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CHEMICAL MANUFACTURERS ASSOCIATION

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ATTN: TSCA 8(e) Coordinator



89960000172

Dear TSCA 8(e) Coordinator:

The Chemical Manufacturers Association (CMA) hereby submits one copy of the final study report on cyclohexane (CAS No. 110-82-7) titled:

"Two Week Inhalation Range-Finding Study with Cyclohexane in Rats and Mice".

A TSCA 8(e) letter was submitted previously by CMA to EPA on this particular range-finding study (see attached March 30, 1995 8(e) letter). In order to bring closure to this 8(e) letter and to provide EPA with complete study details, CMA is submitting the final report.

The range-finding study was conducted at DuPont Haskell Laboratory for the purpose of determining doses for various studies in a cyclohexane testing program. The testing program was conducted under an enforceable consent agreement (see, OPPTS-42094C; Federal Register, Vol.59, No.222, pp.59660-59663). The enclosed final study report is submitted on behalf of the following test sponsors which comprise the CMA Cyclohexane Panel:

- Chevron Chemical Company
- CITGO Chemical Company
- E.I. du Pont de Nemours & Company
- Huntsman corporation
- Koch Industries, Inc.
- Phillips Petroleum Company
- Sun Company, Inc.

If you have any questions regarding this submission, please contact me by phone at 703/741-5633 or by fax at 703/741-6091.

Sincerely,

Jon Busch
Manager, Cyclohexane Panel



CHEMICAL MANUFACTURERS ASSOCIATION

March 30, 1995

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Langley A. Spurlock, Ph.D., CAE
Vice President, CHEMSTAR

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Washington, DC 20460

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Attention: 8(e) Coordinator

Dear Sir or Madam:

The Chemical Manufacturers Association (CMA) submits this notice on behalf of its Cyclohexane Panel pursuant to Section 8(e) of the Toxic Substances Control Act.

A two-week inhalation range-finding study with rats and mice was conducted on cyclohexane (CAS No. 110-82-7) at the DuPont Haskell Laboratory in Newark, Delaware (DuPont MR Study No. 10160). The purpose of this range-finding study was to determine initial dose levels for further studies on cyclohexane that will be conducted as part of a comprehensive testing program under an Enforceable Consent Agreement (49 CFR Part 799; 59: 59660-59663, 11-18-94; Testing Consent Order for Cyclohexane).

In the two-week inhalation range-finding study, rats and mice (5 animals/sex, each species) were concurrently exposed to cyclohexane at 0 (control), 3000, 6000, or 9000 ppm daily for 6 hours/day. All animals were weighed each day prior to exposure, and were observed each day for clinical signs of toxicity before and after exposure. During exposure, only animals visible from the front of the chamber were observed for clinical signs and for an alerting response to a tap on the chamber wall. The tap was done three times during each exposure period for each chamber.

During exposure, abnormal behavior, consisting of periodic jumping and slow circling, was observed in mice exposed to 6000 and 9000 ppm. The activity occurred more frequently and in a higher incidence (based upon the number of animals observable) in the mice exposed to 9000 ppm than in the group exposed to 6000 ppm. Initially this behavior in mice was observed only briefly on study day 2. By study day 5, it began to occur within the first two hours of exposure initiation. This behavior was not reported for lower exposure levels (Lazarew, K., Arch. F. Exp. Pathol. Pharm. 143: 223, 1929; Flurry, F. and Zernick, F., *Schadliche Gase*. (Berlin), 274-275, 1931).

Ready to go

Rats did not display this behavior at any exposure level.

The behavioral effect noted for mice exposed to approximately 9000 ppm cyclohexane was not reported for lower exposure levels (Lazarew, K., Arch. F. Exp. Pathol. Pharm. 143: 223, 1929; Flurry, F. and Zernick, F., *Schadliche Gase*. (Berlin), 274-275, 1931).



Both rats and mice had diminished alerting responses at 6000 and 9000 ppm. Histopathological evaluation of both rats and mice is currently in progress.

The seven member companies of the CMA Cyclohexane Panel on whose behalf this submission is being made include:

Chevron Chemical Company
1301 McKinney
Room 1016
Houston, TX 77010
Panel Contact: Mr. Mike Liittjohann
Telephone No. 713/754-4425

CITGO Petroleum Corporation
6100 S. Yale Avenue
Tulsa, OK 74136
Panel Contact: Mr. John Grabowski
Telephone: 918/495-4764

DuPont
Chestnut Run Plaza
Lancaster Pike & Centre Road
Wilmington, DE 19880-0705
Panel Contact: Dr. Jorge Olguin
Telephone: 302/999-3483

Huntsman Corporation
3040 Post Oak Blvd.
Room 1846
Houston, TX 77056
Panel Contact: Mr. Raymond Papciak
Telephone: 713/235-6094

Kerr-McGee Refining Corporation
2211 Norfolk, Suite 1100
Houston, TX 77253
Panel Contact: Mr. Steve Simpson
Telephone: 713/638-4638

Phillips Petroleum Company
12C1 Phillips Building
Bartlesville, OK 74004
Panel Contact: Dr. Fred Marashi
Telephone: 918/661-8153

Sun Company, Inc.
Ten Penn Center, 24th Flr.
1801 Market Street
Philadelphia, PA 19103
Panel Contact: Mr. Alan Vanacore
Telephone: 215/977-6066

If you have any questions regarding this letter, please contact Jonathon T. Busch of my staff at 202/887-1189.

Sincerely,



Langley A. Spurlock Ph.D., CAE
Vice President, CHEMSTAR

cc: Chevron Chemical Company/Mr. Mike Liittjohann
CITGO Petroleum Corporation/Mr. John Grabowski
DuPont/Dr. Jorge Olguin
Huntsman Corporation/Raymond Papciak
Kerr-McGee Refining Corporation/Mr. Steve Simpson
Phillips Petroleum Company/Dr. Fred Marashi
Sun Company Inc./Mr. Alan Vanacore
Cyclohexane TRTG

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DuPont HLR 240-95

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Study Title

**Two Week Inhalation Range-Finding Study
with Cyclohexane in Rats and Mice**

Laboratory Project ID

Haskell laboratory Report Number 240-95

Author

Judith C. Stadler, Ph.D., D.A.B.T.

Study Completed on

December 15, 1995

Contains No CBI

Performing Laboratory

**E. I. du Pont de Nemours and Company
Haskell Laboratory for Toxicology and Industrial Medicine
Elkton Road, P.O. Box 50
Newark, Delaware 19714**

Medical Research Number 10160-001

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE IN RATS AND MICE

GENERAL INFORMATION

Test Substance: Cyclohexane

Synonyms/Codes: Hexahydrobenzene
Hexamethylene
Hexanaphthene
SOR#025
Tank #19

Haskeil Number(s): 21052

CAS Registry Number: 110-82-7

Purity: 99.97%

Physical Form: liquid

Sponsor: Cyclohexane Panel
Chemical Manufacturers Association
2501 M. Street, N.W.
Washington, DC 20037

Study
Initiated - Completed: 2/16/95 - 12/15/95

In-Life Study
Initiated - Completed: 2/27/95 - 3/10/95

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE IN RATS AND MICE

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TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE IN RATS AND MICE

SUMMARY

Groups of five male and five female Crl:CD®BR rats and five male and five female Crl:CD-1®(ICR)BR mice were exposed by inhalation to cyclohexane at concentrations targeted to 0, 3000, 6000 or 9000 ppm. Exposures were six hours per day, for a total of nine exposures over a two-week period. Rats and mice were weighed prior to exposure each day and were observed for clinical signs of toxicity both prior to and following each exposure. The response to an alerting stimulus was determined during exposures. A functional observational battery was conducted on the rats prior to the first exposure and on test days 4 and 11. Clinical pathology evaluations were conducted on surviving animals prior to the end of the study. Rats and mice were sacrificed and necropsied on the day following the last exposure, and all rats were examined for gross and microscopic pathological changes.

The analytically determined mean concentrations \pm SEM of cyclohexane for the nine exposures were 3000 ± 17 , 6000 ± 13 and 9000 ± 7.2 ppm in the chambers targeted to 3000, 6000, or 9000 ppm, respectively. Relative humidity was slightly lower than targeted; however, all environmental conditions in the exposure chambers were within acceptable ranges for the study.

Rats exposed to 9000 ppm cyclohexane had low body weight gains due to compound exposure; however, none of the cyclohexane-exposed mice had body weight effects. There were no compound-related mortalities in the study. Pre- and post-exposure clinical observations and functional observational battery assessments did not identify any effects due to compound toxicity. During exposure, rats and mice exposed to 6000 or 9000 ppm had a diminished response to the alerting stimulus, and mice in these exposure groups had sporadic abnormal jumping and circling behavior.

There were no compound-related effects in either rats or mice noted during clinical pathology evaluations, and no abnormalities were seen during gross pathology examinations. There were no compound-related organ weight effects in rats; however, biologically significant elevated lung weights in male mice

exposed to 6000 or 9000 ppm and elevated liver weights in female mice exposed to 6000 and 9000 ppm cyclohexane were observed. No microscopic correlate occurred for lungs; however, liver effects were seen in both rats and mice during microscopic evaluations. When compared to controls, there were increases in mitotic figures in the liver for all groups of rats and mice exposed to 9000 ppm, in male rats and female mice exposed to 6000 ppm and in female mice exposed to 3000 ppm.

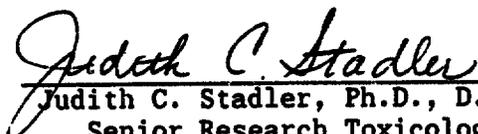
Under the conditions of this study, the no-observed-effect level (NOEL) was 3000 ppm for rats, based on the clinical signs observed during exposure and the microscopic observations in the liver in rats exposed to 6000 ppm. Additionally, there was no no-observed-effect level (NOEL) for mice, based on the increase in mitotic figures in the livers of female mice exposed to the lowest concentration, 3000 ppm cyclohexane.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE IN RATS AND MICE

SIGNATURES

Date

Authored, Reviewed, and
Approved for Issue
by Study Director:



Judith C. Stadler, Ph.D., D.A.B.T.
Senior Research Toxicologist
Inhalation Toxicology

12/19/95

QUALITY ASSURANCE DOCUMENTATION

(H-21052)

Dates of Inspection:

Conduct - 2/27/95

Records, Report(s) - 4/24-25;8/17,24-25,28-29/95

Date(s) Findings Reported to:

Study Director - 5/1;8/29,30/95

Management - 5/1;8/30;12/11/95

Reported by: Donna R Holt
Donna R. Holt
Quality Assurance Auditor

12/11/95
Date

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE IN RATS AND MICE

ACKNOWLEDGMENTS

The following individuals were responsible for conduct of the study:

Management: Scott E. Loveless, Ph.D.
Study Director: Judith C. Stadler, Ph.D., D.A.B.T.
Primary Technician: Scott M. Krenzel, A.A.
Toxicology Report
Preparation: Maryanne M. Wilford, B.A.

The following individuals were responsible for the functional observational battery evaluations:

Management: Greg R. Christoph, Ph.D.
Neurotoxicologist: Linda A. Malley, Ph.D., D.A.B.T.
Primary Technician: Kathleen A. Mikles, B.A.

The following individuals were responsible for the clinical pathology evaluations:

Management: Glenn S. Elliott, D.V.M., Ph.D.
Clinical Pathologist: Glenn S. Elliott, D.V.M., Ph.D.
Clinical Pathology
Report Preparation: Cheryl L. Samson, A.A.S.

The following individuals were responsible for the gross pathology examinations, slide preparation, and microscopic evaluations:

Management: Paul E. Ross, D.V.M.
Pathologist: John Hansen, D.V.M., Ph.D.
Peer Review
Pathologist: Glen E. Marrs, Jr., D.V.M., M.S.
Pathology
Report Preparation: Wanda F. Dinbokowitz

ACKNOWLEDGMENTS (Continued)

The following individuals were responsible for quality assurance:

Auditor: Donna R. Holt, A.A.S

Coordinator: Joseph C. Hamill

The following individual was responsible for assessing the health status of the animals on study:

Laboratory
Veterinarian: Charles E. Cover, V.M.D.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE IN RATS AND MICE

INTRODUCTION

This study was conducted to determine the toxic effects of repeated inhalation of sublethal concentrations of cyclohexane in rats and mice. The study results provided guidance for selection of exposure concentrations in subsequent inhalation toxicity studies.

MATERIALS AND METHODS

A. Test Substance

The test substance, cyclohexane, was supplied as a liquid by Phillips Petroleum Company, Sweeney Facility, Brazoria, Texas. The purity of the test substance was determined prior to study start and following the inhalation exposures. Purity results were compared to determine stability of the sample. Analyses were by gas chromatography.

B. Animals

A total of 25 male and 25 female Crl:CD®BR rats, and 25 male and 25 female Crl:CD-1®(ICR)BR mice was received from Charles River Breeding Laboratories, Raleigh, North Carolina. The rats and mice were approximately 42 days old on the day of arrival.

Rats and mice have historically been used in safety evaluation studies. The Crl:CD®BR rat and Crl:CD-1®(ICR)BR mouse were selected based on consistently acceptable health status and on extensive experience with these strains at this laboratory.

C. Animal Husbandry

Quarantine. When the animals arrived, they were quarantined for six days prior to test initiation. During the quarantine period they were weighed and observed three times for clinical signs of disease.

Animal Identification. Upon arrival, each rat was assigned a unique six-digit animal number, and each mouse was assigned a temporary, one- to two-digit identification number, which was recorded on a card affixed to the cage.

After grouping, each mouse was assigned a unique six-digit animal number. Each animal was tattooed with a three-digit identification number. Both the animal number and the identification number of each animal were recorded on a card affixed to the cage.

Housing. During the test period, animals were housed either singly or in pairs in suspended, stainless steel, wire-mesh cages.

Animal Room Environment. Animal rooms were maintained on a timer-controlled, 12-hour light/12-hour dark cycle. Environmental conditions of the rooms were targeted to a temperature range of $23 \pm 2^{\circ}\text{C}$ and a relative humidity range of $50 \pm 10\%$. Excursions outside of these ranges were of insufficient magnitude and/or duration to have adversely affected the validity of the study.

Animal Selection. Prior to the end of the quarantine period, animals were assigned to four groups of five males and five females each. Animals were divided into groups with the aid of a computerized, stratified, randomization program, so that mean body weights for each group were similar. Animals were approximately seven weeks old at the start of exposures. Male rats weighed between 188 and 212 grams; female rats weighed between 163 and 183 grams; male mice weighed between 27 and 31 grams; female mice weighed between 17 and 26 grams at the start of the exposures.

Feed and Water. Except during exposure, Purina Certified Rodent Chow® #5002 and tap water from United Water Delaware were available ad libitum. Prior to blood collection and necropsy, rats were fasted overnight for approximately 14 to 16 hours; however, water was available ad libitum.

Haskell Laboratory has an animal health monitoring program. As part of this program, water samples are analyzed for total bacterial counts, and the presence of coliforms, lead, and other contaminants.

The laboratory uses certified animal feed, which is guaranteed by the manufacturer to meet specified nutritional requirements and to be free of a list of specified contaminants.

This monitoring program is administered by the laboratory animal veterinarian. Data are maintained separately from study records and are not included in the final report. Evaluation of these data did not indicate any conditions that affected the validity of the study.

D. Study Design

Four groups of five male and female rats each and five male and female mice each were exposed to concentrations of cyclohexane targeted to 0, 3000, 6000, or 9000 ppm. Animal exposures were whole-body for six hours/day for a total of nine exposures. All animals were weighed and individually observed for clinical signs of toxicity throughout the exposure period. On the day after the last exposure, blood samples were collected from all surviving animals, and all animals were sacrificed for pathologic examination.

B. Inhalation Exposure System (Figure 1)

During exposure, animals were placed within wire-mesh cages and exposed whole-body inside the exposure chamber.

1. Atmosphere Generation

Atmospheres of cyclohexane were generated by metering the liquid test substance into a heated, glass Instatherm flask with a Fluid Metering, Inc. model QSXY Pump. Nitrogen introduced into the flask, and high pressure air introduced into the transfer line carried the resulting atmosphere into the exposure chamber. Desired atmospheric concentrations of cyclohexane were achieved by regulating the flow of the test substance to the flask.

Nitrogen and high pressure air were passed through the control chamber at approximately the same flow rate as that used in the test substance chambers.

All chamber exhausts were discharged directly into the fume hood.

2. Chamber Construction and Design

Each exposure chamber was constructed of stainless steel and glass. The internal nominal volume of the chambers was approximately 150 liters. Directly inside the chamber inlet, a stainless steel baffle was positioned to provide uniform distribution of the test substance within the exposure chamber. Homogeneous distribution of cyclohexane in the test chamber was verified during prestudy method development.

F. Characterization of the Test Atmospheres

1. Test Substance Sampling and Analysis

The atmospheric concentration of cyclohexane was determined by gas chromatography at approximately 30-minute intervals during each six-hour exposure. Approximately 250 μ L samples were drawn by vacuum pump from representative areas of the chamber where animals were exposed.

Chamber atmosphere samples were directly injected into a Hewlett Packard model 5880 Gas Chromatograph equipped with a flame ionization detector for

analysis of cyclohexane concentration. All samples were chromatographed isothermally at 100°C on a 30 M x 0.53 mm CAP column.

The atmospheric concentration of cyclohexane was determined from a standard curve derived from gas standards. The gas standards were prepared prior to each exposure by injecting known volumes of liquid cyclohexane into gas bags that contained known volumes of air.

2. Chamber Environment

Chamber temperature, relative humidity, and airflow were monitored continually with a Lander Control Systems Toxicology Monitoring System and measurements were recorded at approximately 15-minute intervals. Chamber airflow was targeted to provide more than 10 to 12 air changes per hour. Chamber temperature was targeted at $23 \pm 2^\circ\text{C}$. Chamber relative humidity was targeted at $50 \pm 10\%$. Chamber oxygen concentration was targeted to at least 19%. During the study, chamber oxygen concentration was measured only in the 9000 ppm chamber, with a Biosystems model 3100R Oxygen Monitor, and was recorded three times during each exposure. In addition, on test day 1, the oxygen concentration was also determined one time for the control chamber.

G. Body Weights and Clinical Observations

Each animal was weighed and individually observed for clinical signs of toxicity before each six-hour exposure. Group clinical observations were made during exposures. After each exposure, each animal was individually observed for clinical signs of toxicity. Animals were observed daily for mortality.

During exposures, the animals visible through the chamber window were visually checked for viability at approximately one-hour intervals. At least three times during each exposure, animals were also checked for alerting behavior in response to a standardized auditory stimulus.

H. Functional Observational Battery Evaluations (FOB)

Abbreviated functional observational battery (FOB) assessments were conducted on three separate days. To establish baseline measures, all rats were evaluated prior to the initiation of exposures. During the exposure period, the abbreviated FOB was performed prior to and following exposure on test days 4 and 11.

FOB testing consisted of a series of quantified behavioral observations conducted in a sequence that proceeded from the least interactive to the most interactive. The order of testing of the rats and the order of the assessments in the FOB was the same on all days of neurobehavioral assessment. The experimenter who conducted the FOB assessments was "blind" with respect to the group designations of the animals.

During the FOB assessments, each rat was evaluated in two "environments": inside the home cage and in a standard "open field" arena (approx. 85 x 59 x 20 cm).

The following parameters were assessed during the abbreviated FOB in the order that they are listed.

Home Cage:	Posture Palpebral Closure	
Open Field:	Righting Reflex Convulsions Gait Characteristics Vocalizations	Labored Breathing Coordination Arousal Palpebral Closure
Manipulations:	Approach & Touch Response Auditory Response (clicker) Tail Pinch	

I. Clinical Laboratory Evaluations

Clinical pathology evaluations were performed on all surviving rats and mice on the day after the ninth exposure. Rats were fasted overnight for

approximately 14 to 16 hours between the end of the ninth exposure and the time blood samples were taken. Mice were not fasted. At the sampling time, blood was taken from the orbital sinus of each animal while it was under light carbon dioxide anesthesia.

1. Hematology

The following hematologic parameters were measured or calculated in rats and mice: number of erythrocytes (RBC), leukocytes (WBC), and platelets (PLAT); hemoglobin concentration (Hb), hematocrit (Ht), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC); relative numbers of neutrophils (Neut), band neutrophils (Band), lymphocytes (Lymph), atypical lymphocytes (Alym), monocytes (Mono), eosinophils (Eosin), and basophils (Baso). Absolute values for the various types of leukocytes were calculated from the leukocytic data. Blood cell counts, hemoglobin concentration, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were determined on a Serono Baker 9000[®] hematology analyzer. Differential cell counts were determined on a Hematrak[®] Automated Differential System cell counter. Reticulocyte smears were prepared on all rats and mice.

2. Clinical Chemistry

In conjunction with hematological measurements, the following serum chemical parameters were measured or calculated for each rat: activities of alkaline phosphatase, (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), sorbitol dehydrogenase (SDH); concentrations of glucose (GLUCO), urea nitrogen (BUN), calcium (CALC), phosphate (PHOS), bilirubin (BILRN), cholesterol (CHOL), creatinine (CREAT), triglycerides (TRIG), total protein (TPROT), albumin (ALBMN), sodium (Na), potassium (K), chloride (Cl). Clinical chemical parameters were measured on a Boehringer Mannheim/Hitachi 717 clinical chemistry analyzer using Boehringer Mannheim reagents. Serum globulin (GLOBN) concentration was calculated from the total protein and albumin concentrations. In addition, to the parameters measured for rats, plasma protein concentrations, on mice only, were determined by refractometry.

J. Pathology Evaluations

All surviving rats and mice were sacrificed by carbon dioxide anesthesia and exsanguination and necropsied the day following the last exposure. The liver, kidneys, lungs, testes, and brain were weighed at necropsy. Each rat or mouse was given a complete gross examination and representative samples of the following tissues were saved: liver (including gallbladder for mice), kidneys, urinary bladder, lungs, heart, spleen, thymus, brain, spinal cord, stomach, duodenum, jejunum, ileum, pancreas, cecum, colon, rectum, mesenteric lymph node, adrenal glands, sciatic nerve, thyroid gland with parathyroids, trachea, esophagus, pharynx/larynx (for rats only), eyes, sternum (with bone marrow), nose, gross lesions, and prostate, seminal vesicles, testes, and epididymides for males, and ovaries, uterus, and vagina for females.

Testes, epididymides, and eyes were fixed in Bouin's solution. All other tissues were fixed in 10% neutral buffered formalin. Processed tissues were embedded in paraffin, cut at an approximate thickness of 5 microns, and stained with hematoxylin and eosin (H&E).

Gross lesions for which microscopic examination was not appropriate (e.g., fluid, ruffled fur, missing, cannibalized, etc.) were not collected. Selected gross lesions for which a microscopic diagnosis would not be additive (pododermatitis, osteoarthritis, tail chronic dermatitis, urinary calculi, and deformities of the pinna, toe, tail, or teeth) were saved but were generally not processed for microscopic evaluation.

All animals in the control and 9000 ppm concentration groups received a full microscopic examination. Additional organs (liver) were examined from animals in intermediate concentration groups as required to determine no-effect levels.

K. Statistical Analyses

Mean body weights, body weight gains, clinical pathology measurements, and organ weights were statistically analyzed by one-way analysis of variance

(ANOVA). Pairwise comparisons between test and control groups were made with the Dunnett's test. For the clinical pathology data and mean absolute and relative organ weights, the Bartlett's test was used to test for homogeneity of variance, and, if significant, non-parametric procedures were employed. Results of Bartlett's test analysis with the pathology data indicated that parametric procedures were appropriate for data analysis for all organs weighed.

Descriptive FOB parameters were evaluated by the Cochran-Armitage test for trend and a test to determine lack of fit to a monotonic concentration-response relationship. If a significant trend was found, the highest dose group was dropped and the trend test was repeated. This process continued until no significant effects were found. If a significant trend was not found but the lack of fit was significant, then a Fishers test with a Bonferroni correction was used to compare each concentration level to control. The use of the word "significant" or "significantly" indicated a statistically significant difference between the control and the experimental groups. Data were evaluated with the individual rat as the unit of analysis.

Males and females were analyzed separately for all parameters. Except for the Bartlett's test ($p < 0.005$), significance was judged at the $p < 0.05$ probability level.

RECORDS AND SAMPLE MANAGEMENT

All original data and the original of this final report will be retained at Haskell Laboratory, Newark, Delaware, or at the Records Management Center, E.I. du Pont de Nemours and Company, Wilmington, Delaware. An archived sample of the test substance as well as preserved wet tissues, paraffin blocks, histological slides, and blood and bone marrow smears will be retained at Haskell Laboratory.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE IN RATS AND MICE

RESULTS AND DISCUSSION

REPORT A. In-Life Animal Measurements

This section was reported by the Study Director. See Test Substance, Animals, Animal Husbandry, Study Design, Inhalation Exposure System, Characterization of the Test Atmospheres, and Body Weights and Clinical Observations in the MATERIALS AND METHODS section of the main report for the procedures used in this portion of the study.

A., Test Substance Analyses and Exposure Conditions

(Tables 1-2; Appendices A-B)

1. Purity and Stability of the Test Substance

A sample of the test substance (H-21052) was analyzed for purity prior to study start. The mean purity obtained from three analyses was 99.97%. Based on these results, the test substance was considered acceptable for use in the two-week study.

Following the study, a second analysis of the test substance also indicated a mean purity of 99.97% from three analyses. As a result, the cyclohexane test sample was considered stable over the duration of the study.

2. Chamber Concentrations of Cyclohexane

The analytically determined mean concentrations \pm SEM of cyclohexane in the exposure chambers targeted to 3000, 6000, or 9000 ppm were 3000 ± 17 , 6000 ± 13 and 9000 ± 7.2 ppm for the nine exposures (Table 1). Daily mean concentrations for six hours of exposure were consistent throughout the two-week study, with minimal day-to-day variability. All exposures were six hours long except on test day 4, when animals in the 9000 ppm chamber received a five-hour exposure due to a damaged pump. The mean daily concentrations were within $\pm 3\%$ of the

targeted exposure concentrations. The analytically determined concentrations were considered acceptable for evaluating the toxicity of cyclohexane at the selected target concentrations.

3. Chamber Environmental Conditions

The daily mean temperatures for the nine exposure days of this study were 22-23°C in each of the four inhalation chambers (Table 2). These temperatures fell within the targeted ranges, and they were considered acceptable for the welfare of the study animals.

The daily mean relative humidity readings were between 34 and 39% (Table 2). The humidity was slightly lower than targeted, due, in part, to the use of dry make-up air in the generation system. Although slightly below the desired range of 40 to 60% relative humidity, study results indicate that the health of the animals was not adversely affected.

The daily mean chamber airflows ranged from 34 to 40 L/min (Table 2). These airflows ensured more than 12 air changes per hour in the 150-liter exposure chambers.

The percent of oxygen in each exposure chamber was determined during level-setting procedures prior to study initiation. The oxygen concentration was shown to be stable at each given cyclohexane concentration and lowest in the 9000 ppm chamber. During the study, measurements indicated that oxygen content was maintained at or above 19%.

Overall, the environmental parameters were considered adequate for maintaining suitable animal exposure conditions during the study.

B. Body Weights

(Tables 3-10; Figures 2-5; Appendix C)

Male and female rats exposed to cyclohexane and those in the control groups gained weight from Day 1 to Day 11 during the exposure period and lost weight

between Days 11 and 12, due to the fast imposed prior to blood collection for clinical pathology evaluations (Tables 3-4). Male rats in the 9000 ppm exposure group had a statistically significant low mean body weight gain from Days 1-11 when compared to controls (Table 7). Additionally, the mean body weight gain for females in the 9000 ppm group was somewhat lower than controls; however, the difference was not statistically significant (Table 8). During the study there were some statistically significant differences in day-to-day mean body weight gains for male rats, but none of the other male or female groups showed clear evidence of compound-related effects on body weight.

Mice in the study did not show consistent weight gains in any of the exposure groups (Tables 5-6). Small mean weight gains and/or losses were evident each day. Although there were some statistically significant differences in mean weight gains of exposed groups when compared to controls (Tables 9-10), none of these differences could be considered biologically important or related to test compound exposure.

The no-observed-effect levels for body weight effects in animals exposed to cyclohexane were 6000 ppm for rats and 9000 ppm for mice.

C. Clinical Observations and Mortality

(Tables 11-16; Appendix D)

There were no rat mortalities during the study; however, several mouse deaths occurred. One mouse originally designated for the study was removed and sacrificed prior to the first exposure due to excessive weight loss that occurred during the interval between grouping and test day 1. One male mouse in the 3000 ppm group was found dead on test day 5 and one male in the 9000 ppm group died prior to necropsy on test day 12. Gross and microscopic evaluations showed no remarkable effects, and the deaths were considered not to be compound-related.

During the clinical observation period prior to exposure each day, there were no signs of toxicity that could be attributed to cyclohexane. Signs observed were incidental findings, and considered typical of rats or mice

subjected to inhalation exposures (Tables 11-14). Similarly, no clinical signs specifically attributable to test substance were observed when animals were examined immediately after they were removed from the exposure chambers.

During exposures, all animals were observed for their reaction to an alerting stimulus, and those in test substance chambers were compared to the control animals. Prior to exposures each day, all rats and mice reacted normally to the stimulus. On the day of the second exposure and on subsequent exposure days, the rats and mice exposed to 9000 ppm had generally diminished responses (Tables 15-16). In addition, the mice in this exposure group displayed sporadic incidences of jumping and/or slow circling behavior. Animals in the 6000 ppm groups showed diminished response beginning on the seventh day of exposure. Circling behavior was also noted among mice exposed to 6000 ppm, although the movements were not as frequent or as remarkable as those observed in the 9000 ppm group. No effects on alerting behavior were observed in rats or mice exposed to 3000 ppm, and no abnormal behavior was seen in mice in this group. None of these signs were evident when the exposures ceased.

The no-observed-effect level for clinical signs of toxicity based on response to alerting stimulus in rats and mice and abnormal behavior in mice during exposure was 3000 ppm cyclohexane.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE IN RATS AND MICE

REPORT B. Functional Observational Battery Evaluations
(Tables 17-18; Appendix E)

Date

Reported by: Linda A. Malley 12/12/95
Linda A. Malley, Ph.D., D.A.B.T.
Senior Research Toxicologist
Neurotoxicology

See Functional Observational Battery Evaluations (FOB) in the MATERIALS AND METHODS section of the main report for the procedures used in this portion of the study.

Functional Observational Battery Evaluations

There were no compound-related effects on any parameters evaluated in the abbreviated functional observational battery assessment at any exposure concentration. On test day 11, the incidence of decreased arousal at the post-exposure evaluation was significantly lower for 9000 ppm male rats than for controls (2/5, 1/5, 0/5, and 0/5 for 0, 3000, 6000, and 9000 ppm males, respectively, Table 17). However, this was considered to be a spurious statistical difference since a lower incidence of decreased arousal is not biologically relevant. Similarly, 9000 ppm female rats had a significantly lower incidence of decreased arousal on test day 4 at the post-exposure evaluation (2/5, 0/5, 0/5, and 0/5 for 0, 3000, 6000, and 9000 ppm females, respectively, Table 18). This was considered to be a spurious statistical difference since a lower incidence of decreased arousal is not biologically relevant.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE IN RATS AND MICE

REPORT C. Clinical Laboratory Evaluations

Date

Reported by:



Glenn S. Elliott, D.V.M., Ph.D.

Diplomate A.C.V.P.

Staff Clinical Pathologist

Clinical Pathology

12-12-95

See Clinical Laboratory Evaluations in the MATERIALS AND METHODS section of the main report for the procedures used in this portion of the study.

A. Rats, Hematology (Tables 19-20; Appendix F)

Toxicologically important hematologic changes did not occur in male or female rats. Some statistically significant hematology changes were observed in female rats, but they were not considered to be toxicologically important for the following reasons:

- Significantly increased mean RBC in 3000 ppm females was not considered to be compound related because mean RBC values did not exhibit a dose-response relationship.
- Significantly decreased mean WBC and lymphocyte counts in 3000 and 9000 ppm females and decreased neutrophil counts in 3000 and 6000 ppm females were not considered to be compound related because the mean values for these parameters did not exhibit a dose-response relationship.

B. Rats, Clinical Chemistry (Tables 21-22, Appendix F)

Toxicologically important clinical chemical changes did not occur in male or female rats during this study. Several parameters were statistically significantly different from the control group, but they were not considered to

be toxicologically important for the following reasons:

- Significantly decreased mean serum enzyme activity (ALP and AST in 6000 ppm males and AST in 9000 ppm males) and mean serum bilirubin concentration (6000 and 9000 ppm males) were not important because mild decreases in liver enzyme activity or bilirubin concentration are not biologically relevant. Conversely, it is increases in liver enzyme activity or bilirubin concentration which generally indicate toxicologically important hepatocellular injury.
- Significantly decreased mean serum triglyceride concentration in 9000 ppm males was not considered to be a biologically adverse change. Even though the change may have been compound related, the mild decrease does not portend adverse consequences.
- Significantly decreased mean total protein concentrations in 6000 and 9000 ppm females were not considered to be important because the changes were minuscule and not biologically important.
- Significantly decreased mean BUN concentration in 6000 ppm males and females and in 9000 ppm females were not important because mild decreases in BUN concentration are not indicative of organ dysfunction.
- Minuscule, statistically significant changes in serum chloride concentration were not considered to be important because of a lack of a dose-response relationship (males) or because the magnitude of the change was biologically inconsequential.

C. Mice, Hematology and Plasma Protein (Tables 23-26, Appendix F)

Compound-related changes in plasma protein concentration were not evident in this study. A few statistically significant changes in hematology parameters were observed in male and female mice, but they were not considered to be toxicologically important for the following reasons:

- Significantly decreased MCV in the 3000 ppm male group was not compound related because a relevant dose-response relationship was not evident.
- Significantly decreased mean platelet count in 9000 ppm females was not important because mean platelet counts did not exhibit a dose-response relationship and the changes were minuscule and biologically inconsequential.

For the clinical pathology parameters measured, the NOEL was 9000 ppm for male and female rats and mice. The NOEL was based on the lack of toxicologically important changes in any group of rats or mice.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE IN RATS AND MICE

REPORT D. Pathology Evaluations

Date

Reported by: John Hansen 12/13/95
John Hansen, D.V.M., Ph.D.
Diplomate A.C.V.P.
Staff Pathologist
Pathology

Peer Reviewed by: Glen E. Marrs, Jr. 12/12/95
Glen E. Marrs, Jr., D.V.M., M.S.
Diplomate A.C.V.P.
Staff Pathologist
Pathology

See Pathology Evaluations in the MATERIALS AND METHODS section of the main report for the procedures used in this portion of the study.

A. Organ Weights

(Tables 27-30; Appendix G)

There were no compound-related organ weight changes in male or female rats. Mean absolute brain and lung weights were significantly increased in female rats in the 3000 ppm and 6000 ppm exposure groups, respectively. Since there were neither correlative microscopic findings nor an apparent dose relationship with either of these organ weight changes, they were considered to be unrelated to compound exposure.

Male mice had compound-related increases in the mean relative (% of body weight, and organ to brain ratio) lung weights in the 9000 and 6000 ppm exposure groups (6000 ppm group not statistically significant, but considered adverse). There was no microscopic correlate detected for the increased lung

weights. It is possible that edema of the lung, which would not be microscopically detected in fixed tissues, could account for the increased lung weights. Relative mean liver weights (% of body weight, and organ to brain ratio) were significantly increased in the 6000 ppm exposure group and were considered not to be compound-related since there was no apparent dose relationship.

Female mice in the 6000 and 9000 ppm exposure groups had significantly increased mean absolute and mean relative (% of body weight) liver weights, which were considered to be compound-related.

B. Gross Lesions

(Tables 31-34; Appendix H)

There were no compound-related gross lesions in rats or mice.

C. Microscopic Observations

(Tables 35-38; Appendix H)

There was a minimal compound-related increase in mitotic figures detected in hepatocytes of male rats in the 9000 and 6000 ppm exposure groups (2 and 1 rats from these groups, respectively), and in one female rat from the 9000 ppm group.

Male mice in the 9000 ppm exposure group (2 mice) had a minimal compound-related increase in hepatocellular mitotic figures and in hepatocellular centrilobular hypertrophy. Minimally increased hepatocellular mitotic figures and minimal hepatocellular centrilobular hypertrophy were observed in one or more female mice from all test concentrations.

Other microscopic observations in rats and mice were considered to be commonly occurring spontaneous lesions unrelated to compound exposure.

The mouse was the more sensitive of the species tested, as compound-related microscopic effects were detected within the livers of females at all test concentrations.

The NOEL (no-observed-effect level) for rats, based on microscopic changes in the liver was 3000 ppm. There was no NOEL determined for pathological findings in mice.

CONCLUSIONS

The test substance received for the study had acceptable purity and stability, and the daily mean chamber concentrations of cyclohexane were maintained within $\pm 3\%$ of targeted concentrations. Environmental conditions were considered acceptable for animal health and welfare.

In study rats, there were no mortalities during the study, and no effects on clinical pathology or functional observational battery parameters. Compound-related body weight effects (males only), diminished alerting responses during exposure, and microscopic abnormalities occurred in rats exposed to 9000 ppm cyclohexane. In male and female groups exposed to 6000 ppm, there were diminished alerting responses and significant microscopic liver abnormalities.

In study mice, two animals were found dead during the study, but the mortalities were not considered compound related. There were also no compound-related effects on clinical pathology parameters or body weights. In the 6000 and 9000 ppm exposure groups, there were abnormal clinical signs and diminished alerting responses during exposure, as well as mean lung and liver weight effects and microscopic abnormalities in the liver. Mice exposed to 3000 ppm also had significant microscopically observed increases in mitotic figures in the liver.

Under the conditions of the study, the no-observed-effect level for rats was 3000 ppm, based on a lack of startle response during exposure and microscopic liver effects in animals exposed to 6000 ppm. There was no no-observed-effect level for mice in the study, based on the increase in mitotic figures in the livers of mice exposed to 3000 ppm cyclohexane.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOPHOSPHAMIDE

TABLES

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 1

CHAMBER CONCENTRATIONS OF CYCLOHEXANE

DESIGN CONCENTRATION (ppm)	MEASURED CONCENTRATION ^a (ppm)			
	MEAN	SEM	RANGE	n
0	0	0	0 - 0	9
3000	3000	17	2900 - 3100	9
6000	6000	13	6000 - 6100	9
9000	9000	7.2	9000 - 9100	9

^a Values represent the mean and range of the daily mean concentrations from nine, six-hour exposures.

TABLE 2

CHAMBER ENVIRONMENTAL CONDITIONS^a

DESIGN CONCENTRATION (ppm)	TOTAL CHAMBER AIRFLOW (L/min)	TEMPERATURE (°C)	RELATIVE HUMIDITY (%)
0	35 - 37	22 - 23	37 - 39
3000	34 - 40	22 - 23	35 - 38
6000	37 - 39	22 - 23	34 - 38
9000	34 - 36	22 - 23	34 - 35

^a Values represent the ranges for the mean of samples obtained from nine, six-hour exposures.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 3

MEAN BODY WEIGHTS OF MALE RATS

DAYS ON TEST	GROUP: CONCENTRATION (ppm):	MEAN BODY WEIGHTS (g)			
		I 0	III 3000	V 6000	VII 9000
1		198.1(8.7) ^a	194.5(5.3)	197.2(4.8)	198.0(4.3)
2		207.0(9.6)	202.4(4.7)	202.1(6.8)	200.0(4.1)
3		214.7(10.8)	212.8(5.9)	208.9(6.3)	206.8(4.7)
4		224.3(12.3)	220.3(6.6)	218.7(8.0)	214.2(5.9)
5		227.9(14.6)	224.2(7.2)	221.2(7.6)	217.2(6.1)
8		255.9(16.8)	251.7(6.1)	250.3(9.4)	245.8(8.7)
9		263.0(17.2)	258.8(9.3)	256.5(11.8)	248.2(9.8)
10		271.7(18.1)	265.2(7.9)	261.5(11.8)	253.2(10.0)
11		278.8(17.1)	271.4(8.8)	266.0(12.8)	259.2(10.2)
12		247.9(14.9)	243.1(7.8)	238.9(9.4)	228.8(9.5)

^a Standard deviation is reported in parentheses

Statistical methods: One-way Analysis of Variance and Dunnett's tests were performed on daily interval data. (See Statistical Analyses)

There were no statistically significant differences at alpha = 0.05.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 4

MEAN BODY WEIGHTS OF FEMALE RATS

DAYS ON TEST	GROUP: CONCENTRATION (ppm):	MEAN BODY WEIGHTS (g)			
		II 0	IV 3000	VI 6000	VIII 9000
1		174.2(6.7) ^a	173.0(3.4)	173.7(5.1)	173.2(7.5)
2		177.4(6.5)	174.3(4.6)	179.6(4.5)	171.8(8.2)
3		181.9(8.2)	180.2(4.7)	179.7(6.4)	177.3(6.5)
4		185.6(7.6)	183.4(5.1)	184.5(5.8)	180.0(6.8)
5		186.2(9.9)	185.4(4.4)	186.2(5.0)	179.0(7.4)
8		192.8(10.4)	198.9(6.7)	195.2(5.5)	190.2(10.5)
9		202.0(8.7)	200.8(8.4)	198.2(5.8)	194.4(7.5)
10		202.1(13.1)	198.9(6.6)	200.4(7.2)	194.1(8.1)
11		206.8(8.7)	206.8(7.1)	205.4(8.1)	201.1(10.2)
12		182.9(9.1)	183.2(9.1)	183.4(4.9)	179.1(11.0)

^a Standard deviation is reported in parentheses

Statistical methods: One-way Analysis of Variance and Dunnett's tests were performed on daily interval data. (See Statistical Analyses)

There were no statistically significant differences at alpha = 0.05.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 5
MEAN BODY WEIGHTS OF MALE MICE

DAYS ON TEST	GROUP: CONCENTRATION (ppm):	MEAN BODY WEIGHTS (g)			
		I 0	III 3000	V 6000	VII 9000
1		29.1(1.0) ^a	28.9(0.9)	28.1(0.9)	29.0(1.4)
2		28.6(0.9)	28.6(1.2)	27.7(0.8)	27.6(1.3)
3		28.7(1.0)	29.0(1.0)	27.8(1.2)	27.4(1.4)
4		28.2(1.2)	28.6(1.3)	27.4(1.2)	27.1(1.1)
5		28.1(0.8)	29.0(1.4)	28.1(1.3)	27.7(1.3)
8		29.5(0.7)	30.5(0.8)	28.7(0.9)	29.5(1.5)
9		29.2(0.6)	30.3(0.6)	28.5(1.1)	28.3(1.0)
10		29.2(0.6)	30.3(0.7)	28.7(1.4)	28.3(1.0)
11		28.5(0.7)	30.1(0.6)	28.6(1.2)	27.9(1.1)
12		29.2(0.6)	29.8(1.4)	28.8(1.5)	28.0(1.2)

^a Standard deviation is reported in parentheses

Statistical methods: One-way Analysis of Variance and Dunnett's tests were performed on daily interval data. (See Statistical Analyses)

There were no statistically significant differences at alpha = 0.05.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 6

MEAN BODY WEIGHTS OF FEMALE MICE

DAYS ON TEST	GROUP: CONCENTRATION (ppm):	MEAN BODY WEIGHTS (g)			
		II 0	IV 3000	VI 6000	VIII 9000
1		24.4(1.1) ^a	24.9(0.9)	24.5(0.7)	23.7(3.2)
2		24.2(1.4)	23.7(0.7)	23.6(0.4)	23.4(0.3)
3		23.5(1.2)	23.5(1.4)	23.6(0.7)	23.5(0.3)
4		23.8(1.4)	23.5(1.0)	23.5(0.3)	23.8(0.8)
5		23.9(1.9)	23.7(0.8)	23.5(1.0)	23.9(0.3)
8		24.9(1.7)	23.4(2.9)	24.8(0.6)	24.7(0.9)
9		24.9(1.2)	23.9(1.1)	24.1(0.8)	24.5(0.6)
10		24.5(1.5)	23.7(1.6)	24.2(1.0)	24.3(1.0)
11		24.0(1.2)	23.4(1.7)	24.3(1.2)	24.2(1.3)
12		24.3(1.7)	23.8(1.0)	24.8(1.4)	24.6(1.4)

a Standard deviation is reported in parentheses

Statistical methods: One-way Analysis of Variance and Dunnett's tests were performed on daily interval data. (See Statistical Analyses)

There were no statistically significant differences at alpha = 0.05.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 7

MEAN BODY WEIGHT GAINS OF MALE RATS

		MEAN BODY WEIGHT GAINS (g)			
CONCENTRATION	GROUP: (ppm):	I 0	III 3000	V 6000	VII 9000
DAYS ON TEST					
1- 2		8.9(2.3) ^a	7.9(0.7)	4.8(2.3)*	2.0(1.4)*
2- 3		7.7(2.2)	10.4(2.5)	6.8(1.7)	6.9(1.3)
3- 4		9.6(1.7)	7.5(1.4)	9.8(1.9)	7.3(2.1)
4- 5		3.6(3.0)	3.9(2.1)	2.5(2.6)	3.0(2.4)
5- 8		28.0(4.8)	27.5(3.5)	29.1(2.2)	28.7(4.6)
8- 9		7.1(1.4)	7.1(3.6)	6.2(3.5)	2.4(1.4)*
9-10		8.7(1.0)	6.4(1.6)	5.0(2.1)	5.1(3.2)
10-11		7.1(3.3)	6.2(2.4)	4.5(1.9)	6.0(1.6)
11-12 ^b		-30.8(2.3)	-28.3(1.2)	-27.1(3.7)	-30.4(1.6)
1-11		80.7(13.1)	76.9(9.7)	68.8(10.0)	61.2(9.1)*

^a Standard deviation is reported in parentheses

^b Weight loss due to fasting.

Statistical methods: One-way Analysis of Variance and Dunnett's tests were performed on both daily and summary interval data. (See Statistical Analyses)

* Statistically significant difference from control at $p < 0.05$.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 8

MEAN BODY WEIGHT GAINS OF FEMALE RATS

CONCENTRATION	GROUP: (ppm):	MEAN BODY WEIGHT GAINS (g)			
		II 0	IV 3000	VI 6000	VIII 9000
	DAYS ON TEST				
	1- 2	3.2(5.5) ^a	1.3(3.2)	5.9(3.1)	-1.4(3.7)
	2- 3	4.6(3.9)	5.9(2.7)	0.1(2.7)	5.5(3.0)
	3- 4	3.7(3.6)	3.2(1.5)	4.8(3.0)	2.7(1.5)
	^a 4- 5	0.6(10.4)	2.0(2.7)	1.7(2.7)	-1.0(4.1)
	5- 8	6.6(5.3)	13.5(3.4)	9.0(1.3)	11.2(4.0)
	8- 9	9.2(3.8)	1.9(3.5)	3.0(2.0)	4.2(8.9)
	9-10	0.1(5.3)	-1.9(2.1)	2.1(1.5)	-0.3(3.3)
	10-11	4.7(5.4)	7.9(1.6)	5.1(4.5)	7.0(4.9)
	11-12 ^b	-23.9(2.5)	-23.6(3.9)	-22.0(4.4)	-22.0(4.2)
	1-11	32.7(11.2)	33.8(4.9)	31.7(6.9)	27.9(7.2)

^a Standard deviation is reported in parentheses

^b Weight loss due to fasting.

Statistical methods: One-way Analysis of Variance and Dunnett's tests were performed on both daily and summary interval data. (See Statistical Analyses)

There were no statistically significant differences at alpha = 0.05.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 9

MEAN BODY WEIGHT GAINS OF MALE MICE

		MEAN BODY WEIGHT GAINS (g)			
		I	III	V	VII
CONCENTRATION	GROUP: (ppm):	0	3000	6000	9000
DAYS ON TEST					
1- 2		-0.5(0.7)*	-0.4(0.6)	-0.4(0.8)	-1.3(0.9)
2- 3		0.1(0.9)	0.4(0.8)	0.1(0.7)	-0.3(0.8)
3- 4		-0.5(0.5)	-0.4(0.6)	-0.4(0.5)	-0.3(0.7)
4- 5		-0.1(0.3)	0.4(0.4)	0.7(0.4)*	0.6(0.3)*
5- 8		1.4(0.8)	1.1(0.8)	0.6(0.5)	1.9(1.0)
8- 9		-0.3(0.5)	-0.2(0.2)	-0.2(0.4)	-1.2(1.0)
9-10		0.0(0.2)	-0.1(0.3)	0.3(1.0)	0.0(0.3)
10-11		-0.6(0.2)	-0.2(0.6)	-0.1(0.4)	-0.4(0.4)
11-12		0.7(0.4)	-0.3(0.8)	0.3(0.3)	0.1(0.5)
1-12		0.1(0.9)	0.5(1.0)	0.8(0.9)	-0.9(0.8)

* Standard deviation is reported in parentheses

Statistical methods: One-way Analysis of Variance and Dunnett's tests were performed on both daily and summary interval data. (See Statistical Analyses)

* Statistically significant difference from control at $p < 0.05$.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 10

MEAN BODY WEIGHT GAINS OF FEMALE MICE

DAYS ON TEST	GROUP: CONCENTRATION (ppm):	MEAN BODY WEIGHT GAINS (g)			
		II 0	IV 3000	VI 6000	VIII 9000
1- 2		-0.2(0.7) ^a	-1.1(0.7)	-0.9(0.5)	-1.5(0.7)*
2- 3		-0.7(0.9)	-0.2(1.3)	0.0(0.8)	0.0(0.3)
3- 4		0.3(0.5)	0.0(0.6)	-0.1(0.5)	0.4(0.6)
4- 5		0.1(0.5)	0.2(0.4)	0.0(0.7)	0.1(0.7)
5- 8		1.0(1.0)	-0.3(3.2)	1.3(0.6)	0.8(0.9)
8- 9		0.0(0.6)	0.5(3.7)	-0.7(0.3)	-0.2(0.5)
9-10		-0.4(0.8)	-0.2(0.6)	0.1(0.4)	-0.2(0.8)
10-11		-0.5(0.8)	-0.4(0.4)	0.0(0.5)	0.0(0.4)
11-12		0.3(0.6)	0.5(1.1)	0.5(0.7)	0.4(0.8)
1-12		-0.1(1.0)	-1.1(1.1)	0.3(1.1)	-0.3(1.1)

^a Standard deviation is reported in parentheses

Statistical methods: One-way Analysis of Variance and Dunnett's tests were performed on both daily and summary interval data. (See Statistical Analyses)

* Statistically significant difference from control at $p < 0.05$.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 11

SUMMARY OF PRE- AND POST-EXPOSURE CLINICAL OBSERVATIONS IN MALE RATS

GROUP*: CONCENTRATION (ppm):	NUMBER OF RATS WITH GIVEN SIGN			
	I 0	III 3000	V 6000	VII 9000
<u>PRE-EXPOSURE OBSERVATIONS</u>				
NO ABNORMALITIES DETECTED				
<u>POST-EXPOSURE OBSERVATIONS</u>				
COLORED DISCHARGE EYE(S)	0	1 (9) ^b	0	0
COLORED DISCHARGE NOSE	0	0	1 (9)	0
STAINED FUR	0	0	3 (10)	4 (10)
WEAKNESS	0	0	0	0
WET FUR	0	0	0	4 (8)

a Total number of rats per group at study start = 5.

^b Numbers in parentheses are the medians for days-on-test when the given signs were first observed.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 12

SUMMARY OF PRE- AND POST-EXPOSURE CLINICAL OBSERVATIONS IN FEMALE RATS

GROUP ^a : CONCENTRATION (ppm):	NUMBER OF RATS WITH GIVEN SIGN			
	I 0	III 3000	V 6000	VII 9000
<u>PRE-EXPOSURE OBSERVATIONS</u>				
COLORED DISCHARGE EYE(S)	1 (6) ^b	0	0	0
COLORED DISCHARGE NOSE	1 (6)	0	0	0
HUNCHED OVER	1 (5)	0	0	0
IRREGULAR RESPIRATION	1 (5)	0	0	0
STAINED FUR	1 (5)	0	0	0
WEAKNESS	1 (5)	0	0	0
WET FUR	1 (5)	0	0	0
<u>POST-EXPOSURE OBSERVATIONS</u>				
HUNCHED OVER	1 (5)	0	0	0
IRREGULAR RESPIRATION	1 (5)	0	0	0
STAINED FUR	1 (5)	0	1 (9)	4 (10)
WEAKNESS	1 (5)	0	0	0
WET FUR	1 (5)	0	1 (8)	2 (10)

^a Total number of rats per group at study start = 5.

^b Numbers in parentheses are the medians for days-on-test when the given signs were first observed.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 13

SUMMARY OF PRE- AND POST-EXPOSURE CLINICAL OBSERVATIONS IN MALE MICE

GROUP ^a : CONCENTRATION (ppm):	NUMBER OF MICE WITH GIVEN SIGN			
	I 0	III 3000	V 6000	VII 9000
<u>PRE-EXPOSURE OBSERVATIONS</u>				
NO ABNORMALITIES DETECTED				
<u>POST-EXPOSURE OBSERVATIONS</u>				
ALOPECIA	0	1 (11)	0	0
RUFFLED FUR	0	0	0	2 (8)
SORE	0	1 (11)	0	0
STAINED FUR	0	0	0	3 (10)

^a Total number of mice per group at study start = 5.

^b Numbers in parentheses are the medians for days-on-test when the given signs were first observed.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 14

SUMMARY OF PRE- AND POST-EXPOSURE CLINICAL OBSERVATIONS IN FEMALE MICE

GROUP ^a : CONCENTRATION (ppm):	NUMBER OF MICE WITH GIVEN SIGN			
	II 0	IV 3000	VI 6000	VIII 9000
<u>PRE-EXPOSURE OBSERVATIONS</u>				
HYPERREACTIVE	0	0	1 (4) ^b	0
SORE	0	0	1 (5)	0
<u>POST-EXPOSURE OBSERVATIONS</u>				
HYPERREACTIVE	0	0	1 (3)	0
SORE	0	0	1 (5)	0
STAINED FUR	0	0	1 (10)	1 (10)

^a Total number of mice per group at study start = 5.

^b Numbers in parentheses are the medians for days-on-test when the given signs were first observed.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 15

SUMMARY OF OBSERVATIONS IN RATS DURING EXPOSURE

EXP. NO.	TEST DAY	GROUPS: I and II III and IV V and VI VII and VIII			
		CONC. (ppm): 0 3000 6000 9000			
		RESPONSE TO ALERTING STIMULUS			
1	1	NORMAL	NORMAL	NORMAL	NORMAL
2	2	NORMAL	NORMAL	NORMAL	DIMINISHED (5) ^b
3	3	NORMAL	NORMAL	NORMAL	DIMINISHED (3) ^c
4	4	NORMAL	NORMAL	NORMAL	DIMINISHED (2) ^d
5	5	NORMAL	NORMAL	NORMAL	DIMINISHED (1)
6	8	NORMAL	NORMAL	NORMAL	DIMINISHED (2)
7	9	NORMAL	NORMAL	DIMINISHED (5) ^a	DIMINISHED (2)
8	10	NORMAL	NORMAL	DIMINISHED (3)	DIMINISHED (2)
9	11	NORMAL	NORMAL	DIMINISHED (2)	DIMINISHED (2)

^a Numbers in parentheses are the approximate hours after exposure initiation when response was first observed.

^b One rat was lying low and appeared lethargic.

^c All animals appeared active prior to time when response was first observed.

^d All animals appeared active when response was first observed.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 16

SUMMARY OF OBSERVATIONS IN MICE DURING EXPOSURE

EXP. NO.	TEST DAY	GROUPS: I and II III and IV V and VI VII and VIII			
		CONC. (ppm): 0 3000 6000 9000			
		RESPONSE TO ALERTING STIMULUS			
1	1	NORMAL	NORMAL	NORMAL	NORMAL
2	2	NORMAL	NORMAL	NORMAL ^b	DIMINISHED (5) ^c
3	3	NORMAL	NORMAL	NORMAL	DIMINISHED (3) ^d
4	4	NORMAL	NORMAL	NORMAL	DIMINISHED (2) ^e
5	5	NORMAL	NORMAL	NORMAL	DIMINISHED (1) ^c
6	8	NORMAL	NORMAL	NORMAL	DIMINISHED (2) ^c
7	9	NORMAL	NORMAL	DIMINISHED (5) ^a	DIMINISHED (2) ^b
8	10	NORMAL	NORMAL	DIMINISHED (3)	DIMINISHED (2)
9	11	NORMAL	NORMAL	DIMINISHED (2)	DIMINISHED (2)

- ^a Numbers in parentheses are the approximate hours after exposure initiation when response was first observed.
- ^b Some or all mice exhibited jumping and/or slow circling behavior approximately six hours after exposure initiation.
- ^c All mice exhibited jumping and/or slow circling behavior when response was first observed.
- ^d All mice exhibited jerking movements approximately one hour after exposure initiation.
- ^e All mice were active and exhibited jerking movements when the response was first observed.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 17

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS FOR MALE RATS ^a

	Baseline			Pre-exposure Day 4			Post-exposure Day 4			Pre-exposure Day 11			Post-exposure Day 11			
	I	III	V	I	III	V	I	III	V	I	III	V	I	III	V	VII
Dose Group:	0	3000	6000	0	3000	6000	0	3000	6000	0	3000	6000	0	3000	6000	9000
Concentration (ppm):	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Number Examined:																
PARAMETER:																
^b																
Home Cage	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Posture - curled up	0	0	0	0	0	0	1	0	3	0	0	0	0	0	0	0
Palpebral Closure	0	0	0	0	0	0	1	0	2	0	0	0	0	0	0	0
rat appears to be sleeping																
Open Field	0	0	0	0	0	0	1	0	0	2	0	0	0	0	0	0
Slow Righting Reflex	0	0	0	0	0	0	2	1	0	1	1	0	0	0	2	1
Decreased Arousal	0	1	0	0	0	0	0	1	0	0	1	0	0	1	0	0
Increased Tail Pinch																

^a The incidence reflects those animals that showed some response other than that which would be considered "normal".
^b Only those parameters that are affected are presented. For a listing of all parameters assessed, see the main text.

Statistical Methods: The Cochran-Armitage test for trend was performed. If a significant trend was found, the test was repeated dropping the highest dose until no significance was found. If no significance was found with the Cochran-Armitage test but a lack of fit was significant, then Fisher's Exact test with a Bonferroni correction was performed to compare each dose group with the control group.

- Statistically significant difference from the control group.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 18

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS FOR FEMALE RATS ^a

	Baseline			Pre-exposure Day 4			Post-exposure Day 4			Pre-exposure Day 11			Post-exposure Day 11		
	II	IV	VIII	II	IV	VIII	II	IV	VIII	II	IV	VIII	II	IV	VIII
Dose Group:	0	3000	6000	0	3000	6000	0	3000	6000	0	3000	6000	0	3000	6000
Concentration (ppm):	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Number Examined:															
PARAMETER: ^b															
Home Cage															
Posture - curled up	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral Closure	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
rat appears to be sleeping	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Open Field															
Decreased Arousal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Increased Arousal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Increased Tail Pinch	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0

^a The incidence reflects those animals that showed some response other than that which would be considered "normal".
^b Only those parameters that are affected are presented. For a listing of all parameters assessed, see the main text.

Statistical Methods: The Cochran-Armitage test for trend was performed. If a significant trend was found, the test was repeated dropping the highest dose until no significance was found. If no significance was found with the Cochran-Armitage test but a lack of fit was significant, then Fisher's Exact test with a Bonferroni correction was performed to compare each dose group with the control group.

• Statistically significant difference from the control group.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 19

SUMMARY OF HEMATOLOGIC FINDINGS FOR MALE RATS

TESTS	CONCENTRATION (ppm)	SAMPLING TIME 2-WEEK
RBC x10 ⁶ /ul	0	6.75 (0.23) ^a
	3,000	6.58 (0.45)
	6,000	6.89 (0.27)
	9,000	6.85 (0.59)
Hb g/dl	0	14.9 (0.8)
	3,000	14.7 (0.5)
	6,000	15.0 (0.1)
	9,000	15.3 (0.8)
Ht %	0	44. (3.)
	3,000	43. (1.)
	6,000	45. (2.)
	9,000	45. (3.)
MCV fl	0	65. (2.)
	3,000	66. (3.)
	6,000	65. (1.)
	9,000	65. (2.)
MCH pg	0	22. (1.)
	3,000	23. (1.)
	6,000	22. (0.)
	9,000	23. (1.)
MCHC g/dl	0	34. (1.)
	3,000	34. (0.)
	6,000	34. (1.)
	9,000	34. (1.)

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 19 (continued)

SUMMARY OF HEMATOLOGIC FINDINGS FOR MALE RATS

TESTS	CONCENTRATION (ppm)	SAMPLING TIME 2-WEEK
PLAT x10 ³ /ul	0	1301. (114.)
	3,000	1200. (94.)
	6,000	1279. (117.)
	9,000	1253. (136.)
WBC x10 ³ /ul	0	15.9 (3.7)
	3,000	13.5 (2.5)
	6,000	11.0 (3.1)
	9,000	15.0 (4.2)
Neut WBCx%	0	1953. (1364.)
	3,000	1229. (290.)
	6,000	984. (468.)
	9,000	1655. (885.)
Band WBCx%	0	0. (0.)
	3,000	0. (0.)
	6,000	0. (0.)
	9,000	0. (0.)
Lymph WBCx%	0	13017. (2689.)
	3,000	11471. (2318.)
	6,000	9488. (2966.)
	9,000	12278. (3467.)
Alym WBCx%	0	0. (0.)
	3,000	0. (0.)
	6,000	0. (0.)
	9,000	61. (136.)

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 19 (continued)

SUMMARY OF HEMATOLOGIC FINDINGS FOR MALE RATS

TESTS	CONCENTRATION (ppm)	SAMPLING TIME 2-WEEK
	0	833. (407.)
Mono WBCx%	3,000	800. (350.)
	6,000	548. (267.)
	9,000	986. (623.)
	0	57. (79.)
Eosin WBCx%	3,000	0. (0.)
	6,000	0. (0.)
	9,000	20. (45.)
	0	0. (0.)
Baso WBCx%	3,000	0. (0.)
	6,000	0. (0.)
	9,000	0. (0.)

^a Group means and standard deviations (SD)

No statistically significant differences were found by Dunnett or Mann-Whitney U criteria

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 20

SUMMARY OF HEMATOLOGY FINDINGS FOR FEMALE RATS

TESTS	CONCENTRATION (ppm)	SAMPLING TIME 2-WEEK
RBC x10 ⁶ /ul	0	6.56 (0.68) ^a
	3,000	7.37 (0.07) [*]
	6,000	6.96 (0.34)
	9,000	7.30 (0.48)
Hb g/dl	0	14.4 (1.7)
	3,000	15.4 (0.6)
	6,000	14.8 (0.8)
	9,000	15.4 (0.6)
Ht %	0	44. (5.)
	3,000	48. (2.)
	6,000	46. (2.)
	9,000	48. (3.)
MCV fl	0	66. (2.)
	3,000	65. (2.)
	6,000	66. (3.)
	9,000	66. (2.)
MCH pg	0	22. (1.)
	3,000	21. (1.)
	6,000	22. (1.)
	9,000	21. (1.)
MCHC g/dl	0	33. (1.)
	3,000	32. (0.)
	6,000	32. (1.)
	9,000	33. (1.)

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 20 (continued)

SUMMARY OF HEMATOLOGIC FINDINGS FOR FEMALE RATS

TESTS	CONCENTRATION (ppm)	SAMPLING TIME 2-WEEK
PLAT x10 ³ /ul	0	1311. (347.)
	3,000	1267. (174.)
	6,000	1186. (63.)
	9,000	1064. (106.)
WBC x10 ³ /ul	0	15.0(5.6)
	3,000	8.7(2.7)*
	6,000	11.3(2.6)
	9,000	8.2(1.2)*
Neut WBCx%	0	2089. (2352.)
	3,000	646. (276.)+
	6,000	646. (283.)+
	9,000	719. (335.)
Band WBCx%	0	48. (108.)
	3,000	0. (0.)
	6,000	0. (0.)
	9,000	0. (0.)
Lymph WBCx%	0	11776. (2673.)
	3,000	7607. (2285.)*
	6,000	10153. (2704.)
	9,000	6855. (1035.)*
Alym WBCx%	0	18. (41.)
	3,000	0. (0.)
	6,000	0. (0.)
	9,000	0. (0.)

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 20 (continued)

SUMMARY OF HEMATOLOGIC FINDINGS FOR FEMALE RATS

TESTS	CONCENTRATION (ppm)	SAMPLING TIME 2-WEEK
Mono WBCx%	0	1062.(947.)
	3,000	417.(345.)
	6,000	472.(301.)
	9,000	547.(179.)
Eosin WBCx%	0	27.(60.)
	3,000	49.(68.)
	6,000	49.(67.)
	9,000	80.(48.)
Baso WBCx%	0	0.(0.)
	3,000	0.(0.)
	6,000	0.(0.)
	9,000	0.(0.)

* Group means and standard deviations(SD)

+ Significantly different from control at 5% level by Dunnett criteria

+ Significantly different from control at 5% level by Mann-Whitney U criteria

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 21

SUMMARY OF CLINICAL CHEMICAL FINDINGS FOR MALE RATS

TESTS	CONCENTRATION (ppm)	SAMPLING TIME 2-WEEK
ALP U/L	0	264. (56.) ^a
	3,000	256. (46.)
	6,000	180. (20.) [*]
	9,000	241. (54.)
ALT U/L	0	42. (5.)
	3,000	39. (8.)
	6,000	35. (3.)
	9,000	40. (5.)
AST U/L	0	122. (26.)
	3,000	95. (19.)
	6,000	86. (7.) [*]
	9,000	82. (11.) [*]
SDH U/L	0	22.8(6.7)
	3,000	20.9(5.1)
	6,000	20.3(2.9)
	9,000	17.3(2.0)
BILRN mg/dl	0	0.10(0.01)
	3,000	0.10(0.02)
	6,000	0.08(0.02) [*]
	9,000	0.08(0.01) [*]
CHOL mg/dl	0	61. (16.)
	3,000	67. (9.)
	6,000	87. (28.)
	9,000	70. (15.)
TRIG mg/dl	0	70. (17.)
	3,000	81. (10.)
	6,000	82. (17.)
	9,000	44. (16.) [*]

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 21 (continued)

SUMMARY OF CLINICAL CHEMICAL FINDINGS FOR MALE RATS

TESTS	CONCENTRATION (ppm)	SAMPLING TIME 2-WEEK
TPROT g/dl	0	6.0(0.2)
	3,000	6.0(0.2)
	6,000	6.1(0.2)
	9,000	6.2(0.4)
ALBMN g/dl	0	4.7(0.2)
	3,000	4.5(0.1)
	6,000	4.5(0.1)
	9,000	4.6(0.2)
GLOBN g/dl	0	1.4(0.2)
	3,000	1.5(0.1)
	6,000	1.6(0.2)
	9,000	1.6(0.2)
GLUCO mg/dl	0	80.(13.)
	3,000	90.(5.)
	6,000	75.(12.)
	9,000	85.(8.)
BUN mg/dl	0	13.(1.)
	3,000	13.(1.)
	6,000	11.(1.)*
	9,000	13.(1.)
CREAT mg/dl	0	0.3(0.1)
	3,000	0.3(0.0)
	6,000	0.3(0.0)
	9,000	0.3(0.1)

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 21 (continued)

SUMMARY OF CLINICAL CHEMICAL FINDINGS FOR MALE RATS

TESTS	CONCENTRATION (ppm)	SAMPLING TIME 2-WEEK
PHOS mg/dl	0	11.2(0.4)
	3,000	10.6(0.4)
	6,000	10.3(0.5)
	9,000	10.3(0.7)
CALC mg/dl	0	10.7(0.3)
	3,000	10.4(0.2)
	6,000	10.4(0.1)
	9,000	10.5(0.3)
Na mmol/L	0	147.(1.)
	3,000	146.(2.)
	6,000	146.(1.)
	9,000	146.(1.)
K mmol/L	0	6.2(0.4)
	3,000	6.1(0.4)
	6,000	6.2(0.2)
	9,000	6.1(0.1)
Cl mmol/L	0	96.(1.)
	3,000	98.(1.)*
	6,000	96.(1.)
	9,000	99.(1.)*

* Group means and standard deviations(SD)

* Significantly different from control at 5% level by Dunnett criteria

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 22

SUMMARY OF CLINICAL CHEMICAL FINDINGS FOR FEMALE RATS

TESTS	CONCENTRATION (ppm)	SAMPLING TIME 2-WEEK
ALP U/L	0	141. (41.) ^a
	3,000	119. (30.)
	6,000	129. (34.)
	9,000	133. (37.)
ALT U/L	0	31. (6.)
	3,000	32. (5.)
	6,000	32. (7.)
	9,000	31. (4.)
AST U/L	0	97. (34.)
	3,000	84. (2.)
	6,000	82. (11.)
	9,000	89. (11.)
SDH U/L	0	15.7 (6.4)
	3,000	16.7 (2.2)
	6,000	17.2 (1.9)
	9,000	17.7 (2.6)
BILRN mg/dl	0	0.11 (0.02)
	3,000	0.09 (0.01)
	6,000	0.08 (0.03)
	9,000	0.10 (0.01)
CHOL mg/dl	0	69. (9.)
	3,000	70. (12.)
	6,000	71. (8.)
	9,000	74. (9.)
TRIG mg/dl	0	53. (19.)
	3,000	35. (4.)
	6,000	44. (13.)
	9,000	34. (12.)

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 22 (continued)

SUMMARY OF CLINICAL CHEMICAL FINDINGS FOR FEMALE RATS

TESTS	CONCENTRATION (ppm)	SAMPLING TIME 2-WEEK
TPROT g/dl	0	6.7(0.3)
	3,000	6.3(0.2)
	6,000	6.1(0.3)*
	9,000	6.3(0.2)*
ALBMN g/dl	0	4.7(1.0)
	3,000	4.9(0.1)
	6,000	4.6(0.3)
	9,000	4.7(0.2)
GLOBN g/dl	0	2.1(0.9)
	3,000	1.5(0.2)
	6,000	1.5(0.1)
	9,000	1.5(0.1)
GLUCD mg/dl	0	95.(11.)
	3,000	98.(5.)
	6,000	98.(3.)
	9,000	99.(8.)
BUN mg/dl	0	18.(3.)
	3,000	17.(1.)
	6,000	15.(2.)*
	9,000	12.(2.)*
CREAT mg/dl	0	0.3(0.1)
	3,000	0.3(0.0)
	6,000	0.3(0.0)
	9,000	0.3(0.1)

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 22 (continued)

SUMMARY OF CLINICAL CHEMICAL FINDINGS FOR FEMALE RATS

TESTS	CONCENTRATION (ppm)	SAMPLING TIME 2-WEEK
PHOS mg/dl	0	9.0(0.6)
	3,000	9.0(0.7)
	6,000	8.8(0.8)
	9,000	9.2(0.7)
CALC mg/dl	0	10.4(0.2)
	3,000	10.1(0.1)
	6,000	10.1(0.3)
	9,000	10.2(0.2)
Na mmol/L	0	144.(2.)
	3,000	143.(0.)
	6,000	144.(1.)
	9,000	144.(1.)
K mmol/L	0	5.8(0.2)
	3,000	5.7(0.3)
	6,000	5.8(0.3)
	9,000	5.9(0.5)
Cl mmol/L	0	97.(2.)
	3,000	98.(1.)
	6,000	99.(2.)
	9,000	100.(1.)*

• Group means and standard deviations(SD)

* Significantly different from control at 5% level by Dunnett criteria

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 23

SUMMARY OF HEMATOLOGIC FINDINGS FOR MALE MICE

TESTS	CONCENTRATION (ppm)	SAMPLING TIME 2-WEEK
RBC x10 ⁶ /ul	0	9.66(0.45) ^a
	3,000	10.13(1.31)
	6,000	11.16(1.16)
	9,000	10.68(1.22)
Hb g/dl	0	15.8(0.8)
	3,000	16.3(1.9)
	6,000	18.1(1.6)
	9,000	17.9(1.8)
Ht %	0	46.(3.)
	3,000	46.(6.)
	6,000	52.(5.)
	9,000	51.(5.)
MCV fl	0	48.(1.)
	3,000	46.(1.) [*]
	6,000	46.(1.)
	9,000	48.(2.)
MCH pg	0	16.(1.)
	3,000	16.(0.)
	6,000	16.(1.)
	9,000	17.(1.)
MCHC g/dl	0	34.(1.)
	3,000	36.(1.)
	6,000	35.(1.)
	9,000	35.(1.)

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 23 (continued)

SUMMARY OF HEMATOLOGIC FINDINGS FOR MALE MICE

TESTS	CONCENTRATION (ppm)	SAMPLING TIME 2-WEEK
PLAT x10 ³ /ul	0	1075. (140.)
	3,000	1057. (316.)
	6,000	948. (100.)
	9,000	890. (178.)
WBC x10 ³ /ul	0	5.0(2.0)
	3,000	5.0(0.7)
	6,000	5.0(1.7)
	9,000	5.0(1.0)
Neut WBCx%	0	350. (218.)
	3,000	632. (479.)
	6,000	315. (98.)
	9,000	458. (128.)
Band WBCx%	0	6. (14.)
	3,000	13. (25.)
	6,000	0. (0.)
	9,000	0. (0.)
Lymph WBCx%	0	4204. (1546.)
	3,000	4033. (824.)
	6,000	4307. (1417.)
	9,000	4119. (975.)
Atym WBCx%	0	0. (0.)
	3,000	0. (0.)
	6,000	0. (0.)
	9,000	0. (0.)

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 23 (continued)

SUMMARY OF HEMATOLOGIC FINDINGS FOR MALE MICE

TESTS	CONCENTRATION (ppm)	SAMPLING TIME 2-WEEK
Mono WBCx%	0	434. (353.)
	3,000	348. (180.)
	6,000	376. (283.)
	9,000	384. (173.)
Eosin WBCx%	0	6. (14.)
	3,000	0. (0.)
	6,000	23. (34.)
	9,000	19. (27.)
Baso WBCx%	0	0. (0.)
	3,000	0. (0.)
	6,000	0. (0.)
	9,000	0. (0.)

^a Group means and standard deviations(SD)

* Significantly different from control at 5% level by Dunnett criteria

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 24

SUMMARY OF HEMATOLOGIC FINDINGS FOR FEMALE MICE

TESTS	CONCENTRATION (ppm)	SAMPLING TIME 2-WEEK
RBC x10 ⁶ /ul	0	10.13 (0.64) ^a
	3,000	10.68 (1.24)
	6,000	9.53 (0.42)
	9,000	10.00 (0.81)
Hb g/dl	0	16.1 (0.5)
	3,000	18.0 (2.3)
	6,000	16.2 (0.8)
	9,000	17.1 (1.8)
Ht %	0	47. (3.)
	3,000	50. (6.)
	6,000	46. (2.)
	9,000	48. (3.)
MCV fl	0	47. (2.)
	3,000	46. (1.)
	6,000	48. (1.)
	9,000	48. (1.)
MCH pg	0	16. (1.)
	3,000	17. (1.)
	6,000	17. (1.)
	9,000	17. (1.)
MCHC g/dl	0	34. (2.)
	3,000	36. (1.)
	6,000	36. (1.)
	9,000	36. (2.)

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 24 (continued)

SUMMARY OF HEMATOLOGIC FINDINGS FOR FEMALE MICE

TESTS	CONCENTRATION (ppm)	SAMPLING TIME 2-WEEK
PLAT x10 ³ /ul	0	1044. (179.)
	3,000	753. (205.)
	6,000	974. (140.)
	9,000	725. (197.)*
WBC x10 ³ /ul	0	6.8 (2.6)
	3,000	5.2 (1.3)
	6,000	5.1 (1.2)
	9,000	4.6 (1.1)
Neut WBCx%	0	610. (281.)
	3,000	485. (143.)
	6,000	325. (151.)
	9,000	280. (165.)
Band WBCx%	0	0. (0.)
	3,000	0. (0.)
	6,000	0. (0.)
	9,000	12. (26.)
Lymph WBCx%	0	5664. (2330.)
	3,000	4374. (862.)
	6,000	4288. (947.)
	9,000	4044. (856.)
Alym WBCx%	0	0. (0.)
	3,000	0. (0.)
	6,000	0. (0.)
	9,000	0. (0.)

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 24 (continued)

SUMMARY OF HEMATOLOGIC FINDINGS FOR FEMALE MICE

TESTS	CONCENTRATION (ppm)	SAMPLING TIME 2-WEEK
	0	557. (252.)
Mono WBCx%	3,000	345. (333.)
	6,000	404. (164.)
	9,000	243. (197.)
	0	8. (19.)
Eosin WBCx%	3,000	37. (52.)
	6,000	44. (43.)
	9,000	21. (30.)
	0	0. (0.)
Baso WBCx%	3,000	0. (0.)
	6,000	0. (0.)
	9,000	0. (0.)

a Group means and standard deviations(SD)

* Significantly different from control at 5% level by Dunnett criteria

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 25

SUMMARY OF PLASMA PROTEIN FINDINGS FOR MALE MICE

TESTS	CONCENTRATION (ppm)	SAMPLING TIME 2-WEEK
PLASMA PROTEIN g/dl	0	6.2(0.3) ^a
	3,000	6.0(0.9)
	6,000	6.5(0.4)
	9,000	6.6(0.6)

^a Group means and standard deviations(SD)

No statistically significant differences found by Dunnett or Mann-Whitney
U criteria

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 26

SUMMARY OF PLASMA PROTEIN FINDINGS FOR FEMALE MICE

TESTS	CONCENTRATION (ppm)	SAMPLING TIME 2-WEEK
PLASMA PROTEIN g/dl	0	6.3(0.3) ^a
	3,000	6.2(0.4)
	6,000	5.9(0.4)
	9,000	5.9(0.3)

^a Group means and standard deviations(SD)

No statistically significant differences found by Dunnett or Mann-Whitney U criteria

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 27
MEAN FINAL BODY AND ORGAN WEIGHTS FROM MALE RATS

MEAN FINAL BODY WEIGHTS (grams)		FINAL BODY		NUMBER OF ANIMALS	
GROUP	CONCENTRATION (ppm)				
I	0	247.9	{ 14.9 }	5	
III	3000	243.1	{ 7.8 }	5	
V	6000	238.9	{ 9.4 }	5	
VII	9000	228.8	{ 9.5 }	5	

MEAN ABSOLUTE ORGAN WEIGHTS (grams)		LIVER		KIDNEYS		LUNGS		TESTES		BRAIN	
GROUP	CONCENTRATION (ppm)										
I	0	8.872	{ 0.893 }	2.381	{ 0.252 }	1.703	{ 0.318 }	2.532	{ 0.150 }	1.923	{ 0.095 }
III	3000	9.319	{ 0.876 }	2.354	{ 0.093 }	1.554	{ 0.198 }	2.767	{ 0.142 }	1.839	{ 0.077 }
V	6000	9.301	{ 1.051 }	2.402	{ 0.180 }	1.557	{ 0.242 }	2.622	{ 0.220 }	1.914	{ 0.043 }
VII	9000	9.402	{ 1.600 }	2.398	{ 0.183 }	1.400	{ 0.137 }	2.466	{ 0.294 }	1.915	{ 0.083 }

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)		LIVER		KIDNEYS		LUNGS		TESTES		BRAIN	
GROUP	CONCENTRATION (ppm)										
I	0	3.573	{ 0.196 }	0.961	{ 0.097 }	0.690	{ 0.152 }	1.023	{ 0.068 }	0.779	{ 0.078 }
III	3000	3.829	{ 0.266 }	0.969	{ 0.049 }	0.640	{ 0.086 }	1.140	{ 0.085 }	0.757	{ 0.028 }
V	6000	3.886	{ 0.314 }	1.005	{ 0.042 }	0.651	{ 0.092 }	1.100	{ 0.109 }	0.802	{ 0.017 }
VII	9000	4.110	{ 0.676 }	1.048	{ 0.060 }	0.612	{ 0.057 }	1.078	{ 0.122 }	0.838	{ 0.048 }

MEAN RELATIVE ORGAN WEIGHTS (organ to brain weight ratio)		LIVER		KIDNEYS		LUNGS		TESTES	
GROUP	CONCENTRATION (ppm)								
I	0	4.638	{ 0.649 }	1.243	{ 0.159 }	0.882	{ 0.128 }	1.321	{ 0.119 }
III	3000	5.062	{ 0.341 }	1.281	{ 0.032 }	0.848	{ 0.126 }	1.509	{ 0.125 }
V	6000	4.853	{ 0.444 }	1.254	{ 0.070 }	0.813	{ 0.124 }	1.371	{ 0.124 }
VII	9000	4.910	{ 0.803 }	1.255	{ 0.112 }	0.730	{ 0.050 }	1.286	{ 0.122 }

STANDARD DEVIATION IN PARENTHESES
- SIGNIFICANTLY DIFFERENT (p < 0.05) FROM CONTROL GROUP BY DUNNETT'S TEST

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 28
MEAN FINAL BODY AND ORGAN WEIGHTS FROM FEMALE RATS

MEAN FINAL BODY WEIGHTS (grams)		FINAL BODY	NUMBER OF ANIMALS	-----		
GROUP	CONCENTRATION (ppm)			LUNGS	KIDNEYS	BRAIN
II	0	182.9 { 9.1 }	5	1.223 { 0.117 }	1.721 { 0.216 }	1.688 { 0.048 }
IV	3000	183.2 { 9.1 }	5	1.218 { 0.091 }	1.754 { 0.158 }	1.844 { 0.072 } #
VI	6000	183.4 { 4.9 }	5	1.393 { 0.062 } #	1.746 { 0.105 }	1.761 { 0.025 }
VIII	9000	179.1 { 11.0 }	5	1.205 { 0.061 }	1.671 { 0.072 }	1.758 { 0.033 }
MEAN ABSOLUTE ORGAN WEIGHTS (grams)						
GROUP	CONCENTRATION (ppm)	LIVER	KIDNEYS	LUNGS	BRAIN	
II	0	6.709 { 0.773 }	1.721 { 0.216 }	1.223 { 0.117 }	1.688 { 0.048 }	
IV	3000	6.677 { 0.930 }	1.754 { 0.158 }	1.218 { 0.091 }	1.844 { 0.072 } #	
VI	6000	6.699 { 0.817 }	1.746 { 0.105 }	1.393 { 0.062 } #	1.761 { 0.025 }	
VIII	9000	6.474 { 0.425 }	1.671 { 0.072 }	1.205 { 0.061 }	1.758 { 0.033 }	
MEAN RELATIVE ORGAN WEIGHTS (% of body weight)						
GROUP	CONCENTRATION (ppm)	LIVER	KIDNEYS	LUNGS	BRAIN	
II	0	3.679 { 0.508 }	0.944 { 0.141 }	0.671 { 0.075 }	0.924 { 0.033 }	
IV	3000	3.639 { 0.393 }	0.957 { 0.058 }	0.666 { 0.059 }	1.008 { 0.051 }	
VI	6000	3.647 { 0.371 }	0.952 { 0.043 }	0.760 { 0.039 }	0.961 { 0.036 }	
VIII	9000	3.618 { 0.195 }	0.935 { 0.048 }	0.675 { 0.047 }	0.984 { 0.063 }	
MEAN RELATIVE ORGAN WEIGHTS (organ to brain weight ratio)						
GROUP	CONCENTRATION (ppm)	LIVER	KIDNEYS	LUNGS		
II	0	3.980 { 0.496 }	1.021 { 0.141 }	0.725 { 0.065 }		
IV	3000	3.624 { 0.518 }	0.952 { 0.086 }	0.660 { 0.029 }		
VI	6000	3.808 { 0.511 }	0.992 { 0.068 }	0.791 { 0.039 }		
VIII	9000	3.684 { 0.265 }	0.951 { 0.054 }	0.686 { 0.044 }		

STANDARD DEVIATION IN PARENTHESES
- SIGNIFICANTLY DIFFERENT (p < 0.05) FROM CONTROL GROUP BY DUNNETT'S TEST

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 29
MEAN FINAL BODY AND ORGAN WEIGHTS FROM MALE MICE

MEAN FINAL BODY WEIGHTS (grams)		FINAL BODY		NUMBER OF ANIMALS	
GROUP	CONCENTRATION (ppm)	WEIGHT	STANDARD DEVIATION	GROUP	NUMBER
I	0	29.2	{ 0.6	I	5
III	3000	29.8	{ 1.4	III	4
V	6000	28.8	{ 1.5	V	5
VII	9000	27.8	{ 1.2	VII	4

MEAN ABSOLUTE ORGAN WEIGHTS (grams)		LIVER		KIDNEYS		LUNGS		TESTES		BRAIN	
GROUP	CONCENTRATION (ppm)	WEIGHT	STANDARD DEVIATION	WEIGHT	STANDARD DEVIATION	WEIGHT	STANDARD DEVIATION	WEIGHT	STANDARD DEVIATION	WEIGHT	STANDARD DEVIATION
I	0	1.527	{ 0.072	0.547	{ 0.060	0.227	{ 0.034	0.216	{ 0.018	0.478	{ 0.022
III	3000	1.630	{ 0.126	0.532	{ 0.045	0.279	{ 0.056	0.191	{ 0.018	0.458	{ 0.031
V	6000	1.694	{ 0.131	0.546	{ 0.079	0.298	{ 0.052	0.213	{ 0.022	0.459	{ 0.044
VII	9000	1.563	{ 0.105	0.501	{ 0.029	0.334	{ 0.077	0.193	{ 0.021	0.458	{ 0.021

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)		LIVER		KIDNEYS		LUNGS		TESTES		BRAIN	
GROUP	CONCENTRATION (ppm)	WEIGHT	STANDARD DEVIATION	WEIGHT	STANDARD DEVIATION	WEIGHT	STANDARD DEVIATION	WEIGHT	STANDARD DEVIATION	WEIGHT	STANDARD DEVIATION
I	0	5.228	{ 0.206	1.874	{ 0.194	0.774	{ 0.100	0.739	{ 0.049	1.637	{ 0.064
III	3000	5.478	{ 0.302	1.791	{ 0.171	0.937	{ 0.170	0.644	{ 0.074	1.544	{ 0.138
V	6000	5.875	{ 0.378}#	1.900	{ 0.327	1.033	{ 0.162	0.740	{ 0.068	1.597	{ 0.189
VII	9000	5.622	{ 0.145	1.806	{ 0.113	1.195	{ 0.237}#	0.693	{ 0.064	1.651	{ 0.078

MEAN RELATIVE ORGAN WEIGHTS (organ to brain weight ratio)		LIVER		KIDNEYS		LUNGS		TESTES	
GROUP	CONCENTRATION (ppm)	WEIGHT	STANDARD DEVIATION	WEIGHT	STANDARD DEVIATION	WEIGHT	STANDARD DEVIATION	WEIGHT	STANDARD DEVIATION
I	0	3.199	{ 0.199	1.143	{ 0.087	0.474	{ 0.065	0.451	{ 0.029
III	3000	3.565	{ 0.308	1.160	{ 0.025	0.609	{ 0.110	0.417	{ 0.036
V	6000	3.705	{ 0.291}#	1.188	{ 0.114	0.654	{ 0.134	0.468	{ 0.062
VII	9000	3.413	{ 0.241	1.096	{ 0.097	0.730	{ 0.180}#	0.420	{ 0.033

STANDARD DEVIATION IN PARENTHESES
- SIGNIFICANTLY DIFFERENT (p < 0.05) FROM CONTROL GROUP BY DUNNETT'S TEST

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE
 TABLE 30
 MEAN FINAL BODY AND ORGAN WEIGHTS FROM FEMALE MICE

MEAN FINAL BODY WEIGHTS (grams)		FINAL BODY	NUMBER OF			
GROUP	CONCENTRATION (ppm)	WEIGHT	ANIMALS	LIVER	KIDNEYS	BRAIN
II	0	24.3	5	0.333	0.217	0.451
IV	3000	23.8	5	0.328	0.292	0.443
VI	6000	24.8	5	0.346	0.211	0.467
VIII	9000	24.6	5	0.359	0.259	0.460
MEAN ABSOLUTE ORGAN WEIGHTS (grams)						
GROUP	CONCENTRATION (ppm)	LIVER	KIDNEYS	LUNGS	BRAIN	
II	0	1.108	0.333	0.217	0.451	
IV	3000	1.149	0.328	0.292	0.443	
VI	6000	1.247	0.346	0.211	0.467	
VIII	9000	1.241	0.359	0.259	0.460	
MEAN RELATIVE ORGAN WEIGHTS (% of body weight)						
GROUP	CONCENTRATION (ppm)	LIVER	KIDNEYS	LUNGS	BRAIN	
II	0	4.568	1.375	0.892	1.862	
IV	3000	4.826	1.376	1.238	1.861	
VI	6000	5.027	1.401	0.844	1.887	
VIII	9000	5.051	1.457	1.062	1.876	
MEAN RELATIVE ORGAN WEIGHTS (organ to brain weight ratio)						
GROUP	CONCENTRATION (ppm)	LIVER	KIDNEYS	LUNGS	BRAIN	
II	0	2.458	0.739	0.481	0.135	
IV	3000	2.594	0.739	0.656	0.191	
VI	6000	2.668	0.741	0.451	0.111	
VIII	9000	2.698	0.781	0.566	0.122	

STANDARD DEVIATION IN PARENTHESES
 # - SIGNIFICANTLY DIFFERENT (p < 0.05) FROM CONTROL GROUP BY DUNNETT'S TEST

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 31
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS

SITE/LESION:	GROUP DESIGNATION:		III		V		VII	
	I	0	3000	5	6000	5	9000	5
CONCENTRATION (ppm):	0	5	3000	5	6000	5	9000	5
NUMBER IN GROUP:	0	5	3000	5	6000	5	9000	5
KIDNEYS	0	0	0	0	1	1	0	0
DILATATION	0	0	0	0	1	1	0	0

NOTE: 0 INCIDENCES REFLECT THE NUMBER OF ANIMALS WITH A GIVEN LESION.

TWO-WEEK INHALATION RANGE-FINDINGS STUDY WITH CYCLOHEXANE

DuPont HLR 240-95

TABLE 32
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS

SITE/LESION:	GROUP DESIGNATION: CONCENTRATION (ppm): NUMBER IN GROUP:	II 0 5	IV 3000 5	VI 6000 5	VIII 9000 5
PERITONEAL CAVITY MASS		1	0	0	0
KIDNEYS DILATATION DISCOLORATION		1 1	0 0	0 0	0 0
SPLEEN LARGE		1	0	0	0

NOTE: 0 INDICENCES REFLECT THE NUMBER OF ANIMALS WITH A GIVEN LESION.

TWO-WEEK INHALATION RANGE-FINDINGS STUDY WITH CYCLOHEXANE

TABLE 33
INCIDENCES OF GROSS OBSERVATIONS IN MALE MICE

SITE/LESION:	GROUP DESIGNATION:						
	I	III	V	VII	CONCENTRATION (ppm):	NUMBER IN GROUP:	
FOOTPAD LARGE	0	1	0	0	3000	5	0
TAIL MISSING	0	1	0	0	6000	5	0
SKIN EDEMA	0	1	0	0			0
WHOLE BODY CANNIBALIZED	0	1	0	0			0

NOTE: 0 INCIDENCES REFLECT THE NUMBER OF ANIMALS WITH A GIVEN LESION.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

DuPont HLR 240-95

TABLE 34
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE MICE

SITE/LESION: EARS	GROUP DESIGNATION: CONCENTRATION (ppm): NUMBER IN GROUP:	II 0 5	IV 3000 5	VI 6000 5	VIII 9000 6
DEFORINITY		0	0	1	0

NOTE: 0 INCIDENCES REFLECT THE NUMBER OF ANIMALS WITH A GIVEN LESION.

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE
 TABLE 35
 INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS

TISSUE/LESION (P,1,2,3,4)	GROUP DESIGNATION: CONCENTRATION (ppm):		III 3000 5	V 6000 5	VII 9000 5
	I 0	5			
LIVER	5	5	5	5	5
MITOTIC FIGURES, INCREASED	-	-	-	1 (-,1,-,-,-)	2 (-,2,-,-,-)
KIDNEYS	5	5	0	0	5
HYPERPLASIA, TRANSITIONAL CELL	1	1	-	-	1 (-,-,1,-,-)
HYPERTROPHY, TUBULAR	1	1	-	-	1 (-,-,1,-,-)
INFLAMMATION, SUBACUTE/CHRONIC	1	1	-	-	1 (-,-,1,-,-)
URINARY BLADDER	5	5	0	0	5
HYPERPLASIA, SIMPLE TRANSITIONAL CELL	-	-	-	-	1 (-,-,1,-,-)
INFLAMMATION, SUBACUTE/CHRONIC	-	-	-	-	1 (-,-,1,-,-)
LUNGS	5	5	0	0	5
HEART	5	5	0	0	5
SPLEEN	5	5	0	0	5
THYMUS	5	5	0	0	5
BRAIN	5	5	0	0	5
SPINAL CORD	5	5	0	0	4
STOMACH	5	5	0	0	5
DUODENUM	5	5	0	0	5
JEJUNUM	5	5	0	0	5
ILEUM	5	5	0	0	5
PANCREAS	5	5	0	0	5
CECUM	5	5	0	0	5
COLON	5	5	0	0	5
RECTUM	5	5	0	0	5
MESENTERIC LYMPH NODE	5	5	0	0	5

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 35 (Continued)
INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS

TISSUE/LESION (P, 1, 2, 3, 4)	GROUP DESIGNATION: CONCENTRATION (ppm):		III 3000 5	V 6000 5	VII 9000 5
	NUMBER IN GROUP:				
ADRENAL GLANDS	5	5	0	0	5
SCIATIC NERVE	5	5	0	0	5
THYROID GLAND	5	5	0	0	5
PARATHYROID GLANDS	5	5	0	0	3
TRACHEA	5	5	0	0	5
ESOPHAGUS	5	5	0	0	5
PHARYNX/LARYNX	5	5	0	0	5
STERNUM & MARROW	5	5	0	0	5
EYES	5	5	0	0	5
FOLD/ROSETTE, RETINAL	1	1	-	-	1
PROSTATE	5	5	0	0	5
INFLAMMATION, SUBACUTE/CHRONIC	-	-	-	-	1
SEMINAL VESICLES	5	5	0	0	5
TESTES	5	5	0	0	5
EPIDIDYMIDES	5	5	0	0	5
NOSE I & II	5	5	0	0	4
NOSE III & IV	5	5	0	0	4
OTHER	0	0	0	0	0

NOTES:
 0 THE NUMBER OF ORGANS EXAMINED FOR EACH GROUP IS UNDERLINED.
 0 LESION GRADES: P = PRESENT; 1 = MINIMAL; 2 = MILD; 3 = MODERATE; 4 = SEVERE.
 0 LESION GRADES CORRESPOND BY POSITION WITH THE NUMBERS IN PARENTHESES, WHICH INDICATE HOW OFTEN EACH GRADE WAS OBSERVED. FOR EXAMPLE: (-, 1, 2, -) MEANS NO LESIONS WERE GRADED "PRESENT" (NON-GRADED LESIONS).
 1 LESION WAS GRADED "MINIMAL", 2 LESIONS WERE GRADED "MILD", NO LESIONS WERE GRADED "MODERATE" AND NO LESIONS WERE GRADED "SEVERE".

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 36 (Continued)
INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS

TISSUE/LESION (P,1,2,3,4)	GROUP DESIGNATION: CONCENTRATION (ppm):		IV 3000 5	VI 6000 5	VIII 9000 5
	LESION GRADES (P,1,2,3,4)	NUMBER IN GROUP:			
ADRENAL GLANDS	5	0	0	0	5
SCIATIC NERVE	5	0	0	0	5
THYROID GLAND INFLAMMATION, SUBACUTE/CHRONIC	5	0	0	0	5 1 (-,1,-,-,-)
PARATHYROID GLANDS	3	0	0	0	5
TRACHEA	5	0	0	0	5
ESOPHAGUS	5	0	0	0	5
PHARYNX/LARYNX	5	0	0	0	5
STERNUM & MARROW	5	0	0	0	5
EYES FOLD/ROSETTE, RETINAL	5	0	0	0	5 1 (-,1,-,-,-)
OVARIES	5	0	0	0	5
UTERUS INFLAMMATION, PERITONEAL	5 1 (-,-,-,-,1)	0	0	0	5 -
VAGINA	5	0	0	0	5
NOSE I & II	5	0	0	0	5
NOSE III & IV	5	0	0	0	5
OTHER MESENTERY/PERITONEUM: INFLAMMATION	1 1 (-,-,-,-,1)	0	0	0	0 -

NOTES:
 0 THE NUMBER OF ORGANS EXAMINED FOR EACH GROUP IS UNDERLINED.
 0 LESION GRADES: P = PRESENT; 1 = MINIMAL; 2 = MILD; 3 = MODERATE; 4 = SEVERE.
 0 LESION GRADES CORRESPOND BY POSITION WITH THE NUMBERS IN PARENTHESES, WHICH INDICATE HOW OFTEN EACH GRADE WAS OBSERVED. FOR EXAMPLE: (-,1,2,-,-) MEANS NO LESIONS WERE GRADED "PRESENT" (NON-GRADED LESIONS).
 1 LESION WAS GRADED "MINIMAL"; 2 LESIONS WERE GRADED "MILD"; NO LESIONS WERE GRADED "MODERATE" AND NO LESIONS WERE GRADED "SEVERE".

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 37
INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE MICE

TISSUE/LESION	GROUP DESIGNATION:		I	III 3000	V 6000	VII 9000
	LESION GRADES (P,1,2,3,4)	CONCENTRATION (ppm): NUMBER IN GROUP:				
LIVER			5	0	5	5
HYPERTROPHY, HEPATOCYTE MITOTIC FIGURES, INCREASED			-	-	-	2 (-,2,-,-,-,-)
GALL BLADDER			5	0	0	5
KIDNEYS CYST			5	0	0	5
LUNGS			1 (1,-,-,-,-,-)	-	-	2 (-,2,-,-,-,-)
HEART			5	0	0	5
SPLEEN			5	0	0	5
BRAIN			5	0	0	5
SPINAL CORD			5	0	0	5
STOMACH			5	0	0	5
DUODENUM			5	0	0	5
JEJUNUM			5	0	0	5
ILEUM			5	0	0	5
PANCREAS			5	0	0	5
CECUM			5	0	0	5
COLON			5	0	0	5
RECTUM			5	0	0	5
MESENTERIC LYMPH NODE			5	0	0	5
THYMUS			5	0	0	5
ADRENAL GLANDS			5	0	0	5

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE
 TABLE 37 (Continued)
 INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE MICE

TISSUE/LESION (P,1,2,3,4)	GROUP DESIGNATION: CONCENTRATION (ppm):		III 3000 5	V 6000 5	VII 9000 5
	1	0			
SCIATIC NERVE	5	0	0	0	5
THYROID GLAND	5	0	0	0	5
PARATHYROID GLANDS	2	0	0	0	4
TRACHEA	5	0	0	0	5
ESOPHAGUS	5	0	0	0	5
EYES	5	0	0	0	5
INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE)	1 (-, -, 1, -, -)	-	-	-	-
PROSTATE	5	0	0	0	5
SEMINAL VESICLES	5	0	0	0	5
URINARY BLADDER	5	0	0	0	5
TESTES	5	0	0	0	5
EPIDIDYMIDES	5	0	0	0	5
STERNUM & MARROW	5	0	0	0	5
NOSE I & II	5	0	0	0	5
NOSE III & IV	5	0	0	0	5
OTHER	0	0	0	0	0

NOTES:
 0 THE NUMBER OF ORGANS EXAMINED FOR EACH GROUP IS UNDERLINED.
 0 LESION GRADES: P = PRESENT; 1 = MINIMAL; 2 = MILD; 3 = MODERATE; 4 = SEVERE.
 0 LESION GRADES CORRESPOND BY POSITION WITH THE NUMBERS IN PARENTHESES, WHICH INDICATE HOW OFTEN EACH GRADE WAS OBSERVED. FOR EXAMPLE: (-, 1, 2, -) MEANS NO LESIONS WERE GRADED "PRESENT" (NON-GRADED LESIONS)
 1 LESION WAS GRADED "MINIMAL", 2 LESIONS WERE GRADED "MILD", NO LESIONS WERE GRADED "MODERATE" AND NO LESIONS WERE GRADED "SEVERE".

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE
 TABLE 38
 INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE MICE

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: CONCENTRATION (ppm): NUMBER IN GROUP:	II	IV 3000 5	VI 6000 5	VIII 9000 5
LIVER			5	5	5	5
HYPERTROPHY, HEPATOCYTE MITOTIC FIGURES, INCREASED			-	1 (-,1,-,-,-,-) 3 (-,3,-,-,-,-)	1 (-,1,-,-,-,-) 4 (-,4,-,-,-,-)	4 (-,4,-,-,-,-) 4 (-,4,-,-,-,-)
GALL BLADDER			5	0	0	5
KIDNEYS CYST			5	0	0	5
LUNGS			-	-	-	1 (1,-,-,-,-,-)
HEART			5	0	0	5
SPLEEN			5	0	0	5
BRAIN			5	0	0	5
SPINAL CORD			5	0	0	5
STOMACH			5	0	0	5
DUODENUM			5	0	0	5
JEJUNUM			5	0	0	5
ILEUM			5	0	0	5
PANCREAS			5	0	0	5
CECUM			5	0	0	5
COLON			5	0	0	5
RECTUM			5	0	0	5
MESENTERIC LYMPH NODE			5	0	0	5
THYMUS			5	0	0	5
ADRENAL GLANDS FATTY CHANGE, DIFFUSE CORTICAL			5	1 (-,1,-,-,-,-)	0	5

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

TABLE 38 (Continued)
INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE MICE

TISSUE/LESION (P,1,2,3,4)	GROUP DESIGNATION: CONCENTRATION (ppm):		IV 3000 5	VI 6000 5	VIII 9000 5
	II 0	5			
SCIATIC NERVE	5	5	0	0	5
THYROID GLAND	5	5	0	0	5
PARATHYROID GLANDS	4	4	0	0	3
TRACHEA	5	5	0	0	5
ESOPHAGUS	5	5	0	0	5
EYES	5	5	0	0	5
OVARIES	5	5	0	0	5
UTERUS	5	5	0	0	5
VAGINA	5	5	0	0	5
URINARY BLADDER	5	5	0	0	5
STERNUM & MARROW	5	5	0	0	5
NOSE I & II	5	5	0	0	5
NOSE III & IV	5	5	0	0	5
OTHER	0	0	0	0	0

NOTES:
 O THE NUMBER OF ORGANS EXAMINED FOR EACH GROUP IS UNDERLINED.
 O LESION GRADES: P = PRESENT; 1 = MINIMAL; 2 = MILD; 3 = MODERATE; 4 = SEVERE.
 O LESION GRADES CORRESPOND BY POSITION WITH THE NUMBERS IN PARENTHESES, WHICH INDICATE HOW OFTEN EACH GRADE WAS OBSERVED. FOR EXAMPLE: (-,1,2,-,-) MEANS NO LESIONS WERE GRADED "PRESENT" (NON-GRADED LESIONS).
 O 1 LESION WAS GRADED "MINIMAL", 2 LESIONS WERE GRADED "MILD", NO LESIONS WERE GRADED "MODERATE" AND NO LESIONS WERE GRADED "SEVERE".

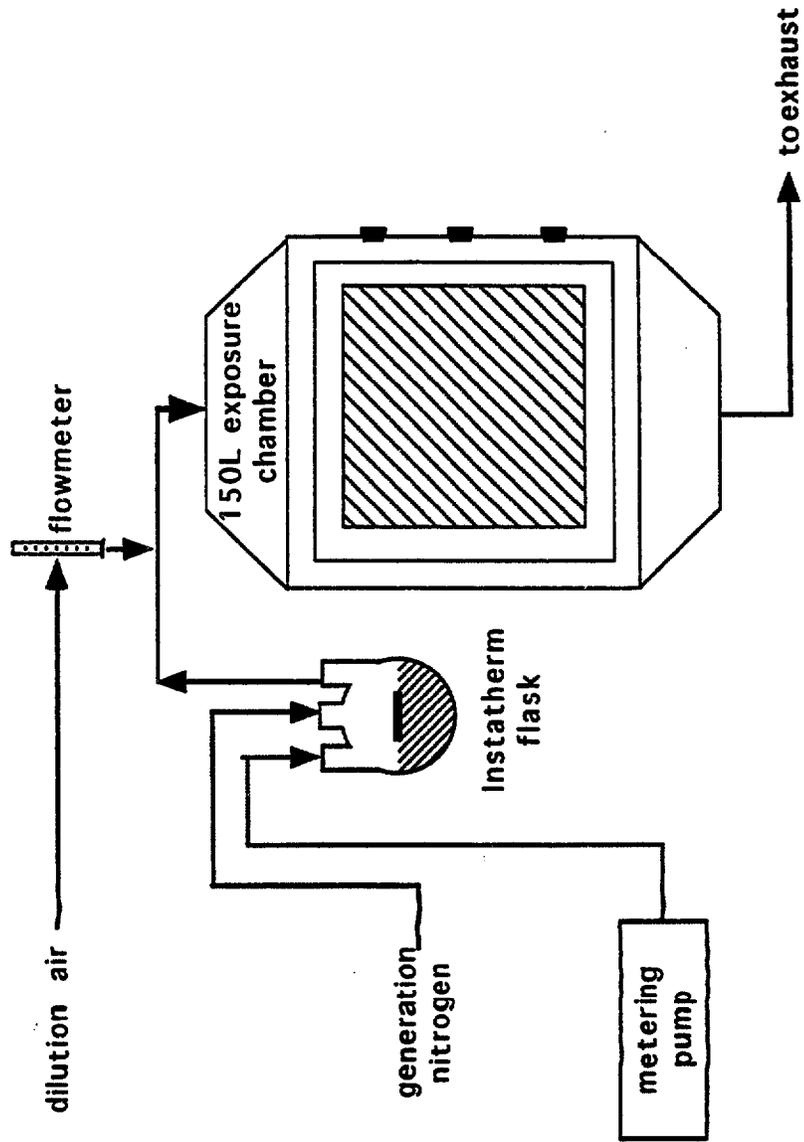
TWO-WEEK INSULATION MASS-STEERING STUDY WITH CYPLOHEXIMIDE

FIGURES

TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

FIGURE 1

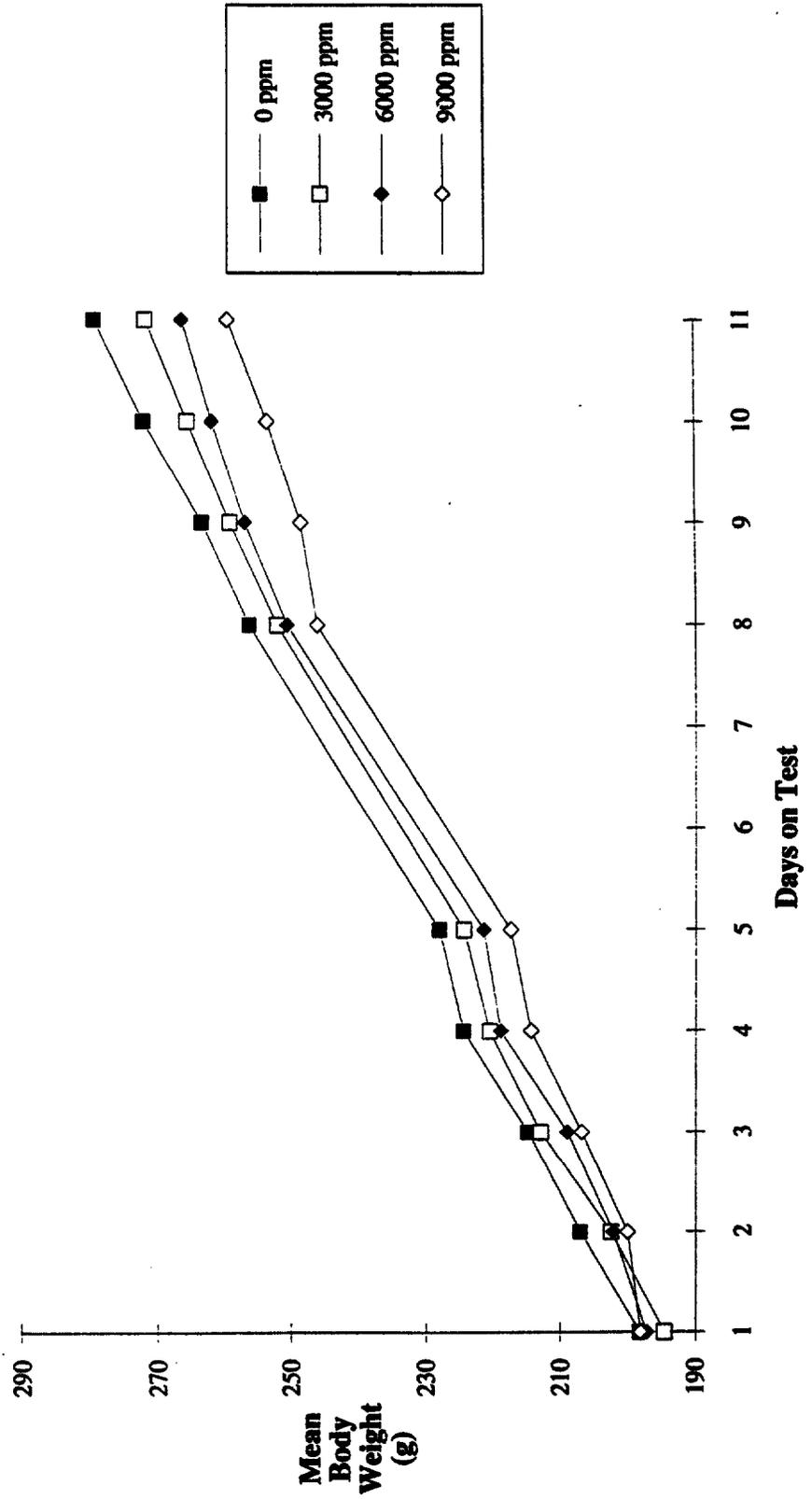
SCHEMATIC OF EXPOSURE SYSTEM



TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

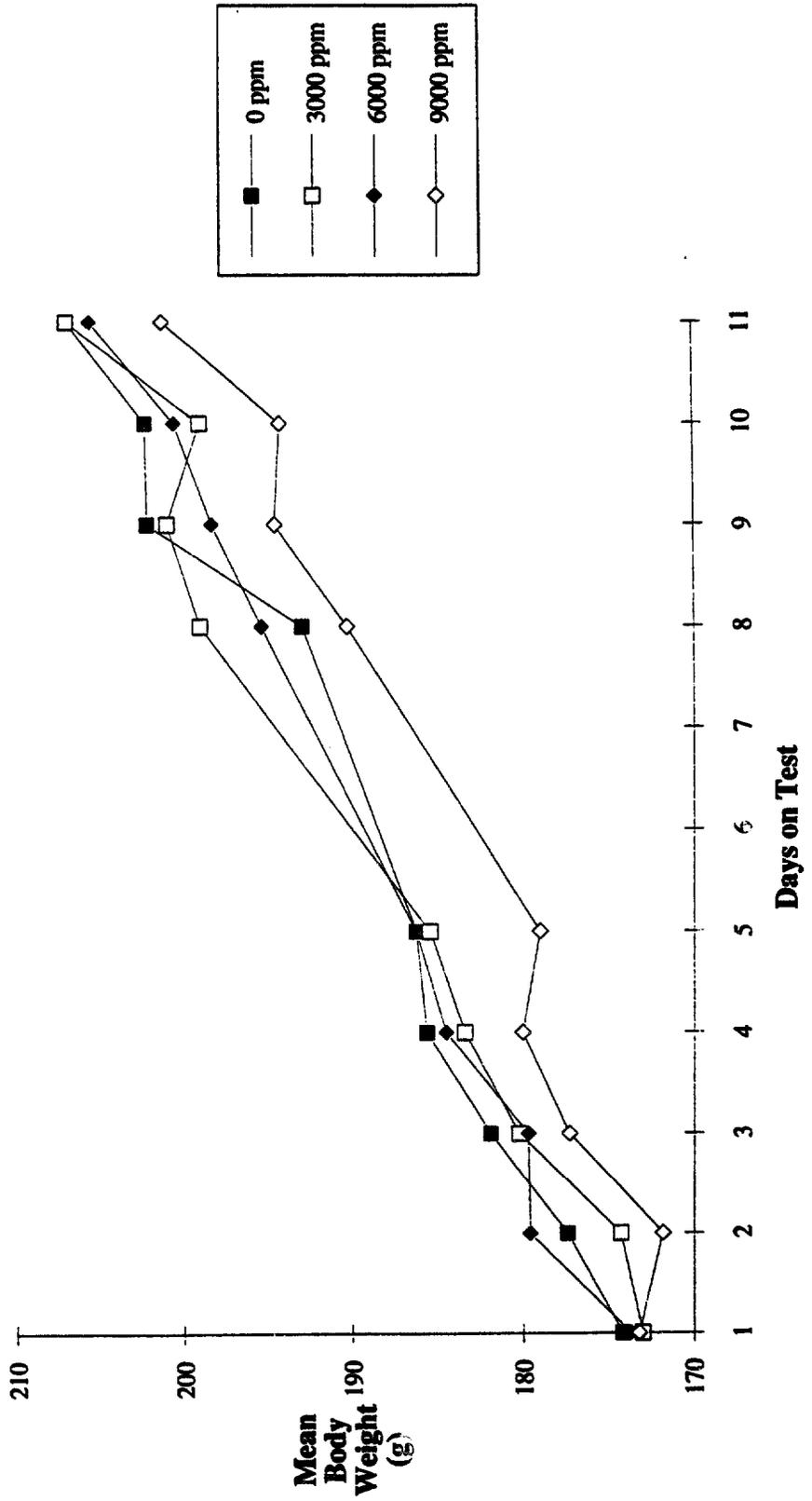
FIGURE 2

MEAN BODY WEIGHTS OF MALE RATS



TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

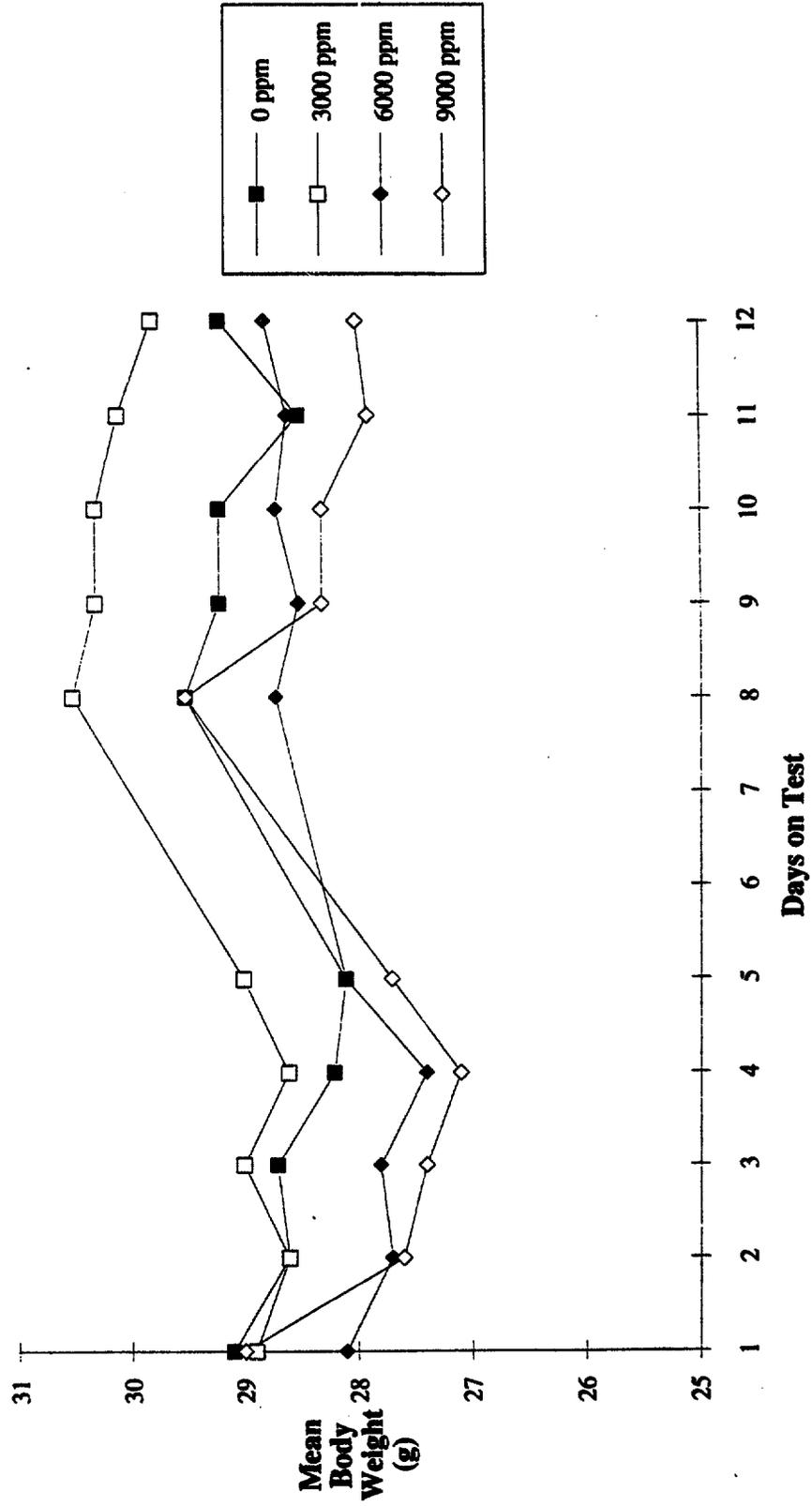
FIGURE 3
MEAN BODY WEIGHTS OF FEMALE RATS



TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

FIGURE 4

MEAN BODY WEIGHTS OF MALE MICE



TWO-WEEK INHALATION RANGE-FINDING STUDY WITH CYCLOHEXANE

FIGURE 5
MEAN BODY WEIGHTS OF FEMALE MICE

