2	0.8						
200	78-8112	42.5	6.09	15.6	10.1	48	3/0	37	5	7	0
	78-8113	42.5	6.50	15.4	11.6	59	4/0	32	4	1	0
	78-8114	52.0	7.19	18.2	12.5	54	4/0	31	9	2	0
	Mean	45.7	6.59	16.4	11.4	54	4/0	33	6	3	0
	±S.D.	5.5	0.56	1.6	1.2						
500	78-8109	49.0	6.99	17.1	8.9	61	2/0	28	5	4	0
	78-8115	52.5	7.58	17.1	9.4	58	3/0	29	3	7	0
	78-8117	41.5	6.07	15.0	11.6	48	3/0	36	3	10	0
	Mean	47.7	6.88	16.4	10.0	56	3/0	31	4	6	0
	±S.D.	5.6	0.76	1.2	1.4						

000040

TABLE 16

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Post-Exposure V: Individual and Mean Hematologic Values of Dogs

Exposure Conc. (ppm)	Animal Number	PCV %	RBC $x10^6/mm^3$	Hgb gm/100ml	WBC $x10^3/mm^3$	WBC Differential Count (%) Neut Seg.	Neut B/J	Lym.	Mon.	Eos.	Bas.
0	78-8110	41.5	6.36	15.4	14.1	60	2/0	28	5	5	0
	78-8111	43.5	6.52	15.7	14.6	59	2/0	25	9	5	0
	79-447	43.5	6.45	15.5	11.8	65	3/0	33	6	3	0
	Mean	[illegible].8	6.44	15.5	13.5	58	2/0	29	7	4	0
	±S.D.	1.2	0.08	0.2	1.5						
200	78-8112	44.0	6.32	16.5	10.8	62	1/0	32	7	8	0
	78-8113	47.0	6.79	16.4	11.5	65	4/0	23	6	2	0
	78-8114	51.0	7.11	18.3	13.7	58	3/0	30	5	4	0
	Mean	47.3	6.74	17.1	12.0	58	3/0	28	6	5	0
	±S.D.	3.5	0.40	1.1	1.5						
500	78-8109	44.0	6.54	15.7	8.5	57	3/0	32	6	2	0
	78-8115	46.5	7.23	16.9	9.7	62	5/0	24	2	7	0
	78-8117	42.5	6.17	15.6	11.6	53	6/0	27	7	7	0
	Mean	44.3	6.65	16.1	9.9	5[illegible]	5/0	28	5	5	0
	±S.D.	2.0	0.54	0.7	1.6						

000041

TABLE 17

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Pre-Exposure I: Individual and Mean Hematologic Values of Cats

Exposure Conc. (ppm)	Animal Number	PCV %	RBC $x10^6/mm^3$	Hgb gm/100ml	WBC $x10^3/mm^3$	WBC Differential Count (%) Neut Seg.	Neut B/J	Lym.	Mon.	Eos.	Bas.
0	78-8100	34.0	8.77	11.6	27.4	46	11/0	28	4	12	0
	78-8101	32.0	8.08	11.7	23.1	53	5/0	32	2	8	0
	78-8102	35.0	9.00	12.2	8.7	11	0/0	82	4	3	0
	Mean	33.7	8.62	11.8	19.7	36	5/0	47	3	9	0
	±S.D.	1.5	0.48	0.3	9.8						
200	78-8103	34.5	8.55	11.8	16.0	37	2/0	47	1	13	0
	78-8104	35.5	9.61	12.9	9.6	42	1/0	51	4	2	0
	78-8105	39.0	9.64	14.0	14.8	30	2/0	61	1	6	0
	Mean	36.3	9.27	12.9	13.5	36	2/0	53	2	7	0
	±S.D.	2.4	0.62	1.1	3.4						
500	78-8106	25.0	6.78	9.4	7.8	19	0/0	75	3	3	0
	78-8107	37.5	9.64	12.9	13.8	44	2/0	49	2	3	0
	78-8108	38.5	9.69	13.5	12.5	33	1/0	63	2	1	0
	Mean	33.7	8.70	11.9	11.4	32	1/0	62	2	3	0
	±S.D.	7.5	1.7	2.2	3.2						

000042

TABLE 18

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Pre-Exposure II: Individual and Mean Hematologic Values of Cats

Exposure Conc. (ppm)	Animal Number	PCV %	RBC $x10^6/mm^3$	Hgb gm/100ml	WBC $x10^3/mm^3$	WBC Differential Count (%) Neut Seg.	Neut B/J	Lym.	Mon.	Eos.	Bas.
0	78-8100	32.5	8.60	11.5	19.7	49	3/0	41	1	6	0
	78-8101	34.0	8.29	12.3	9.8	61	0/0	35	2	2	0
	78-8102	32.0	8.17	11.3	16.5	52	6/0	42	0	1	0
	Mean	32.8	8.35	11.7	15.3	54	3/0	39	1	3	0
	±S.D.	1.0	0.22	0.6	5.1						
200	78-8103	34.0	8.30	11.8	13.4	36	5/0	43	3	13	0
	78-8104	35.5	9.03	12.6	13.6	52	2/0	38	4	4	0
	78-8105	40.6	9.74	14.7	22.6	31	1/0	65	1	2	0
	Mean	36.7	9.02	13.0	16.5	40	3/0	49	2	6	0
	±S.D.	3.4	0.72	1.5	5.3						
500	78-8106	27.0	6.84	9.4	12.6	46	0/0	44	0	10	0
	78-8107	34.5	9.10	12.1	16.0	48	2/0	46	4	0	0
	78-8108	33.0	8.58	12.0	8.2	26	3/0	67	3	2	0
	Mean	31.5	8.17	11.2	12.2	40	2/0	52	2	4	0
	±S.D.	4.0	1.18	1.6	3.9						

000043

TABLE 19

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS & CATS

Pre-Exposure I & II: Average of Individual Hematologic Values for Cats

Exposure Conc. (ppm)	Animal Number	PCV %	RBC $x10^6/mm^3$	Hgb gm/100ml	WBC $x10^3/mm^3$	WBC Differential Count (%)					
						Neut Seg.	Neut B/J	Lym.	Mon.	Eos.	Bas.[a]
	78-8100	33.25	8.685	11.55	23.55	47.0	7.0	34.5	2.5	9.0	0
	78-8101	33.00	8.185	12.00	16.45	57.0	2.5	33.5	2.0	5.0	0
	78-8102	33.50	8.585	11.75	12.60	31.5	2.5	62.0	2.0	2.0	0
	Mean	33.25	8.485	11.77	17.53	45.2	4.0	43.3	2.2	5.3	0
	± S.D.	0.25	0.265	0.23	5.55	12.8	2.6	16.2	0.3	3.5	0
200	78-8103	34.25	8.425	11.80	14.70	36.5	3.5	45.0	2.0	13.0	0
	78-8104	35.50	9.320	12.65	11.60	47.0	1.5	44.5	4.0	3.0	0
	78-8105	39.75	9.690	14.35	18.70	30.5	1.5	63.0	1.0	4.0	0
	Mean	36.50	9.145	12.93	15.00	38.0	2.2	50.8	2.3	6.7	0
	± S.D.	2.88	0.650	1.30	3.55	8.4	1.2	10.5	1.5	5.5	0
500	78-8106	26.00	6.810	9.40	10.15	32.5	0.0	59.5	1.5	6.5	0
	78-8107	36.00	9.370	12.50	14.90	46.0	2.0	47.5	3.0	1.5	0
	78-8108	35.75	9.135	12.75	10.35	29.0	2.0	65.0	2.5	1.5	0
	Mean	32.58	8.438	11.55	11.80	35.8	1.3	57.3	2.3	3.2	0
	± S.D.	5.70	1.415	1.87	2.69	9.0	1.2	8.9	0.8	2.9	0

[a]Not evaluated statistically

NOTE: The Pre-Exposure III and IV hematologic data was averaged for use in the statistical analysis of pre- and post-exposure data by two way (time and exposure concentration) repeated measures ANOVA.

000044

TABLE 20

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Post-Exposure I: Individual and Mean Hematologic Values of Cats

Exposure Conc. (ppm)	Animal Number	PCV %	RBC $x10^6/mm^3$	Hgb gm/100ml	WBC $x10^3/mm^3$	WBC Differential Count (%) Neut Seg.	Neut B/J	Lym.	Mon.	Eos.	Bas.
0	78-8100	30.0	7.76	10.4	24.2	52	1/0	42	4	1	0
	78-8101	38.0	9.03	13.3	21.6	47	4/0	36	6	7	0
	78-8102	30.0	7.58	10.1	11.3	47	2/0	48	0	3	0
	Mean	32.7	8.12	11.3	19.0	49	2/0	42	3	4	0
	±S.D.	4.6	0.79	1.8	6.8						
200	78-8103	33.5	8.23	11.5	13.0	55	3/0	29	2	11	0
	78-8104	37.0	9.22	12.5	7.9	55	2/0	39	3	1	0
	78-8105	37.5	8.71	12.9	12.0	31	0/0	58	5	6	0
	Mean	36.0	8.72	12.3	11.0	47	2/0	42	3	6	0
	±S.D.	2.2	0.50	0.7	2.7						
500	78-8106	32.5	8.29	10.8	10.8	38	3/0	50	1	8	0
	78-8107	38.0	9.82	13.3	11.0	60	4/0	30	1	6	0
	78-8108	38.0	9.29	13.3	8.0	50	0/0	45	2	3	0
	Mean	36.2	9.13	12.5	9.9	49	2/0	42	1	6	0
	±S.D.	3.2	0.78	1.4	1.7						

Parameters found to be significantly altered by a two way repeated measures ANOVA included: PCV. A discussion of these findings and their interpretation may be found in the text.

000045

TABLE 21

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Post-Exposure II: Individual and Mean Hematologic Values of Cats

Exposure Conc. (ppm)	Animal Number	PCV %	RBC $x10^6/mm^3$	Hgb gm/100ml	WBC $x10^3/mm^3$	WBC Differential Count (%) Neut Seg.	Neut B/J	Lym.	Mon.	Eos.	Bas.
0	78-8100	35.5	8.48	11.5	16.9	33	1/0	58	4	5	0
	78-8101	37.5	9.10	13.6	15.5	36	3/0	50	5	6	0
	78-8102	33.0	8.82	11.9	12.2	40	1/0	47	5	7	0
	Mean	34.7	8.80	12.3	14.9	36	2/0	52	5	5	0
	±S.D.	2.5	0.31	1.1	2.4						
200	78-8103	30.0	7.35	10.6	5.2	16	0/0	76	3	6	0
	78-8104	33.0	8.49	11.8	12.6	10	0/0	83	5	2	0
	78-8105	37.0	8.62	13.0	9.6	61	3/0	32	3	11	0
	Mean	33.3	8.15	11.8	9.4	26	1/0	63	4	6	0
	±S.D.	3.5	0.70	1.2	3.2						
500	78-8106	30.0	7.88	16.9	11.9	28	3/0	61	3	5	0
	78-8107	35.5	9.47	12.7	13.4	53	4/0	35	5	3	0
	78-8108	38.0	9.22	13.5	8.4	32	1/0	61	5	1	0
	Mean	34.5	8.86	12.4	11.2	38	3/0	52	4	3	0
	±S.D.	4.1	0.86	1.3	2.6						

000046

TABLE 22

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Post-Exposure III: Individual and Mean Hematologic Values of Cats

Exposure Conc. (ppm)	Animal Number	PCV %	RBC $x10^6/mm^3$	Hgb gm/100ml	WBC $x10^3/mm^3$	WBC Differential Count (%) Neut Seg.	Neut B/J	Lym.	Mon.	Eos.	Bas.
0	78-8100	36.5	9.03	12.6	11.8	43	5/0	34	4	14	0
	78-8101	37.0	9.74	14.9	14.9	42	4/0	46	4	4	0
	78-8102	30.5	9.11	12.3	12.2	42	5/0	43	5	5	0
	Mean	34.7	9.29	13.3	13.0	42	5/0	41	4	8	0
	±S.D.	3.6	0.39	1.4	1.7						
200	78-8103	31.0	7.77	10.7	23.1	55	10/0	24	4	7	0
	78-8104	35.0	8.77	13.3	9.7	14	1/0	79	6	0	0
	78-8105	37.0	9.45	13.3	14.7	27	2/0	61	6	4	0
	Mean	34.3	8.66	12.4	15.8	32	4/0	55	5	4	0
	±S.D.	3.1	0.85	1.5	6.8						
500	78-8106	38.0	9.69	13.5	5.3	15	0/0	79	6	0	0
	78-8107	40.0	9.03	12.6	13.4	58	3/0	29	4	6	0
	78-8108	41.0	9.94	13.6	12.0	67	8/0	22	2	1	0
	Mean	39.7	9.55	13.2	10.2	47	4/0	43	4	2	0
	±S.D.	1.5	0.47	0.6	4.3						

000047

TABLE 23

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Pre-Exposure III: Individual and Mean Clinical Chemistry Values of Dogs

Exposure Conc. (ppm)	Animal Number		BUN mg/100 ml	SGPT mU/ml	AP mU/ml	SGOT mU/ml	Glucose mg/100 ml	Total Bilirubin mg/100 ml
0	78-8110		20	17	77	19	96	0.2
	78-8111		21	22	61	19	90	0.3
	79-447		20	38	107	21	126	0.3
		Mean	20	26	82	20	104	0.3
		±S.D.	1	11	23	1	19	0.1
200	78-8112		16	18	61	17	108	0.3
	78-8113		13	17	100	13	115	0.2
	78-8114		20	16	83	16	111	0.6
		Mean	16	17	81	15	111	0.4
		±S.D.	4	1	20	2	4	0.2
500	78-8109		23	29	124	26	105	0.4
	78-8115		23	21	77	28	109	0.9
	78-8117		19	24	61	22	111	0.7
		Mean	22	25	84	25	108	0.7
		±S.D.	2	4	37	3	3	0.3

000048

TABLE 24

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Pre-Exposure IV: Individual and Mean Clinical Chemistry Values of Dogs

Exposure Conc. (ppm)	Animal Number		BUN mg/100 ml	SGPT mU/ml	AP mU/ml	SGOT mU/ml	Glucose mg/100 ml	Total Bilirubin mg/100 ml
0	78-8110		22	17	78	21	91	0.4
	78-8111		20	28	57	20	101	0.3
	79-447		22	39	101	22	115	0.6
		Mean	21	28	79	21	102	0.4
		±S.D.	1	11	22	1	12	0.2
200	78-8112		15	20	65	24	102	0.4
	78-8113		17	17	99	16	120	0.2
	78-8114		24	15	92	21	104	0.5
		Mean	19	17	85	20	109	0.4
		±S.D.	5	3	18	4	10	0.2
500	78-8109		13	24	99	27	119	0.2
	78-8115		13	36	95	37	110	0.3
	78-8117		21	29	52	18	117	0.2
		Mean	16	30	82	27	115	0.2
		±S.D.	5	6	26	10	5	0.1

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TABLE 25

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Pre-Exposure III & IV: Average of Individual Clinical Chemistry Values for Dogs

Exposure Conc. (ppm)	Animal Number		BUN mg/100 ml	SGPT mU/ml	AP mU/ml	SGOT mU/ml	Glucose mg/100 ml	Total Bilirubin mg/100 ml
0	78-8110		21.0	17.0	77.5	20.0	93.5	0.30
	78-8111		20.5	25.0	59.0	19.5	95.5	0.30
	79-447		21.0	38.5	104.0	21.5	120.5	0.45
		Mean	20.8	26.8	80.2	20.3	103.2	0.35
		±S.D.	0.3	10.9	22.6	1.0	15.0	0.09
200	78-8112		15.5	19.0	63.0	20.5	105.0	0.35
	78-8113		15.0	17.0	99.5	14.5	117.5	0.20
	78-8114		22.0	15.5	87.5	18.5	107.5	0.55
		Mean	17.5	17.2	83.3	17.8	110.0	0.37
		±S.D.	3.9	1.3	18.6	3.1	6.6	0.18
500	78-8109		18.0	26.5	111.5	26.5	112.0	0.30
	78-8115		18.0	28.5	86.0	32.5	109.5	0.60
	78-8117		20.0	26.5	51.5	20.0	114.0	0.45
		Mean	18.7	27.2	83.0	26.3	111.8	0.45
		±S.D.	1.2	1.2	30.1	6.3	2.3	0.15

NOTE: The Pre-Exposure III & IV clinical chemistry data was averaged for use in the statistical analysis of pre- and post-exposure data by two way (time and exposure concentration) repeated measures ANOVA, $p < 0.05$.

000050

TABLE 26

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Post-Exposure I: Individual and Mean Clinical Chemistry Values of Dogs

Exposure Conc. (ppm)	Animal Number		BUN mg/100 ml	SGPT mU/ml	AP mU/ml	SGOT mU/ml	Glucose mg/100 ml	Total Bilirubin mg/100 ml
0	78-8110		9	18	81	17	123	0.3
	78-8111		13	21	50	10	107	0.3
	79-447		21	35	81	17	123	0.7
		Mean	14	25	71	15	118	0.4
		±S.D.	6	9	18	4	9	0.2
200	78-8112		8	17	53	10	126	0.2
	78-8113		13	15	86	9	120	0.2
	78-8114		11	14	77	10	130	0.3
		Mean	11	15	72	10	125	0.2
		±S.D.	3	2	17	1	5	0.1
500	78-8109		12	24	100	10	129	0.2
	78-8115		11	28	85	11	181	0.3
	78-8117		21	58	45	12	143	0.4
		Mean	15	37	77	11	151	0.3
		±S.D.	6	19	28	1	27	0.1

Parameters found to be significantly altered by a two way repeated measures ANOVA were: SGPT, SGOT and total bilirubin. A discussion of these observations and their interpretation may be found in the text.

000051

TABLE 27

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Post-Exposure II: Individual and Mean Clinical Chemistry Values of Dogs

Exposure Conc. (ppm)	Animal Number		BUN mg/100 ml	SGPT mU/ml	AP mU/ml	SGOT mU/ml	Glucose mg/100 ml	Total Bilirubin mg/100 ml
0	78-8110		16	19	68	18	102	0.3
	78-8111		23	23	60	12	92	0.4
	79-447		27	47	89	19	112	0.5
		Mean	22	30	69	16	102	0.4
		±S.D.	6	15	20	4	10	0.1
200	78-8112		9	19	50	15	105	0.3
	78-8113		15	17	79	11	111	0.1
	78-8114		22	14	68	16	107	0.8
		Mean	15	17	66	14	108	0.4
		±S.D.	7	3	15	3	3	0.4
500	78-8109		26	20	68	15	98	0.4
	78-8115		16	18	57	15	117	0.2
	78-8117		18	22	34	15	94	0.4
		Mean	20	20	53	15	103	0.3
		±S.D.	5	2	17	0	12	0.1

00052

TABLE 28

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Post-Exposure III: Individual and Mean Clinical Chemistry Values of Dogs

Exposure Conc. (ppm)	Animal Number		BUN mg/100 ml	SGPT mU/ml	AP mU/ml	SGOT mU/ml	Glucose mg/100 ml	Total Bilirubin mg/100 ml
0	78-8110		23	16	64	14	94	0.4
	78-8111		16	22	46	10	99	0.2
	79-447		11	36	83	19	120	0.3
		Mean	16	25	64	14	104	0.3
		±S.D.	6	10	19	5	14	0.1
200	78-8112		12	17	50	13	117	0.2
	78-8113		19	16	82	11	112	0.2
	78-8114		18	12	59	12	108	0.3
		Mean	16	15	64	12	112	0.2
		±S.D.	4	3	17	1	5	0.1
500	78-8109		20	14	51	12	110	0.2
	78-8115		21	17	46	15	111	0.6
	78-8117		19	16	32	14	117	0.6
		Mean	20	16	43	14	113	0.5
		±S.D.	1	2	10	2	4	0.2

000053

TABLE 29

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Post-Exposure IV: Individual and Mean Clinical Chemistry Values of Dogs

Exposure Conc. (ppm)	Animal Number		BUN mg/100 ml	SGPT mU/ml	AP mU/ml	SGOT mU/ml	Glucose mg/100 ml	Total Bilirubin mg/100 ml
0	78-8110		16	14	64	15	89	0.5
	78-8111		21	28	45	13	103	0.5
	79-447		19	24	78	14	120	0.5
		Mean	19	22	62	14	104	0.5
		±S.D.	3	7	17	1	16	0.0
200	78-8112		10	18	43	14	112	0.3
	78-8113		15	15	78	10	115	0.2
	78-8114		18	12	56	13	116	0.3
		Mean	14	15	59	12	114	0.3
		±S.D.	4	3	18	2	2	0.1
500	78-8109		21	13	54	14	112	0.4
	78-8115		18	13	48	14	127	0.6
	78-8117		20	16	33	13	115	0.5
		Mean	20	14	45	14	118	0.5
		±S.D.	2	2	11	1	8	0.1

000054

TABLE 30

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Post-Exposure V: Individual and Mean Clinical Chemistry Values of Dogs

Exposure Conc. (ppm)	Animal Number		BUN mg/100 ml	SGPT mU/ml	AP mU/ml	SGOT mU/ml	Glucose mg/100 ml	Total Bilirubin mg/100 ml
0	78-8110		27	17	65	17	105	0.6
	78-8111		22	20	44	13	99	0.5
	79-447		27	33	77	16	117	0.6
		Mean	25	23	62	15	107	0.6
		±S.D.	3	9	17	2	9	0.1
200	78-8112		17	18	44	17	104	0.8
	78-8113		20	17	77	12	119	0.5
	78-8114		22	12	53	15	106	0.7
		Mean	20	16	58	15	110	0.7
		±S.D.	3	3	17	3	8	0.2
500	78-8109		17	13	46	15	115	0.1
	78-8115		26	17	37	14	123	0.5
	78-8117		13	12	50	15	127	0.4
		Mean	19	14	44	15	122	0.3
		±S.D.	7	3	7	1	6	0.2

000055

TABLE 31

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Pre-Exposure I: Individual and Mean Clinical Chemistry Values of Cats

Exposure Conc. (ppm)	Animal Number		BUN mg/100 ml	SGPT mU/ml	AP mU/ml	SGOT mU/ml	Glucose mg/100 ml	Total Bilirubin mg/100 ml
0	78-8100		32	17	49	12	65	0.6
	78-8101		42	13	66	9	89	0.3
	78-8102		34	19	86	15	163	0.5
		Mean	36	16	67	12	106	0.5
		±S.D.	5	3	19	3	51	0.2
200	78-8103		33	17	93	7	91	0.2
	78-8104		31	32	57	11	82	0.2
	78-8105		38	17	70	11	77	0.5
		Mean	34	22	73	10	83	0.3
		±S.D.	4	9	18	2	7	0.2
500	78-8106		38	25	118	20	337	0.4
	78-8107		41	19	53	8	88	0.2
	78-8108		27	14	74	9	159	0.3
		Mean	35	19	82	12	194	0.3
		±S.D.	7	6	33	7	128	0.1

000056

TABLE 32

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Pre-Exposure II: Individual and Mean Clinical Chemistry Values of Cats

Exposure Conc. (ppm)	Animal Number		BUN mg/100 ml	SGPT mU/ml	AP mU/ml	SGOT mU/ml	Glucose mg/100 ml	Total Bilirubin mg/100 ml	Other
0	78-8100		26	12	61	9	158	0.2	
	78-8101		34	11	78	9	143	0.2	
	78-8102		34	20	101	10	100	0.1	
		Mean	31	14	77	9	134	0.2	
		±S.D.	5	5	26	1	30	0.1	
200	78-8103		30	17	87	6	109	0.2	
	78-8104		31	30	55	11	93	0.3	
	78-8105		34	33	86	38	273	0.6	Slight hemolysis
		Mean	32	27	76	18	168	0.4	
		±S.D.	2	9	18	17	100	0.2	
500	78-8106		27	21	88	8	115	0.2	
	78-8107		45	19	50	8	92	0.2	
	78-8108		24	17	59	6	112	0.2	
		Mean	32	19	66	7	106	0.2	
		±S.D.	11	2	20	1	13	0.0	

000057

TABLE 33

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS & CATS

Pre-Exposure I & II: Average of Individual Clinical Chemistry Values for Cats

Exposure Conc. (ppm)	Animal Number		BUN mg/100 ml	SGPT mU/ml	AP mU/ml	SGOT mU/ml	Glucose mg/100 ml	Total Bilirubin mg/100 ml
0	78-8100		29.0	14.5	50.0	10.5	111.5	0.40
	78-8101		38.0	12.0	72.0	9.0	116.0	0.25
	78-8102		34.0	19.5	93.5	12.5	131.5	0.30
		Mean	33.7	15.3	71.8	10.7	119.7	0.32
		± S.D.	4.5	3.8	21.8	1.8	10.5	0.08
200	78-8103		31.5	17.0	90.0	6.5	100.0	0.20
	78-8104		31.0	31.0	56.0	11.0	87.5	0.25
	78-8105		36.0	25.0	78.0	24.5	175.0	0.30
		Mean	32.8	24.3	74.7	14.0	120.8	0.25
		± S.D.	2.8	7.0	17.2	9.4	47.3	0.05
500	78-8106		32.5	23.0	103.0	14.0	226.0	0.30
	78-8107		43.0	19.0	51.5	8.0	90.0	0.20
	78-8108		25.5	15.5	66.5	7.5	135.5	0.25
		Mean	33.7	19.2	73.7	9.8	150.5	0.25
		± S.D.	8.8	3.8	26.5	3.6	69.2	0.05

NOTE: The Pre-Exposure II & II clinical chemistry data was averaged for use in the statistical analysis of pre- and post-exposure data by two way (time and exposure concentration) repeated measures ANOVA, $p < 0.05$.

0058

TABLE 34

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Post-Exposure I: Individual and Mean Clinical Chemistry Values of Cats

Exposure Conc. (ppm)	Animal Number		BUN mg/100 ml	SGPT mU/ml	AP mU/ml	SGOT mU/ml	Glucose mg/100 ml	Total Bilirubin mg/100 ml
0	78-8100		26	13	42	6	82	0.4
	78-8101		37	12	55	7	90	0.1
	78-8102		28	16	81	6	94	0.3
		Mean	30	14	59	6	89	0.3
		±S.D.	6	2	20	1	6	0.2
200	78-8103		30	18	75	6	103	0.3
	78-8104		31	24	67	9	94	0.2
	78-8105		34	33	77	18	88	0.2
		Mean	32	25	70	11	95	0.2
		±S.D.	2	8	11	6	8	0.1
500	78-8106		36	18	100	5	91	0.2
	78-8107		43	24	54	9	83	0.2
	78-8108		33	16	66	6	85	0.3
		Mean	37	19	73	7	86	0.2
		±S.D.	5	4	24	2	4	0.1

None of the clinical chemistry parameters revealed statistically significant alterations when evaluated by two-way repeated measures ANOVA.

000059

TABLE 35

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Post-Exposure II: Individual and Mean Clinical Chemistry Values of Cats

Exposure Conc. (ppm)	Animal Number		BUN mg/100 ml	SGPT mU/ml	AP mU/ml	SGOT mU/ml	Glucose mg/100 ml	Total Bilirubin mg/100 ml
0	78-8100		25	12	51	4	92	0.1
	78-8101		39	12	54	10	92	0.2
	78-8102		28	15	89	6	81	0.1
		Mean	31	13	65	7	88	0.1
		±S.D.	7	2	21	3	6	0.1
200	78-8103		26	17	83	7	106	0.1
	78-8104		31	25	51	9	77	0.2
	78-8105		30	17	70	7	89	0.1
		Mean	29	20	68	8	91	0.1
		±S.D.	3	5	16	1	15	0.1
500	78-8106		34	11	62	5	93	0.1
	78-8107		40	21	46	8	84	0.2
	78-8108		23	13	62	6	94	0.2
		Mean	32	15	57	6	90	0.2
		±S.D.	9	5	9	2	6	0.1

000060

TABLE 36

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Post-Exposure III: Individual and Mean Clinical Chemistry Values of Cats

Exposure Conc. (ppm)	Animal Number		BUN mg/100 ml	SGPT mU/ml	AP mU/ml	SGOT mU/ml	Glucose mg/100 ml	Total Bilirubin mg/100 ml
0	78-8100		25	13	56	7	72	0.2
	78-8101		40	14	63	14	89	0.3
	78-8102		27	17	99	13	84	0.3
		Mean	31	15	73	11	82	0.3
		±S.D.	8	2	23	4	9	0.1
200	78-8103		28	16	85	9	103	0.4
	78-8104		32	23	56	10	73	0.3
	78-8105		28	16	75	10	94	0.3
		Mean	29	18	72	10	90	0.3
		±S.D.	2	4	15	1	15	0.1
500	78-8106		34	14	100	9	208	0.2
	78-8107		51	20	50	10	88	0.4
	78-8108		24	11	67	5	87	0.1
		Mean	36	15	72	8	128	0.2
		±S.D.	14	5	25	3	70	0.2

C-C61

TABLE 37

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Pre-Exposure III: Individual and Mean Urinalysis Values of Dogs

Exposure Conc. (ppm)	Animal Number	Color	Appearance	Specific Gravity	pH	Glucose	Protein mg/100 ml	Ketones	Bilirubin	Blood	Uro-Bilinogen	WBC/HPF	RBC/HPF	Casts/LPF	Crystals	Bacteria	Mucous	Epithelial	Other
0	78-0110	Red	Hazy	1.032	8	-	100	-	-	4+	1	Many	Many	-	-	-	trace	-	-
	78-0111	Yellow	Clear	1.026	6	-	7	-	-	-	1	-	-	-	-	-	1+	0-1	-
	79-447	Yellow	Clear	1.036	5	-	6	-	-	-	1	1-2	-	-	-	-	-	0-2	-
	Mean			1.031															
				0.006															
200	78-0112	Yellow	Slt Hazy	1.032	8	-	6	-	-	-	1	-	-	-	tri phos	-	trace	0-1	-
	78-0113	Yellow	Clear	1.038	6	-	6	-	-	-	1	0-1	-	-	tri phos	-	1+	0-1	-
	78-0114	Yellow	Clear	1.044	5	-	6	-	-	-	-	0-1	-	-	-	-	1+	0-1	-
	Mean			1.030															
	±S.D.			0.006															
500	78-0100	Yellow	Clear	1.052	8	-	5	-	-	-	1	0-1	-	-	tri phos	few red	1+	0-1	-
	78-0115	Yellow	Clear	1.050	8	-	5	-	-	-	1	0-1	-	-	tri phos	-	1+	-	occ sperm seen
	78-0117	Yellow	Clear	1.040	5	-	5	-	-	-	1	1-2	-	-	-	-	1+	0-3	-
	Mean			1.050															
	±S.D.			0.000															
0	78-0110[a]	Yellow	Hazy	1.052	9	-	76	-	-	4+	1	9-12	Many	-	many tri phos	many red	1+	0-1	-

[a]A second analysis was done on this dog later in the day because of the blood seen in his urine.

- = negative finding

tri phos = triple phosphate

occ = occasional

slt = slight

Pre-Exposure IV: Individual Urinalysis Values of Dog 78-0110[a]

0	78-0110	Yellow	Hazy	1.036	6	-	76	-	-	4+	1	6-7	Many	-		rare red	trace	3-4	

[a]Urinalysis was performed on only this dog because of the blood found previously in his urine in Pre-Exposure III. Since blood was not found here, the blood found earlier was probably traumatically induced by the catherization.

TABLE 30

[illegible]: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Post-Exposure I: Individual and Mean Urinalysis Values of Dogs

Exposure Conc. (ppm)	Animal Number	Color	Appearance	Specific Gravity[a]	pH	Glucose	Protein mg/100 ml	Ketones	Bilirubin	Blood	Uro-bilino-gen	WBC/HPF	RBC/HPF	Casts/LPF	Crystals	Bacteria	Mucus	Epithelial	Other
0	70-0110	Yellow	Clear	1.022	6	-	5	-	-	-	1	1-2	-	-	occ tri phos	-	1+	2-3	-
	70-0111	Yellow	Hazy	1.042	8	-	20	-	-	-	1	0-1	-	-	many tri phos	occ rod	1+	-	-
	70-447	Yellow	Clear	1.032	7	-	5	-	-	-	1	0-1	-	-	many tri phos	rare rod	1+	-	-
	Mean			1.032															
	±S.D.			0.010															
200	70-0112	Yellow	Clear	1.030	6	-	5	-	-	-	1	1-2	-	-	-	-	1+	0-2	-
	70-0113	Yellow	Clear	1.046	7	-	5	-	-	-	1	-	-	-	-	-	1+	-	-
	70-0114	Yellow	Clear	1.016	6	-	10	-	-	-	1	0-1	-	-	-	-	1+	2-3	-
	Mean			1.031															
	±S.D.			0.015															
500	70-0109	Yellow	Clear	1.030	6	-	10	-	-	-	1	0-1	-	-	occ tri phos	-	1+	0-1	-
	70-0115	Yellow	Clear	1.058	6	-	5	-	-	-	1	-	-	-	-	occ rod	1+	0-1	-
	70-0117	Yellow	Clear	1.050	6	-	0	-	-	-	1	0-1	-	-	rare tri phos	occ rod	1+	2-3	-
	Mean			1.050															
	±S.D.			0.023															

[a]Statistical analysis was performed on this data only

There were no statistically significant deviations in urinalysis parameters evaluated by two-way repeated measures ANOVA.

- = negative finding

tri phos = triple phosphates; occ (occasional)

00063

TABLE 30

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Post-Exposure II: Individual and Mean Urinalysis Values of Dogs

Exposure Conc. (ppm)	Animal Number	Color	Appearance	Specific[a] Gravity	pH	Glucose	Protein mg/100 ml	Ketones	Bilirubin	Blood	Uro-Bilinogen	WBC/HPF	RBC/HPF	Casts/LPF	Crystals	Bacteria	Mucous	Epithelial	Other
0	78-8110	Yellow	Cloudy	1.040	8	-	100	-	-	4+	1	2-3	Many	-	many tri phos	occ rod	1+	0-1	-
	78-8111	Yellow	Clear	1.050	6	-	6	-	-	-	1	-	-	-	occ tri phos	-	rare	-	-
	78-8117	Yellow	Clear	1.056	7	-	5	-	-	-	1	0-2	-	-	many tri phos	-	2+	-	-
	Mean			1.052															
	±S.D.			0.013															
200	78-8112	Yellow	Clear	1.034	6	-	10	-	-	-	1	0-1	-	-	mod tri phos	-	-	-	-
	78-8113	Yellow	Cloudy	1.038	9	-	100	-	-	4+	1	2-3	Many	-	many tri phos	occ rod	1+	0-1	-
	78-8114	Yellow	Clear	1.052	6	-	5	-	-	-	1	0-1	-	-	many tri phos	-	1+	0-1	-
	Mean			1.045															
	±S.D.			0.015															
500	78-8109	Yellow	Clear	1.056	6	-	5	-	-	-	1	2-3	-	-	-	-	2+	0-1	-
	78-8115	Yellow	Hazy	1.050	7	-	5	-	-	-	1	2-3	0-2	-	many tri phos	occ rod	2+	0-1	-
	78-8117	Yellow	Clear	1.052	6	-	5	-	-	-	1	0-1	-	-	many tri phos	rare rod	1+	-	-
	Mean			1.056															
	±S.D.			0.001															

[a]Statistical analysis was performed on this data only

- = negative finding

tri phos = triple phosphate; occ (occasional), mod (moderate)

TABLE 40

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Post-Exposure III: Individual and Mean Urinalysis Values of Dogs

Exposure Conc. (ppm)	Animal Number	Color	Appearance	Specific[a] Gravity	pH	Glucose	Protein mg/100 ml	Ketones	Urobilinogen	Blood	Uro-Bilin-ogen	WBC/HPF	RBC/HPF	Casts/LPF	Crystals	Bacteria	Mucus	Epithelial	Other
0	70-0110	Yellow	Clear	1.040	5	-	5	-	-	-	1	0-1	-	-	-	-	1+	2-3	-
	70-0111	Yellow	Clear	1.024	6	-	5	-	-	-	1	0-1	-	-	-	-	2+	2-4	-
	70-0112	Yellow	Clear	1.032	6	-	5	-	-	-	1	-	-	-	-	-	1+	-	-
	Mean			1.036											-	-	1+	-	-
	±S.D.			0.012												-			
200	70-0112	Yellow	Clear	1.040	7	-	5	-	-	-	1	0-1	-	-	many tri phos	-	1+	-	-
	70-0113	Yellow	Clear	1.046	6	-	10	-	-	3+	1	2-3	Many	-	occ tri phos	-	1+	0-1	-
	70-0114	Yellow	Clear	1.032	6	-	5	-	-	-	1	0-2	-	-	-	-	1+	0-1	-
	Mean			1.039															
	±S.D.			0.007															
500	70-0100	Yellow	Clear	1.052	6	-	-	-	-	-	1	0-1	-	-	many tri phos	-	1+	0-1	-
	70-0115	Yellow	Clear	1.050	6	-	5	-	-	-	1	0-1	-	-	-	-	1+	-	-
	70-0117	Yellow	Clear	1.030	7	-	5	-	-	-	1	0-1	-	-	many tri phos	-	1+	-	-
	Mean			1.044															
	±S.D.			0.016															

[a]Statistical analysis was performed on this data only

- = negative finding

tri phos = triple phosphates occ (occasional)

000065

TABLE 41

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (7-22-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Post-Exposure IV: Individual and Mean Urinalysis Values of Dogs

Exposure Conc. (ppm)	Animal Number	Color	Appearance	Specific[a] Gravity	pH	Glucose	Protein mg/100 ml	Ketones	Bilirubin	Blood	Uro-bilino-gen	WBC/HPF	RBC/HPF	Casts/LPF	Crystals	Bacteria	Mucus	Epithelial	Other
0	70-0110	Yellow	Hazy	1.046	6	-	6	-	-	-	1	0-2	-	-	many tri phos	rare rod	1+	0-1	-
	70-0111	Yellow	Hazy	1.052	8	-	10	-	-	-	1	2-3	-	-	many tri phos	-	1+	1-2	-
	70-0117	Yellow	Clear	1.040	7	-	6	-	-	-	1	1-2	-	-	many tri phos	rare rod	1+	0-1	-
	Mean			1.042															
	±S.D.			0.006															
200	70-0112	Yellow	Clear	1.032	6	-	6	-	-	-	1	1-2	-	-	occ tri phos	occ rod	1+	0-1	-
	70-0113	Yellow	Hazy	1.040	6	-	50	-	-	1+	1	0-1	0-10	-	-	-	2+	0-1	-
	70-0114	Yellow	Clear	1.040	6	-	6	-	-	-	1	0-1	-	-	-	-	-	-	-
	Mean			1.040															
	±S.D.			0.008															
600	70-0109	Yellow	Clear	1.054	7	-	6	-	-	-	1	1-2	-	-	occ tri phos	rare rod	1+	0-1	-
	70-0115	Yellow	Hazy	1.052	8	-	20	-	-	1+	1	1-2	Many	-	many tri phos	-	1+	0-1	-
	70-0117	Yellow	Clear	1.048	6	-	6	-	-	-	1	2-3	-	-	-	-	1+	2-3	-
	Mean			1.055															
	±S.D.			0.007															

[a]Statistical analysis was performed on this data only

- = negative finding

tri phos = triple phosphates; occ (occasional)

000066

TABLE 42

MERCURY CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Post-Exposure 91: Individual and Mean Urinalysis Values of Dogs

Exposure Conc. (mg/m³)	Animal Number	Color	Appearance	Specific[a] Gravity	pH	Glucose	Protein mg/100 ml	Ketones	Bilirubin	Blood	Uro-bilinogen	WBC/HPF	RBC/HPF	Casts/LPF	Crystals	Bacteria	Mucus	Epithelial	Other
0	70-0110	Yellow	Cloudy	1.040	6.5	-	30	-	-	-	1	1-3	10-16	-	occ Ca. ox.	-	-	minimal	spora term
	70-0111	Yellow	Sl. Cloudy	1.036	7.0	-	5	-	-	-	1	2-6	-	-	and tri phos	1+	-	minimal	spora term
	70-007	Yellow	Clear	1.042	6.0	-	0	-	-	-	1	0-4	-	-	-	few	-	-	spora term
	Mean			1.042															
	±S.D.			0.007															
200	70-0112	Yellow	Clear	1.042	4.5	-	5	-	-	-	1	0-2	1-4	-		few	-	minimal	
	70-0113	Yellow	Cloudy	1.052	7.0	-	10	-	-	3+	1	-	loaded	-	mic Ca. ox.	-	-	moderate	spora term
	70-0114	Yellow	Hazy	1.050	6.0	-	30	-	-	-	1	2-4	0-3	0-1 granular	-	3+	-	minimal	spora term
	Mean			1.045															
	±S.D.			0.011															
501	70-0109	Yellow	Sl. Cloudy	1.034	7.0	-	5	-	-	-	1	2-4	-	-	and tri phos	-	-	minimal	spora term
	70-0115	Yellow	Clear	1.023	6.0	-	5	-	-	-	1	1-3	-	-	mic tri phos	few	-	-	-
	70-0117	Yellow	Clear	1.040	7.5	-	5	-	-	-	1	0-2	-	-	and tri phos	few	-	-	spora term
	Mean			1.037															
	±S.D.			0.008															

[a]Statistical analysis was performed on this data only

- = negative finding

Ca ox = Calcium oxalate; occ (occasional), mic (minimal)

tri phos = triple phosphate; mic (minimal), and (moderate)

sl. = slight

00067

TABLE 43

METHYL CHLORIDE: A 72 HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

At Necropsy: Individual and Mean Urinalysis Data of Cats

Exposure Conc. (ppm)	Animal Number	Color	Appearance	Specific Gravity[a]	pH	Glucose	Protein mg/100 ml	Ketones	Bilirubin	Blood	Uro-Bilinogen	WBC/HPF	RBC/HPF	Casts/LPF	Crystals	Bacteria	Mucous	Epithelial	Other
0	78-8100	Yellow	Hazy	1.056	8	-	6	-	-	-	1	3-8	-	-	-	-	trace	0-1	-
	78-8101	Yellow	Clear	1.038	8	-	6	-	-	-	1	0-1	-	-	rare tri. phos.	-	1+	2-3	-
	78-8102	Yellow	Hazy	1.062	8	-	6	-	-	-	1	0-1	-	-	rare tri. phos	rare rod	1+	-	sperm seen
	Mean			1.052															
	±S.D.			0.013															
200	78-8103	Yellow	Hazy	1.075	6	-	5	-	-	-	1	6-8	-	-	-	-	trace	0-3	-
	78-8104	Yellow	Clear	1.061	6	-	5	-	-	-	1	-	-	-	-	-	trace	-	-
	78-8105	Yellow	Clear	1.028	8	-	5	-	-	-	1	0-3	0-1	-	-	rare rod	1+	1-2	sperm seen
	Mean			1.054															
	±S.D.			0.023															
500	78-8106	Yellow	Hazy	1.056	7	-	5	-	-	2+	1	1-2	10-14	-	-	-	1+	1-2	sperm seen
	78-8107	Pale Yellow	Hazy	.058	7	-	6	-	-	-	1	3-6	-	-	-	occ rod	1+	0-1	sperm seen
	78-8108	Yellow	Clear	1.064	7	-	6	-	-	-	1	0-1	-	-	rare tri. phos.	rare rod	trace	2-3	sperm seen
	Mean			1.049															
	±S.D.			0.019															

[a]Statistical analysis was performed on this data only

- = negative finding

rare tri phos. = rare triple phosphate

occ. = occasional

TABLE 44

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Results of a Neurologic Examination on Dogs

Animal Tattoo (Path Number)	MeCl Exposure ppm	Number of Days post exposure	General Observations	Results of Neurologic Examination
HTEBX-1 (79-447)	0	4	Alert and apprehensive	No neurological abnormalities were observed.
HOLAR-1 (78-8111)	0	4	Normal demeanor	No neurological abnormalities were observed.
HUVAF-1 (78-8110)	0	4	Alert and inquisitive	No neurological abnormalities were observed.
HUUAF-1 (78-8112)	200	4	Alert and normal	No neurological abnormalities were observed.
HTOGV-1 (78-8113)	200	4	Inquisitive and hyperactive	No neurological abnormalities were observed.
HNOBX-2 (78-8114)	200	4	Alert and apprehensive	Showed a slight exaggeration of the patella reflex ("knee-jerk").
HTBBX-2 (78-8115)	500	4	Alert and good natured	Dog would not walk. Was lateral recumbent. All limbs had voluntary movement. The dog could raise head and reposition itself by thrashing around using neck, forelimbs and torso. Often an opisthotonus positioning of the neck was observed when the dog tried to relocate or became excited. When coaxed to lift head or forced to stand, intention tremors were noted along the cervical and forelimb regions. -Cranial nerve evaluation resulted in normal responses. -Front limbs were slow to respond to proprioception positioning. -Rear limbs showed no response to proprioception positioning. -Front limbs were slow to respond to the forced "hopping" evaluation. -Forced "hopping" of the rear limbs was difficult to evaluate, however, there was a very weak response in both rear limbs. -No righting reflex. -After attempting passive manipulation, the rear limbs were rigid and extended. This was only temporary and the rear limbs gradually relaxed with continued manipulation.
		26	Alert, good natured and inquisitive. Protested being held in lateral recumbency	Dog walked with intermittent rear limb ataxia. Slight ventriflexion of the rear digits was noted. Extension and flexion of rear limb joints was noted when dog walked or ran. Position and balance was maintained when dog was pushed. Cranial nerves, spinal reflexes and postural reactions were all normal.

TABLE 44 (cont.)

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Results of a Neurologic Examination on Dogs

Animal Tattoo (Data Number)	MeCl Exposure ppm	Number of Days post exposure	General Observations	Results of Neurologic Examination
RCSBF-1 (78-8117)	500	4	Nervous, apprehensive and protested being handled	-Rear limb ataxia and poor placement of rear limbs. Appeared stiff when walking or running causing an appearance of a "hopping" gait. Rear digits appeared ventriflexed. Could be pushed off balance easily. -Would not recognition rear feet after proprioception positioning evaluation. -All four limbs were slow to respond to the forced "hopping" evaluation. -Only the torso was used for righting itself. Dog would not right itself immediately. -Tremors were brought about over the left half of the cervical, thoracic, and left forelimb regions during evaluation of the flexor spinal reflexes. -Rear limb positioning and ataxia appeared more severe in this dog than in dog RCSBK-1.
		26	Alert and inquisitive. Did not protest being handled. Very submissive	Overall there has been a significant improvement in this animal's demeanor, gait, and posture. However, a slight rigidity and ataxia of the rear limbs were still apparent. Reactions to neurologic tests were considered normal.
RCSBK-1 (78-8109)	500	4	Alert and active in examination room. Slight excessive salivation noted.	-Slight ataxia and poor placement of rear limbs. When walking or running a slight "hopping" gait was apparent. When walking the rear digits appear ventriflexed and had a "walking on toes" appearance. -Could be pushed off balance easily. -Bilateral exaggerated patellar reflex. -Slow response to proprioceptive positioning of rear limbs. -Slow response to placing reflex with or without occluded vision. -Nonresponsive to righting reflex. -Initially limbs were rigid during passive manipulation, however, normal movement was apparent soon after continued manipulation.
		26	Alert and slightly apprehensive	Gait and posture appeared normal. Normal movement of the hip and stifle joints was noted. No abnormal responses or behavior were observed during the neurologic examination.

TABLE 45

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Summary of the Gross and Histopathologic Findings in Dogs

Pathology Number	Exposure Concentration (ppm)	Summary of Gross and Histopathologic Findings
79-447	0	**Gross:** Liver - Pale focus. **Histopathology:** Liver - Multifocal extramedullary hematopoiesis. Kidney - Bilateral mineralization in medulla. Stomach - Aggregate of mononuclear cells in submucosa. Lungs - Nematode parasite (probably Dirofilaria) in pulmonary artery. Slight chronic active inflammation, perivasculitis, peribronchiolitis and interstitial pneumonia, probably secondary to infection by the nematode parasite Filaroides Hirthi. Tongue: Foreign body granuloma. Nasal Turbinates - Aggregate of mononuclear cells in submucosa.
78-8110	0	**Gross:** Urinary Bladder - Petechia on mucosal surface. **Histopathology:** Liver - Aggregates of reticuloendothelial cells. Kidneys - Aggregate of reticuloendothelial cells in cortex. Bilateral mineralization of medulla. Testicles - Mineralization of individual seminiferous tubule. Urinary Bladder - Acute cystitis, probably secondary to catheterization. Lungs - Focal granuloma, peribronchiolitis and interstitial pneumonia, all of which are slight and probably secondary to infection by the nematode parasite Filaroides Hirthi. Skin - Subacute perifollicular inflammation.
78-8111	0	**Gross:** NVL **Histopathology:** Liver - Aggregates of reticuloendothelial cells. Kidneys - Bilateral mineralization of the medulla. Stomach - Aggregate of mononuclear granular lymphoid cells in the submucosa. Prostate - Subacute inflammation. Urinary Bladder - Subacute inflammation of the submucosa. Lungs - Subacute inflammation, very slight. Nasal Turbinates - Aggregates of mononuclear predominantly lymphoid cells in the submucosa.
78-8112	200	**Gross:** Lungs - Two gray foci suggestive of parasites. **Histopathology:** Liver - Multifocal extramedullary hematopoiesis. Kidneys - Bilateral mineralization of the medulla. Stomach - Aggregate of mononuclear predominantly lymphoid cells in the submucosa. Lungs - Chronic active inflammation, predominantly peribronchial and perivascular consistent with infection due to the nematode parasite Filaroides Hirthi. Mesenteric Lymph Nodes - Multifocal hemorrhage in the medullary sinuses. Nasal Turbinates - Aggregates of mononuclear, predominantly lymphoid cells in the submucosa.

TABLE 45 (cont.)

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Summary of the Gross and Histopathologic Findings in Dogs

Pathology Number	Exposure Concentration (ppm)	Summary of Gross and Histopathologic Findings
78-8113	200	Gross: Urinary Bladder - Thickened wall. Numerous petechial and ecchymotic hemorrhages on the mucosal surface. Histopathology: Liver - Focal microgranuloma. Multifocal extramedullary hematopoiesis. Spleen - Siderotic nodule, focal. Kidneys - Bilateral mineralization of the medulla. Stomach - Aggregates of mononuclear, predominantly lymphoid, cells in the submucosa. Urinary Bladder - Submucosal edema, multifocal hemorrhage and acute inflammation, all moderate and probably secondary to catheterization. Lungs - Chronic active inflammation probably secondary to infection by the nematode parasite Filaroides Hirthi. Tongue - Foreign body granuloma. Nasal Turbinates - Aggregates of mononuclear, predominantly lymphoid, cells in the submucosa.
78-8118	200	Gross: Externally - Multiple areas of alopecia especially prominent on the dorsal neck region and probably secondary to fighting with cage mates. Internally: Spleen - One cm area on capsular surface with adhesions to the abdominal wall. Lungs - Firm dark elevated 2 mm focus probably parasitic in origin. Histopathology: Liver - Multifocal extramedullary hematopoiesis. Kidneys - Bilateral mineralization of the medulla. Stomach - Aggregates of mononuclear, predominantly lymphoid, cells in the submucosa. Lungs - Focal foreign body granuloma. Multifocal chronic active inflammation probably secondary to infection by the nematode parasite Filaroides Hirthi. Nasal Turbinates - Aggregates of mononuclear, predominantly lymphoid, cells in the submucosa. Spleen - Fibrous capsular adhesions, focal.
78-8109	500	Gross: Heart - Slight thickening of mitral valve. Multifocal pale areas in left ventricular wall. Focal pale area 5 mm in diameter constricting the myocardium, suggestive for fibrosis. Histopathology: Heart - Valvular endocarditis of the mitral valve. Fibrosis with mineralization of left ventricular wall. Brain - Multifocal degeneration and demyelinization of the midbrain (medulla). Spinal Cord - Multifocal degeneration and demyelinization of the lateral and ventral funiculi. Stomach - Aggregates of mononuclear, predominantly lymphoid cells, in the submucosa.

TABLE 45 (cont.)

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Summary of the Gross and Histopathologic Findings in Dogs

Pathology Number	Exposure Concentration (ppm)	Summary of Gross and Histopathologic Findings
78-8115	500	**Gross:** Urinary Bladder - Two linear hemorrhages on serosal surface. **Histopathology:** Liver - Multifocal extramedullary hematopoiesis. Brain - Multifocal degeneration and demyelination of the midbrain (pons). Spinal Cord - Multifocal degeneration and demyelinization of the lateral and ventral funiculi. Kidneys - Bilateral mineralization of the medulla. Testicles - Bilateral diffuse atrophy, moderate. Epididymides - Bilateral decreased sperm in the tubular lumina. Lungs - Multifocal chronic active inflammation, consistent with the migration of the nematode parasite *Filaroides Hirthi*. Tongue - Multifocal foreign body granulomata. Nasal Turbinates - Multifocal subacute inflammation in the submucosa.
78-8117	500	**Gross:** Lungs - One cm pale area on right cardiac lobe. Irregularly shaped area of atelectasis and one cm diameter area of emphysema on right apical lobe. Multiple subpleural raised foci. **Histopathology:** Liver - Multifocal aggregates of reticuloendothelial cells. Brain - Multifocal degeneration and demyelination of the brain stem (pons). Spinal Cord - Multifocal degeneration and demyelinization of the lateral and ventral funiculi. Tongue - Multifocal foreign body granulomata. Lungs - Multifocal chronic active inflammation consistent with infection by the nematode parasite *Filaroides Hirthi*.

TABLE 46

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Summary of the Gross and Histopathologic Findings in Cats

Pathology Number	Exposure Concentration (ppm)	Summary of Gross and Histopathologic Findings
78-8100	0	Gross: NVL Histopathology: Kidneys - Unilateral mineralization of cortico-medullary junction. Stomach - Multifocal aggregates of mononuclear lymphoid cells in the mucosa.
78-8101	0	Gross: NVL Histopathology: Liver - Focal aggregate of mononuclear lymphoid cells. Brain - Focal perivascular aggregate of mononuclear, predominantly lymphoid, cells in medulla. Multifocal degeneration and demyelinization in midbrain. Spinal Cord - Multifocal perivascular aggregates of mononuclear, predominantly lymphoid, cells. Degeneration and demyelinization of the lateral and ventral funiculi. Stomach - Focal aggregate of mononuclear lymphoid cells in mucosa. Lungs - Multifocal perivascular and focal peribronchial aggregates of mononuclear lymphoid cells. Nasal Turbinates - Multifocal suppurative rhinitis.
78-8102	0	Gross: NVL. Histopathology: Stomach - Multifocal aggregates of mononuclear lymphoid cells in mucosa. Lungs - Focal peribronchial aggregate of mononuclear lymphoid cells.
78-8103	200	Gross: Externally - Remnant of persistent papillary membrane in left eye. Histopathology: Liver - Multifocal aggregates of mononuclear, predominantly lymphoid, cells. Kidneys - Unilateral mineralization of cortico-medullary junction. Stomach - Multifocal aggregates of mononuclear, predominantly lymphoid, cells in mucosa. Lungs - Focal peribronchial aggregate of mononuclear, predominantly lymphoid, cells. Thyroid - Multifocal aggregates of mononuclear, predominantly lymphoid, cells. Spinal Cord - Multifocal degeneration and demyelinization of the lateral and ventral funiculi.

TABLE 46 (cont.)

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Summary of the Gross and Histopathologic Findings in Cats

Pathology Number	Exposure Concentration (ppm)	Summary of Gross and Histopathologic Findings
78-8104	200	Gross: NVL Histopathology: Liver - Focal aggregate of mononuclear lymphoid cells. Kidneys - Multifocal mineralization of cortico-medullary junction. Stomach - Multifocal aggregates of mononuclear lymphoid cells. Lungs - Multifocal peribronchial aggregates of mononuclear lymphoid cells.
78-8105	200	Gross: NVL Histopathology: Liver - Focal periportal aggregate of mononuclear lymphoid cells. Kidneys - Multifocal mineralization of cortico-medullary junction. Stomach - Multifocal aggregates of mononuclear lymphoid cells. Pancreas - Focal aggregate of mononuclear lymphoid cells. Lungs - Multifocal perivascular aggregates of mononuclear lymphoid cells.
78-8106	500	Gross: NVL Histopathology: Pancreas - Focal subacute inflammation associated with focal ductal hyperplasia. Brain - Multifocal perivascular aggregates of mononuclear lymphoid cells in the medulla and cerebellum. Multifocal degeneration and demyelinization in the cerebrum, cerebellum, and midbrain regions. Spinal Cord - Multifocal perivascular aggregates of mononuclear predominantly lymphoid cells. Multifocal degeneration and demyelinization of the lateral and ventral funiculi. Lungs - Multifocal perivascular aggregates of mononuclear lymphoid cells.
78-8107	500	Gross: NVL Histopathology: Brain - Perivascular aggregates of mononuclear lymphoid and plasma cells and multifocal gliosis. Multifocal degeneration and demyelinization of the cerebrum and midbrain regions. Spinal Cord - Moderate multifocal perivascular aggregates of mononuclear lymphoid and plasma cells and slight multifocal gliosis. Multifocal degeneration and demyelinization of the lateral and ventral funiculi. Kidneys - Bilateral multifocal mineralization of the cortico-medullary junction. Stomach - Multifocal aggregates of mononuclear lymphoid cells in the mucosa and submucosa. Thyroid - Focal colloid cyst.

TABLE 46 (cont.)

METHYL CHLORIDE: A 72-HOUR CONTINUOUS (~23-1/2 HR/DAY) INHALATION TOXICITY STUDY IN DOGS AND CATS

Summary of the Gross and Histopathologic Findings in Cats

Pathology Number	Exposure Concentration (ppm)	Summary of Gross and Histopathologic Findings
78-8108	500	Gross: NVL Histopathology: Liver - Multifocal aggregates of mononuclear, predominantly lymphoid, cells. Spinal Cord - Focal gliosis. Multifocal degeneration and demyelinization of the lateral and ventral funiculi. Kidneys - Mineralization of the cortico-medullary junction. Testicles - Juvenile . pearance, bilateral. Thyroid - Focal colloid cyst.

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Description

METHYL CHLORIDE 48 AND 12 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Chemical Name (Type or Name)	CAS No. (10)
CHLOROMETHANE (METHYL CHLORIDE)	14-27-3

D519

87210221

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

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Final Report

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SUMMARY

Male and female Sprague Dawley rats were exposed by inhalation to methyl chloride gas for 48 or 72 continuous hours. Exposure concentrations were 0, 200, 500, 1000 or 2000 ppm. Some rats were immediately sacrificed after exposure and some were held for a recovery period of up to 12 days. Animal evaluations included general observations, body weights, organ weights, hematologic parameters, urinalysis parameters, clinical chemistry parameters, gross necropsy observations and histopathologic observations.

Exposure to 2000 ppm of methyl chloride for 48 or 72 hours resulted in 100% mortality either during or soon after the exposure period. The primary cause of death appeared to be kidney toxicity and subsequent renal failure. A lesser degree of liver toxicity was also evident.

Exposure to 1000 ppm of methyl chloride for 48 or 72 hours resulted in some mortality after the exposures. Surviving rats sacrificed immediately after exposure to 1000 ppm for 48 or 72 hours showed decreased body weights, and kidney toxicity was evident in the rats immediately after the exposure period. A lesser degree of liver toxicity was also present. Following the recovery period, most parameters were normal and definite signs of renal tubular regeneration were evident indicating an active process of repair from the toxicity.

In addition, the epididymides were affected in male rats exposed to 500, 1000, or 2000 ppm for 48 or 72 hours and in those males that survived the recovery period. The effects included degeneration, inflammation, sperm granuloma formation, scarring, and obstructive changes. Testicular atrophy was also present apparently occurring secondarily to the epididymal alterations.

Exposure-related effects were minimal in male and female rats exposed to 200 ppm for 48 or 72 continuous hours and consisted of slight reversible liver effects.

INTRODUCTION

Methyl chloride (CH_3Cl, chloromethane or monochloromethane) is a widely used industrial chemical. It is used in silicone manufacturing, as a blowing agent in polyurethane and polystyrene foams, as an aerosal propellant and as an intermediate in numerous chemical reactions. Methyl chloride is a colorless gas at ordinary temperature and pressures, but is commercially handled in the liquid form.

Betso (1974) and Repko and Lasley (1979) have reviewed the literature on the toxicity of methyl chloride. As is evident from their reviews, a considerable amount of information is available on the toxicity of methyl chloride in humans and animals following inhalation exposure. As summarized by Patty (1963), acute exposures of 500 to 1000 ppm for 8 hours or 7000 ppm for 1 hour do not produce serious effects in animals while exposures to 150,000 to 300,000 ppm produced death in a short period of time.

Methyl chloride has been reported to affect several organs or organ systems in animals including the liver, kidney, respiratory system and central nervous system. For example, Dunn and Smith (1947), Smith and von Oettingen (1947a,b), and Smith (1947) exposed several animal species 6 hours per day, 6 days per week to concentrations ranging from 300 to 1000 ppm of methyl chloride for up to 175 days. At 500 ppm, rats showed no effects, however mice, dogs, guinea pigs, rabbits, and a monkey showed some evidence of central nervous system effects. They also demonstrated effects in the liver, kidney or lungs at exposure concentrations greater than 500 ppm.

McKenna, et al. (1981a) exposed mice, rats and dogs to exposure concentrations of 0, 50, 150 or 400 ppm of methyl chloride for 6 hours per day, 5 days per week for 3 months. Exposure to 400 ppm resulted in slightly increased relative liver weights in male and female rats and male mice, but without histopathological liver alterations or changes in

other clinical laboratory parameters indicative of liver function. Dogs were unaffected. Therefore, target organ toxicity appears to result only after exposure concentrations of about 400 to 500 ppm for 6 hours a day, 5 or 6 days a week are exceeded. However, little is known about the effects of continuous inhalation exposure at these exposure concentrations over several days. In order to address this issue, two studies (identical except for exposure concentrations) were designed to evaluate the possible effects in rats of continuous inhalation exposure of methyl chloride for 48 or 72 hours and to evaluate the potential for recovery from any observed effect. One study consisted of exposures to 0, 200 or 500 ppm, the second to 0, 1000 or 2000 ppm. Following the exposures, groups of rats were maintained for a recovery period of up to 12 days. This report presents the results of those two studies.

MATERIALS AND METHODS

Test Material. The methyl chloride used was obtained from Matheson Gas Products, Joliet, Illinois, in the form of 100 lb. (net weight) gas cylinders. The following specifications for methyl chloride were provided by the supplier:

Component	Specification
Methyl Chloride	99.5 (mole %) minimum
Water	0.015 (weight %) maximum
Acidity (as HCl)	0.005 (weight %) maximum
Residue in evaporation	0.01 (weight %) maximum

The test material was obtained in 3 gas cylinders with the following serial numbers (filling dates): J262 (5/6/76), J888 (8/10/76) and J2001 (9/23/76). A gas sample from each cylinder was analyzed by mass spectrometry. The analyses by mass spectrometry indicated the test material was >99.9% pure. Furthermore, there was no indication of methyl chloride decomposition during the exposure period.

Exposure Chambers. Three 4.1m^3 stainless steel exposure chambers were used for the exposures. Air supply for the chambers was taken from air conditioning ducts, so that tempered air at approximately 70°F and 50% relative humidity was supplied to the chambers. Appropriate amounts of methyl chloride were added to the air supply streams to achieve chamber concentrations of 0, 200, 500, 1000 or 2000 ppm methyl chloride.

Atmosphere Generation. Methyl chloride was metered directly from the methyl chloride cylinder through a regulator valve and through a needle valve, then through a rotameter and finally introduced into the chamber air supply duct where it was diluted to the desired concentration. Total airflow through the chambers was approximately 760 liters/minute.

Each rotameter used was calibrated for methyl chloride gas. During exposure, the needle valve was set so that methyl chloride flow, as

measured by the rotameter, was at the rate calculated to provide the target concentration in that chamber. Slight adjustments in the needle valve were made as required to keep the analytical concentration as close as possible to the target concentration.

Vapor Analysis. For the exposures at 0, 200 and 500 ppm (Part I of the study), analysis was made by gas chromatography. The column used was a 6' by 1/8" stainless steel column packed with 10% UCW-98 on 80/100 mesh Chromosorb W-HP. The carrier gas was helium at 40 ml/minute. A series of timed electrical valves was arranged so that each chamber was sampled for a period of 20 minutes (the control chamber was not sampled). The gas chromatograph (Varian Model 2400) was equipped with an 8-port sample valve and two 1 ml sample loops. While the contents of one loop was being analyzed the other loop was being flushed with a gas sample. The valve was electrically activated and driven by a timing mechanism such that an analysis was automatically made once every 1-1/2 minutes during the sampling period.

The gas chromatograph was standardized by injecting 20 ml or 50 ml of methyl chloride into a 100-liter Saran air bag, to yield 200 or 500 ppm standards, respectively. Repeatability and linearity of the standards were within a relative ±2%. The gas chromatograph was standardized once each day during the study (standards were repeatable to within ±2% relative).

For the exposures at 0, 1000, and 2000 ppm (Part II of the study), analyses were made by infrared spectrometry. The sampling cycle was 40 minutes (13-1/3 minutes per chamber) including the control chamber.

The infrared spectrophotometer was a Miran Model IA-CVF (Foxboro-Wilks) equipped with a variable pathlength gas cell. The pathlength was 5.25 meters. The analytical wavelength was 13.4 microns. Recording was made with a Varian Model A-25 recorder, input range 1.0 volt full scale.

Methyl chloride standards were prepared as described above. Linearity and repeatability of the instrument was within a relative ±4%.

Experimental Design and Animal Exposures. Male and female Sprague Dawley rats (Spartan Research Animals, Haslett, Michigan) were used. They were approximately 5-6 weeks old when they arrived and weighed between 125-135 grams (females) and 185-200 grams (males). They were acclimated for approximately 5 to 10 days and were randomized using a computer program-derived table of random numbers (GRAND.CLIST from the Computation Laboratory, Dow Chemical, U.S.A.) and placed in wire-bottom stainless steel cages. They were then individually identified with metal ear tags. Food (Purina Laboratory Chow) and water were available ad libitum throughout the study, including during the exposure period. The animals were maintained on a 12-hour light-dark cycle in facilities fully accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC).

This study consisted of exposing the male and female rats to 0, 200, 500, 1000, or 2000 ppm of methyl chloride by inhalation for 48 or 72 continuous hours. In order to conduct the study, exposures were conducted during 2 separate exposure periods. Part I included exposure concentrations of 0, 200, or 500 ppm. Part II included exposure concentrations of 0, 1000, or 2000 ppm.

Both parts consisted of exposing 40 rats/sex/exposure level for 48 hours at which time the exposures were stopped and 20 rats/sex/exposure level were removed from the chambers. Ten were sacrificed soon after exposure for blood, urine and pathological evaluation, and ten were held for up to 12 days of recovery. The exposures were restarted and the remaining rats/sex/exposure level were again exposed for an additional 24 hours (total of approximately 72 hours exposure). After the 72 hours of exposure, 10 rats/sex/exposure level were sacrificed for blood, urine and pathological evaluation. The remaining 10 were held for up to 12 days of recovery. At the end of each recovery period, each surviving rat was sacrificed for blood, urine and pathological evaluation.

During the first 24 hours of exposure, the methyl chloride gas in the 200 ppm chambers was pumped from a plenum flask supplied with methyl chloride from the supply tank. However, difficulty with the pumps (they had a tendency to "seize" and malfunction) led to the decision to supply the chambers as described under the description of sample generation. Because of uncertainty in the first 24 hours of exposure to 200 ppm methyl chloride as a result of pump failure, that exposure was discontinued, the rats discarded, and the exposure restarted. Therefore, these rats were exposed for the same length of time (48 or 72 hours) as the other exposure groups but the exposures were one day later than the other groups. As a result, they had one less day of recovery (11 days) than their corresponding cohorts exposed to 0 or 500 ppm (12 days).

Observations and Criteria of Response. During and after the exposure periods, the rats were examined periodically for overt signs of toxicity. All rats were weighed prior to the start of exposure, just after being removed from exposure, and three times per week during the recovery period. Rats that died or were found moribund during or after exposure were submitted for a gross necropsy examination.

Hematology, urinalysis, and clinical chemistry parameters were obtained from all rats killed immediately after the exposure period and all rats killed at the end of the recovery period. The "sacrifice" groups had blood samples taken for hematology determinations, and urine samples taken for urinalysis directly after removal from the inhalation chambers. Blood samples for clinical chemistry parameters were taken at necropsy following decapitation (animals were not fasted). The "recovery" groups were fasted overnight prior to the day of necropsy.

The blood samples for hematology determinations and the urine for urinalysis were collected on the morning of necropsy. The blood samples for clinical chemistry determinations were obtained at necropsy following decapitation.

Blood samples for hematologic determinations were collected from the tail vein. The packed cell volume (PCV), total erythrocyte counts (RBC), total and differential leukocyte counts (WBC), and hemoglobin (Hgb) concentration were determined using automated[1] or manual procedures.

Urine samples were collected at the time of necropsy and the urine specific gravity[2], pH, and the presence or absence of glucose, protein, ketones, bilirubin, occult blood, and urobilinogen were determined[3].

Blood for serum was collected from the severed cervical blood vessels of rats following decapitation at necropsy and the blood urea nitrogen (BUN), alkaline phosphatase (AP), and serum glutamic pyruvic transaminase (SGPT), serum glutamic oxalacetic transaminase (SGOT), and total bilirubin concentration were determined using automated procedures[4].

Gross necropsy examinations were conducted on all animals. Rats not dying spontaneously were anesthetized with methoxyflurane prior to clamping the trachea and decapitation. Fasting body weights and organ weights for liver, kidneys, brain, heart, and testes (male) were obtained from all animals of the "recovery groups" at necropsy, and organ-body weight ratios were calculated. Organ weights were not obtained on animals sacrificed at the end of the 48 or 72 hour exposure periods.

The eyes from all rats were examined by gently pressing a glass slide against the cornea and examining the eye under bright fluorescent illumination. A complete gross pathologic examination was performed by a veterinary pathologist. In addition, the lungs and trachea from all

[1]PCV - Microhematocrit Centrifuge - Clay Adams Co., New York; RBC, WBC - Coulter Counter ZBI - Coulter Electronics, Hialeah, Florida; and Hgb - Hemoglobinometer.
[2]U.S. Meter, American Optical Company, Buffalo, New York.
[3]Ames Multilabistix, Ames Company, Elkhart, Indiana.
[4]Centrifichem System 400, Methods File, Union Carbide Corporation, Rye, New York.

animals were removed as a unit and expanded with phosphate buffered 10% formalin by hand using a syringe. Representative sections of all major organs and tissues were collected and preserved in phosphate buffered 10% formalin. The tissues collected included: adipose tissue, adrenal glands, accessory sex glands, aorta, brain (cerebrum, cerebellum, and brain stem), epididymides, esophagus, eyes, heart, kidneys, large intestine, liver, lungs (bronchi), lymph nodes (thoracic, mesenteric), mammary tissue, nasal turbinates, ovaries, pancreas, parathyroid, peripheral nerve (sciatic), pituitary, salivary glands, skeletal muscle, skin, small intestine, spinal cord, spleen, sternum and sternal bone marrow, stomach, testes, thymus, thyroid, trachea, urinary bladder, uterus, and any gross lesions or mass.

Representative specimens of organs and tissues were taken from all animals and fixed in phosphate buffered 10% formalin. Histopathologic examination of significant gross lesions, liver, kidney, lung, and brain were conducted on all rats, and testes and epididymides on male rats. The above tissues were processed by conventional methods, embedded in paraffin blocks, sectioned (6-8μm), stained with hematoxylin and eosin and evaluated by light microscopy. In some cases, Oil-Red-O staining of liver and kidneys were done to determine the degree of fat accumulation.

<u>Statistical Evaluations</u>. Hematology, urinary and clinical chemistry parameters, body weights, and organ to body weight ratio data were statistically analyzed by a one-way analysis of variance followed by Dunnett's Test (Steel and Torrie, 1960). The level of significance chosen was $p<0.05$.

RESULTS

Chamber Concentrations. The actual time-weighted averages (± standard deviations) of chamber concentrations calculated from the analytical data were: 196(±6) and 198(±8) ppm for the 48 and 72 hour exposures at the 200 ppm target concentration; 501(±10) and 504(±11) ppm for the 48 and 72 hour exposures at the 500 ppm target concentration; 972(±21) and 976(±20) ppm for the 48 and 72 hour exposures at the 1000 ppm target concentration and 1968(±18) and 1950(±96) ppm for the 48 and 72 hour exposures at the 2000 ppm concentration. Therefore, all exposure levels were within the expected ranges.

Animal Observation. Male and female rats exposed to 0, 200, or 500 ppm methyl chloride showed no overt signs of toxicity during the exposure, nor were any untoward signs noted when they were examined directly after exposure or during the recovery period.

Both male and female rats exposed to 1000 or 2000 ppm had signs of toxicity. After 24 hours of continuous exposure the animals exhibited a slightly less alert demeanor and apparently drank less water than the control animals. After 30 hours of exposure, they appeared to be less alert than controls, and this was again noted after 40 hours of exposure. At 48 hours of exposure, when half the animals in each group were withdrawn, the groups exposed to 1000 ppm appeared lethargic. However, the rats exposed to 2000 ppm methyl chloride were either lethargic, moribund, or dead after 48 hours. At 52 hours of exposure the group exposed to 1000 ppm remained lethargic, while those in the 2000 ppm exposure groups were all dead or moribund. At the end of 72 hours exposure, those rats exposed to 1000 ppm appeared worse than at 48 or 52 hours and although none were dead, all were either sick or moribund. All the rats exposed to 2000 ppm were dead at the end of 72 hours of exposure.

Mortality. Table 1 summarizes the mortality data for all of the exposure groups. The data are listed in two parts. First are those rats

that were found dead or were killed moribund at the end of each respective exposure or those that died the same day the exposures were stopped (post-exposure day 0). Second are those that died or were killed moribund starting on the day after the exposures were stopped (post-exposure day 1) and continuing through the end of the study (post-exposure day 11 or 12).

Continuous exposure of rats to 2000 ppm of methyl chloride for 72 hours produced 100% mortality during exposure while 48 hours exposure to this concentration produced approximately 50-70% (14 of 20 males and 10 of 20 females) mortality, with the remainder in the recovery groups dying within a day post-exposure.

Exposure to 1000 ppm for 72 continuous hours produced no fatalities during exposure, but many deaths occurred during the post-exposure "recovery" period. The deaths occurred on post-exposure days 1 through 7 leaving only 4 males and 2 females surviving until the end of the recovery portion of the study. Exposure to 1000 ppm for 48 hours produced no fatalities during exposure and only one (female) post-exposure death occurred on post-exposure day six.

No deaths occurred in the groups exposed to 0, 200, or 500 ppm for 48 or 72 hours and none occurred during the 11 or 12 day post-exposure recovery period.

Body Weights. Mean body weight data derived from male and female rats are given in Tables 2-5. Table 2 shows the data for rats exposed to 200 or 500 ppm methyl chloride for 48 hours along with their corresponding controls. Table 3 gives similar data for those exposed to 0, 200, or 500 ppm for 72 hours. Tables 4 and 5 summarize the data for rats exposed to 0, 1000, or 2000 ppm for 48 and 72 hours, respectively. Most of the animals exposed to 2000 ppm for 48 hours were either dead or moribund and as a result, body weight data were collected from only 3 males and 3 females after the exposure was stopped. None of the rats

exposed to 2000 ppm for 48 or 72 hours survived beyond post-exposure day 1 and as a result, no body weight data were collected.

No body weight decreases occurred in either males or females exposed to 200 ppm for 48 hours (Table 2). Both males and females exposed to 500 ppm for 48 hours had significantly decreased body weights (5-6% decrease) after exposure (post-exposure day 0) but the values returned to normal by post-exposure day 2.

In the females exposed to 200 ppm for 72 hours (Table 3), two female rats apparently had difficulty in drinking from the water bottle, and their low body weights depressed the mean for the group to a point that showed a statistically significant decrease from the control mean. The mean of the remaining 8 rats did not show a statistically significant difference from the control mean. This inability to obtain water was noted by the animal caretaker, and once corrected these 2 rats regained weight, such that within 6 days the mean body weight value of the group showed no statistically significant deviation from the control mean. Furthermore, there was a lack of a similar response in females at 500 ppm. Therefore, the low mean body weights for this group were not clearly exposure-related.

The males exposed to 200 ppm for 72 hours (Table 3) showed a statistically significantly decreased mean body weight value (4%) compared to the control mean after the exposure (post-exposure day 0). Therefore, males exposed to 200 ppm for 72 hours had slightly decreased mean body weight gains during the exposure with values returning to normal within 3 days post-exposure.

Both males and females exposed to 500 ppm for 72 hours had statistically significant decreased mean body weight values at the end of their exposure periods. The group means represented a 6 to 8% decrease compared to their respective pre-exposure weights. Males exposed to 500 ppm for 72 hours had statistically significantly decreased mean body weights until post-exposure day 11. However, the rats had regained all

lost weight by post-exposure day 4 and continued to gain weight throughout the rest of the recovery period. Females exposed to 500 ppm regained their initial lost weight so that the groups exposed for 48 or 72 hours had mean weights comparable to their respective controls by post-exposure day 2 and 1, respectively.

Males exposed to 1000 ppm for 48 hours showed a 14% decrease in mean body weights compared to their pre-exposure values and approximately 20% decreased compared to the control data (Table 4). By post-exposure day 4, they had regained their initial lost weight, but the mean values remained statistically significantly less than the controls throughout the recovery period.

Females exposed to 1000 ppm for 48 hours had a 10% decrease in mean body weights compared to their pre-exposure values and approximately 9% decreased when compared to the control values. Therefore, the decrease was less severe than the males from the same exposure group. Furthermore, the females regained their lost weight by post-exposure day 4 and values were similar to control data throughout the remainder of the recovery period.

The males and females exposed to 1000 ppm for 72 hours, where most of the male and female rats died post-exposure, showed severe weight losses which were 23 to 25% decreased from pre-exposure values and 28 to 30% decreased compared to respective control values (Table 5). However, those rats which did survive gained weight, with the values for males statistically significantly decreased even at the end of the recovery period while the values for females were statistically significantly decreased throughout most of the recovery period.

Three males and 3 females exposed to 2000 ppm survived 48 hours of exposure. Their mean body weight values were statistically significantly decreased compared to their pre-exposure values (males were decreased by 20% and females by 17%) and to their respective controls (males decreased by 25% and females by 18%).

Fasted Body Weights and Organ Weights. The data on the mean fasted body weights, mean organ weights, and relative mean organ weights obtained on all rats at the end of the recovery period are summarized in Table 6.

Fasted body weights were statistically significantly decreased in males exposed to 1000 ppm for 48 or 72 hours and held for up to 12 days of recovery. Males exposed to 500 ppm for 72 hours also had statistically significantly decreased fasted body weights at the end of the recovery period. Furthermore, the males exposed to 500 ppm for 48 hours had fasted body weights less than their respective controls, but the group mean was not statistically significant. These values were all considered to be exposure-related decreases in the mean fasted body weights for males exposed to 500 or 1000 ppm of methyl chloride for either 48 or 72 hours.

None of the groups of exposed females had statistically significantly decreased mean fasted body weights when compared to their respective control groups.

Several statistically significantly altered values are shown in Table 6 for absolute organ weights, relative organ weights, or both. In most cases, the alteration appeared to be secondary to decreased body weights. For example, males exposed to 1000 ppm for 48 or 72 hours had decreased absolute and increased relative mean brain weights, decreased absolute mean kidney weights, decreased absolute mean liver weights, decreased absolute heart weights, and decreased absolute and relative mean testicular weights. In addition, males exposed to 500 ppm for 72 hours had decreased absolute mean kidney and liver weights. Therefore, most values correlated well with the decreased body weight gains in the males.

Mean testicular weights (absolute and relative) were decreased by about 50% in males exposed to 1000 ppm for 72 hours. This effect appeared to

be secondary to epididymal lesions (see results of Gross and Histopathologic Observations) and represented an exposure-related alteration.

Although clearly evident in males exposed to 1000 ppm for 72 hours, the decrease in mean testicular weights was not apparent in males exposed to 1000 ppm for 48 hours nor was this effect evident in males exposed to 200 or 500 ppm for either 48 or 72 hours.

Mean liver weights (absolute, relative, or both) were statistically significantly decreased in males exposed to 200, 500, or 1000 ppm for either 48 or 72 hours and held for up to 12 days of recovery. Furthermore, body weights (see results section on Body Weights) and histopathologic parameters (see results section on Histopathologic Observations) were altered in rats examined immediately after exposure to 200, 500, or 1000 ppm. Therefore, the mean liver weight decreases appear to represent a slight exposure-related effect in male rats exposed to 200, 500, or 1000 ppm followed by up to 12 days of recovery. Absolute mean liver weights were not statistically significantly decreased in females except for the relative liver weight of females exposed to 1000 ppm for 72 hours and killed after the recovery period.

Hematology. The hematology data obtained from rats that were sacrificed at the end of their respective exposure periods and from rats that were killed at the end of the recovery period are summarized in Tables 7 and 8.

Most of the statistically significant data points appeared to be due to biological variability. The values were clearly within the range of normal for rats of this strain and sex. Although significantly different from their corresponding controls they were not different from the other control groups of this study. Therefore, most values were considered to be toxicologically insignificant.

However, a few values were considered biologically significant. These included the increased hematocrit, red blood cell counts, and hemoglobin values in males and females in the sacrifice groups at 48 hours for the 1000 and 2000 ppm exposures and the sacrifice groups at 72 hours for the 1000 ppm exposure. These values were probably the result of dehydration and resultant hemoconcentration in these exposure groups where rats were either lethargic or moribund at the end of the exposure period when the blood samples were collected. Also, there appeared to be a slight neutrophilia in male and female rats exposed to 1000 ppm for 72 hours (Table 8), but the biological significance of this response is uncertain.

Clinical Chemistry Determinations. Analyses of serum samples collected by decapitation from rats sacrificed immediately after exposure and those killed after the recovery periods are shown in Table 9. Striking differences are present in the values for alkaline phosphatase between the sacrificed groups and the recovery groups. These differences are the result of overnight fasting of the recovery rats prior to collecting their sera and the result of not fasting the sacrifice groups that were sacrificed immediately after the exposures. This is an expected variation between fasted and nonfasted rats and is not related to the methyl chloride exposure. In addition, there were a few statistically significantly altered data points that were within the range of normal for rats of this age and strain. Some points were increased when compared to their respective controls, but were decreased when compared to other control data. These alterations represented normal biological variability.

A few values appeared to be treatment-related alterations which were the result of methyl chloride exposure. Treatment-related changes were most evident in males and females exposed to 2000 ppm and sacrificed at 48 hours. All parameters were altered. The BUN values in males and females were increased indicating renal failure. The SGPT, SGOT, and total bilirubin values were increased in males and females indicating liver toxicity. The alkaline phosphatase values were decreased, probably secondary to the rats not eating.

Rats exposed to 1000 ppm for 72 hours also had altered clinical chemistry values but of a lesser degree of severity than those exposed to 2000 ppm. BUN values were slightly increased in males (not statistically significant) and in females indicating renal toxicity. Alkaline phosphatase values were decreased, probably as a result of not eating. Alkaline phosphatase was also decreased in those exposed to 1000 ppm for 48 hours and sacrificed. All of the values returned to normal by the end of the recovery period.

Serum alkaline phosphatase activity was significantly decreased in males sacrificed after 48 or 72 hours exposure to 500 ppm when compared to their respective controls. Similarly, the females exposed to 500 ppm for 48 or 72 hours and those exposed to 200 ppm for 48 or 72 hours had values lower than their respective controls (only the value in the 200 ppm exposure for 72 hours was statistically significantly decreased). These were considered to be exposure-related decreases in serum alkaline phosphatase values in males and females exposed to 500 ppm for either 48 or 72 hours and in females exposed to 200 ppm for 48 or 72 hours. The cause of the decrease is unknown, however it is likely the result of decreased food intake.

<u>Urinalysis</u>. Urinalysis data from the rats from Part I and Part II of the study are summarized in Tables 10 and 11, respectively. Both males and females exposed to 1000 or 2000 ppm for either 48 or 72 hours had alterations in urine values. The altered urine values included one or more of the following: decreased specific gravity (1.015) in males exposed to 2000 ppm; a trend for decreased pH in males and females exposed to 1000 or 2000 ppm; increased glucose in females exposed to 1000 or 2000 ppm; a trend for increased protein in males and females exposed to 1000 or 2000 ppm; a trend for increased blood in males exposed to 1000 or 2000 ppm; and increased ketones in males and females exposed to 1000 or 2000 ppm. The values were consistent with an exposure-related effect and were consistent with renal failure and kidney lesions observed in these rats (see results section on Gross and Histopathologic Observations).

None of the other values in the exposed groups (either 200 or 500 ppm exposure groups) were considered to be treatment-related. The other values were within the normal range and the variations observed were considered to be within the expected range of variability for rats of this age and strain.

Gross Necropsy and Histopathologic Observations. Several gross necropsy and histopathologic observations were made on control and methyl chloride exposed rats in Part I and Part II of the study. Many were typical of spontaneous, naturally-occurring lesions commonly observed in rats of this age and strain. The summaries of the gross necropsy observations, actual number of tissues examined and the histopathologic findings are summarized in Tables 12-44. The findings that were considered related to the exposure to methyl chloride at each exposure level are discussed below.

Exposure to 200 ppm for 48 (Tables 12-17)

There were no exposure-related gross or histopathologic alterations in any of the male or female rats exposed to 200 ppm for 48 hours. There were no effects after the exposure or following the 11 day recovery period.

Exposure to 200 ppm for 72 hours (Tables 18-23)

Slight effects were present in the livers of males and females exposed to 200 ppm for 72 hours and sacrificed after the exposure (Table 20). The effect was an altered tinctorial appearance to hepatocytes in 200 ppm exposed males (4 of 5) compared to the control males (0 of 5). Females had an increased amount of fat based on Oil-Red-O staining with slight lipid present in 4 of 5 females after 72 hours of exposure compared to 0 of 5 in the controls (Table 20). These effects were reversible and were not present in the rats killed at the end of their respective recovery periods (Table 23).

Exposure to 500 ppm for 48 hours (Tables 12-17)

Exposure to 500 ppm for 48 hours followed by immediate sacrifice produced histopathological effects in the epididymides of males (Table 14). The alterations included changes in the appearance of the luminal contents with increased proteinaceous and cellular aggregates. One rat also had focal suppurative inflammation and 2 of 5 had interstitial edema. In addition, 5 of 5 males had altered tinctorial properties to the liver hepatocytes.

Following the 12-day recovery period, the epididymal effects were more pronounced and in addition, the testicles were also affected. In males, the effects were recognized at the time of gross necropsy (Table 15). Histologically the effects in the epididymides consisted of sperm granuloma formation, decreased sperm in the lumina of the tubules, interstitial edema, coagulated proteinaceous debris or inflammation (Table 17). The changes also appeared to be obstructive causing at least partial occlusion of affected lumina. The total number of rats with one or more of these changes was 3 of the 5 examined. Testicles were also affected in 3 of 5 rats which included unilateral atrophy which appeared to be secondary to the obstructive changes occurring in the epididymides.

The histologically observed liver alterations observed immediately after the exposure (Table 14) were no longer present following 12 days of recovery (Table 17).

No gross necropsy or histopathologic effects were recognized in the females exposed to 500 ppm for 48 hours, nor were effects observed in these groups following the 12-day recovery period.

Exposure to 500 ppm for 72 hours (Tables 18-23)

Epididymal effects were present in the males exposed to 500 ppm for 72 hours and in those exposed for 72 hours followed by a 12-day recovery period. The effects in the group sacrificed immediately after 72 hours

of exposure were similar to those present after 48 hours exposure, but the severity was more pronounced (Table 20). Following the 12-day recovery period, grossly observed alterations were seen in the testicles and epididymides of exposed males (Table 21). Histologically epididymal effects consisted primarily of inflammation with sperm granuloma formation and were unilateral in some rats and bilateral in others (Table 23). Two rats had unilateral testicular atrophy. Two of the five rats examined had normal testicles and epididymides.

In addition, a slight liver effect was present in male, but not female, rats that were sacrificed after 72 hours of exposure to 500 ppm (Table 20). The effect consisted of altered tinctorial properties to hepatocytes in males (3 of 5). This alteration was not evident in either male or female rats killed after the 12-day recovery period (Table 23).

Exposure to 1000 ppm for 48 hours (Tables 24-30)

Exposure to 1000 ppm for 48 hours produced definite signs of toxicity. Grossly 3 of 10 females had decreased adipose tissue (Table 24). Histologically (Table 25), the kidneys were affected in males and females with the renal lesions consisting of renal tubular cell necrosis and increased renal tubular cytoplasmic homogeneity. In addition, 3 of 5 females had increased lipid accumulations in renal tubular cells. Lipid accumulations were also apparent in liver hepatocytes of males based on Oil-Red-O staining. Also, the epididymides of all 5 males had treatment-related alterations that were similar to, but more severe than, the epididymal effects in the 500 ppm exposed males.

During the recovery period, 1 female rat exposed to 1000 ppm for 48 hours died with nonspecific gross necropsy observations (Table 28). The remaining recovery rats from the 48 hour 1000 ppm exposure groups survived until the end of the 12-day recovery period. Grossly observed treatment-related effects were present only in males and included decreased adipose tissue, dark livers, dark kidneys, testicular alterations, and epididymal changes (Table 27). Histologically both males and

females had evidence of toxicity (Table 30). Both sexes appeared to have slightly more lipid in cells of the liver based on Oil-Red-O staining. Kidneys of 3 of 5 males and 4 of 5 females had regenerative tubular epithelium. Also 3 of 5 males and 1 of 5 females had increased lipid in renal tubular epithelial cells. Finally, testicular atrophy and epididymal alterations were present. These alterations were similar to those observed in male rats exposed to 500 ppm followed by a 12-day recovery period.

Exposure to 1000 ppm for 72 hours (Tables 31-37)

Exposure to 1000 ppm for 72 hours resulted in signs of toxicity in all males and females that were sacrificed immediately after the exposure. Grossly (Table 31), there were many nonspecific signs including loss of adipose tissue, soiling of hair around body orifices, and decreased food in the intestinal tract. In addition, all 10 males and females had dark livers and approximately one-half of each sex also had dark kidneys. Histologically (Table 33), renal lesions were present in all males and females. The changes included varying degrees of renal tubular necrosis, increased renal tubular cytoplasmic homogeneity and increased lipid (based on Oil-Red-O stain) in the tubular epithelium. Evidence of liver toxicity was also present, but the effect was confined to an alteration in the tinctorial properties of hepatocytes. This change in the staining characteristics of the liver cells was most likely the result of hepatocellular glycogen depletion which most likely occurred secondary to the apparent anorexia observed in these animals. The epididymides of all 5 exposed males had inflammatory and degenerative alterations that were similar to those observed in the males exposed to 500 ppm for 48 or 72 hours or 1000 ppm for 48 hours.

All males in the 72 hour 1000 ppm exposure group survived the exposure period, but 6 males and 8 females died or were killed moribund during the first week of recovery. These rats were examined grossly and had many nonspecific observations as well as grossly observed evidence of kidney or liver toxicity (Table 34).

The rats that survived the 72 hours of exposure followed by 12 days of recovery were evaluated grossly and histopathologically and they had definite signs of toxicity. Gross alterations were present in males only which consisted of decreased adipose tissue, decreased size of testicles and 1 of 4 rats had pale foci in the epididymides and 1 of 4 had dark livers (Table 35). Histopathologic observations (Table 37) were present in the kidneys of males and females. The changes included evidence of renal tubular regeneration, renal tubular degeneration, and lipid accumulations in renal tubular epithelium (based on Oil-Red-O staining). Also all 4 males had testicular atrophy and epididymal lesions consisting of edema, inflammation, sperm granuloma formation, decreased sperm in tubules or proteinaceous debris in tubular lumina.

Exposure to 2000 ppm for 48 hours (Tables 38-41)

The grossly observed alterations in the male and female rats from the 2000 ppm 48 hour exposure groups are shown in Tables 38 and 39. Table 38 shows the findings in the rats that were found dead or moribund at the end of the exposure period and Table 39 for the rats that died after that. All rats died or were killed within a few days of each other. As a result, the data in Tables 38 and 39 are combined to include the observations from the rats predesignated for the sacrifice after the 48 hour exposure and those predesignated for sacrifice after recovery. Grossly, there were many nonspecific alterations including decreased adipose tissue, perineal soiling, decreased food in gastrointestinal tract, dark liver and dark kidneys.

Of those rats that were alive after the 48 hour exposure period, 4 males and 8 females were still alive and were sacrificed. Of those, 4 males and 5 females were evaluated histopathologically (Table 41). They showed evidence of liver and kidney toxicity. Kidney alterations included necrosis, increased cytoplasmic homogeneity of renal tubules and increased lipid in renal tubular epithelium (based on Oil-Red-O staining). Liver lesions were less extensive but included degenerative (increased lipid, variable size of nucleus, and altered tinctorial

properties), necrotic and inflammatory changes. Epididymal lesions were prominent in all 4 males which were similar to the epididymal alterations observed in males exposed to 1000 ppm for either 48 or 72 hours.

Exposure to 2000 ppm for 72 hours (Tables 42-44)

All rats exposed to 2000 ppm for 72 hours were dead or were killed moribund by the end of the 72 hour exposure period. The gross findings in these rats are summarized in Table 42 and the histopathologic findings in Table 44. The lesions were similar to those observed in the rats exposed to 2000 ppm for 48 hours. Briefly, the major cause of death appeared to be kidney toxicity and renal failure. Liver effects were also present. Some of these animals also had congestion and edema of the lungs which was probably an agonal event. In addition, all males had evidence of inflammatory or degenerative epididymal lesions.

Summary of Pathologic Findings

In summary, the epididymides were affected in males exposed to 500, 1000 or 2000 ppm for 48 or 72 hours and in those that survived the 12-day recovery period. The effects included degeneration, inflammation, sperm granuloma formation, scarring and obstructive changes in the epididymides. Testicular atrophy was also present, but it appeared to have occurred secondarily as a result of the obstructive epididymal lesions. In rats exposed to 1000 or 2000 ppm for either 48 or 72 hours, the primary cause of death appeared to be kidney toxicity which resulted in renal failure. Also, liver toxicity was evident in both males and females. In rats surviving the 48 or 72 hours of exposure to 1000 ppm, definite signs of renal tubular regeneration (recovery) were evident after 12 days of recovery. Slight liver effects were evident in males and females exposed to 200 ppm or 500 ppm for 72 hours and in males exposed to 500 ppm for 48 hours, but these effects were not apparent after the recovery period. Gross and histopathologic alterations were not present in male or female rats exposed to 200 ppm for 48 hours.

DISCUSSION

The primary cause of death in the rats exposed to 1000 or 2000 ppm for 48 or 72 hours was the result of kidney toxicity and subsequent renal failure. In addition, liver toxicity was also evident. Those rats that survived the exposure had evidence of renal tubular regeneration at the end of the 12-day recovery period thus indicating recovery from the toxic effects. These findings are in general agreement with other reports in humans and animals that have indicated liver and/or kidney toxicity. For example, incidental reports of individual human exposures to methyl chloride have indicated that the liver and kidney can be affected (Wood, 1951; Mackle, 1961). Similarly, Dunn and Smith (1947), Smith (1947), Smith and von Oettingen (1947 a,b), and Mitchell, et al (1979) demonstrated liver and/or kidney effects in animals and that the kidney is the primary target organ for methyl chloride in the rat.

Liver effects, characterized by decreased mean absolute or relative liver weights and by slight histopathologic alterations, were also observed in the rats exposed to 200 or 500 ppm. The effects were slight, were probably reversible, and were not life-threatening. However, these findings do indicate minimal effects in the liver of male and female rats following continuous exposure to 200 or 500 ppm of methyl chloride for 48 or 72 hours and at levels below those that produced definite kidney effects.

Inflammatory and degenerative changes were observed in the epididymides of some or all male rats exposed to 500, 1000 or 2000 ppm of methyl chloride for 48 or 72 hours. The changes present in the rats sacrificed immediately after the exposure period varied in severity from animal to animal, but they tended to be more severe in the rats exposed to 1000 and 2000 ppm. The rats in the recovery groups were exposed for 48 or 72 hours and were then allowed to recover for 12 days and inflammatory changes were observed in the epididymides of some or all of these male rats that had been exposed to 500 or 1000 ppm. Most of the alterations

observed were similar to those seen immediately following the exposure period. In addition, unilateral or bilateral sperm granulomas were observed in the epididymides in the recovery rats from the 500 and 1000 ppm exposure groups. Some rats with epididymal changes also had degenerative testicular changes. None of the rats in the 2000 ppm exposure groups had sperm granulomas; however, all had died during or immediately following the exposure. They did have early inflammatory changes in their epididymides which would suggest that if they had survived, they too would have developed sperm granulomas during the recovery period. Testicular atrophy was also present in some rats, but it appeard to have occurred secondarily as a result of the obstructive epididymal lesions.

Epididymal or testicular alterations have not been previously reported and occurred only at exposure concentrations of 500 ppm or greater. McKenna, et al. (1981) did not find epididymal or testicular effects in dogs, rats, or mice exposed to concentrations of methyl chloride up to 400 ppm, 6 hours per day, 5 days per week for 3 months; nor were epididymal or testicular effects found in dogs or cats exposed to 200 or 500 ppm of methyl chloride for 48 or 72 hours (McKenna, et al., 1981b). Furthermore, no epididymal or testicular effects were reported in rats or mice by Mitchell, et al. (1979) following exposure to 0, 375, 750 or 1500 ppm of methyl chloride for 6 hours per day, 5 days per week for 13 weeks. Therefore, the epididymal effects may represent a species specific response in rats and occurred only under conditions of continuous exposure for 48 hours or more and at concentrations of methyl chloride of 500 ppm or greater.

In summary, continuous inhalation exposure of male and female rats to 0, 200, 500, 1000 or 2000 ppm methyl chloride for 48 or 72 hours resulted in effects at all exposure concentrations (except females exposed to 200 ppm for 48 hours). The effects consisted of decreased body weight gains, decreased mean absolute or relative liver weights and slight histopathologic changes in the liver. These effects were minimal and were reversible. Similar minimal effects were present in rats from the

500 ppm exposure groups, but they were somewhat more pronounced. In addition, inflammatory and degenerative epididymal lesions were also present which progressed to sperm granuloma formation after 12 days of recovery. In rats exposed to 1000 or 2000 ppm for either 48 or 72 hours, the primary cause of death was due to kidney toxicity characterized by tubular necrosis and degeneration and resulting renal failure. Liver toxicity was also evident. In addition, epididymal inflammatory and degenerative lesions were present after the exposure which progressed to sperm granuloma formation after 12 days of recovery.

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QUALITY ASSURANCE STATEMENT

This report represents data generated prior to the enactment of the FDA Good Laboratory Practice Regulations. The study was conducted according to standards used in this laboratory at that time. The report accurately reflects all of the data generated. All data and reports are located at the submitting laboratory.

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TABLE 1

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

CUMULATIVE NUMBER OF MALE AND FEMALE RATS DYING OR KILLED MORIBUND DURING OR WITHIN 24 HOURS OF EXPOSURE AND THE NUMBER DYING OR KILLED MORIBUND DURING THE RECOVERY PERIOD

Part of Study		I												II											
Exposure level (ppm)		200								500				0				1000				2000			
Hours of exposure		48	72	48	72	48	72	48	72	48	72	48	72	48	72	48	72	48	72	48	72	48	72	48	72
Rec (S) or Rec (R)[d]		S	S	R	R	S	S	R	R	S	S	R	R	S	S	R	R	S	S	R	R	S	S	R	R
Number of females tested		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Number of males tested		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	Sex																								
Number dead during exposure or within 24 hours of exposure	M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	10	8	10
	F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	10	8	10
Number dying during recovery period																									
Post-Exposure[a] Day 1	M	-[b]	-	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	2	-	-	10	10
	F	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	4	-	-	10	10
" 2	M	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	3	-	-	10	10
	F	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	7	-	-	10	10
" 3	M	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	4	-	-	10	10
	F	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	7	-	-	10	10
" 4	M	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	4	-	-	10	10
	F	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	7	-	-	10	10
" 5	M	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	5	-	-	10	10
	F	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	7	-	-	10	10
" 6	M	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	5	-	-	10	10
	F	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	1	7	-	-	10	10
" 7	M	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	6	-	-	10	10
	F	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	1	8	-	-	10	10
" 8	M	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	6	-	-	10	10
	F	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	1	8	-	-	10	10
" 9	M	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	6	-	-	10	10
	F	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	1	8	-	-	10	10
" 10	M	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	6	-	-	10	10
	F	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	1	8	-	-	10	10
" 11	M	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	6	-	-	10	10
	F	-	-	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	1	8	-	-	10	10
" 12	M	-	-	0	0	-	-	-[c]	-	-	-	0	0	-	-	0	0	-	-	0	6	-	-	10	10
	F	-	-	0	0	-	-	-	-	-	-	0	0	-	-	0	0	-	-	1	8	-	-	10	10

[a] Post-exposure day 1 is actually the day after the exposures were stopped.
[b] Means not applicable.
[c] The males and females exposed to 200 ppm had 11 post-exposure days rather than 12.
[d] Rec (S) = sacrificed; Rec (R) = recovery.

TABLE 2

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Mean Body Weights of Male and Female Rats Exposed for 48 Hours

Sex	Exposure Concentration (ppm)	N		Just Prior to Exposure	Post-Exposure Day 0[a]	2 (1)[b]	5 (4)	7 (6)	9 (8)	12 (11)
Male	0		Mean	269	279	291	314	324	335	346
			±S.D.	11	12	13	15	19	20	22
	200	10	Mean	277	282	296	316	332	340	347
			±S.D.	14	13	12	14	14	15	18
	500	10	Mean	268	254*	279	304	315	326	335
			±S.D.	11	13	14	13	18	19	21
Female	0	10	Mean	171	176	181	192	189	200	206
			±S.D.	10	11	12	11	19	15	16
	200	10	Mean	167	171	177	185	192	198	203
			±S.D.	5	7	7	8	7	7	9
	500	10	Mean	173	163*	175	189	193	198	201
			±S.D.	9	11	10	9	11	9	10

*Statistically significant deviation from control using Dunnett's test, P<0.05.

[a]Animals were weighed right after the 48-hour exposure on 0 post-exposure day.

[b]The animals of the 200 ppm exposure group started their exposures one day after the 0 and 500 ppm groups, so their body weights were taken one post-exposure day less than the 0 and 500 ppm groups. The number in parentheses is the actual post-exposure day for the 200 ppm groups.

TABLE 3

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Mean Body Weights of Male and Female Rats Exposed for 72 Hours

Sex	Exposure Concentration (ppm)	N		Just Prior to Exposure	Post-Exposure Day 0[a]	1	4 (3)[b]	6 (5)[b]	8 (7)[b]	11 (10)[b]
Male	0	10	Mean	279	295	296	319	327	338	351
			±S.D.	11	11	13	13	10	12	14
	200	10	Mean	278	282*	---	312	329	341	351
			±S.D.	9	9	---	11	12	15	18
	500	10	Mean	273	251*	267*	300*	307*	323*	336
			±S.D.	9	12	9	10	12	12	14
Female	0	10	Mean	176	180	180	193	198	205	209
			±S.D.	7	8	9	8	9	10	10
	200	10	Mean	170	159*	---	180*	185*	196	197
			±S.D.	8	20	---	10	15	10	16
	500	10	Mean	174	163*	172	188	192	199	203
			±S.D.	9	12	11	10	12	11	14

*Statistically significant deviation from control using Dunnett's test, $P<0.05$.

[a]Animals were weighed right after the 72-hour exposure on 0 post-exposure day.

[b]The animals of the 200 ppm exposure group started their exposures one day after the 0 and 500 ppm groups, so their body weights were taken one post-exposure day less than the 0 and 500 ppm groups. The number in parentheses is the actual post-exposure day for the 200 ppm groups.

TABLE 4

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Mean Body Weights of Male and Female Rats Exposed for 48 Hours

Sex	Exposure Concentration (ppm)		Just Prior to Exposure	Post-Exposure Day 0[a]	1	4	6	8	11
Male	0	Mean	198	206	212	236	252	271	294
		±S.D.	7	7	9	11	11	12	13
	1000	Mean	192	165*	170*	201*	220*	240*	260*
		±S.D.	7	9	9	8	9	9	13
	2000	Mean	191	154*	Dead				
		±S.D.	10	7 (n=3)					
Female	0	Mean	164	164	168	176	183	191	197
		±S.D.	10	10	9	9	10	12	9
	1000	Mean	165	149*	154*	167	177	194	198
		±S.D.	7	5	11	28	35	10	11
	2000	Mean	161	134*	Dead				
		±S.D.	14	6 (n=3)					

*Statistically significant deviation from control using Dunnett's test, $P<0.05$.

[a]Animals were weighed right after the 72-hour exposure on 0 post-exposure day.

TABLE 5

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Mean Body Weights of Male and Female Rats Exposed for 72 Hours

Sex	Exposure Concentration (ppm)		Just Prior to Exposure	Post-Exposure Day 0[a]	3	5	7	10
Male	0	Mean	193	214	235	251	270	292
		±S.D.	7	9	10	12	10	12
	1000	Mean	198	149*	128*	145*	190*	218*
		±S.D.	9	9	27	43	20	27
					(n=6)	(n=6)	(n=4)	(n=4)
	2000	Mean	192	Dead				
		±S.D.	11					
Female	0	Mean	166	175	180	189	195	204
		±S.D.	9	10	12	10	11	11
	1000	Mean	162	125*	127*	139*	179*	190
		±S.D.	9	7	26	44	2	5
					(n=3)	(n=3)	(n=2)	(N=2)
	2000	Mean	162	Dead				
		±S.D.	10					

*Statistically significant deviation from control using Dunnett's test, P<0.05.

[a]Animals were weighed right after the 72-hour exposure on 0 post-exposure day.

TABLE 6

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE
IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Mean (±S.D.) Organ Weights and Organ/Body Weight Ratios Obtained at End of the Recovery Period

Part of Study	I						II					
Exposure level (ppm)	0		200		500		0		1000		2000	
Hours of exposure	48	72	48	72	48	72	48	72	48	72	48	72
Recovery (R)	R	R	R	R	R	R	R	R	R	R	R	R
Number of male rats tested	10	10	10	10	10	10	10	10	10	4	0	0
Number of female rats tested	10	10	10	10	10	10	10	10	9	2	0	0
Final body weight												
M	319.9 ±18.0	329.1 ±12.4	320.0 ±17.2	325.0 ±14.1	311.2 ±17.6	313.5* ±12.8	262.4 ±12.8	266.2 ±10.0	234.5* ± 8.9	200.3* ±24.3	-	-
F	187.5 ±13.1	192.3 ± 8.7	183.7 ± 8.2	183.7 ±10.7	184.2 ±10.5	185.2 ±14.0	176.7 ± 9.1	182.3 ±11.1	178.9 ±10.2	172.5 ± 4.9	-	-
Brain												
M g	18.3 ±0.06	1.78 ±0.03	1.82 ±0.08	1.83 ±0.08	1.80 ±0.05	1.79 ±0.06	1.76 ±0.06	1.73 ±0.03	1.68* ±0.07	1.63* ±0.05	-	-
g/100g body weight	0.57 ±0.04	0.54 ±0.02	0.57 ±0.04	0.56 ±0.03	0.58 ±0.03	0.57 ±0.02	0.67 ±0.04	0.65 ±0.03	0.72* ±0.03	0.82* ±0.09	-	-
F g	1.64 ±0.07	1.68 ±0.04	1.69 ±0.07	1.63 ±0.07	1.65 ±0.05	1.65 ±0.04	1.64 ±0.06	1.68 ±0.05	1.60 ±0.04	1.54* ±0.09	-	-
g/100g body weight	0.88 ±0.06	0.91 ±0.04	0.92 ±0.07	0.89 ±0.07	0.90 ±0.05	0.89 ±0.06	0.93 ±0.07	0.92 ±0.05	0.90 ±0.06	0.89 ±0.03	-	-
Heart												
M g	1.20 ±0.07	1.17 ±0.08	1.15 ±0.13	1.13 ±0.05	1.11 ±0.09	1.13 ±0.09	1.02 ±0.07	1.02 ±0.10	0.90* ±0.04	0.78* ±0.09	-	-
g/100g body weight	0.38 ±0.03	0.35 ±0.02	0.36 ±0.04	0.35 ±0.01	0.36 ±0.02	0.36 ±0.02	0.39 ±0.02	0.38 ±0.03	0.38 ±0.03	0.39 ±0.02	-	-
F g	0.74 ±0.07	0.78 ±0.05	0.73 ±0.05	0.76 ±0.05	0.74 ±0.06	0.77 ±0.08	0.70 ±0.04	0.74 ±0.06	0.71 ±0.04	0.71 ±0.02	-	-
g/100g body weight	0.39 ±0.03	0.41 ±0.02	0.40 ±0.03	0.41 ±0.02	0.40 ±0.03	0.42 ±0.04	0.39 ±0.02	0.40 ±0.02	0.40 ±0.02	0.41 ±0.00	-	-

*statistically significant difference from appropriate control value when analyzed using analysis of variance followed by Dunnett's Test, $p<0.05$.

-indicates that all rats had died spontaneously during exposure.

TABLE 6 (continued)

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE
IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Mean (±S.D.) Organ Weights and Organ/Body Weight Ratios Obtained at End of the Recovery Period

Part of Study	I						II					
Exposure level (ppm)	0		200		500		0		1000		2000	
Hours of exposure	48	72	48	72	48	72	48	72	48	72	48	72
Recovery (D)	8	8	8	8	8	8	8	8	8	8	8	8
Number of male rats tested	10	10	10	10	10	10	10	10	10	4	0	0
Number of female rats tested	10	10	10	10	10	10	10	10	9	2	0	0
Kidneys												
M g	2.64 ±0.22	2.72 ±0.21	2.58 ±0.17	2.52 ±0.17	2.56 ±0.22	2.45* ±0.19	2.43 ±0.19	2.32 ±0.24	2.06* ±0.16	1.85* ±0.14	-	-
g/100g body weight	0.83 ±0.05	0.83 ±0.05	0.81 ±0.05	0.78 ±0.03	0.82 ±0.04	0.78 ±0.05	0.93 ±0.07	0.87 ±0.06	0.88 ±0.07	0.93 ±0.09	-	-
F g	1.56 ±0.16	1.62 ±0.08	1.62 ±0.09	1.66 ±0.13	1.56 ±0.13	1.63 ±0.15	1.58 ±0.11	1.60 ±0.08	1.56 ±0.15	1.51 ±0.13	-	-
g/100g body weight	0.83 ±0.05	0.84 ±0.04	0.88 ±0.04	0.90* ±0.04	0.85 ±0.04	0.88 ±0.06	0.89 ±0.06	0.88 ±0.03	0.87 ±0.07	0.87 ±0.05	-	-
Liver												
M g	11.37 ±1.23	10.86 ±0.46	10.37* ±0.89	10.06* ±0.41	10.18* ±0.75	10.19* ±0.76	9.38 ±0.66	9.58 ±0.83	8.56* ±0.33	7.64* ±0.61	-	-
g/100g body weight	3.55 ±0.27	3.30 ±0.17	3.23* ±0.18	3.10* ±0.09	3.27* ±0.10	3.25 ±0.13	3.57 ±0.20	3.60 ±0.20	3.66 ±0.22	3.83 ±0.20	-	-
F g	6.41 ±0.77	6.20 ±0.52	6.27 ±0.51	6.12 ±0.59	6.06 ±0.40	6.29 ±0.82	5.96 ±0.48	6.20 ±0.48	5.91 ±0.64	6.49 ±0.98	-	-
g/100g body weight	3.41 ±0.22	3.22 ±0.16	3.41 ±0.22	3.33 ±0.18	3.29 ±0.08	3.40 ±0.45	3.38 ±0.24	3.40 ±0.16	3.30 ±0.22	3.77* ±0.67	-	-
Testes												
M g	3.68 ±0.27	3.59 ±0.27	3.68 ±0.27	3.71 ±0.26	3.68 ±0.35	3.60 ±0.47	3.34 ±0.22	3.30 ±0.20	3.10 ±0.62	1.49* ±0.04	-	-
g/100g body weight	1.15 ±0.10	1.09 ±0.09	1.15 ±0.09	1.14 ±0.08	1.17 ±0.09	1.15 ±0.16	1.27 ±0.06	1.24 ±0.07	1.32 ±0.26	0.75* ±0.09	-	-

*Statistically significant difference from appropriate control value when analyzed using analysis of variance followed by Dunnett's Test, $p<0.05$.

- Indicates that all rats had died spontaneously during exposure.

TABLE 7

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Mean (±S.D.) Hematology Values

Part of study	1											
Exposure concentration (ppm)	0				200				500			
Hours of exposure	48	72	48	72	48	72	48	72	48	72	48	72
Sacrificed (S) or Recovery (R)	S	S	R	R	S	S	R	R	S	S	R	R
Number of male rats tested	10	10	10	10	10	10	10	10	10	10	10	10
Number of female rats tested	10	10	10	10	10	10	10	10	10	10	10	10
HCT (%)												
M	46.5 ±1.4	44.5 ±1.7	50.1 ±1.1	47.5 ±1.1	48.0 ±2.0	46.9* ±1.4	50.4 ±1.4	47.8 ±1.8	47.7 ±1.6	51.6* ±3.0	48.7 ±2.4	46.1 ±1.6
F	45.7 ±2.2	47.7 ±3.4	47.0 ±1.8	48.0 ±1.6	46.1 ±1.0	47.0 ±1.4	46.8 ±2.9	45.7* ±1.5	48.2* ±1.6	48.9 ±2.7	47.3 ±1.9	46.7 ±1.7
RBC x $10^6/mm^3$												
M	6.90 ±0.23	6.76 ±0.25	7.78 ±0.29	7.63 ±0.28	6.96 ±0.32	7.13* ±0.20	7.60 ±0.22	7.44 ±0.31	7.41* ±0.32	7.61* ±0.48	7.81 ±0.14	7.49 ±0.34
F	6.77 ±0.29	6.93 ±0.33	7.09 ±0.35	7.03 ±0.26	6.92 ±0.27	7.33 ±0.33	7.47* ±0.28	7.15 ±0.27	7.16 ±0.57	7.34 ±0.28	7.48* ±0.26	7.28 ±0.27
Hgb g/100 ml												
M	15.0 ±0.5	14.4 ±0.6	16.1 ±0.5	15.8 ±0.4	15.0 ±0.3	15.0 ±0.3	15.9 ±0.5	15.3 ±0.6	15.5* ±0.6	16.0* ±1.0	15.7 ±0.5	15.1* ±0.6
F	14.7 ±0.4	14.7 ±0.5	15.0 ±0.8	15.3 ±0.6	14.9 ±0.5	15.2 ±0.6	15.3 ±0.7	14.8 ±0.5	15.5* ±1.1	15.7 ±0.6	15.3 ±0.6	15.2 ±0.8
WBC x $10^3/mm^3$												
M	18.8 ±3.6	19.5 ±3.0	24.8 ±5.1	23.6 ±2.0	17.9 ±2.9	21.2 ±4.3	25.3 ±6.6	23.4 ±3.0	20.0 ±4.2	17.6 ±3.5	21.4 ±4.1	22.4 ±2.9
F	14.3 ±2.1	17.7 ±3.6	19.0 ±5.3	16.0 ±3.8	14.1 ±1.7	16.5 ±3.1	27.2* ±8.0	21.8* ±5.0	15.4 ±3.2	16.2 ±3.8	21.5 ±3.1	14.8 ±1.7

*Statistically significant difference from appropriate control value when analysed using analysis of variance followed by Dunnett's Test, $p<0.05$.

TABLE 7 (continued)

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Mean (±S.D.) Hematology Values

Part of study	II											
Exposure concentration (ppm)	0				1000				2000			
Hours of exposure	48	72	48	72	48	72	48	72	48	72	48	72
Sacrificed (S) or Recovery (R)	S	S	R	R	S	S	R	R	S	S	R	R
Number of male rats tested	10	10	10	10	10	9	10	4	5	0	0	0
Number of female rats tested	10	10	10	10	9	10	9	7	8	0	0	0
HCT (%)												
M	46.1 ±3.9	45.1 ±1.3	50.2 ±2.0	50.0 ±1.2	49.8 ±2.3	55.4* ±1.5	49.4 ±1.9	49.5 ±1.9	53.6* ±3.2	-	-	-
F	47.2 ±4.5	46.9 ±2.8	51.0 ±1.6	50.1 ±1.5	50.6 ±2.3	56.2* ±2.0	50.4 ±1.8	48.5 ±0.7	54.1* ±1.0	-	-	-
RBC x $10^6/mm^3$												
M	5.83 ±0.43	6.57 ±0.20	6.00 ±0.42	6.85 ±0.34	6.24 ±0.47	8.32* ±0.37	6.53* ±0.32	6.86 ±0.52	6.90* ±0.87	-	-	-
F	6.28 ±0.57	6.85 ±0.27	7.02 ±0.26	7.18 ±0.40	7.03* ±0.57	8.73* ±0.51	6.80 ±0.32	6.41 ±0.28	7.09* ±0.79	-	-	-
Hgb g/100 ml												
M	14.1 ±1.1	14.0 ±0.3	16.0 ±0.6	16.2 ±0.4	15.9* ±0.8	17.7* ±0.8	16.0 ±0.5	15.7 ±0.8	16.6* ±0.9	-	-	-
F	15.6 ±0.9	14.7 ±0.4	16.0 ±0.5	16.5 ±0.6	16.6 ±0.7	18.7* ±0.7	16.1 ±0.5	15.2* ±0.3	18.4* ±1.4	-	-	-
WBC x $10^3/mm^3$												
M	20.2 ±3.9	16.6 ±2.9	18.7 ±2.3	16.1 ±3.2	15.8 ±3.7	10.6* ±2.9	12.4* ±2.7	15.3 ±3.2	15.7 ±3.3	-	-	-
F	20.0 ±4.0	13.8 ±2.7	18.7 ±2.3	11.2 ±2.7	14.3 ±2.8	18.1* ±5.1	13.7 ±2.6	15.5 ±4.4	19.2 ±5.7	-	-	-

*Statistically significant difference from appropriate control value when analysed using analysis of variance followed by Dunnett's Test, $p<0.05$.
- Indicates all animals died spontaneously during exposure.

TABLE 8

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE
IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Mean Differential White Blood Cell Values

Part of Study	I												II											
Exposure level (ppm)	0				200				500				0				1000				2000			
Hours of exposure	48	72	48	72	48	72	48	72	48	72	48	72	48	72	48	72	48	72	48	72	48	72	48	72
Sac (S) or Rec (R)*	S	S	R	R	S	S	R	R	S	S	R	R	S	S	R	R	S	S	R	R	S	S	R	R
Number of males tested	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	4	5	0	0	0
Number of females tested	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	9	2	8	0	0	0
Neutrophils - segmented																								
M	12	17	16	12	9	15	18	23	19	13	14	15	9	15	12	8	14	51	14	24	15	-	-	-
F	16	15	16	10	10	8	24	26	8	11	15	13	12	10	11	15	13	24	11	8	23	-	-	-
Neutrophils- Band/Juvenile																								
M	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	-	-	-
F	1	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	-	-	-
Lymphocytes																								
M	83	77	80	83	87	80	76	72	75	81	81	79	86	80	85	90	80	44	83	74	79	-	-	-
F	72	79	77	85	87	88	70	69	89	85	80	82	82	86	84	82	82	70	75	88	71	-	-	-
Monocytes																								
M	3	4	4	4	4	5	5	4	5	5	4	5	5	4	3	1	6	5	1	1	6	-	-	-
F	2	5	5	4	2	3	5	4	2	4	4	5	4	3	4	1	5	5	2	2	5	-	-	-
Eosinophils																								
M	1	1	0	1	0	0	1	1	0	1	1	1	0	1	0	1	0	0	2	1	0	-	-	-
F	2	1	1	1	1	1	1	1	1	0	1	0	0	1	1	2	0	1	2	2	1	-	-	-
Basophils																								
M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-	-	-
F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-	-	-

*Sac (S) = sacrificed; Rec (R) = recovery.
Data listed as percent.
- Indicates all animals died spontaneously during exposure.

TABLE 9

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Mean (±S.D.) Clinical Chemistry Values

Part of Study	I												II											
Exposure level (ppm)	0				200				500				0				1000				2000			
Hours of exposure	48	72	48	72	48	72	48	72	48	72	48	72	48	72	48	72	48	72	48	72	48	72	48	72
Sac (S) or Rec (R)[a]	S	S	R	R	S	S	R	R	S	S	R	R	S	S	R	R	S	S	R	R	S	S	R	R
Number of males tested	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	4	4	0	0	0
Number of females tested	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	9	9	2	8	0	0	0
BUN (mg/100 ml)																								
M	22 ±2	25 ±3	16 ±2	14 ±2	20 ±4	20* ±3	19* ±2	16 ±3	21 ±2	27 ±6	16 ±2	12 ±1	15 ±2	19 ±3	15 ±3	18 ±3	18 ±4	41 ±35	17 ±2	17 ±1	170* ±21	-	-	-
F	21 ±2	24 ±3	18 ±3	16 ±1	18 ±3	25 ±4	17 ±1	15 ±2	20 ±3	21 ±3	18 ±4	16 ±2	17 ±2	17 ±3	17 ±2	20 ±2	19 ±4	68* ±54	16 ±2	17 ±1	156* ±69	-	-	-
SGPT (mU/ml)																								
M	30 ±9	26 ±5	16 ±2	15 ±3	27 ±5	24 ±4	18 ±6	15 ±3	25 ±8	31 ±19	14 ±2	13 ±2	23 ±6	24 ±4	14 ±2	25 ±11	28 ±14	27 ±18	13 ±2	28 ±11	123* ±56	-	-	-
F	22 ±3	22 ±3	13 ±2	13 ±3	20 ±4	19 ±3	13 ±1	14 ±3	18 ±4	21 ±5	12 ±1	12 ±2	18 ±7	16 ±3	13 ±2	18 ±5	21 ±6	18 ±7	15 ±4	15 ±2	29* ±12	-	-	-
AP (mU/ml)																								
M	263 ±32	260 ±53	95 ±13	78 ±21	258 ±48	264 ±48	87 ±14	94 ±20	212* ±47	196* ±74	92 ±14	72 ±18	258 ±76	275 ±80	109 ±13	118 ±35	177* ±38	126* ±32	111 ±23	114 ±11	151* ±12	-	-	-
F	207 ±43	224 ±33	87 ±19	87 ±27	186 ±34	182* ±39	83 ±12	86 ±13	182 ±49	187 ±36	88 ±21	80 ±10	196 ±32	181 ±33	84 ±6	75 ±12	143* ±25	103* ±26	77 ±10	86 ±8	119 ±17	-	-	-
SGOT (mU/ml)																								
M	94 ±21	115 ±25	92 ±15	112 ±32	117 ±35	108 ±25	128 ±70	98 ±38	83 ±18	139 ±45	93 ±21	105 ±17	119 ±24	128 ±40	108 ±15	149 ±48	149 ±67	142* ±42	116 ±34	161 ±53	1308* ±876	-	-	-
F	103 ±14	136 ±32	103 ±21	110 ±22	135 ±48	109 ±20	119 ±21	120 ±34	93 ±30	129 ±35	118 ±19	106 ±32	127 ±34	117 ±27	138 ±[illegible]	166 ±51	125 ±30	139 ±41	142 ±41	108 ±13	200* ±81	-	-	-
T Bilirubin (mg/100 ml)																								
M	0.4 ±0.1	0.4 ±0.1	0.3 ±0.0	0.3 ±0.1	0.3* ±0.1	0.4 ±0.1	0.3 ±0.1	0.2 ±0.0	0.3* ±0.1	0.3 ±0.0	0.3 ±0.0	0.3 ±0.1	0.3 ±0.1	0.3 ±0.0	0.3 ±0.2	0.3 ±0.1	0.4 ±0.1	0.4* ±0.1	0.2 ±0.1	0.2 ±0.0	0.9* ±0.5	-	-	-
F	0.4 ±0.1	0.4 ±0.1	0.3 ±0.1	0.2 ±0.1	0.3 ±0.1	0.5 ±0.1	0.3 ±0.0	0.2 ±0.1	0.3 ±0.1	0.3 ±0.0	0.3 ±0.1	0.2 ±0.1	0.2 ±0.0	0.4 ±0.1	0.3 ±0.1	0.3 ±0.2	0.5 ±0.2	0.3 ±0.1	0.2 ±0.0	0.2 ±0.1	0.7* ±0.5	-	-	-

*Statistically significant difference from appropriate control value when analysed using analysis of variance followed by Dunnett's Test, $p<0.05$.
- indicates all animals died spontaneously during exposure.
[a] SAC (S) = sacrificed; Rec (R) = recovery.

TABLE 10

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE
IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Urinalysis Values

Part of Study	I											
Exposure level (ppm)	0				200				500			
Hours of exposure	48	72	48	72	48	72	48	72	48	72	48	72
Sac (S) or Rec (R)[a]	S	S	R	R	S	S	R	R	S	S	R	R
Number of male rats tested	10	10	10	10	5	9	10	9	10	6	9	10
Number of female rats tested	10	10	10	10	10	10	10	10	10	10	10	10
Specified Gravity[b]												
M	1.045 ±0.011	1.047 ±0.016	1.050 ±0.007	1.053 ±0.007	1.030* ±0.013	1.036 ±0.007	1.049 ±0.005	1.055 ±0.005	1.027* ±0.007	1.042 ±0.023	1.047 ±0.013	1.048 ±0.007
F	1.027 ±0.006	1.032 ±0.010	1.022 ±0.008	1.030 ±0.009	1.023 ±0.009	1.036 ±0.012	1.034* ±0.010	1.028 ±0.012	1.016* ±0.008	1.034 ±0.014	1.027 ±0.009	1.026 ±0.011
Bilirubin												
M	7(5) 8(5)	7(6) 8(4)	6(3) 7(4) 8(3)	6(1) 7(9)	7(5) 8(1)	6(3) 7(6)	7(5) 8(5)	7(8) 8(1)	6(10)	6(4) 7(1) 8(1)	6(1) 7(3) 8(5)	7(10)
F	8(10)	7(2) 8(8)	6(1) 7(2) 8(7)	7(8) 8(2)	8(10)	7(8) 8(2)	8(10)	6(1) 7(2) 8(7)	6(5) 7(2) 8(3)	6(2) 7(1) 8(7)	6(1) 8(9)	7(4) 8(6)
Glucose												
M	Neg(10)	Neg(10)	Neg(9)	Neg(10)	Neg(6)	Neg(9)	Neg(10)	Neg(9)	Neg(10)	Neg(6)	Neg(9)	Neg(10)
F	Neg(10)	Neg(10)	Neg(10)	Neg(10)	Neg(10)	Neg(10)	Neg(10)	Neg(10)	Neg(10)	Neg(10)	Neg(10)	Neg(10)
Protein												
M	1+(4) 2+(5) 3+(1)	2+(9)	2+(6) 3+(3)	3+(10)	1+(1) 2+(5)	1+(2) 2+(5) 3+(2)	2+(5) 3+(5)	2+(6) 3+(3)	Trace(2) 1+(7) 2+(1)	2+(6)	2+(9)	2+(2) 3+(8)
F	Trace(10)	1+(1) 2+(9)	1+(3) 2+(6) 3+(1)	Trace(3) 1+(5) 2+(1) 3+(1)	1+(6) 2+(4)	Trace(1) 1+(4) 2+(5)	1+(6) 2+(3) 4+(1)	Trace(1) 1+(3) 2+(6)	1+(7) 2+(1) 3+(2)	1+(6) 2+(3) 3+(1)	Trace(7) 2+(2) 3+(1)	Trace(3) 1+(2) 2+(4) 3+(1)

[a]Sac (S) = sacrificed; Rec (R) = recovery
[b]Data listed as mean±S.D.

*Statistically significant difference from appropriate control value when analysed using analysis of variance followed by Dunnett's Test, $p<0.05$.
( ) indicates number of animals with this value.

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TABLE 10 (continued)

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Urinalysis Values

Part of Study	I (Continued)											
Exposure level (ppm)	0				200				500			
Hours of exposure	48	72	48	72	48	72	48	72	48	72	48	72
Sac (S) or Rec (R)[a]	S	S	R	R	S	S	R	R	S	S	R	R
Number of male rats tested	10	10	10	10	6	9	10	9	10	6	9	10
Number of female rats tested	10	10	10	10	10	10	10	10	10	10	10	10
Ketones												
M	1+(10)	Neg(1) 1+(9)	Neg(1) 1+(7) 2+(1)	1+(8) 2+(2)	Neg(1) 1+(5)	Neg(1) 1+(8)	1+(10)	1+(7) 2+(2)	Neg(1) 1+(9)	Neg(2) 1+(4)	1+(9)	Neg(2) 1+(8)
F	Neg(6) 1+(4)	Neg(4) 1+(6)	Neg(2) 1+(8)	Neg(1) 1+(9)	Neg(2) 1+(8)	Neg(1) 1+(9)	Neg(1) 1+(9)	Neg(3) 1+(7)	Neg(1) 1+(9)	Neg(7) 1+(2) 2+(1)	Neg(2) *1+(8)	Neg(7) 1+(3)
Bilirubin												
M	Neg(10)	Neg(10)	Neg(9)	Neg(10)	Neg(6)	Neg(9)	Neg(10)	Neg(9)	Neg(10)	Neg(6)	Neg(9)	Neg(10)
F	Neg(10)	Neg(10)	Neg(10)	Neg(10)	Neg(10)	Neg(10)	Neg(10)	Neg(10)	Neg(10)	Neg(10)	Neg(10)	Neg(10)
Blood												
M	Neg(10)	Neg(8) Trace(1) 1+(1)	Neg(9)	Neg(9) 1+(1)	Neg(6)	Neg(8) Trace(1)	Neg(10)	Neg(9)	Neg(10)	Neg(3) Trace(3)	Neg(9)	Neg(8) Trace(2)
F	Neg(6) Trace(4)	Neg(8) Trace(2)	Neg(8) Trace(2)	Neg(10)	Neg(10)	Neg(9) 1+(1)	Neg(7) Trace(2) 2+(1)	Neg(9) Trace(1)	Neg(10)	Neg(7) Trace(3)	Neg(9) Trace(1)	Neg(8) Trace(2)
Urobilinogen												
M	1(9) 0.1(1)	1(10)	1(9)	1(10)	1(6)	1(9)	1(10)	1(9)	1(10)	1(6)	1(9)	1(10)
F	1(9) 0.1(1)	1(10)	1(10)	1(10)	1(9) 0.1(1)	1(10)	1(10)	1(10)	1(8) 0.1(2)	1(10)	Neg(10)	1(10)

[a]Sac (S) = sacrificed; Rec (R) = recovery

*Statistically significant difference from appropriate control value when analyzed using analysis of variance followed by Dunnett's Test, $p<0.05$.

( ) indicates number of animals with this value.

TABLE 11

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Urinalysis Values

Part of Study	11											
Exposure level (ppm)	0				1000				2000			
Hours of exposure	48	72	48	72	48	72	48	72	48	72	48	72
Sacrificed (S) or Recovery (R)	S	S	S	S	S	S	S	S	S	S	S	S
Number of male rats tested	10	10	10	10	9	9	10	4	6	0	0	0
Number of female rats tested	10	10	10	10	9	10	9	2	8	0	0	0
Specific Gravity[a]												
M	1.056 ±0.013	1.054 ±0.009	1.021 ±0.010	1.035 ±0.011	1.035* ±0.018	1.037* ±0.008	1.022 ±0.013	1.034 ±0.021	1.015* ±0.002	-	-	-
F	1.024 ±0.010	1.022 ±0.123	1.025 ±0.016	1.017 ±0.007	1.029 ±0.011	1.028 ±0.006	1.024 ±0.003	1.033* ±0.002	1.021 ±0.005	-	-	-
pH												
M	6.5(2) 7.0(1) 7.5(5) 8 (2)	6.5(5) 7.0(1) 7.5(2) 8.0(2)	5.0(1) 6.0(8) 6.5(1)	6.0(10)	5 (3) 6 (6)	5.0(1) 6.0(8)	6.0(3) 6.5(6)	5.5(1) 6.0(3)	5.0(6)	-	-	-
F	7.0(1) 7.5(1) 8.0(8)	6.5(1) 7.0(2) 7.5(4) 8.0(3)	5.0(1) 6.0(6) 6.5(1) 7.0(2)	6.0(4) 6.5(3) 7.0(3)	6.0(8) 7.5(1)	5.0(10)	6.0(1) 6.5(6) 7.0(2)	6.0(1) 7.0(1)	5.0(8)	-	-	-
Glucose												
M	Neg(10)	Neg(10)	Neg(10)	Neg(10)	Neg(9)	Neg(8) 1+(1)	Neg(8)	Neg(4)	Neg(5) 1+(1)	-	-	-
F	Neg(10)	Neg(10)	Neg(10)	Neg(9)	Neg(6) 1+(1) 2+(1) 3+(1)	Neg(4) Trace(2) 1+(1) 2+(2) 3+(1)	Neg(9)	Neg(2)	1+(1) 2+(4) 3+(1) 4+(2)	-	-	-
Protein												
M	Trace(2) 1+(2) 2+(6)	1+(2) 2+(7) 3+(1)	Trace(3) 1+(5) 2+(2)	Trace(1) 1+(3) 2+(5) 3+(1)	1+(7) 2+(2)	1+(2) 2+(3) 3+(4)	Trace(2) 1+(3) 2+(3)	Trace(1) 1+(3)	3+(6)	-	-	-
F	Neg(1) Trace(6) 1+(1) 2+(1) 3+(1)	Neg(4) Trace(2) 1+(3) 2+(1)	Trace(3) 1+(5) 2+(2)	Neg(3) Trace(5) 2+(1)	Trace(1) 1+(3) 2+(2) 3+(3)	2+(1) 3+(9)	Trace(1) 1+(8)	Trace(1) 1+(1)	3+(6) 4+(4)	-	-	-

[a]Data listed as mean±S.D.
*Statistically significant difference from appropriate control value when analyzed using analysis of variance followed by Dunnett's Test, $p<0.05$.
( ) indicates number of animals with this value.
- indicates all rats died during exposure.

TABLE 11 (continued)

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Urinalysis Values

Part of Study	II (Continued)											
Exposure level (ppm)	0				1000				2000			
Hours of exposure	48	72	48	72	48	72	48	72	48	72	48	72
Sacrificed (S) or Recovery (R)	S	S	R	R	S	S	R	R	S	S	R	R
Number of male rats tested	10	10	10	10	9	9	10	4	5	0	0	0
Number of female rats tested	10	10	10	10	9	10	9	2	6	0	0	0
Ketones												
M	Neg(9) 1+(1)	Neg(2) 1+(8)	Neg(10)	Neg(4) 1+(6)	Neg(2) 1+(5) 2+(4)	Neg(4) 1+(3) 2+(1) 3+(3) 4+(1)	Neg(8)	Neg(4)	Neg(4) 1+(2)	-	-	-
F	Neg(10)	Neg(9) 1+(1)	Neg(5) Trace(1) 1+(4)	Neg(7) 1+(1)	Neg(2) 1+(3) 2+(3) 3+(2)	1+(1) 2+(1) 3+(7) 4+(1)	Neg(9)	1+(2)	1+(1) 2+(6) 3+(1)	-	-	-
Bilirubin												
M	Neg(10)	Neg(10)	Neg(10)	Neg(9)	Neg(9)	Neg(9)	Neg(8)	Neg(4)	Neg(6)	-	-	-
F	Neg(10)	Neg(10)	Neg(10)	Neg(8)	Neg(9)	Neg(10)	Neg(9)	Neg(2)	Neg(8)	-	-	-
Blood												
M	Neg(10)	Neg(10)	Neg(9) 2+(1)	Neg(9)	Neg(8) Trace(1)	Neg(5) Trace(4)	Neg(4) Trace(4)	Neg(4)	Neg(5) Trace(1)	-	-	-
F	Neg(8) Trace(2)	Neg(7) Trace(3)	Neg(6) Trace(1) 3+(1)	Neg(7) 2+(1)	Neg(9)	Neg(8) Trace(2)	Neg(7) 1+(2)	Neg(2)	Neg(1) Trace(5) 1+(2)	-	-	-
Urobilinogen												
M	1 (10)	Neg(1) 1+(9)	0.1(7) 1 (3)	0.1(1) 1 (8)	0.1(9) 1.0(4)	1 (9)	1 (8)	1 (4)	0.1(6)	-	-	-
F	Neg(2) 1 (8)	0.1(1) 1 (9)	0.1(6) 1 (4)	0.1(2) 1 (6)	0.1(9)	1 (10)	1 (9)	1 (2)	0.1(1) 1 (7)	-	-	-

*Statistically significant difference from appropriate control value when analyzed using analysis of variance followed by Dunnett's Test, $p<0.05$.
( ) indicates number of animals with this value.
- indicates all rats died during exposure.

TABLE 12

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Gross Necropsy Observations on Rats From the Scheduled Kill at the End of the 48-Hour Exposure

Sex	Male			Female		
Dose in ppm	0	200	500	0	200	500
Original Number of Rats in Group	10	10	10	10	10	10
Number of Rats Examined	10	10	10	10	10	10
LUNGS						
Pinpoint dark red foci in lungs	3	0	5	2	2	1
Dark focus in lungs	1	0	0	0	0	0
Patchy dark red appearance (agonal aspiration of blood)	0	0	0	0	0	1
LIVER						
Linear dark streaks	1	0	0	0	0	0
Pinpoint white capsular focus	1	0	0	0	0	0
Cyst	0	1	0	0	0	0
TESTES						
Decreased size of testicle	1	0	0	-	-	-
UTERUS						
Uterine horns filled with clear fluid	-	-	-	0	1	1
THYMUS						
Multiple pinpint dark foci	1	0	0	0	0	0
Mottled	0	0	1	0	0	0
KIDNEYS						
Dilated renal pelvises	0	0	0	0	1	0

Data listed as number of rats with the listed observation.

TABLE 13

METHYL CHLORIDE: 48 and 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Tissues examined microscopically from Rats from the Scheduled Kill at the End of the 48-Hour Exposure

Sex	Males			Females		
Dose in ppm	0	200	500	0	200	500
Original number of rats in group	10	10	10	10	[illegible]	10
Number of rats examined microscopically	5	5	5	5	5	5
Liver	5	5	5	5	5	5
Brain	5	5	5	5	5	5
Kidneys	5	5	5	5	5	5
Testes	5	5	5	-	-	-
Epididymides	5	5	5	-	-	-
Lungs	5	5	5	5	5	5

Data listed as number of rats for which the listed tissue was examined microscopically.

- Indicates not applicable.

TABLE 14

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Histopathologic Observations from Rats from the Scheduled Kill at the End of the 48-Hour Exposure

Sex	Males			Females		
Dose in ppm	0	200	500	0	200	500
Original number of rats in group	10	10	10	10	10	10
Number of rats examined microscopically	5	5	5	5	5	5
LIVER						
Focal or multifocal extramedullary hematopoiesis - slight	4	3	1	1	2	1
Altered tinctorial properties of hepatocytes	0	0	5	0	1	0
Randomly distributed coarse vacuolization of hepatocytes - very slight	0	0	0	0	1	0
KIDNEYS						
Focal dilated renal tubules with eosinophilic cast formation - slight	1	0	0	0	0	0
Multifocal dilated renal tubules with eosinophilic cast formation - slight	0	1	0	0	0	0
Focal interstitial fibrosis	1	0	0	0	0	0
Focal interstitial mononuclear cell inflammation	1	0	0	0	0	0
Focal basophilic staining of renal tubules - slight	0	2	1	0	2	3
Multifocal basophilic staining of renal tubules - slight	0	0	0	0	2	0
Bilateral hydronephrosis - slight	0	0	0	0	1	0
Focal extramedullary hematopoiesis	0	0	0	0	0	2
LUNGS						
Focal or multifocal peribronchiolar aggregates of mononuclear cells - slight	5	5	5	5	5	4
Perivascular edema	0	0	1	2	1	0
Multifocal suppurative arteritis - slight	1	0	0	0	0	0

Data listed as number of rats with the listed observation.

TABLE 14 (continued)

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Histopathologic Observations from Rats from the Scheduled Kill at the End of the 48-Hour Exposure

Sex	Males			Females		
Dose in ppm	0	200	500	0	200	500
Original number of rats in group	10	10	10	10	10	10
Number of rats examined microscopically	5	5	5	5	5	5
Lungs (Continued)						
Multifocal peribronchiolitis - slight	1	0	0	0	0	0
Focal pleural fibrosis - slight	1	0	0	0	0	0
Focal granuloma - slight	0	1	0	0	0	0
Focal aggregate of alveolar macrophages - slight	0	1	1	0	0	0
Focal or multifocal perivascular aggregates of mononuclear cells - slight	0	5	1	2	1	0
Focal or multifocal perivascular aggregates of polymorphonuclear cells - slight	0	1	0	0	0	0
Multifocal alveolar and terminal bronchiolar hyperplasia - slight	0	1	0	0	0	0
Focal resolving bronchopneumonia - slight	0	1	0	0	0	0
Focal hemorrhage, probably agonal	0	0	0	1	0	0
EPIDIDYMIDES						
Increased eosinophilic intratubular proteinaceous and cellular aggregates - slight or moderate	0	0	4	-	-	-
Coagulated intratubular proteinaceous and spermatic elements - moderate	0	0	2	-	-	-
Focal suppurative inflammation	0	0	1	-	-	-
Interstitial mononuclear cell inflammation	0	0	1	-	-	-
Interstitial edema	0	0	2	-	-	-

Data listed as number of rats with the listed observation.

- Indicates not applicable.

TABLE 15

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Gross Necropsy Observations on Rats from the Scheduled Kill at the End of the Recovery Period Which Followed 48 Hours of Exposure

Sex	Male			Female		
Dose in ppm	0	200	500	0	200	500
Original Number of Rats in Group	10	10	10	10	10	10
Number of Rats Examined	10	10	10	10	10	10
EYES						
Slightly cloudy cornea(s)	7	7	5	4	3	1
Enlarged and reddened eye	0	1	0	0	0	0
Mottled discoloration of cornea	0	1	0	0	0	0
LIVER						
Herniation of diaphragm involving a nodular portion of liver	1	0	0	0	0	0
KIDNEYS						
Dilated renal pelvis	1	0	2	0	0	0
Focal white opacity in renal pelvis	0	0	0	0	1	0
TESTES						
Decreased size of testicle	0	0	2	-	-	-
Dark color in testicle	0	0	2	-	-	-
Flaccid testicle	0	0	1	-	-	-
EPIDIDYMIDES						
Decreased size of epididymis - unilateral	0	0	1	-	-	-
Pale area on epididymis - unilateral	0	0	2	-	-	-
Pinpoint white foci in fat of spermatic cord 0	0	1	-	-	-	
UTERUS						
Uterine horns distended with clear fluid	-	-	-	2	1	1
THYMUS						
Mottled (probably agonal hemorrhage)	0	0	1	0	0	0
LUNGS						
Dark red foci in lungs	0	0	2	0	0	0

Data listed as number of rats with the listed observation.

TABLE 16

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Tissues Examined Microscopically from Rats from the Scheduled Kill at the End of the Recovery Period Which Followed 48 Hours of Exposure

Sex	Males			Females		
Dose in ppm	0	200	500	0	200	500
Original number of rats in group	10	10	10	10	10	10
Number of rats examined microscopically	5	5	5	5	5	5
Liver	5	5	5	5	5	5
Brain	5	5	5	5	5	5
Kidneys	5	5	5	5	5	5
Testes	5	5	5	-	-	-
Epididymides	5	5	5	-	-	-
Lungs	5	5	5	5	5	5

Data listed as number of rats for which the listed tissue was examined microscopically.

- Indicates not applicable.

TABLE 17

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Histopathologic Observations From Rats From the Scheduled Kill at the End of the Recovery Period Which Followed 48 Hours of Exposure

Sex	Males			Females		
Dose in ppm	0	200	500	0	200	500
Original number of rats in group	10	10	10	10	10	10
Number of rats examined microscopically	5	5	5	5	5	5
LIVER						
Focal or multifocal extramedullary hematopoiesis - slight	3	5	2	5	4	4
Randomly distributed coarse vacuolization - very slight to slight	0	0	2	5	5	4
- slight to moderate	0	0	0	0	0	1
Focal capsular fibrosis - slight	0	0	0	1	0	0
Focal coagulation necrosis - slight	0	0	0	0	1	0
KIDNEYS						
Focal basophilic staining of renal tubules - slight	2	0	1	2	0	1
Multifocal basophilic staining of renal tubules - slight	0	1	0	2	1	0
Focal dilated renal tubules with eosinophilic cast formation - slight	1	1	1	1	0	0
Multifocal dilated renal tubules with eosinophilic cast formation - slight	2	2	0	0	1	0
Multifocal vacuolization of cytoplasm of renal tubular epithelium	0	1	0	0	0	0
Focal interstitial mononuclear cell inflammation - slight	1	0	0	0	0	0
Bilateral calcification in pelvis - slight	0	0	0	0	1	[illegible]
LUNGS						
Multifocal peribronchiolar aggregates of mononuclear cells - slight	5	5	5	5	5	4
Focal aggregates of alveolar macrophages - slight	2	1	0	0	0	0

Data listed as number of rats with the listed observation.

TABLE 17 (continued)

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Histopathologic Observations From Rats From the Scheduled Kill at the End of the Recovery Period Which Followed 48 Hours of Exposure

Sex	Males			Females		
Dose in ppm	0	200	500	0	200	500
Original number of rats in group	10	10	10	10	10	10
Number of rats examined microscopically	5	5	5	5	5	5
LUNGS (Continued)						
Focal terminal bronciolar suppurative inflammation - slight	1	0	0	0	0	0
Perivascular edema - slight	0	1	0	0	0	1
Multifocal suppurative perivasculitis - slight	0	0	1	0	0	0
Focal subpleural aggregates of mononuclear cells - slight	0	0	0	1	1	0
Focal chronic active interstitial pneumonia - slight	0	0	0	0	0	1
TESTES						
Unilateral atrophy - moderate	0	0	3	-	-	-
Unilateral atrophy - severe	0	0	1	-	-	-
Numerous multinucleated spermatids	0	0	1	-	-	-
Unilateral interstitial edema	0	0	1	-	-	-
EPIDIDYMIDES						
Unilateral sperm granuloma	0	0	3	-	-	-
Unilateral decreased spermatogenic elements	0	0	3	-	-	-
Unilateral interstitial edema	0	0	2	-	-	-
Unilateral coagulated proteinaceous and spermatic elements in tubules - moderate	0	0	1	-	-	-
Unilateral chronic inflammation	0	0	1	-	-	-
Unilateral increased eosinophilic intratubular proteinaceous and cellular aggregates - slight	0	0	1	-	-	-

Data listed as number of rats with the listed observation.

- Indicates not applicable.

TABLE 18

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Gross Necropsy Observations on Rats From the Scheduled Kill at the End of the 72-Hour Exposure

Sex	Male			Female		
Dose in ppm	0	200	500	0	200	500
Original Number of Rats in Group	10	10	10	10	10	10
Number of Rats Examined	10	10	10	10	10	10
GENERAL						
Decreased adipose tissue	0	0	1	0	0	1
LUNGS						
Pinpoint dark red foci	4	2	3	1	1	0
LIVER						
Herniation of diaphragm involving a nodular portion of liver	1	0	0	0	0	0
THYMUS						
Mottled	2	0	0	1	0	0
Hemorrhage (probably agonal)	0	0	1	0	0	0
GASTROINTESTINAL						
Decreased ingesta	0	0	2	0	0	6
Pinworms in cecum	0	1	0	0	0	0
KIDNEYS						
Dilated renal pelvis	1	0	1	1	0	0
Pinpoint dark foci on kidney	0	0	0	1	0	0
White mineral deposits in renal pelvis	0	0	0	1	0	0
TESTES						
Decreased size of testicle	0	1	0	-	-	-
UTERUS						
Uterine horns distended with clear fluid	-	-	-	4	0	1

Data listed as number of rats with the listed observation.

TABLE 25

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Tissues Examined Microscopically From Rats From the Scheduled Kill at the End of the 48-Hour Exposure

Sex	Males		Females	
Dose in ppm	0	1000	0	1000
Original number of rats in group	10	10	10	10
Number of rats examined microscopically	5	5	5	5
Liver	5	5	5	5
Brain	5	5	5	5
Kidneys	5	5	5	5
Testes	5	5	-	-
Epididymides	5	5	-	-
Lungs	5	5	5	5
Oil Red O Stain - liver	5	5	5	5
Oil Red O Stain - kidney	5	5	5	5

Data listed as number of rats for which the listed tissue was examined microscopically.

- Indicates not applicable.

TABLE 20

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Histopathologic Observations From Rats From the Scheduled Kill at the End of the 72-Hour Exposure

Sex	Males			Females		
Dose in ppm	0	200	500	0	200	500
Original number of rats in group	10	10	10	10	10	10
Number of rats examined microscopically	5	5	5	5	5	5
LIVER						
Focal or multifocal extramedullary hematopoiesis	3	1	1	1	4	3
Nodular architecture of portions of liver secondary to diaphragmatic hernia showing no visible lesions	1	0	0	0	0	0
Randomly distributed coarse vacuolization of hepatocytes - slight	0	0	0	1	1	1
Altered tinctorial properties of the hepatocytes - slight	0	4	3	0	0	0
Oil Red O Stain for lipid content - increased lipid accumulation within hepatocytes - very slight	0	0	0	5	1	1
- slight	0	0	0	0	4	2
KIDNEYS						
Focal interstitial fibrosis - slight	1	0	0	0	0	0
Focal interstitial mononuclear cell inflammation - slight	1	1	1	0	0	0
Focal dilated renal tubules with eosinophilic cast formation - slight	1	0	0	1	1	0
Multifocal dilated renal tubules with eosinophilic cast formation - slight	0	0	0	1	0	0
Focal basophilic staining of renal tubules - slight	0	1	0	2	2	1
Multifocal basophilic staining of renal tubules - slight	0	1	0	0	1	1
Multifocal calcification - slight	0	0	0	1	0	0
Oil Red O Stain for lipid content - increased lipid accumulation within renal tubular epithelium - slight	0	0	0	0	1	0

Data listed as number of rats with the listed observation.

TABLE 20 (continued)

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Histopathologic Observations From Rats From the Scheduled Kill at the End of the 72-Hour Exposure

Sex	Males			Females		
Dose in ppm	0	200	500	0	200	500
Original number of rats in group	10	10	10	10	10	[illegible]
Number of rats examined microscopically	5	5	5	5	5	[illegible]
LUNGS						
Focal subpleural aggregates of mononuclear cells - slight	1	2	1	0	0	[illegible]
Multifocal peribronchiolar aggregates of mononuclear cells - slight	5	5	5	5	5	5
Focal aggregates of alveolar macrophages - slight	0	1	1	0	1	[illegible]
Focal perivascular aggregates of mononuclear and/or polymorphonuclear cells - slight	0	1	2	0	0	[illegible]
Focal aggregate of mucus - slight	0	0	1	0	0	[illegible]
Focal perivascular edema	0	0	0	0	0	[illegible]
Multifocal perivascular edema	0	0	0	1	1	[illegible]
TESTES						
Unilateral congenital hypoplasia - severe	0	1	0	-	-	-
EPIDIDYMIDES						
Unilateral interstitial edema with slight suppurative inflammation	0	0	2	-	-	
Bilateral interstitial edema with slight suppurative inflammation	0	0	2	-	-	
Unilateral tubules with coagulated proteinaceous and spermatic elements in lumen - moderate	0	0	1	-	-	-
Bilateral tubules with coagulated proteinaceous and spermatic elements in lumen - moderate	0	0	2	-	-	-
Unilateral increased eosinophilic proteinaceous and cellular aggregates	0	0	1	-	-	-
Unilateral loss and necrosis of tubular epithelium	0	0	1	-	-	-
Pericapsular inflammation - slight	0	0	1	-	-	

Data listed as number of rats with the listed observation.

- Indicates not applicable.

TABLE 21

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Gross Necropsy Observations on Rats From the Scheduled Kill at the End of the Recovery Period Which Followed 72 Hours of Exposure

Sex	Male			Female		
Dose in ppm	0	200	500	0	200	500
Original Number of Rats in Group	10	10	10	10	10	10
Number of Rats Examined	10	10	10	10	10	10
EYES						
Slightly cloudy cornea(s)	4	5	5	1	1	1
THYMUS						
Mottled (probably due to agonal hemorrhage)	1	0	0	0	0	0
Fresh and clotted blood in thymus and mediastinum	0	0	0	0	0	1
LUNGS						
Pinpoint dark foci in lung	0	1	0	0	0	0
Focal patchy dark area in lung (agonal)	0	0	0	0	1	0
TESTES						
Decreased size of testicle - unilateral	0	0	3	-	-	-
Decreased size of testes - bilateral	0	0	1	-	-	-
Dark-colored testicle	0	0	1	-	-	-
Flaccid testicle	0	0	1	-	-	-
EPIDIDYMIDES						
White foci on epididymis - unilateral	0	0	2	-	-	-
White foci on epididymis - bilateral	0	0	2	-	-	-
UTERUS						
Uterine horns distended with clear fluid	-	-	-	3	0	3

Data listed as number of rats with the listed observation.

- Indicates not applicable.

TABLE 22

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Tissues Examined Microscopically From Rats From the Scheduled Kill at the End of the Recovery Period Which Followed 72 Hours of Exposure

Sex	Males			Females		
Dose in ppm	0	200	500	0	200	500
Original number of rats in group	10	10	10	10	10	10
Number of rats examined microscopically	5	5	5	5	5	5
Liver	5	5	5	5	5	5
Brain	5	5	5	5	5	5
Kidneys	5	5	5	5	5	5
Testes	5	5	5	-	-	-
Epididymides	5	5	5	-	-	-
Lungs	5	4	5	5	5	5
Oil Red O Stain - liver	5	5	5	5	5	5
Oil Red O Stain - kidney	5	5	5	5	5	5

Data listed as number of rats for which the listed tissue was examined microscopically.

- Indicates not applicable.

TABLE 24

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Gross Necropsy Observations on Rats From the Scheduled Kill at the End of the 48-Hour Exposure

Sex	Males		Females	
Dose in ppm	0	1000	0	1000
Original Number of Rats in Group	10	10	10	10
Number of Rats Examined	10	10	10	10
No visible lesions	6	9	6	6
GENERAL				
Decreased amounts of adipose tissue in abdominal cavity	0	0	0	3
EYES				
Focal corneal cloudiness	0	0	1	0
Slight hyperemia at junction of cornea and sclera	0	0	0	2
KIDNEYS				
Slight dilatation of renal pelvis - unilateral	0	1	1	0
Mineralized deposits in renal pelvis	0	0	1	0
LUNGS				
Area of atelectasis	1	0	0	0
Few red foci	0	0	1	0
THYMUS				
Hemorrhage (probably agonal)	3	0	0	0
SALIVARY				
Diffuse edematous appearance	0	0	1	0
CERVICAL LYMPH NODES				
Enlarged, moist, darkened	0	0	1	0
UTERUS				
Slight distention with clear fluid	-	-	1	0

Data listed as number of rats with the listed observation.

TABLE 23 (continued)

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Histopathologic Observations From Rats From the Scheduled Kill at the End of the Recovery Period Which Followed 72 Hours of Exposure

Sex	Males			Females		
Dose in ppm	0	200	500	0	200	500
Original number of rats in group	10	10	10	10	10	10
Number of rats examined microscopically	5	5	5	5	5	5
LUNGS						
Focal suppurative interstitial pneumonia	1	0	0	0	0	0
Multifocal peribronchiolar aggregates of mononuclear cells - slight	5	4	5	5	4	5
Focal perivascular aggregates of mononuclear cells - slight	0	0	1	0	0	1
Focal subpleural aggregates of mononuclear cells - slight	0	0	2	0	0	1
Focal aggregates of alveolar macrophages - slight	0	0	1	1	0	0
Focal perivascular edema	0	0	0	0	0	1
EPIDIDYMIDES						
Bilateral interstitial edema	0	0	2	-	-	-
Bilateral suppurative inflammation	0	0	2	-	-	-
Unilateral decreased sperm in tubules	0	0	1	-	-	-
Bilateral decreased sperm in tubules	0	0	3	-	-	-
Increased eosinophilic intratubular proteinaceous and cellular aggregates - slight or moderate	0	0	3	-	-	-
Increased necrotic cellular debris in tubules	0	0	1	-	-	-
Unilateral sperm granuloma	0	0	2	-	-	-
Bilateral sperm granuloma	0	0	1	-	-	-
TESTES						
Unilateral moderate atrophy	0	0	2	-	-	-

Data listed as number of rats with the listed observation.

- Indicates not applicable.

TABLE 26

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Histopathologic Observations From Rats From the Scheduled Kill at the End of the 48-Hour Exposure

Sex	Males		Females	
Dose in ppm	0	1000	0	1000
Original number of rats in group	10	10	10	10
Number of rats examined microscopically	5	5	5	5
LIVER				
Focal or multifocal extramedullary hematopoiesis - slight	4	4	5	4
Randomly distributed coarse vacuolization of hepatocytes - very slight or slight	1	0	2	0
Focal necrosis and suppurative inflammation - slight	0	1	0	0
Multifocal necrosis and suppurative inflammation - slight	0	2	0	0
Oil Red O Stain for lipid content - lipid accumulations within hepatocytes				
- very slight	2	0	1	0
- slight	1	2	2	0
- slight to moderate	0	3	0	0
KIDNEYS				
Focal interstitial fibrosis	1	1	0	0
Focal interstitial mononuclear cell inflammation	1	0	0	0
Focal basophilic staining of renal tubules - slight	1	0	3	0
Unilateral hydronephrosis - slight	0	0	1	0
Focal extramedullary hematopoiesis	0	0	0	1
Individual renal tubular cell necrosis - very slight or slight	0	3	0	2
Multifocal renal tubular cell necrosis - slight	0	0	0	2
Focal dilated renal tubules	0	0	2	0
Multifocal calcification	0	0	1	0
Increased renal tubular cytoplasmic homogeneity	0	0	0	4
Oil Red O Stain for lipid content - lipid accumulations within renal tubular cells - very slight	0	0	0	3

Data listed as number of rats with the listed observation.

TABLE 25

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Tissues Examined Microscopically From Rats From the Scheduled Kill at the End of the 48-Hour Exposure

Sex	Males		Females	
Dose in ppm	0	1000	0	1000
Original number of rats in group	10	10	10	10
Number of rats examined microscopically	5	5	5	5
Liver	5	5	5	5
Brain	5	5	5	5
Kidneys	5	5	5	5
Testes	5	5	-	-
Epididymides	5	5	-	-
Lungs	5	5	5	5
Oil Red O Stain - liver	5	5	5	5
Oil Red O Stain - kidney	5	5	5	5

Data listed as number of rats for which the listed tissue was examined microscopically.

- Indicates not applicable.

TABLE 27

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Gross Necropsy Observations on Rats From the Scheduled Kill at the End of the Recovery Period Which Followed 48 Hours of Exposure

Sex	Males		Females	
Dose in ppm	0	1000	0	1000
Original Number of Rats in Group	10	10	10	10
Number of Rats Examined	10	10	10	9
No visible lesions	6	0	5	6
GENERAL				
Decreased adipose tissue	0	9	0	0
Perineal soiling	0	1	0	0
LIVER				
Dark	0	7	0	0
White focus	0	1	0	0
KIDNEYS				
Dark	0	4	0	0
Dilatation of renal pelvis - unilateral	0	2	0	0
Dilatation of renal pelvis - bilateral	0	0	0	1
TESTES				
Decreased size - unilateral	0	2	-	-
Decreased size - bilateral	0	1	-	-
Dark - unilateral	0	1	-	-
Dark - bilateral	0	1	-	-
EPIDIDYMIS(IDES)				
White focus or foci in head - unilateral	0	4	-	-
White focus or foci in head - bilateral	0	1	-	-
Enlarged and moist appearance of head - unilateral	0	2	-	-
THYMUS				
Mottled or hemorrhagic (probably agonal)	4	1	0	1

Data listed as number of rats with the listed observation.

TABLE 26 (continued)

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Histopathologic Observations From Rats From the Scheduled Kill at the End of the 48-Hour Exposure

Sex	Males		Females	
Dose in ppm	0	1000	0	1000
Original number of rats in group	10	10	10	10
Number of rats examined microscopically	5	5	5	5
LUNGS				
Focal or multifocal peribronchiolar aggregates of mononuclear cells - slight	5	5	4	5
Focal aggregate of alveolar macrophages - slight	1	0	0	0
Focal or multifocal perivascular aggregates of mononuclear cells - slight	1	1	1	0
Focal or multifocal perivascular aggregates of polymorphonuclear cells - slight	0	0	1	0
EPIDIDYMIDES				
Decreased spermatic elements in tubules (sexual immaturity)	5	5	-	-
Increased eosinophilic intratubular proteinaceous and cellular aggregates - slight or moderate	0	5	-	-
Coagulated intratubular proteinaceous and spermatic elements - moderate	0	3	-	-
Focal suppurative inflammation	0	3	-	-
Interstitial edema	0	4	-	-
Focal inflammation and edema surrounding capsule	0	3	-	-

Data listed as number of rats with the listed observation.

- Indicates not applicable.

TABLE 28

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Gross Necropsy Observations on Rats Dead or Killed Moribund Following 48 Hours of Exposure, But Predesignated as Part of Recovery Group

Sex	Female
Dose in ppm	1000
Original Number of Rats in Group	10
Number of Rats Dying Spontaneously	1
GENERAL	
Soiling around external nares	1
Perineal soiling	1
Postmortem autolysis - moderate	1
GASTROINTESTINAL	
Multiple erosions or ulcerations with hemorrhage on glandular mucosa of stomach	1
Hemolyzed blood throughout gastrointestinal tract	1

Data listed as number of rats with the listed observation.

TABLE 27 (continued)

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Gross Necropsy Observations on Rats From the Scheduled Kill at the End of the Recovery Period Which Followed 48 Hours of Exposure

Sex	Males		Females	
Dose in ppm	0	1000	0	1000
Original Number of Rats in Group	10	10	10	10
Number of Rats Examined	10	10	10	9
UTERUS				
Slight distention with clear fluid	-	-	4	1
EYES				
Cloudy corneas - bilateral	0	1	0	0
Pinpoint focus on lens - unilateral	0	0	1	0
LUNGS				
Dark focus	0	0	1	0

Data listed as number of rats with the listed observation.

TABLE 30

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Histopathologic Observations From Rats From the Scheduled Kill at the End of the Recovery Period Which Followed 48 Hours of Exposure

Sex	Males		Females	
Dose in ppm	0	1000	0	1000
Original number of rats in group	10	10	10	10
Number of rats examined microscopically	5	5	5	5
LIVER				
Focal or multifocal extramedullary hematopoiesis				
- slight	2	2	1	2
Coarse vacuolization of hepatocytes consistent with fatty change				
- very slight	0	1	0	1
- slight	0	0	5	2
- slight to moderate	0	0	0	1
Altered tinctorial properties				
- slight	0	2	0	0
Oil Red O Stain for lipid content - lipid accumulations within hepatocytes:				
- very slight	2	0	1	1
- slight	1	1	2	1
- slight to moderate	0	3	2	0
- moderate	0	0	0	2
KIDNEYS				
Focal basophilic staining of renal tubules				
- slight	1	1	0	2
Focal dilated renal tubules with eosinophilic cast formation				
- slight	2	0	0	0
Regenerative renal epithelial cells (increased cytoplasmic eosinophilia)				
- slight	0	3	0	4
Oil Red O Stain for lipid content - lipid accumulation in renal tubular epithelium				
- slight	0	3	0	1

Data listed as number of rats with the listed observation.

TABLE 29

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Tissues Examined Microscopically From Rats From the Scheduled Kill at the End of the Recovery Period Which Followed 48 Hours of Exposure

Sex	Males		Females	
Dose in ppm	0	1000	0	1000
Original number of rats in group	10	10	10	10
Number of rats examined microscopically	5	5	5	5
Liver	5	5	5	5
Brain	5	5	5	5
Kidneys	5	5	5	5
Testes	5	5	-	-
Epididymides	5	5	-	-
Lungs	5	5	5	5
Oil Red O Stain - liver	5	5	5	5
Oil Red O Stain - kidney	5	5	5	5

Data listed as number of rats for which the listed tissue was examined microscopically.

- Indicates not applicable.

TABLE 31

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Gross Necropsy Observations on Rats From the Scheduled Kill at the End of the 72-Hour Exposure

Sex	Males		Females	
Dose in ppm	0	1000	0	1000
Number of Rats in Group	10	10	10	10
No visible lesions	8	0	8	0
GENERAL				
Perineal soiling	1	4	0	0
Decreased adipose tissue	0	9	0	10
Soiling around external nares and/or mouth, eyes or front feet	0	3	0	5
Convulsive seizure and excessive salivation prior to decapitation	0	1	0	0
GASTROINTESTINAL				
Decreased ingesta in gastrointestinal tract	0	10	0	9
Hyperemia of small intestine	0	0	0	1
Slight distention of stomach with watery ingesta	0	0	0	1
THYMUS				
Mottled (probably agonal hemorrhage)	1	0	0	0
LUNGS				
Few dark foci	1	0	0	1
Multiple dark foci	0	1	0	0
Dark discoloration of one lobe	0	1	0	0
CERVICAL LYMPH NODES				
Slightly enlarged and dark	1	0	0	0
LIVER				
Dark	0	10	0	10
KIDNEYS				
Dark	0	5	0	4

Data listed as number of rats with the listed observation.

TABLE 30 (continued)

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Histopathologic Observations From Rats From the Scheduled Kill at the End of the Recovery Period Which Followed 48 Hours of Exposure

Sex	Males		Females	
Dose in ppm	0	1000	0	1000
Original number of rats in group	10	10	10	10
Number of rats examined microscopically	5	5	5	5
LUNGS				
Multifocal peribronchial aggregates of mononuclear cells - slight	5	5	5	5
Perivascular edema	0	1	2	0
Focal aggregate of mucus	0	1	0	0
Focal or multifocal aggregate of alveolar macrophages - slight	0	1	0	1
Focal subpleural aggregate of mononuclear cells - slight	0	1	0	0
Focal perivascular aggregate of mononuclear cells - slight	0	0	2	0
EPIDIDYMIDES				
Decreased sperm in tubules	0	5	-	-
Interstitial edema - slight	0	5	-	-
Increased intratubular proteinaceous and cellular aggregates - slight	0	4	-	-
Unilateral sperm granuloma	0	1	-	-
Bilateral sperm granuloma	0	1	-	-
TESTES				
Unilateral atrophy - severe	0	1	-	-
Bilateral atrophy - moderate	0	2	-	-
Unilateral increased multinucleated spermatids in tubules - moderate	0	2	-	-
Unilateral focal spermatocele	0	1	-	-

Data listed as number of rats with the listed observation.

- Indicates not applicable.

TABLE 32

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Tissues Examined Microscopically From Rats From the Scheduled Kill at the End of the 72-Hour Exposure

Sex	Males		Females	
Dose in ppm	0	1000	0	1000
Original number of rats in group	10	10	10	10
Number of rats examined microscopically	5	5	5	5
Liver	5	5	5	5
Brain	5	5	5	5
Kidneys	5	5	5	5
Testes	5	5	-	-
Epididymides	5	5	-	-
Lungs	5	5	5	5
Oil Red O Stain - liver	5	5	5	5
Oil Red O Stain - kidney	5	5	5	5

Data listed as number of rats for which the listed tissue was examined microscopically.

- Indicates not applicable.

TABLE 31 (continued)

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Gross Necropsy Observations on Rats From the Scheduled Kill at the End of the 72-Hour Exposure

Sex	Males		Females	
Dose in ppm	0	1000	0	1000
Number of Rats in Group	10	10	10	10
EYES				
Focal lenticular opacities - bilateral	0	1	0	0
ADRENALS				
Mottled	0	1	0	0
Dark foci - unilateral	0	0	0	1
Dark foci - bilateral	0	0	0	1
UTERUS				
Distention with clear fluid	-	-	2	0

Data listed as number of rats with the listed observation.

TABLE 33 (continued)

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Histopathologic Observations From Rats From the Scheduled Kill at the End of the 72-Hour Exposure

Sex	Males		Females	
Dose in ppm	0	1000	0	1000
Original number of rats in group	10	10	10	10
Number of rats examined microscopically	5	5	5	5
LUNGS				
Multifocal peribronchiolar aggregates of mononuclear cells - slight	5	5	5	5
Focal aggregates of alveolar macrophages - slight	0	1	0	0
Focal subpleural aggregates of mononuclear cells - slight	2	2	1	0
Focal perivascular aggregates of mononuclear cells - slight	1	0	0	0
Multifocal perivascular aggregates of mononuclear cells - slight	1	0	0	0
Focal pleural fibrosis - slight	0	1	1	0
Perivascular edema	0	1	0	3
TESTES				
NVL, but juvenile in appearance	0	5	-	-
EPIDIDYMIDES				
Decreased sperm in tubules (immaturity)	5	5	-	-
Interstitial edema in head	0	5	-	-
Suppurative inflammation in the head	0	4	-	-
Increased eosinophilic intratubular proteinaceous and cellular aggregates - slight to moderate	0	5	-	-
Coagulated proteinaceous and spermatic elements within tubules - moderate	0	3	-	-
BRAIN				
Perivascular and perineural edema	0	0	0	1

Data listed as number of rats with the listed observation.

- Indicates not applicable.

TABLE 33

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Histopathologic Observations From Rats From the Scheduled Kill at the End of the 72-Hour Exposure

Sex	Males		Females	
Dose in ppm	0	1000	0	1000
Original number of rats in group	10	10	10	10
Number of rats examined microscopically	5	5	5	5
LIVER				
Multifocal or focal extramedullary hematopoiesis - slight	2	1	3	0
Individual hepatocellular necrosis - slight	0	0	0	1
Focal coagulative necrosis - slight	0	1	0	0
Randomly distributed coarse vacuolization - very slight to slight	0	1	2	3
Altered tinctorial properties of hepatocytes	0	2	0	5
Oil Red O Stain for lipid content - increased lipid within hepatocytes:				
- very slight	1	0	2	0
- slight	0	1	3	3
- slight to moderate	0	1	0	0
KIDNEYS				
Focal dilated renal tubules - slight	0	0	1	0
Focal dilated renal tubules with eosinophilic cast formation - slight	1	0	1	0
Focal basophilic staining of renal tubules - slight	1	0	1	0
Increased renal tubular cytoplasmic homogeneity	0	3	0	5
Renal tubular epithelial necrosis and sloughing				
- slight to moderate	0	1	0	0
- moderate	0	1	0	4
- severe	0	0	0	1
Oil Red O Stain for lipid content - increased lipid within renal tubular epithelium generally at corticomedullary junction:				
- slight	0	2	0	0
- slight to moderate	0	3	0	0
- moderate	0	0	0	4
- moderate to severe	0	0	0	1

Data listed as number of rats with the listed observation.

TABLE 34 (continued)

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Gross Necropsy Observations on Rats Dead or Killed Moribund Following 72 Hours of Exposure, But Predesignated as Part of the Recovery Phase

Sex	Males	Females
Dose in ppm	1000	1000
Original Number of Rats in Group	10	10
Number of Rats Dying Spontaneously	6	8
LUNGS		
Mottled	1	2
ADRENALS		
Dark focus	0	1

Data listed as number of rats with the listed observation.

TABLE 34

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Gross Necropsy Observations on Rats Dead or Killed Moribund Following 72 Hours of Exposure, But Predesignated as Part of the Recovery Phase

Sex	Males	Females
Dose in ppm	1000	1000
Original Number of Rats in Group	10	10
Number of Rats Dying Spontaneously	6	8
GENERAL		
Lacerations or encrusted areas on tail	2	0
Unkempt appearance	1	1
Decreased adipose tissue	5	8
Exudate lateral to nares, eyes, facial region, or front feet	4	7
Dehydrated appearance	2	1
Red coloration of extremities	1	1
Perineal soiling	2	3
Cannibalism	0	2
Matting of haircoat (perineal region)	0	1
GASTROINTESTINAL		
Decreased ingesta in gastrointestinal tract	5	6
Hemolyzed blood in gastrointestinal tract	1	1
Distention of stomach or intestines with gas and/or watery ingesta	1	2
Dark foci on glandular mucosa of stomach	1	0
THYMUS		
Decreased size	1	1
Hemorrhage (probably agonal)	1	1
LIVER		
Dark	4	7
Firm	2	1
KIDNEYS		
Dark or mottled	4	6

Data listed as number of rats with the listed observation.

TABLE 36

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Tissues Examined Microscopically From Rats From the Scheduled Kill at the End of the Recovery Period Which Followed 72 Hours of Exposure

Sex	Males		Females	
Dose in ppm	0	1000	0	1000
Original number of rats in group	10	10	10	10
Number of rats examined microscopically	5	4	5	2
Liver	5	4	5	2
Brain	5	4	5	2
Kidneys	5	4	5	2
Testes	5	4	-	-
Epididymides	5	4	-	-
Lungs	5	4	5	2
Oil Red O Stain - liver	5	4	5	2
Oil Red O Stain - kidney	5	4	5	2

Data listed as number of rats for which the listed tissue was examined microscopically.

- Indicates not applicable.

TABLE 35

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Gross Necropsy Observations on Rats From the Scheduled Kill at the End of the Recovery Period Which Followed 72 Hours of Exposure

Sex	Males		Females	
Dose in ppm	0	1000	0	1000
Original Number of Rats in Group	10	10	10	10
Number of Rats Examined	10	4	10	2
No visible lesions	6	0	7	2
GENERAL				
Decreased adipose tissue	0	4	0	0
EYES				
Mottled cornea with hemorrhagic areas	0	1	0	0
THYMUS				
Mottled (probably agonal)	1	1	2	0
LUNGS				
Few dark foci	2	1	0	0
Multiple dark foci	1	0	0	0
TESTES				
Decreased size - bilateral	0	4	-	-
Dark - unilateral	0	1	-	-
Dark - bilateral	0	2	-	-
EPIDIDYMIS(IDES)				
Pale foci in head - bilateral	0	1	-	-
KIDNEYS				
Pale	0	1	0	0
UTERUS				
Distention with clear fluid	-	-	1	0
LIVER				
Dark	0	1	0	0

Data listed as number of rats with the listed observation.

TABLE 37 (continued)

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Histopathologic Observations From Rats From the Scheduled Kill at the End of the Recovery Period Which Followed 72 Hours of Exposure

Sex	Males		Females	
Dose in ppm	0	1000	0	1000
Original number of rats in group	10	10	10	10
Number of rats examined microscopically	5	4	5	2
LUNGS				
Focal or multifocal peribronchiolar aggregates of mononuclear cells - slight	5	3	5	2
Focal or multifocal perivascular aggregates of mononuclear cells - slight	0	1	0	0
Focal subpleural aggregates of mononuclear cells - slight	1	0	0	0
Focal aggregates of alveolar macrophages - slight	0	0	0	1
Focal perivascular edema	0	0	0	1
Focal atelectasis	0	0	0	1
EPIDIDYMIDES				
Bilateral interstitial edema	0	4	-	-
Bilateral suppurative inflammation	0	2	-	-
Unilateral decreased sperm in tubules (juvenile)	1	0	-	-
Bilateral decreased sperm in tubules	0	4	-	-
Increased eosinophilic intratubular proteinaceous and cellular aggregates - slight or moderate	0	3	-	-
Bilateral sperm granuloma	0	1	-	-
Focal intertubular calcification	0	1	-	-
TESTES				
Bilateral atrophy - moderate or severe	0	4	-	-
Unilateral focal interstitial edema	0	2	-	-
Increased multinucleated spermatids in tubules	0	2	-	-

Data listed as number of rats with the listed observation.

- Indicates not applicable.

TABLE 37

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Histopathologic Observations From Rats From the Scheduled Kill at the End of the Recovery Period Which Followed 72 Hours of Exposure

Sex	Males		Females	
Dose in ppm	0	1000	0	1000
Original number of rats in group	10	10	10	10
Number of rats examined microscopically	5	4	5	2
LIVER				
Focal or multifocal extramedullary hematopoiesis - slight	4	2	3	1
Coarse vacuolization of hepatocytes consistent with fatty change - very slight or slight	0	0	4	2
Altered tinctorial properties of the hepatocytes	3	4	0	0
Focal aggregates of mononuclear inflammatory cells - slight	0	1	0	0
Oil Red O Stain for lipid content - lipid accumulations within hepatocytes				
- very slight	0	1	1	0
- slight	5	0	1	1
- slight to moderate	0	0	1	1
KIDNEYS				
Focal basophilic staining of renal tubules - slight	3	0	0	0
Multifocal basophilic staining of renal tubules - slight	0	2	0	1
Focal calcification - slight	0	0	0	1
Multifocal tubules with an accentuated granularity and eosinophilia - slight	0	1	0	0
Multifocal renal tubular cells suggestive of regeneration or degeneration - slight	0	1	0	2
Multinucleated renal tubular cells suggestive of degeneration	0	1	0	0
Oil Red O Stain for lipid content - lipid accumulations with renal tubular cells				
- very slight	1	0	0	0
- slight	0	0	0	2
- slight to moderate	0	1	0	0

Data listed as number of rats with the listed observation.

TABLE 39

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Gross Necropsy Observations on Rats Dead or Killed Moribund Following 48 Hours of Exposure, But Predesignated for a Scheduled Kill

Sex	Males	Females
Dose in ppm	2000	2000
Original Number of Rats in Group	20	20
Number of Rats Dying Spontaneously or Killed in a Moribund Condition After 48 Hours	6	8
GENERAL		
Cyanotic appearance of extremities	1	0
Perineal soiling	4	3
Decreased adipose tissue	4	6
GASTROINTESTINAL		
Decreased ingesta in gastrointestinal tract	5	7
Stomach distended with gas and/or watery ingesta	4	7
Hyperemia or hemorrhagic appearance of glandular mucosa of stomach	2	0
Diffuse reddening of ileum	0	1
LIVER		
Dark	4	8
KIDNEYS		
Dark, congested	2	5
LUNGS		
Multiple dark foci	0	1
ADRENALS		
Mottled	1	0
THYMUS		
Hemorrhage (probably agonal)	0	1
EYES		
Hyperemia at junction of cornea and sclera	4	5

Data listed as number of rats with the listed observation.

TABLE 38

METEYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Gross Necropsy Observations on Rats Dead or Killed Moribund During 48 Hours of Exposure, But Predesignated for a Scheduled Kill

Sex	Males	Females
Dose in ppm	2000	2000
Original Number of Rats in Group	20	20
Number of Rats Dying During 48-Hr. Exposure	14	12
GENERAL		
Darkened cyanotic appearance of extremities	7	5
Decreased adipose tissue in abdominal cavity	10	5
Perineal soiling	2	3
Dark staining around mouth and on forepaws	0	1
GASTROINTESTINAL		
Decreased ingesta in gastrointestinal tract	13	11
Stomach and/or intestine distended with gas and/or watery ingesta	12	4
Marked hyperemia of serosal blood vessels of stomach	1	0
Mottled, dark, congested, hyperemic or hemorrhagic appearance of glandular mucosa of stomach	6	2
Depressed areas on glandular gastric mucosa	1	0
LIVER		
Dark, congested, or mottled	13	9
Herniation of diaphragm involving a nodular portion of liver	0	1
THYMUS		
Hemorrhage (probably agonal)	9	5
KIDNEYS		
Darkened appearance	2	2
LUNGS		
Dark, mottled or congested	2	5
URINARY BLADDER		
Proteinaceous plug in lumen	3	0
TESTES		
Decreased size - unilateral	1	-

Data listed as number of rats with the listed observation.

TABLE 41

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Histopathologic Observations From Rats Predesignated for a Scheduled Kill Following 48 Hours of Exposure

Sex	Males	Females
Dose in ppm	2000	2000
Original number of rats in scheduled recovery group	10	10
Number of rats examined microscopically	4	5
LIVER		
Altered tinctorial properties of the hepatocytes (increased homogeneity, decreased basophilia)	4	5
Degeneration of the hepatocytes consisting of either vacuolization, feathery type change, or change in staining characteristics	0	1
Increased vacuolization of hepatocytes - slight	1	1
Swollen appearance of hepatocytes	0	1
Variability of hepatocellular nuclear clumping and/or size	4	3
Individual hepatocellular necrosis - slight	4	3
Multifocal individual hepatocellular necrosis	0	2
Multifocal centrilobular hepatocellular necrosis - slight	1	0
Inflammatory cells associated with necrosis - slight	1	0
Focal extramedullary hematopoiesis - slight	0	1
Oil Red O Stain for lipid - lipid accumulation within hepatocytes - slight	0	1
- slight to moderate	2	0
KIDNEYS		
Renal tubular necrosis and epithelial sloughing - moderate or severe	4	5
Individual cell necrosis	2	0
Calcium-like material within tubules	2	0
Increased basophilic staining of renal tubules	1	0
Increased cytoplasmic eosinophilic homogeneity of renal tubules (decreased granularity)	0	2

Data listed as number of rats with the listed observation.

TABLE 40

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Tissues Examined Microscopically From Rats Predesignated for a Scheduled Kill Following 48 Hours of Exposure

Sex	Males	Females
Dose in ppm	2000	2000
Original number of rats in group	10	10
Number of rats examined microscopically	4	5
Liver	4	5
Brain	4	5
Kidneys	4	5
Testes	4	-
Epididymides	4	-
Lungs	4	5
Oil Red O Stain - liver	4	5
Oil Red O Stain - kidney	4	5

Data listed as number of rats for which the listed tissue was examined microscopically.

- Indicates not applicable.

TABLE 42

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Gross Necropsy Observations on Rats Dead or Killed Moribund Following 72 Hours of Exposure, But Predesignated for a Scheduled Kill

Sex	Males	Females
Dose in ppm	2000	2000
Original Number of Rats in Group	20	20
Number of Rats Dying During 72-Hr. Exposure	20	20
GENERAL		
Darkened, cyanotic appearance of extremities	20	19
Decreased adipose tissue	19	16
Perineal soiling	4	3
GASTROINTESTINAL		
Decreased ingesta in gastrointestinal tract	18	17
Distention of stomach with gas and/or watery ingesta	14	10
Mottled or hemorrhagic appearance of glandular mucosa of stomach	2	1
Multiple reddened areas suggestive of erosion or ulceration on glandular mucosa of stomach	2	1
Soft consistency of fecal contents	0	2
LIVER		
Dark or mottled	19	17
Herniation of diaphragm involving reddened nodular portion of liver	1	0
KIDNEYS		
Dark	5	3
LUNGS		
Dark or mottled	9	13
ADRENALS		
Mottled	1	0
Dark focus(foci) - unilateral	1	1
Dark focus(foci) - bilateral	2	0
THYMUS		
Hemorrhagic (probably agonal)	10	5
MESENTERIC LYMPH NODE		
Enlarged and edematous	1	0

Data listed as number of rats with the listed observation.

TABLE 41 (continued)

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Histopathologic Observations From Rats Predesignated for a Scheduled Kill Following 48 Hours of Exposure

Sex	Males	Females
Dose in ppm	2000	2000
Original number of rats in scheduled recovery group	10	10
Number of rats examined microscopically	4	5
KIDNEYS (Continued)		
Oil Red O Stain for lipid content - lipid accumulation in renal tubules		
- ungraded	0	1
- slight to moderate	2	0
- moderate	0	4
LUNGS		
Multifocal or focal peribronchial aggregates of mononuclear cells		
- slight	4	5
Focal accumulation of mucus	0	1
Focal atelectasis	0	1
TESTES		
Slight juvenile appearance	3	-
EPIDIDYMIDES		
Bilateral decreased sperm in the tubules (juvenile)	4	-
Bilateral interstitial edema	4	-
Bilateral suppurative inflammation	4	-
Coagulated proteinaceous and spermatic elements in tubules		
- moderate or severe	4	-
Eosinophilic intratubular proteinaceous and cellular aggregates		
- moderate	3	-
Extension of edema and inflammation into surrounding fat	1	-

Data listed as number of rats with the listed observation.

- Indicates not applicable.

TABLE 44

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Histopathologic Observations From Rats Predesignated for a Scheduled Kill Following 72 Hours of Exposure

Sex	Males	Females
Dose in ppm	2000	2000
Original number of rats in the scheduled recovery group	10	10
Number of rats examined microscopically	5	5
LIVER		
Altered tinctorial properties of the hepatocytes (increased homogeneity, decreased basophilia)	4	2
Degeneration of the hepatocytes consisting of either vacuolization, feathery type change, or change in staining characteristics	0	3
Increased vacuolization of hepatocytes - slight	2	2
Decreased eosinophilia and increased granularity of the hepatocytes - severe	0	1
Increased basophilia of hepatocytes	1	0
Variability of hepatocellular nuclear clumping and/or size	5	1
Individual hepatocellular necrosis - slight or moderate	5	2
Multifocal individual hepatocellular necrosis - slight or moderate	0	3
Focal hepatocellular necrosis - slight of moderate	1	1
Multifocal hepatocellular necrosis - slight	0	1
Inflammatory cells associated with necrosis - slight	0	1
Generalized congestion	0	3
Oil Red O Stain for lipid - lipid accumulation within hepatocytes		
- slight	2	4
- slight to moderate	1	0
- moderate	2	1

Data listed as number of rats with the listed observation.

TABLE 43

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Tissues Examined Microscopically From Rats Predesignated for a Scheduled Kill Following 72 Hours of Exposure

Sex	Males	Females
Dose in ppm	2000	2000
Original number of rats in group	10	10
Number of rats examined microscopically	5	5
Liver	5	5
Brain	5	5
Kidneys	5	5
Testes	5	-
Epididymides	5	-
Lungs	5	5
Oil Red O Stain - liver	5	5
Oil Red O Stain - kidney	5	5

Data listed as number of rats for which the listed tissue was examined microscopically.

-Indicates not applicable.

TABLE 44 (continued)

METHYL CHLORIDE: 48 AND 72 HOUR CONTINUOUS INHALATION EXPOSURE IN RATS FOLLOWED BY UP TO 12 DAYS OF RECOVERY

Histopathologic Observations From Rats Predesignated for a Scheduled Kill Following 72 Hours of Exposure

Sex	Males	Females
Dose in ppm	2000	2000
Original number of rats in the scheduled recovery group	10	10
Number of rats examined microscopically	5	5
KIDNEYS		
Renal tubular necrosis and epithelial sloughing - moderate or severe	5	5
Increased cytoplasmic eosinophilic homogeneity of renal tubules (decreased granularity)	0	5
Oil Red O Stain for lipid content - lipid accumulations in renal tubules		
- slight	0	1
- moderate	5	4
LUNGS		
Multifocal or focal peribronchiolar aggregates of mononuclear cells - slight	5	4
Focal atelectasis	0	1
Perivascular edema - slight	5	5
Generalized congestion	2	5
Focal subpleural aggregates of mononuclear cells - slight	0	1
TESTES		
Slight juvenile appearance	3	-
EPIDIDYMIDES		
Bilateral decreased sperm in the tubules	5	-
Bilateral interstitial edema	5	-
Bilateral suppurative inflammation - slight	4	-
Coagulated proteinaceous and spermatic elements in tubules - moderate or severe	5	-
Eosinophilic intratubular proteinaceous and cellular aggregates - moderate	5	-

Data listed as number of rats with the listed observation.

-Indicates not applicable.

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PULOMONARY PHYSIOLOGY AND INHALATION DOSIMETRY IN RATS: DEVELOPMENT OF A METHOD WITH TWO EXAMPLES

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ABSTRACT

Methods were developed to quantitate the net uptake of an inhaled material in rats under apparent steady state conditions, and to simultaneously measure respiratory frequency, tidal volume, and minute volume. During steady state, if metabolism is the only significant means of elimination, the net uptake rate of an inhaled material will equal its rate of metabolism. The rates of metabolism of methyl chloride (MeCl) in 50 and 1000 ppm exposed rats were 0.20 and 3.3 nM/min/g; the rates of metabolism of methylene chloride ($MeCl_2$) in 50 and 1500 ppm exposed rats were 0.57 and 2.8 nM/min/g. The uptake values obtained for both solvents were consistent with pharmacokinetic and metabolism data that was previously obtained in our laboratory. A pharmacokinetic model incorporating the metabolic rate at steady state, blood concentration vs time, and respiratory minute volume was used to describe the fate of inhaled MeCl in F344 rats, and to estimate the inhaled "effective" dose in 50 and 1000 ppm 6 hr-exposed rats (3.8 and 67 mg/kg respectively). The approach used in these studies appears to be a useful method for the evaluation of metabolic rates and for inhalation dosimetry.

INTRODUCTION

Pharmacokinetic data have been used extensively in evaluating exposure concentration-response relationships of inhaled materials. One parameter that is not routinely measured in toxicity studies is the uptake of parent compound. This is a potentially useful means for assessing the rate of metabolism and, in conjunction with pharmacokinetic data, the cumulative net uptake during exposure (effective dose). At steady state, the rate of uptake is equal to the rate of metabolism plus non-pulmonary excretion of parent compound (i.e., by definition input must equal output at steady state). If there is no significant non-pulmonary excretion of parent compound, steady state uptake rate must equal the metabolism rate. Two potentially important applications of these determinations are the comparisons between routes of administration made possible by knowing the inhaled dose, and the assessment of possible exposure concentration dependent (or saturation) kinetics. The latter phenomenon has been shown to profoundly influence the relationship between administered dose and toxicity (Ramsey and Gehring, 1980).

Inhaled materials can cause changes in pulmonary physiological parameters. Alarie (1973) has reviewed the phenomenon of sensory irritation by airborne chemicals. Irritants, according to Alarie, produce a protective reflex designed to reduce exposure of the respiratory tract. A chronic inhalation toxicity study of formaldehyde provides an example in which the relative sensitivity of mice and rats to nasal carcinoma appears to be related to the irritant reflex producing potential in the two species (Chang, et al., 1981). Mice reduce respiratory frequency and minute volume in response to formaldehyde to a greater extent than rats, and mice also have a smaller incidence of formaldehyde induced nasal carcinomas.

Likens and Mauderly (1979) have reviewed methods that have been used for respiratory measurements in small laboratory animals. One method was volume displacement plethysmography. Barrows (1980) used this method in a system that utilized an animal restraining tube with a plethysmograph tube that slipped over the restraining tube when measurements were made. An advantage of this procedure is that the animal is unlikely to become overheated while in the ventilated restraining tube. Long periods within a small closed plethysmograph potentially cause animal heat stress which can have marked effects on respiration.

We developed an apparatus to utilize whole body plethysmography in conjunction with a low dead volume, head only, dynamic inhalation exposure apparatus. This system allowed inhalation exposure of a rat to a known concentration of a material, and simultaneous measurement of vapor uptake and ventilatory functions.

Our system was tested by performing repeated respiratory physiological measurements in rodents to assess the optimal time(s) for sampling and to determine the precision and repeatability of the procedure. Steady state uptake of methyl chloride (MeCl) and methylene chloride ($MeCl_2$) were determined, and ventilatory function measurements were made during exposure. These chemicals were selected because blood concentration data from exposed rats were already available for comparisons (Landry, et al., 1981; McKenna, et. al., 1979). Methyl chloride provided an example of chemical that exhibits linear kinetics from 50 to 1000 ppm exposure in rats (Landry et al., 1981) and $MeCl_2$ was an example of a chemical displaying saturable kinetics in rats exposed to 50 and 1500 ppm (McKenna et al., 1979).

MATERIALS AND METHODS

A. Test Materials and Analysis

Methyl chloride was obtained from Matheson Gas Products (Joliet, IL). Purity was specified to be >99.5%; this was confirmed by GC analysis with a flame ionization detector. Technical grade $MeCl_2$ was obtained from Dow Chemical USA. The stabilizer and principle impurities identified (those above 10 ppm) in the test material were cyclohexane (a stabilizer, 383 ppm), trans-1,2-dichloroethylene (100 ppm), vinylidene chloride (42 ppm), and water (22 ppm).

Test atmospheres were analyzed with a Varian 2400 gas chromatograph (Varian Instrument Co., Sunnyvale, CA). A six-port valve with a 1 ml sampling loop was used to load samples on the columns (6' x 1/8"; 60/80 mesh Tenax GC for MeCl and Poropak QS for $MeCl_2$), and peak height response of the flame ionization detector was used to quantitate MeCl and $MeCl_2$ concentrations. Standard curves were made prior to exposures by preparing a series of known concentrations of MeCl or $MeCl_2$ in 100 ℓ gas sampling bags made of Saran resin.

B. Animals

Male Fischer 344 rats (200 to 250 g when exposed) were obtained from the Charles River Breeding Laboratory. Rats were acclimated to the laboratory for at least one week prior to exposure. Animals were provided water and certified Purina Rodent Chow *ad libitum* (except during exposure) and were housed and exposed in rooms designed to maintain ~22°C, 40 to 60% relative humidity, and a 12 hour photocycle. Body weights were recorded prior to plethysmography measurements or inhalation exposures. Animals were assigned to test groups so that differences in mean body weights and variance would be minimized.

C. Exposure Apparatus

This apparatus (Figure 1a) employed a wire mesh restraining tube to support the body of the rat. The rat's head was exposed in an acrylic plastic chamber. The conical-shaped exposure chamber was designed to minimize dead volume and rebreathing of test atmosphere. A rubber diaphragm was placed around the rat's neck to seal the exposure chamber from the plethysmograph chamber. A dual exhaust manifold prevented the rat from inadvertently blocking the chamber exhaust.

The test atmosphere was pumped from a gas sampling bag containing the desired concentration of test material. An FMI pump (Fluid Metering Inc., Oyster Bay, NY) was used to produce a 300 ml/min chamber airflow, as measured with a soap bubble flowmeter. Since the FMI positive displacement pump could cause displacement of the rubber diaphragm seal around the rat's neck, a 4 ℓ ballast reservoir was placed in the airstream to reduce significant pressure fluctuations due to the pump. The head-only exposure apparatus was tested for possible adsorption of test material by passing known concentrations of MeCl and $MeCl_2$ through the device without a rat. No uptake of either material was detected.

D. Plethysmography

An aluminum tube (Figure 1b) was placed over the rat restraining tube 1 to 2 minutes prior to making ventilatory function measurements. The aluminum tube had a brass port (7 mm i.d.) that allowed connection with a Fleisch pneumotachograph (Gould Inc., Oxnard, CA). A pressure transducer (Grass PT5A; Grass Instrument Co., Quincy, MA) created an electrical signal proportionate to the pressure produced by airflow in the pneumotachograph. The signal from the pressure transducer was processed by a Beckman Dynograph strain gage coupler and amplifier (Beckman Instrument Inc., Schiller Park, IL). The amplifier output was connected to an LLL 8080 microcomputer with an analogue to digital convertor. The digitalized airflow data were used to calculate respiratory frequency, tidal volume, and minute volume (RMV).

E. Vapor Uptake Measurements

Air entering and leaving the exposure chamber (provided at 300 ml/min) was sampled at 12 ml/min via 1/8" Teflon tubing. A stainless steel 2-way valve (Whitey Co., Cleveland, OH) was used to select the sampling line.

The concentrations entering the chamber were normally measured in duplicate before and after measuring the test material concentration in the air leaving the chamber (also measured in duplicate). This procedure maximized the sensitivity to small differences between intake concentration and exhaust concentration.

The uptake of test material was calculated according to equation (1):

$$\mu M/min = (a-b)c \div 24\ \ell/M \qquad (1)$$

where a equals concentration entering chamber (ppm, i.e. μM(test material)/M(air)), b equals concentration leaving chamber (ppm), and c equals chamber airflow (0.3 ℓ/min).

The ratio of expired to inspired concentrations of test material (R) was also calculated:

$$R = 1-[(1-b/a)(c/RMV)] \qquad (2)$$

where RMV is the respiratory minute volume in ℓ/min.

Vapor uptake was measured at 1.5 and 2 hours (MeCl) and at 2.5 and 3 hrs ($MeCl_2$). These times corresponded to an apparent steady state of parent compound in blood for inhaled MeCl (Landry, et al., 1981) and $MeCl_2$ (McKenna, et al., 1979). At the end of the $MeCl_2$ exposures, air from the chamber exhaust was collected for ∿10 min in a gas sampling bag and the carbon monoxide concentration was measured with an Ecolyzer (Energetics Science, Inc., Elmsford, NY). The instrument was calibrated with a known concentration of CO and checked for interferences with chamber exhaust air from a nonexposed rat.

RESULTS

A. Plethysmograph Optimization

Calibration of the airflow measurement device (consisting of the pneumotachograph, pressure transducer, amplifier, and microcomputer) was routinely checked by pumping air from a syringe through the pneumotachograph. The microcomputer then calculated the volume of the air displaced by the syringe by integrating the airflow through the pneumotachograph. This system was also calibrated with a rat carcass inside the plethysmograph, and a piston displacement pump (FMI model RP G-150) connected to the plethysmograph to simulate breathing. The volume of air calculated by the microcomputer was 15% lower than that indicated by the calibration check with the syringe. This difference was incorporated into the calculations as a correction factor.

Because uptake measurements are dependent on quantitating the difference in concentration entering and leaving the exposure chamber, the minimun adequate airflow for normal respiration was desired to maximize sensitivity. Alterations in respiratory frequency and RMV reflect the adequacy of the air supply. Airflows of 200, 300, and 500 ml/min were then evaluated with 5 rats/group. Each rat was placed in the restraining device and measurements were made at 5, 10, 15 and 20 min (Table 1). A two-way repeated measures ANOVA of these data indicated an airflow-related effect on RMV, and a time-related effect on variance of respiratory parameters. RMV values in rats provided 200 ml/min were considerably greater than those of rats provided 300 or 500 ml/min (Table 1). However, the difference in RMV between the groups provided 300 ml/min or 500 ml/min was not statistically significant ($p < 0.05$). Rats provided 300 (or 500) ml/min airflow (without test material) initially struggled within the restraining device, and had elevated respiratory frequency and RMV (Figure 2). After ~10 min, the respiratory parameters appeared to have decreased in magnitude, and were somewhat stabilized. Since 300 ml/min was approximately 1.5 to 2x the rat's RMV, and it resulted in similar respiratory physiology values to rats provided 500 ml/min; 300 ml/min was selected as a minimum adequate airflow.

B. Uptake and Respiratory Measurements

Methyl chloride uptake rate and the ratio of MeCl concentrations in expired and inspired air are provided in Table 2. Measurements made at 1.5 and 2.0 hr of exposure revealed no detectable change in uptake rate. The uptake rate was 16.5 fold greater in rats exposed to 1000 ppm versus rats exposed to 50 ppm. This ratio was of borderline statistical significance ($0.05 < p < 0.1$, t test) when tested for a difference from the ratio of 20 as predicted by a linear model. Respiratory frequency, tidal volume, and RMV were measured concomitantly with uptake (Table 3). Mean tidal volume and RMV were significantly less (t test, $p < 0.05$) in rats exposed to 1000 vs 50 ppm MeCl.

Methylene chloride uptake rate, ratios of inspired to expired air concentrations, and expired air CO concentrations are provided in Table 4. Measurements made at 2.5 and 3.0 hr of exposure revealed no detectable change in uptake. Neither the $MeCl_2$ uptake rate nor the end exposure expired air CO concentrations were proportionate to exposure concentration. There was only a 5 fold difference in uptake rate and 3 fold difference in expired air CO concentration despite a 30 fold difference in exposure concentration. There were statistically significant differences in mean respiratory frequency, tidal volume, and RMV between rats exposed to 1500 versus 50 ppm $MeCl_2$. The mean RMV was 28% less in 1500 ppm exposed rats.

DISCUSSION

An important feature of the exposure device/plethysmograph combination is that simultaneous measurement of uptake (i.e. metabolism) and respiratory parameters is possible. Exposure concentration dependent reduction of RMV will reduce the rate at which a test atmosphere is inspired. This effect will reduce uptake of the material, if uptake is limited by ventilation.

A pharmacokinetic model describing the fate of inspired MeCl allowed a quantitative analysis of the interrelationships of MeCl exposure concentration, RMV, uptake, and blood MeCl concentration. (Blood MeCl concentrations were measured in male Fischer 344 rats under similar exposure conditions by Landry, et al., 1981). In this pharmacokinetic model (Figure 3)[1], MeCl inspiration rate was equal to chamber concentration times RMV. Blood concentration and steady-state uptake data were used to obtain the least squares estimate of rate constants for expiration and metabolism of MeCl and intercompartment exchange, and the volume of the central compartment (V1). The values obtained for these parameters are provided in Table 5. The simulations of blood concentration data are provided in Figure 4. After data from the 1000 ppm exposure were fit, estimates were made for the rate of expiration and metabolism of MeCl during and after a 50 ppm exposure. The RMV measured during the 50 ppm exposure was incorporated into these estimates. Attempts to obtain reasonable fits with other combinations of V1 and rate constants were not successful.

This model showed that although RMV was diminished by 20% in 1000 ppm exposed rats relative to 50 ppm exposed rats, the relative decrease in MeCl inspiration did not entirely account for the apparently non-linear uptake rates. (The mean uptake rate in 1000 ppm exposed rats was 16.5 fold, not 20 fold greater than in 50 ppm exposed rats.) Rate constants for both metabolism (k_m) and expiration (k_{1E}) were affected by exposure concentration (Table 5). This suggests that, <u>at steady state</u>, MeCl uptake rate was not strictly ventilation limited.

Methyl chloride inspiration rate (chamber concentration times RMV), metabolism rate (k_m times the amount of MeCl in compartment 1 according

[1]The computer program is provided in Appendix A.

to the model), and expiration rate (k_{1E} times the amount of MeCl in Cl) are shown in Figure 5. The expiration rate is depicted in Figure 5 to illustrate that, at steady state, expiration plus metabolism equals MeCl inspiration. An analagous depiction of the fate of inhaled carbon disulfide (CS_2) in humans was made by Demus (1967), who plotted concentration of inspired and expired CS_2. Division of MeCl inspiration and expiration rates (Figure 5) by RMV gives concentration of MeCl in inspired and expired air. The integration of rates of MeCl inspiration, metabolism and expiration yielded values for the amount of MeCl that was inspired, metabolized during and after exposure, or expired unchanged. These amounts are illustrated in Figure 5.

The amount of MeCl inspired during exposure (areas B plus M plus E in Figure 5) may be considered to be the administered dose of MeCl. The effective dose is the amount of MeCl that remains in the body at the end of exposure (B) plus the amount that has been metabolized (M). The pharmacokinetic model used to describe MeCl allowed an estimate of the effective dose to be made for rats exposed to 50 or 1000 ppm MeCl (Table 5). The effective dose resulting from exposing 226 g F344 rats to 50 or 1000 ppm were estimated to be 3.8 and 67 mg/kg, and were nearly proportionate (67/3.8=17.6) to the exposure concentrations. The small difference from the ratio of exposure concentrations (1000/50=20) apparently reflects slightly less MeCl inspiration and metabolism (relative to exposure concentration) in the 1000 ppm exposed rats. As indicated in Figure 5, most of the effective dose consists of MeCl metabolized during exposure, rather than retained as parent compound.

Methylene chloride metabolism was saturable in male Sprague-Dawley rats: apparent steady state plasma $MeCl_2$ concentrations were disproportionately greater in 1500 versus 50 ppm exposed rats, and post-exposure excretion of $MeCl_2$, CO_2, and CO were consistent with a marked degree of exposure concentration dependent metabolism in animals exposed to 1500 vs 50 ppm (McKenna et al., 1979). Although the values provided by McKenna are not directly comparable to our uptake measurements, the demonstration of exposure concentration dependent metabolism by different methods helps to confirm the value of the uptake and CO expiration measurements.

The marked exposure-concentration dependence of $MeCl_2$ uptake cannot be accounted for by the 28% decrease in mean RMV of 1500 versus 50 ppm exposed rats. The uptake is largely related to saturable $MeCl_2$ metabolism, and not simply a physiological response to inhaled $MeCl_2$.

Andersen, et al. (1980) and Filser and Bolt (1981) have described methods that utilize the recirculation of test atmosphere in a closed system. These methods have been used to measured uptake of a number of materials, and are somewhat similar to the methods described in this paper. However, our dynamic exposure apparatus measures uptake at steady state, and respiratory physiology parameters can be evaluated during exposure with the whole body plethysmograph. Other differences include the possible interaction of dessicants and adsorbents with test material in the recirculating system, and the potential differences in measurement sensitivity of the two systems.

Andersen (1980) measured uptake in male Fischer 344 rats exposed to MeCl in a closed recirculating system. Based on Andersen's equation, the metabolic rate in 50 and 1000 ppm exposed rats would be 0.17 and 1.8 nM/min/g. There appears to be reasonable agreement in estimated rates of metabolism (our values were 0.20 and 3.3 nM/min/g) despite the differences between the methods.

Cahalan et al. (1982) have demonstrated the utility of uptake measurements to determine metabolic rates in humans. These authors measure RMV and anesthetic concentration in inspired and expired air to estimate clearance and metabolism of isoflurane and halothane. These data allowed determination of V_{max} and K_m for halothane which was related to the clinical use of this anesthetic.

The measurement of uptake under dynamic exposure conditions is suitable for a variety of chemicals that are rapidly metabolized (so that the difference between inspired and expired concentrations is quantifiable), and that attain steady-state in a reasonable period of time. Elimination of parent compound must either be predominantly via exhalation, or other routes of elimination must be quantitated. For example, urinary excretion of parent compound might be erroneously interpreted as metabolism.

Important features of gas uptake measurements make it a useful tool. Precise measurement of vapors or gases in a test atmosphere normally much easier than other assessments of metabolism rates (eg radiotracer disposition studies or analysis of parent compound in blood). Also, uptake (and dose) have not been commonly measured in inhalation studies. When sufficient pharmacokinetic information is

available, gas uptake measurements allow the evaluation of dose in relation to exposure concentration utilizing measured respiratory minute volume and uptake.

The device and methods described here provide a useful means of assessing apparent steady-state metabolism of an inhaled vapor and respiratory physiological parameters (frequency, tidal volume, and minute volume). These determinations were applied to MeCl and $MeCl_2$, and resulted in values for metabolic rates that were consistent with what is currently known. Methyl chloride metabolism was predominantly linear, and $MeCl_2$ was markedly non-linear over the concentrations tested. Incorporation of uptake values into a pharmacokinetic model allowed an estimation of dose in rats exposed to 50 or 1000 ppm MeCl.

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LIST OF FIGURES

Figure 1 Head-only exposure apparatus (Figure 1a), including wire mesh restraining tube, conical exposure chambers, and stand. Exposure apparatus with plethysmograph tube in place (Figure 1b). The vent on top of the plethysmograph is connected to a pneumotachograph.

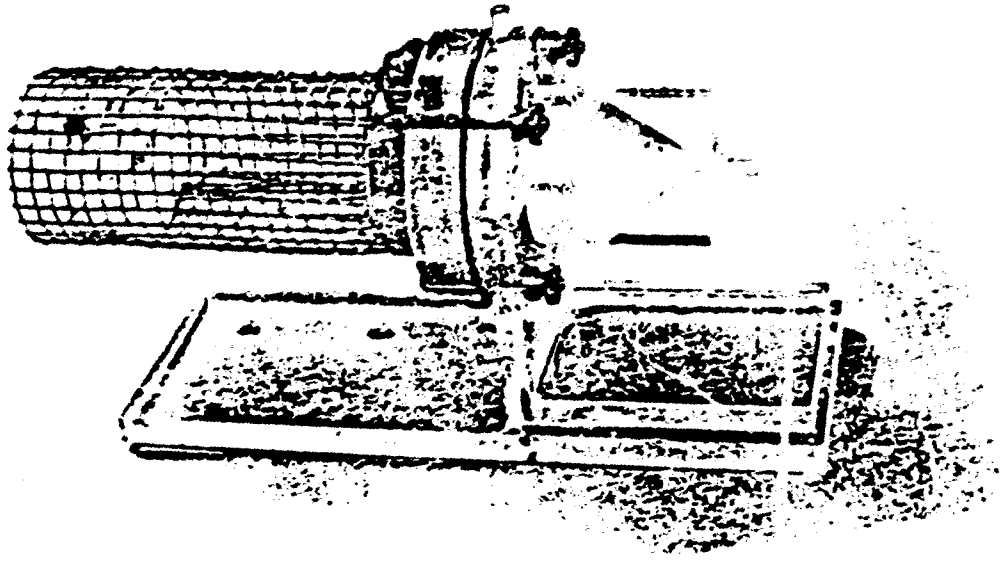
Figure 2 Respiratory frequency (Figure 2a) and RMV (Figure 2b) in 5 rats provided 300 ml/min of chamber airflow each (Values are $\bar{X}\pm SD$).

Figure 3 Pharmacokinetic model for inhaled MeCl. Input = chamber concentration (CC) times RMV. First order rate constants include k_{1E} (exhalation of MeCl), k_m (metabolism), and k_{12} and k_{21} (transport constants between compartments). Compartment 1 includes blood.

Figure 4 Blood MeCl concentrations in rats during and after a 3[illegible] min MeCl exposure to 50 ppm (■) or 1000 ppm (●). Data points are from individual rats from groups of 4 per exposure concentration (data from Landry, et al., 1981). The lines drawn through the data points correspond to the pharmacokinetic model in Figure 3.

Figure 5 Fate of inhaled MeCl in rats exposed to 50 ppm or 1000 ppm. The lines represent MeCl inspiration rate (----), metabolism rate (———), and expiration rate (—— ——). The shaded area corresponds to the dose of inhaled MeCl. These lines are derived from a computer model that utilized chamber concentration and RMV to calculate MeCl inspiration, MeCl uptake in 50 (■) and 1000 ppm (●) exposed rats measured in duplicate 6 times/exposure concentration, and blood MeCl concentrations (as shown in Figure 4). Area B is equivalent to the amount of MeCl remaining in the body as parent compound when the exposure ends. Area M is equivalent to the amount of MeCl metabolized during exposure. Area E is the amount of MeCl that is expired during the exposure. The amount of MeCl inspired equals the sum of B, M, and E. When the exposure is terminated the MeCl in the body (B) can be expired as parent compound (Ep) or metabolized (Mp). The effective dose (B+M) is the area that is shaded grey.

FIGURE 1



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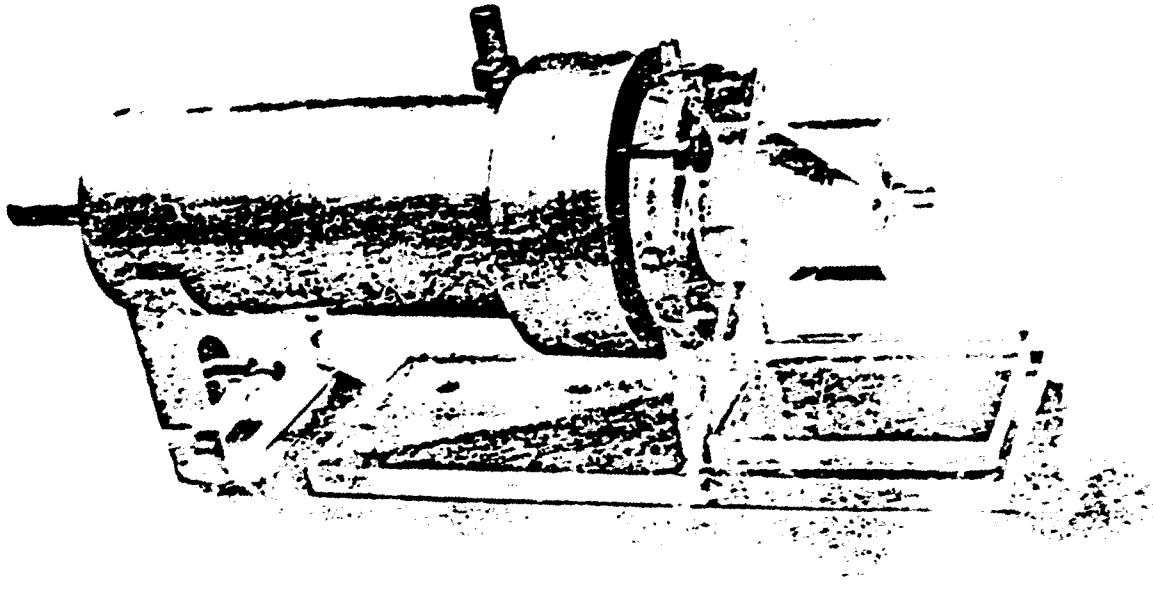

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FIGURE 2a

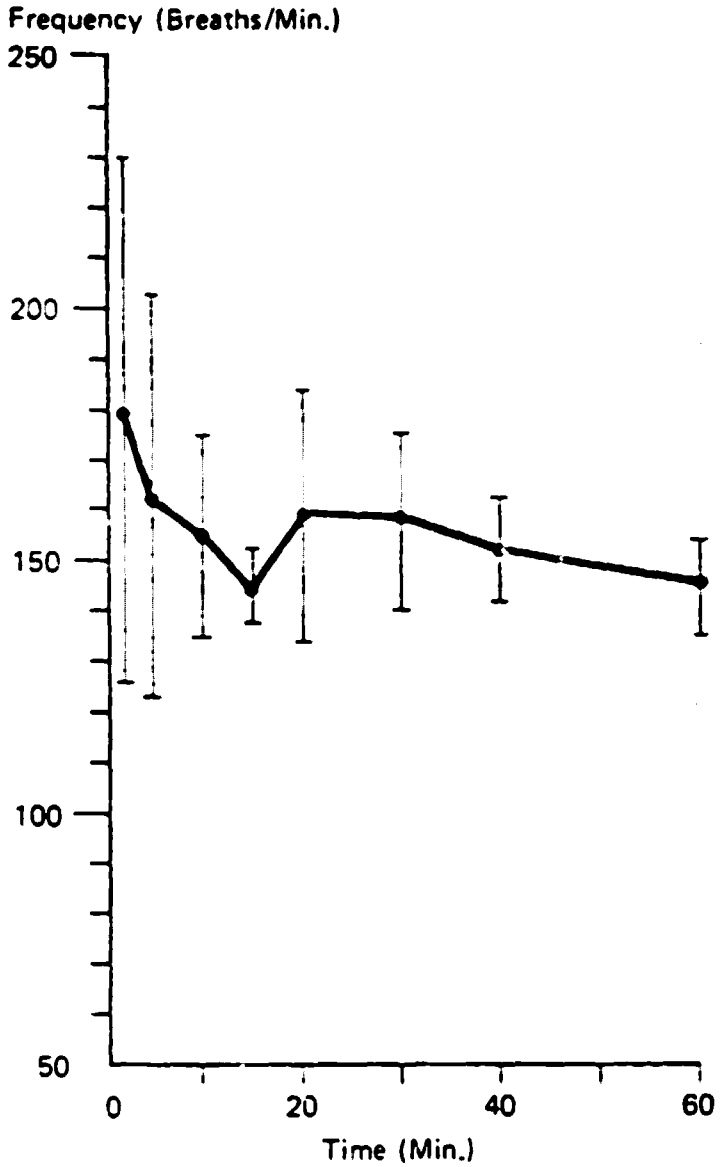


FIGURE 2b

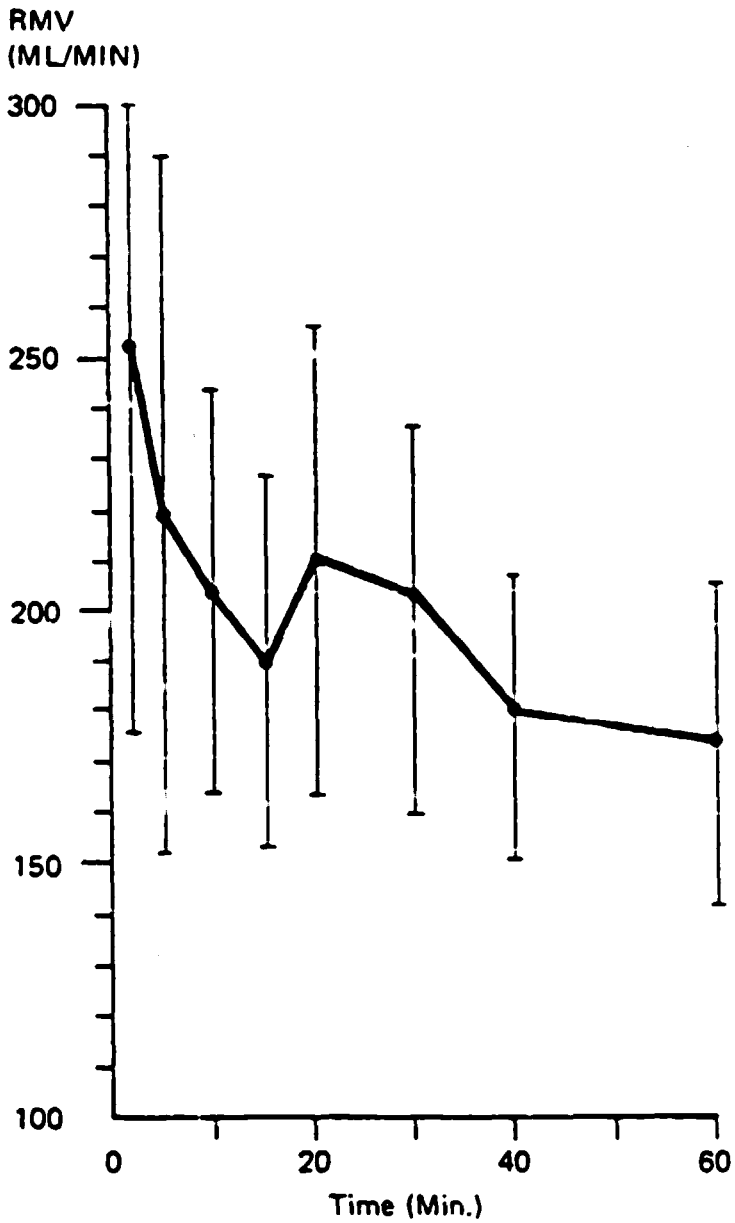


FIGURE 3

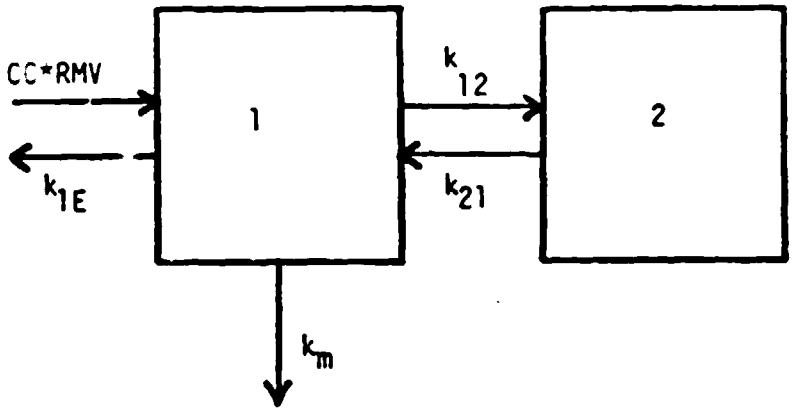


FIGURE 4

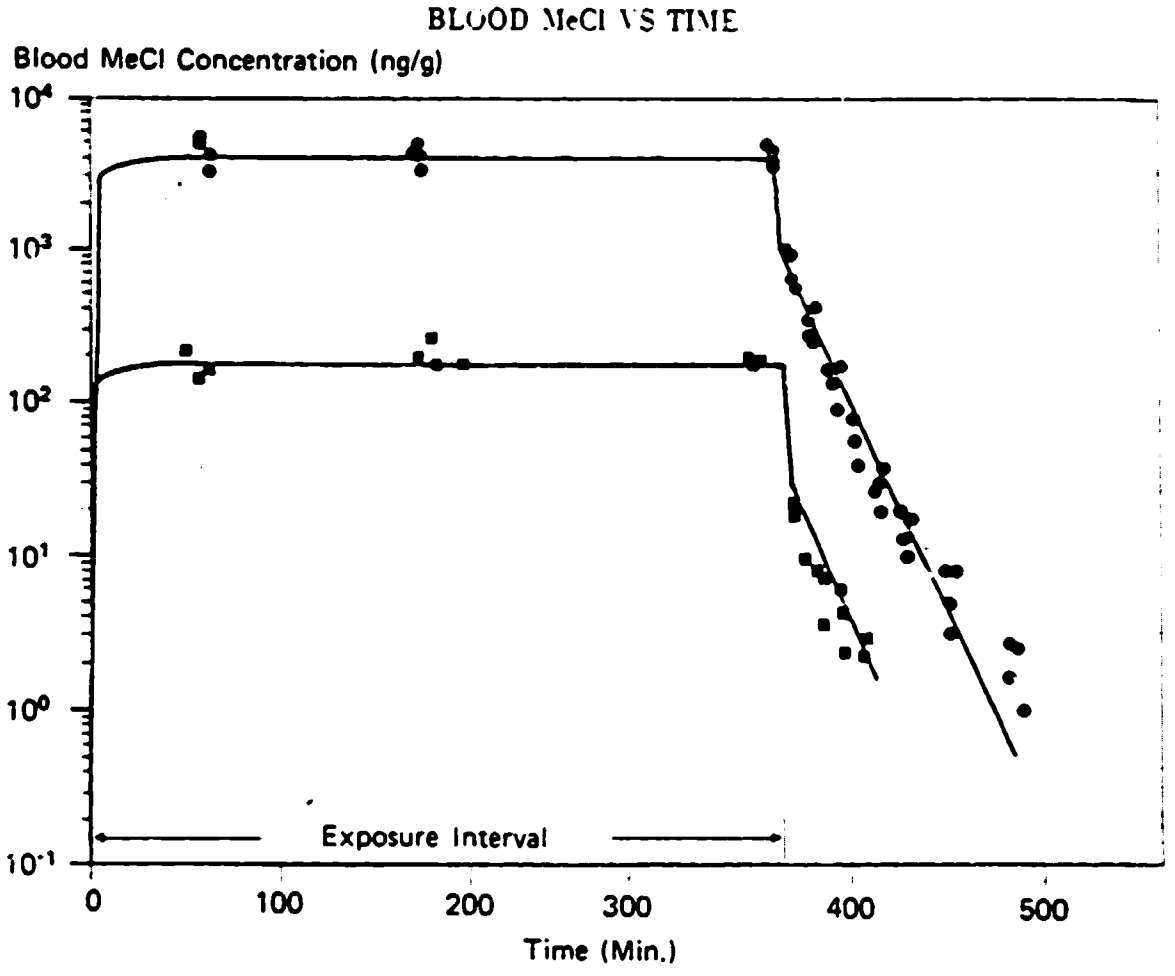
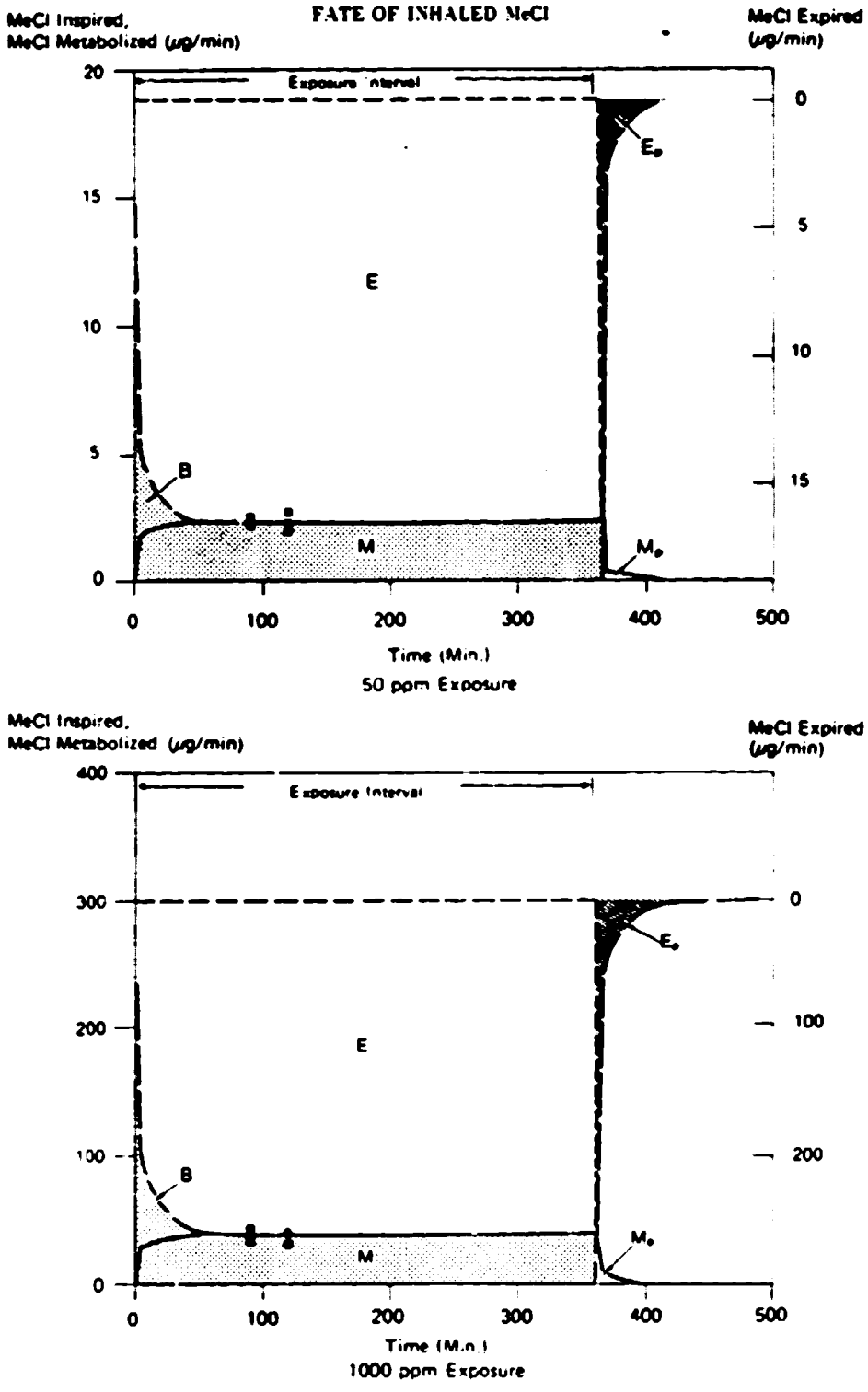

BLOOD MeCl VS TIME
Blood MeCl Concentration (ng/g)
10^4
10^3
10^2
10^1
10^0
10^{-1}
Exposure Interval
0
100
200
300
400
500
Time (Min.)

FIGURE 5


FATE OF INHALED MeCl
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MeCl Metabolized (μg/min)
MeCl Expired
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Exposure Interval
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Time (Min.)
50 ppm Exposure
MeCl Inspired,
MeCl Metabolized (μg/min)
MeCl Expired
(μg/min)
Exposure Interval
E
B
M
E_e
M_e
Time (Min.)
1000 ppm Exposure

TABLE 1

Respiratory Frequency and Minute Volume in Rats Provided 200, 300, or 500 ml/min Chamber Airflow

Sampling Time (min):	Respiratory Frequency (breaths/min)				RMV (ml/min)			
	5	10	15	20	5	10	15	20
Chamber Airflow (ml/min)								
200	156 22	159 20	167 33	156 40	265 49	255 36	268 32	250 65
300	156 24	163 37	170 35	156 25	196 52	201 39	204 49	193 19
300	163 40	155 20	145 7	160 24	221 69	203 40	190 38	210 46
500	155 29	123 13	152 37	122 19	231 66	184 27	174 39	174 26

Values are the mean (±SD) of 5 rats.

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TABLE 2

MeCl Uptake and Proportion of MeCl in Expired Air

[MeCl] (ppm)	MeCl Uptake nM/min/rat at 1.5 hr	2 hr	nM/min/g[a]	conc. expired/conc. inspired
50	48.5	52.5	0.22	0.84
50	43.9	38.9	0.19	0.86
50	40.9	43.2	0.19	0.88
$\bar{X}$±SD	44.7 ± 5.0		0.20 ± 0.02	0.86 ± 0.02
1000	774	774	3.55	0.85
1000	649	624	2.67	0.87
1000	809	786	3.58	0.86
$\bar{X}$±SD	736 ± 79		3.27 ± 0.51	0.86 ± 0.01

(Uptake values are provided as nM/min per rat and per gram body weight.)

[a]Mean of values obtained at 1.5 and 2 hr.

000024

TABLE 3

Respiratory Parameters in Rats Exposed to MeCl or $MeCl_2$

	MeCl		$MeCl_2$	
	50 ppm	1000 ppm	50 ppm	1000 ppm
Respiratory Frequency (breaths/min)	122±13	135±34	121±20	166±25
Tidal Volume (ml)	1.5±0.1	1.1±0.3	1.4±0.1	0.8±0.1
RMV (ml/min)	179±18	143±13	173±30	124±17

Values are $\bar{X}$ ± SD, n = 3 rats with duplicate measurements

000025

TABLE 4

$MeCl_2$ Uptake and CO Expiration

$[MeCl_2]$ (ppm)	$MeCl_2$ Uptake nM/min/rat at 2.5 hr	3 hr	nM/min/g[a]	conc. expired/conc. inspired	Expired Air [CO] ppm
50	133	131	0.55	0.65	5.3
50	1[illegible]	111	0.52	0.66	3.1
50	1[illegible]8	139	0.63	0.61	6.0
$\bar{X}$±SD	129 ±11		0.56±0.05	0.64±0.03	4.8 ±1.5
1500	606	789	3.05	0.91	14.3
1500	771	645	3.12	0.90	15.3
1500	436	504	2.23	0.95	10.6
$\bar{X}$±SD	625 ±141		2.80±0.50	0.92±0.03	13.4 ±2.5

[a]Mean of values obtained at 2.5 and 3 hr.

000026

TABLE 5

Pharmacokinetic Parameters Describing the Fate of Inhaled MeCl in Rats

MeCl Exposure Concentration (ppm)	Steady-State Blood [MeCl] (ng/g)	MeCl Uptake Rate[a] (nM/min/g)	k_M (min^{-1})	k_{1E} (min^{-1})	Effective dose for 6 hr exposure (mg/kg)
50	173	0.20	0.19	1.38	3.8
1000	3920	3.3	0.14	0.96	67

[a]Rats in both exposure groups averaged 226 g, values are nM MeCl/min/g of rat.

Values in this table, except exposure concentration, were obtained from the computer optimization.

APPENDIX A1

DACSL Program for MeCl Pharmacokinetics

(1000 ppm Exposure)

```
00000100 PROGRAM - 'GMIA.FCCL'
00000200            'THREE COMPARTMENT'
00000300            'UPTAKE MEASURED'
00000400            'MECL BLOOD DATA FOR RATS'
00000500       INITIAL
00000600         CONSTANT POINTS    =  98.
00000700         CONSTANT TSTOP     = 490.
00000800         CONSTANT RMV       = 143.
00000900         CONSTANT K12       =   0.4463
00001000         CONSTANT K21       =   0.08885
00001100         CONSTANT KM        =   0.1393
00001200         CONSTANT K1E       =   0.9618
00001300         CONSTANT V1        =  69.54
00001400         CONSTANT CC        =2100.0
00001500           CINT  =  TSTOP / POINTS
00001600       END$'OF INITIAL'
00001700       DYNAMIC
00001800         AKO = CC * RMV * (1. - STEP (359.9))
00001900         CE  =(K1E*A1)/RMV
00002000        DOSE = A1+A2+AM
00002010        D2=MASSIN-AE
00002100       TMASS = A1 + AE + A2 + AM
00002110       RE=(CC * RMV) - DAEDT
00002200      DERIVATIVE
00002300          ALGORITHM IALG=2
00002400          C1     = A1/V1
00002500          DA1DT = AKO - (K12 + KM + K1E) * A1 + K21 * A2
00002600          DA2DT = K12 * A1 - K21 * A2
00002700          DAEDT = K1E * A1
00002810          DAMDT = KM * A1
00002820          MASSIN = INTEG(AKO,0.0)
00002900            A1  =   INTEG(DA1DT,0.0)
00003000            A2  =   INTEG(DA2DT,0.0)
00003100            AE  =   INTEG(DAEDT,0.0)
00003200            AM  =   INTEG(DAMDT,0.0)
00003300         'DEFINE TERMINATION CONDITION'
00003400       TERMT( T .GE. TSTOP )
00003500     END$'OF DERIVATIVE'
00003600     END$'OF DYNAMIC'
00003700     TERMINAL
00003800     END$'OF TERMINAL'
00003900 END$'OF PROGRAM'
```

87821210

APPENDIX A2

DACSL Program for MeCl Pharmacokinetics

(50 ppm Exposure)

```
PROGRAM - 'GMAA.ACSL'
          'THREE COMPARTMENT'
          'UPTAKE MEASURED'
          'MECL BLOOD DATA FOR RATS'
      INITIAL
        CONSTANT POINTS    =  90.
        CONSTANT TSTOP     = 410.
        CONSTANT RMV       = 179.
        CONSTANT K12       =   0.4463
        CONSTANT K21       =   0.08885
        CONSTANT KM        =   0.1050
        CONSTANT K1E       =   1.3750
        CONSTANT V1        =  69.54
        CONSTANT CC        = 105.
          CINT   =  TSTOP / POINTS
      END$'OF INITIAL'
      DYNAMIC
        AKO = CC * RMV * (1. - STEP (359.9))
        CE  =(K1E*A1)/V1
       DOSE = A1+A2+AM
      TMASS = A1 + AE + A2 + AM
      RE    = (CC * RMV) - DAEDT
     DERIVATIVE
         ALGORITHM IALG=2
         C1     = A1/V1
         DA1DT = AKO - (K12 + KM + K1E) * A1 + K21 * A2
         DA2DT = K12 * A1 - K21 * A2
         DAEDT = K1E * A1
         DAMDT = KM * A1
         MASSIN = INTEG(AKO,0.0)
           A1   =   INTEG(DA1DT,0.0)
           A2   =   INTEG(DA2DT,0.0)
           AE   =   INTEG(DAEDT,0.0)
           AM   =   INTEG(DAMDT,0.0)
        'DEFINE TERMINATION CONDITION'
      TERMT( T .GE. TSTOP )
    END$'OF DERIVATIVE'
    END$'OF DYNAMIC'
    TERMINAL
    END$'OF TERMINAL'
END$'OF PROGRAM'
```

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THE DOW CHEMICAL COMPANY

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Dear Sir or Madam:

We are submitting the two attached lists of Health and Safety studies as required by the referenced rule.

The first list, marked D650, is a list of studies in progress as of the date of this submission.

Please note that the study entitled "Acrylamide: A Two-Year Drinking Water Chronic Toxcitity - Onogenicity Study in CDF Fischer 344 Rats" is submitted on behalf of the following companies who are participating in the study:

Dow Chemical
American Cyanamid
Sohio
Nalco

The second list, marked D652, contains references to unpublished studies of which we are aware but do not have a copy.

Very truly yours,

R. L. Hagerman
Regulatory Specialist
Regulatory and Legislative Issues
Health and Environmental Sciences
1803 Building
(517)636-6855

rt

000002

Dow Chemical Company
D-650
Studies in Progress as of Date of Submission

1. A Mortality Study of Men Engaged in the Manufacture of Organic Dyes.
   Purpose: Examine the mortality experience of men assigned to production areas in which aromatic amines were present as raw materials or chemical intermediates.
   Data: Mortality data
   Progress: Report submitted for publication
   Date of Completion: Unknown - when accepted for publication
   CAS Nos: 62533

2. *In Vitro* Reactivity Study of Alkylene Oxides
   Purpose: See title
   Data: Relative kinetic data
   Progress: Started Dec. 1, 1982
   Date of Completion: Report due 1984
   CAS Nos: 106887, 75218, 75569

3. Range-Finding Study of Methylchloroform Formulation XN 50120
   Purpose: See title
   Data: Mammalian toxicity
   Progress: Report being written
   Date of Completion: Jan. '83
   CAS Nos. 71556

4. Propylene Dichloride: Acute and Two-week Inhalation Study
   Purpose: See title
   Data: Toxicity in Rats, Mice and Rabbits
   Progress: Report being written
   Date of Completion: Jan '83
   CAS Nos: 78875

5. Methyl Chloride: Inhalation Toxicity in Female C57BL6 Mice Continuously or Intermittently Exposed for 12 Days
   Purpose: See title
   Data: See title
   Progress: Report to be written
   Date of Completion: First Quarter '83
   CAS Nos. 74873

6. Methylene Chloride: A Comparison of the Pharmacokinetics and Macromolecular Interactions of Inhaled ^{14}C-Methylene Chloride in Hamsters and Rats as Related to Toxicity
   Purpose: Evaluate species differences in the fate of inhaled methylene chloride
   Data: See title
   Progress: Pathology in progress
   Date of Completion: Sept. '84
   CAS Nos: 79061

7. Acrylamide: A Two Year Drinking Water Chronic Toxicity - Onogenicity Study in B/F Fischer 344 Rats
   Purpose: See title
   Data: See title
   Progress: Pathology in progress
   Date of Completion: September '84
   CAS Nos: 79061

8. Acrylamide: Pharmacokinetics in the Rat
   Purpose: See title
   Data: See title
   Progress: Report to be written
   Date of Completion: First quarter '83
   CAS Nos: 79061

9. Acute Range-finding - Diglycidylether of Biphenol A
   Purpose: See title
   Data: See title
   Progress: Report being written
   Date of Completion: First quarter '83
   CAS Nos: 1675543

10. Characterization of Butylene Oxide Blood Levels, Macromolecular Binding and Hepatic Nonprotein Sulfhydryl Levels After Inhalation Exposure in Rats
    Purpose: See title
    Data: See title
    Progress: Report being written
    Date of Completion: First quarter '83
    CAS Nos: 26249207

11. 1,1,1-Trichloroethane: Two-year Inhalation in Rats and Mice
    Purpose: See title
    Data:
    Progress: Awaiting pathology
    Date of Completion: June, '83
    CAS Nos: 71556

12. Reduction Dechlorination of Chlorinated Methanes, Ethanes, & Ethylenes in Aqueous Solutions
    Purpose: Investigate non-biological, reductive dehalogenation of a series of chlorinated hydrocarbons in aqueous solution
    Data: Laboratory analytical data on concentration of chemicals in solution as a function of conditions
    Progress: Underway
    Date of Completion: Mid-1983
    CAS Nos: 75092, 71556

13. A Case-Control Study of Renal Cancer Mortality at a Texas Chemical Plant.
    Purpose: To determine if a possible etiologic agent for human renal cancer can be found related to occupation.
    Data: Mortality and past presumptive exposures to chemicals produced or used in the chemical plant.
    Progess: Preliminary report nearing completion
    Date of Completion: Early 1983

14. A Case-Control Study of Leukemia and Occupational Exposure to Ethylene Oxide.
    Purpose: To determine if past presumptive exposures to ethylene oxide are associated with leukemia.
    Data: Mortality and past presumptive exposures to ethylene oxide.
    Progress: Work histories on cases and controls being collected.
    Date of Completion: Early 1983.

15. A Cross-Sectional Study of Employees with Potential Workplace Exposure to Ethylene Oxide.
    Purpose: To determine whether those with potential exposure to ethylene oxide had a higher prevalence of abnormalities of the hematopoietic, hepatic, renal or reproductive systems than did an unexposed control group.
    Data: Medical surveillance and presumptive occupational exposure
    Progress: Preliminary report in process of review and revision
    Date of Completion: Early 1983

16. Methyl Chloride Mortality Study.
    Purpose To evaluate the mortality patterns of employees with past potential exposure to methyl chloride.
    Data: Mortality and past potential occupational exposure to methyl chloride.
    Progress: Collecting work history and exposure data.
    Date of Completion: Mid-1983

17. 1,1,1-Trichloroethane

Purpose: Define the time course of 1,1,1-trichloroethane in human volunteers following a single six-hour inhalation exposure to 350 and 35 ppm.

Data: Human pharmacokinetic study

Progress: In progress

Date of Completion: February 1983

CAS Nos: 71556

18. Acrylamide

Purpose: Evaluate vibratory sensitivity in an exposed population and controls.

Data: Field survey

Progress: Preliminary data collected.

Date of completion: Unknown; Pending development and validation of methodology.

CAS Nos: 79061

Dow Chemical Company
D-652
References to Unpublished Studies by Others

1. Studies of the visual system in chronic acrylamide poisoned monkeys. Lapham, L.W., et. al.
Dr. L. W. Lapham, University of Rochester Medical Center, Department of Pathology, Division of Neuropathology, Rochester, NY, 14642.

2. The integration of multiple measures in behavioral toxicology. Merison, W.H., et. al.
Dr. W. H. Merison, University of Rochester Medical Center, Division of Toxicology, Rochester, NY, 14642

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