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TSCA CBI STATUS:

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1.0 SUBMISSION TYPE <input type="checkbox"/> Contains CBI Submission date: January 29, 1997 <input type="checkbox"/> 8(d) <input checked="" type="checkbox"/> 8(e) <input type="checkbox"/> FYI <input type="checkbox"/> 4 <input type="checkbox"/> Other: specify <input type="checkbox"/> Initial submission <input type="checkbox"/> Follow-up submission <input checked="" type="checkbox"/> Final report submission Previous EPA Submission or Title if Update or Follow-up: Acute Inhalation Study Docket Number, if any: # of Cyclopropanecarboxaldehyde in Rats <input type="checkbox"/> continuation sheet attached								
2.1 SUMMARY/ABSTRACT ATTACHED <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	2.2 SUBMITTER TRACKING NUMBER OR INTERNAL ID 8E-97-2	2.3 FOR EPA USE ONLY <div style="text-align: right; font-size: 2em; font-weight: bold; transform: rotate(-5deg);"> Contains No CBI </div>						
3.0 CHEMICAL/TEST SUBSTANCE IDENTITY <input type="checkbox"/> Contains CBI <div style="display: flex; justify-content: space-between;"> <div> CAS #: 1489-69-6 Purity: ~100 % <input checked="" type="checkbox"/> Single Ingredient <input type="checkbox"/> Commercial/Technical Grade <input type="checkbox"/> Mixture </div> <div style="text-align: center;"> <u>Reported Chemical Name (speci)</u> Cyclopropanecarboxaldehyde </div> <div style="text-align: center;">  8EHQ-97-13873 Common Name: CPCA </div> </div>								
Other chemical(s) present in tested mixture <input type="checkbox"/> continuation sheet attached	<table style="width:100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left;">CAS Number</th> <th style="text-align: left;">Name</th> <th style="text-align: right;">% WEIGHT</th> </tr> </thead> <tbody> <tr> <td>None known</td> <td style="font-size: 1.5em; font-weight: bold; text-align: center;">8EHQ-0197-13873</td> <td></td> </tr> </tbody> </table>	CAS Number	Name	% WEIGHT	None known	8EHQ-0197-13873		
CAS Number	Name	% WEIGHT						
None known	8EHQ-0197-13873							
4.0 REPORT/STUDY TITLE <input type="checkbox"/> Contains CBI An Acute Inhalation Toxicity Study in the Rat <div style="text-align: center; margin-top: 10px;">  88970000123 </div> <input type="checkbox"/> continuation sheet attached								
5.1 STUDY/TSCATS INDEXING TERMS [CHECK ONE] HEALTH EFFECTS (HE): <input checked="" type="checkbox"/> ENVIRONMENTAL EFFECTS (EE): <input type="checkbox"/> ENVIRONMENTAL FATE (EF): <input type="checkbox"/>								
5.2 STUDY/TSCATS INDEXING TERMS (see instructions f or 4-digit codes) <table style="width:100%; border-collapse: collapse;"> <tr> <td>STUDY TYPE: ATOX <i>Other:</i></td> <td>SUBJECT ORGANISM (HE,EE only): RATS <i>Other:</i></td> <td>ROUTE OF EXPOSURE (HE only): INHL <i>Other:</i></td> <td>VEHICLE OF EXPOSURE (HE only): AIR <i>Other:</i></td> </tr> </table>			STUDY TYPE: ATOX <i>Other:</i>	SUBJECT ORGANISM (HE,EE only): RATS <i>Other:</i>	ROUTE OF EXPOSURE (HE only): INHL <i>Other:</i>	VEHICLE OF EXPOSURE (HE only): AIR <i>Other:</i>		
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6.0 REPORT/STUDY INFORMATION <input type="checkbox"/> Contains CBI <input checked="" type="checkbox"/> Study is GLP Laboratory: <u>Health and Environment Laboratories, Eastman Kodak Company</u> Report/Study Date: <u>December 10, 1996</u> <u>1100 Ridgeway Avenue, Rochester, NY 14652</u> Source of Data/Study Sponsor (if different than submitter) Number of Pages: <u>146</u> <input type="checkbox"/> continuation sheet attached								
7.0 SUBMITTER INFORMATION <input type="checkbox"/> Contains CBI Submitter: <u>Marc G. Schurger</u> Title: <u>Manager, Product Safety and Regulatory Programs</u> Phone: <u>(423) 229-8921</u> Company Name: <u>Eastman Chemical Company</u> Company Address: <u>P. O. Box 1994, Kingsport TN 37664-5144</u> Submitter Address (if different): Technical Contact: <u>Karen R. Miller, Ph.D.</u> Phone: <u>(423) 229-4554</u> <input type="checkbox"/> continuation sheet attached								
8.0 ADDITIONAL/OPTIONAL STUDY COMMENTS <input type="checkbox"/> Contains CBI This is the final report received by Eastman Chemical Company on January 24, 1997 <input type="checkbox"/> continuation sheet attached								

Submitter Signature: Marc G. Schurger Date: 1-29-97
 Page ___ of ___

CSRAD/OPPT
 3/27/97
 mb

FINAL REPORT

CYCLOPROPANECARBOXALDEHYDE
SYNONYM: CPCA

HAEL No. 96-0212
CAS No. 001489-69-6

EAN 023931
PM No. 15653-00

AN ACUTE INHALATION TOXICITY STUDY IN THE RAT

GUIDELINE

U.S. EPA: 40 CFR 798.1150
OECD: TG-403
EEC: Annex V., Test B.2

AUTHORS

Lisa G. Bernard, M.S.
Raymond M. David, Ph.D.

TESTING FACILITY

Toxicological Sciences Laboratory
Health and Environment Laboratories
Eastman Kodak Company
Rochester, New York 14652-6272
USA

LABORATORY PROJECT ID

960212I1

STUDY SPONSOR

Eastman Chemical Company
P.O. Box 1994
First American Center
Kingsport, TN 37662-5394

STUDY COMPLETION DATE

December 10, 1996

QUALITY ASSURANCE INSPECTION STATEMENT
(21 CFR 58.35(B)(7), 40 CFR 792.35(B)(7), AND 40 CFR 160.35(B)(7))

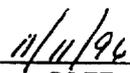
STUDY: 96-0212-1 STUDY DIRECTOR: BERNARD, L.G.
ACCESSION NUMBER: 023931

PAGE 1
11/11/96

STUDY TYPE: ACUTE INHALATION (LC50)



(AUDITOR, QUALITY ASSURANCE UNIT)



DATE

THIS STUDY WAS INSPECTED BY 1 OR MORE PERSONS OF THE QUALITY
ASSURANCE UNIT. WRITTEN STATUS REPORTS WERE SUBMITTED ON THE
FOLLOWING DATES.

INSPECTION DATES -----	PHASE(S) INSPECTED -----	STATUS REPORT DATES -----
04/30/96	PROTOCOL SUBMISSION PROTOCOL AMENDMENT OF 4/29/96 RECEIVED	
05/01/96	CLINICAL SIGNS DURING DOSE CHAMBER AIRFLOW/TEMPERATURE/RELATIVE HUMIDITY READINGS CHAMBER CONCENTRATION ANALYSIS SAMPLE COLLECTION SPECIMEN/SAMPLE WEIGHT SAMPLE ANALYSIS	05/01/96
05/02/96	NECROPSY SPECIMEN COLLECTION	
05/10/96	PROTOCOL AMENDMENT OF 5/7/96 RECEIVED	
05/14/96	CHAMBER CONCENTRATION ANALYSIS CLINICAL SIGNS CHAMBER AIRFLOW/TEMPERATURE/RELATIVE HUMIDITY READINGS SAMPLE COLLECTION	
05/20/96	PROTOCOL AMENDMENT OF 5/7/96 RECEIVED	

QUALITY ASSURANCE INSPECTION STATEMENT
(21 CFR 58.35(B)(7), 40 CFR 792.35(B)(7), AND 40 CFR 160.35(B)(7))

STUDY: 96-0212-1 STUDY DIRECTOR: BERNARD, L.G. PAGE 2
ACCESSION NUMBER: 023931 11/11/96

08/21/96	GROSS PATHOLOGY HISTOPATHOLOGY PATHOLOGY REPORT	08/21/96
09/26/96	RECORDS REVIEW ANALYTICAL REPORT DURING DOSE CLINICAL SIGNS TWA AND NOMINAL CONCENTRATION TEMPERATURE, RELATIVE HUMIDITY AND AIRFLOW	
10/07/96	RECORDS REVIEW CLINICAL SIGNS, ANALYTICAL REPORT, TEMPERATURE, HUMIDITY, AIRFLOW AND CONCENTRATION	10/08/96
10/10/96	FINAL REPORT REVIEW	10/11/96
10/11/96	FINAL REPORT REVIEW	10/11/96
10/21/96	FINAL REPORT REVIEW	10/21/96
11/11/96	FINAL REPORT REVIEW	11/11/96

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study was conducted according to:

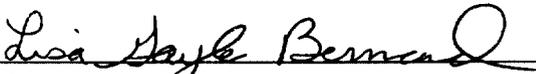
United States Food and Drug Administration, Good Laboratory Practice
Regulations for Nonclinical Laboratory Studies, 21 CFR Part 58;

United States Environmental Protection Agency, Toxic Substances Control Act,
Good Laboratory Practice Standards, 40 CFR Part 792;

Annex 2, Organisation for Economic Cooperation and Development, Guidelines
for Testing of Chemicals [C(81)30(Final)].

With the following reservations:

The stability of the test article under test conditions (during exposure) was not
determined by the performing laboratory and is not included in the final report
[21 CFR Part 58, Section 113 (2); 40 CFR Part 792, Section 105 (a,3); and
Annex 2 (C(81)30(Final), Section 6.2 (4 and 5)].



Lisa G. Bernard, M.S.
Study Director

12-10-96

Month/Day/Year

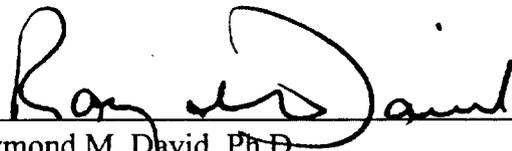


Karen R. Miller, Ph.D.
Sponsor's Representative

November 26, 1996

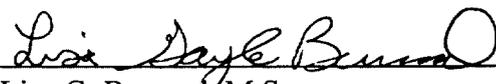
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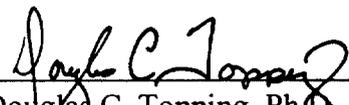
Raymond M. David, Ph.D.
Report Author

11/11/96
Month/Day/Year



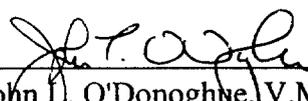
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Month/Day/Year



Douglas C. Topping, Ph.D.
Unit Director, Mammalian Toxicology

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Month/Day/Year



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Month/Day/Year



Karen R. Miller, Ph.D.
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November 26, 1996
Month/Day/Year

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ABSTRACT

**CYCLOPROPANECARBOXALDEHYDE
SYNONYM: CPCA**

**HAEL No. 96-0212
CAS No. 001489-69-6**

**EAN 023931
PM No. 15653-00**

AN ACUTE INHALATION TOXICITY STUDY IN THE RAT

Male and female Sprague-Dawley rats (CRL:CD[®](SD)BR/VAF Plus[™]) were exposed to cyclopropanecarboxaldehyde (CPCA) vapor in three individual tests: Test 1 animals received a single 6 hour exposure to 1892 ppm CPCA, and Test 2 and 3 animals received single 4 hour exposures to 1697 or 368 ppm CPCA, respectively. Separate control groups (Control 1, 2, and 3) were exposed concurrently to the corresponding test group. Samples from the test atmosphere were analyzed by GC/FID for CPCA and cyclopropane carboxylic acid, a potential oxidation product of the test substance. Only CPCA was detected in the chambers. Test 1 consisted of 10 male and 10 female rats and Control 1 consisted of 5 male and 5 female rats. Test 2 and 3 and Control 2 and 3 each consisted of 8 male and 8 female rats. Animals were observed hourly during exposure and twice daily thereafter. Body weights were measured at least weekly. For the Test 1 group, 7/10 male and 10/10 female rats died by the morning following the exposure; the remaining treated and control animals were euthanatized and necropsied on Day 1 to assess short-term effects. For Control/Test 2 and 3 groups, three of each sex per concentration were necropsied on Day 1. In addition, 3/5 male and 4/5 female Test 2 rats were found dead on Days 2 to 8. All surviving Control/Test 2 and 3 animals were necropsied on Day 14. General activity was reduced during exposure to all concentrations of the test substance. The severity of the reduced activity was concentration dependent. In addition, the Test 1 group had rapid, shallow respiration during the second and third exposure hours and labored breathing during the fourth through sixth exposure hours with a slower rate of breathing during the sixth hour. The altered respiratory pattern for these animals may have been a physiological response to the reduced oxygen level (17.5% during the first three hours of exposure). Immediately following exposure, the Test 1 animals had reduced activity levels (moderate to severe severity) and deep, rapid respiration, while the Test 2 animals had reduced activity levels (minimal to moderate severity) and abnormal gait. Immediately following exposure, a single Test 3 male rat had a reduced activity level (minimal severity). For Test 2 animals which survived, an abnormal gait was observed through Day 2, and reduced activity levels were observed through Day 3 (2 male rats) or 4 (one female rat). Additional clinical signs included porphyrin discharges around the nose or eyes, excessive tearing, partially closed eyes, dehydration, decreased fecal volume, softened feces, inguinal haircoats which were wet with urine and/or stained with feces, and/or unkempt haircoats. Two male rats and one female rat from Test 2 had tremors during the 24 - 48 hours prior to death on Days 3 or 4. For the surviving animals, one male rat appeared normal by Day 6; the other surviving male rat and female rat appeared normal by Day 9; these animals

appeared normal for the remainder of the study. By three hours post-exposure and for the remainder of the study, all Test 3 animals appeared normal. All surviving Test 2 group animals lost weight or had reduced weight gain during the first week when compared to the concurrent control group, but appeared to recover during the second week. For the Test 3 group, mean body weights were comparable to those of their respective control group throughout the study. At necropsy, the nasal passages, liver, kidneys, spleen, and gross lesions were preserved and examined histologically. Exposure-related lesions were observed for Test 1 and Test 2 animals only and consisted of eosinophilic cytoplasmic changes and hypertrophy of hepatocytes. Several lesions such as thymic and splenic atrophy were considered secondary to stress. All other lesions were considered to be incidental to treatment. No lesions were observed in the nasal passages.

LC₅₀ values were calculated by plotting the percent mortality (probability scale) versus the exposure concentration (log scale). Due to the unequal group size and the change in length of exposure, the LC₅₀ values were calculated using the 1697 and 638 ppm (4-hour exposure) groups only. The 4-hour LC₅₀ values for male and female rats were 1525 ppm and 1275 ppm, respectively. When the mortality data for male and female rats were combined, the 4-hour LC₅₀ was 1395 ppm.

STUDY AND TEST SUBSTANCE INFORMATION

Testing Facility

Toxicological Sciences Laboratory
Health and Environment Laboratories
Eastman Kodak Company
Rochester, New York 14652-6272
USA

Project Participants

Study Director
Study Technicians

Lisa G. Bernard, M.S.
Reade A. Moulton
James F. Murphy, B.S.
Linda M. Taylor, A.A.S.
Milan S. Vlaovic, D.V.M., Ph.D.
Kathy Staudenmayer, B.S.
Raymond M. David, Ph.D.
Lisa G. Bernard, M.S.

Pathologist/Veterinarian
Analytic Chemist
Report Authors

Sponsor

Eastman Chemical Company
First American Center
P.O. Box 1994
Kingsport, TN 37662-5394

Authorized Representative: Karen R. Miller, Ph.D.

Test Substance Characterization

Test Substance Name: Cyclopropanecarboxaldehyde
Synonym: CPCA
HAEL No.: 96-0212
EAN: 023931
CAS No.: 001489-69-6
PM No.: 15653-00
Lot No.: 3-96 A blend of the two lots of test substance received
(X24557-170-CFR1 and X24557-170-CFR2)
Physical State and Appearance: Liquid, clear and colorless
Source of Test Substance: Eastman Chemical Company

Test Substance Characterization, continued

Laboratory Project ID:	960212I1	Control and Test 1, 6 hour exposure, Target concentrations: 0 and 1750 ppm
	960212I2	Control and Test 2, 4 hour exposure, Target concentrations: 0 and 1500 ppm
	960212I3	Control and Test 3, 4 hour exposure, Target concentrations: 0 and 300 ppm

Study Dates

Study Initiation Date	April 26, 1996
Experimental Start Date	May 1, 1996
Experimental Completion Date	October 2, 1996

Purity, Structure Confirmation, and Stability Determination

The purity of the test substance in each container was determined by gas chromatography with flame ionization detection (GC/FID) to be 99.6% prior to use on the study and 99.0% at study termination. Based on these data, the test substance was considered to be stable during the test period. The structure of the test substance was confirmed using mass spectrometry. The mass spectrum of the test substance was consistent with published spectra for this substance. The analytical report is provided in the appendix beginning on page 101.

PURPOSE

The purpose of this study was to determine the acute inhalation toxicity of the test substance in rats following single inhalation exposures of 4 hours (Test 2 and 3) or 6 hours (Test 1) and to estimate an LC₅₀ value.

MATERIALS AND METHODS

Test System

Male and female Sprague-Dawley rats (CD[®](SD)BR/VAF Plus[™]) obtained from Charles River Kingston (Stone Ridge, NY) were randomly assigned to the exposure groups. Rats were chosen for this study because they are a common representative species for toxicity studies. Also, the rat is one of the two primary rodent species recommended for use in the USEPA and OECD Test guidelines.

Group	Number of Animals		Age (days) ¹		Weight (grams) ¹	
	Males	Females	Males	Females	Males	Females
Control and Test 1	15 (5 Control & 10 Test)	15 (5 Control & 10 Test)	50	57	264 ± 13 ²	208 ± 9
Control and Test 2	16 (8 Control & 8 Test)	16 (8 Control & 8 Test)	46	46	201 ± 6	179 ± 4
Control and Test 3	16 (8 Control & 8 Test)	16 (8 Control & 8 Test)	48	48	223 ± 8	190 ± 6

¹ At the start of the study.

² (mean ± SD)

Husbandry

Housing

Animals were housed in an American Association for Accreditation of Laboratory Animal Care-accredited vivarium in accordance with the Guide for the Care and Use of Laboratory Animals (1996, National Research Council). During nonexposure periods, rats were singly housed in stainless-steel, wire-mesh cages in a room separate from the exposure room. No other study was housed in the same room as this study. Exposure cages were washed daily. Housing cages and racks were washed once a week. Absorbent paper, used to collect excreta, was changed daily.

Husbandry, continued

Environmental Conditions

The study room was maintained at 19 - 22°C and 49 - 68% relative humidity, except for a two day deviation in room relative humidity to 72-74%. A photoperiod of 12 hours light from 6 a.m. to 6 p.m. was maintained.

Acclimation Period

The animals were isolated upon arrival and allowed to acclimate for a period of 5 days. Animals were judged to be healthy prior to testing and were released for testing by the Staff Veterinarian.

Feed

Certified Rodent Diet (PMI #5002, pelleted) was available *ad libitum* except during exposure. Feed containers were cleaned weekly and were refilled at least once a week. No known contaminants which would interfere with the outcome of this study were present in the feed. Analyses of feed are maintained on file within the testing laboratory.

Water

Water was available *ad libitum*, except during exposure, through an automatic watering system. The source of the water was the local public water system. There have been no contaminants identified periodic water analyses that would be expected to interfere with the conduct of the study. Semiannual analyses of water are maintained on file within the testing laboratory.

Identification

Upon arrival, all rats were identified by uniquely-numbered metal ear tags. During randomization, study-specific animal numbers were assigned to each animal. Cage cards, color-coded for each group, contained the study-specific animal numbers and the ear tag number.

Experimental Design

Randomization

The test animals were selected from the stock population based on body weight and were randomly assigned to groups using computer-generated lists. The body weights of individual animals in the selected population did not exceed 20% of the mean for each sex. Following randomization, the body weights of all groups were compared by analysis of variance to insure that there were no statistically significant differences prior to initiation of exposure.

Test Procedures

This study was conducted according to the U.S. EPA Toxic Substances Control Act Health Effects Testing Guidelines: 40 CFR 798.1150, Acute Inhalation Toxicity; Organisation for Economic Cooperation and Development (OECD) Guidelines for Testing of Chemicals Guideline: TG-403, Acute Inhalation Toxicity; and European Economic Community (EEC): Annex V., Test B. 2, Acute Toxicity (Inhalation).

Selection of Exposure Concentrations

The initial exposure concentration was selected based on the limit concentration specified in the OECD guidelines (5 mg/L). Subsequent exposure concentration were selected in consultation with the Sponsor.

Exposure

The inhalation exposures were conducted in 590 L stainless-steel and glass inhalation chambers at target vapor concentrations of 0, 300, 1500, or 1750 ppm. Animals were singly housed during the 6-hour (0 and 1750 ppm) and 4-hour (0, 300, and 1500 ppm) exposures. A diagram of the chamber and placement of cages within the chamber is provided in the Appendix. Cage positions 1 - 3 and 10 - 26 were used for this study. The exposure chambers were maintained under negative pressure relative to room air. The air flow, temperature, and humidity were recorded every 30 minutes. Chamber vapor concentrations were recorded at least once each hour.

Experimental Design, continued

Exposure Atmosphere Generation

The test substance was metered by a pump from an oxygen deprived amber glass bottle to a distillation column packed with glass beads. Nitrogen gas was passed through the glass bead-packed column at 6 - 10 Lpm. The resultant vapor was directed via glass tubing to a tee just upstream of the 590 L inhalation chamber where it was mixed with filtered, conditioned exterior dilution air to produce a total airflow of 84 to 118 Lpm (9 to 12 air changes per hour). A continuous, dynamic test atmosphere was generated using this system. A diagram of the generation system is provided in the Appendix.

A Micro Laser Particle Counter model mLPC-301 (Particle Measuring Systems, Inc., Boulder, CO) was used to measure the number and size of particulates in the chamber. The results indicated that an aerosol of the test substance was not present.

The effluent from the chamber was passed through coarse prefilters, HEPA filters, and charcoal filters.

Vapor Concentration Determination

Chamber vapor concentrations of the test substance were monitored with a multipositional air sampling and analysis system. The system consisted of a single MIRAN[®] IA infrared gas analyzer (Wilks Foxboro Analytical, South Norwalk, CT) and a computer-operated four-port sampling valve (Valco Instruments, Houston, TX). Chamber vapor samples were continuously collected from each chamber through TEFLON[®] tubing (3/16" i.d.). The valve position was periodically changed to sample from each chamber at least once each hour. The voltage output of the MIRAN[®] and chamber concentration were printed in real-time and captured on electronic media. Voltage data were converted to concentration by linear interpolation between the calibration data points immediately on each side of the sampled data.

Chamber vapor concentrations of the test substance and of a potential oxidation product were determined by gas chromatography with flame ionization detection (GC/FID) of gas washing bottle samples. Five liters of the test atmosphere (0.5 L/min for 10 minutes) were passed through two (in series) gas washing bottles, with fritted bubblers, each containing approximately 20 mL of *p*-xylene ($\geq 99\%$) with 0.10% butylated hydroxy-toluene as a stabilizer. Samples were collected from each chamber at least once each hour. The analytical results were reported as total mg test substance/sample and total mg oxidation product/sample. The analytical report is provided in the appendix beginning on page 121.

Experimental Design, continued

Vapor Concentration Determination, continued

These analytical results were converted to chamber concentration using the following formula:

$$C = \frac{(mg)(MV)}{(V)(MW)}$$

where: C = concentration (ppm)
 mg = total mg test substance/sample or total mg oxidation product/sample
 MV = molar volume at 1 atm and 25°C (24.45 L/mole)
 V = volume of air sampled (m³)
 MW = test substance molecular weight (g/mole)

A time-weighted average exposure concentration was calculated using the following formula:

$$TWA = \frac{\Sigma\{[T_2 - T_1]\{(C_1 + C_2)/2\}}}{\Sigma(T_2 - T_1)}$$

where: TWA = time-weighted average exposure concentration (ppm)
 T₁ = the earlier time from each consecutive concentration determination (increment from 2:00 to 2:15)
 T₂ = the later time from each consecutive concentration determination (increment from 2:15 to 2:30)
 C₁ = the concentration at time T₁
 C₂ = the concentration at time T₂

MIRAN® IA Infrared Analyzer Operating Parameters And Calibration

The infrared analyzer operating parameters were as follows:

	Control and Test 1 and 2	Control and Test 3
MIRAN® No.	2	2
Pathlength (m)	2.25	18.75
Wavelength (mm)	3.66	3.66
Slit width (mm)	1	21
Response Time (sec)	4	4
Range (Absorption)	1A	1A
Gain	x10	x10
Cell Temperature (°C)	25	25
Cell Pressure (atm)	0.833	0.833
Cell Volume (L)	5.64	5.64

The wavelength used for monitoring concentration was selected based on a comparison of infrared spectra of the test substance to that of air.

Experimental Design, continued

MIRAN® IA Infrared Analyzer Operating Parameters And Calibration, continued

The infrared analyzer was calibrated by making serial injections (Hamilton microliter syringe) of the test substance into a closed-loop cell. The concentration was determined using the following formula:

$$C = \frac{(\rho)(V_1)(R)(T + 273)(1000)}{(MW)(P)(V_2)}$$

where: C	=	concentration (ppm)
ρ	=	test substance density (g/mL)
V_1	=	serial injection volume
R	=	gas constant (0.08205 atm·L/mole·K)
T	=	MIRAN® cell temperature (25 °C)
1000	=	Conversion from mL to L
MW	=	test substance molecular weight (g/mole)
P	=	MIRAN® cell pressure (0.833 atm)
V_2	=	MIRAN® cell volume (5.64 L)

Three sets of serial injections were made to produce a mean calibration curve of test substance concentration versus infrared analyzer output voltage.

An infrared analyzer calibration check was performed just prior to each exposure by injecting a measured amount of the test substance into the MIRAN® closed loop. The infrared analyzer output voltage was converted to the test substance concentration and compared to the calculated expected concentration. If the variation of the calibration concentrations were within 10% of that expected, the calibration was accepted.

Nominal Concentration Determination

The nominal concentration was calculated by dividing the amount of test substance consumed from the reservoir (determined gravimetrically) by the total chamber air flow using the formula:

$$NC = \frac{(G)(MV)(10^6)}{(V)(MW)}$$

where: NC	=	nominal concentration (ppm)
G	=	amount of test substance vaporized (grams)
MV	=	molar volume at 1 atm and 25°C (24.45 L/mole)
V	=	total daily chamber air flow (L)
MW	=	test substance molecular weight (g/mole)

Experimental Design, continued

Chamber Vapor Homogeneity

A test to determine variations in concentration at different positions within the exposure chambers was conducted prior to study initiation. The air from the breathing zones of cage positions 2, 10, 12, 14, 16, 18, 20, 22, 24, and 25 was sampled using a MIRAN[®] IA infrared gas analyzer as described under Vapor Concentration Determination and compared to the concentration at a fixed reference position (cage 15). Based on deviations from the reference position of less than 10%, the chamber atmosphere was considered to be homogeneous.

Air Flow Measurement

Total chamber air flow was a combination of nitrogen which was used to vaporize the test substance and to carry the vapor from the generation system to the inhalation chamber, and dilution air. The nitrogen flow rate was continuously monitored using a flowmeter. The dilution air flow was adjusted and monitored throughout the exposure using an Omega Air Velocity Transducer (FMA-602-V-S) and Ratemeter (DPF66-RS232). The dilution air flow rate was calculated using the following formula:

$$Q = \frac{(A)(V)}{1000}$$

where: Q = Supply air flow rate (Lpm)
A = Cross sectional area of the dilution air duct (cm²) [πr^2 , r = 1 in.]
V = Supply air linear velocity (cm/min.) [air velocity meter readings are in ft./min.]
1000 = Conversion Factor

Oxygen Level

The oxygen content of the chamber exposure atmosphere was measured during exposure from the reference position using an Model K Oxygen Indicator (Johnson-Williams Products, Bacharach Instrument Co., Mountain View, CA).

Chamber Temperature And Humidity

Chamber temperature and humidity were measured using wet/dry bulb hygrometers and were recorded twice each hour during exposure.

Experimental Design, continued

Disposition of Groups

Animals were distributed into groups as follows:

Group	Exposure		Animal Numbers For		Total Animals per Group
	Target Conc.	Length	Day 1 Necropsy	Day 14 Necropsy	
Control 1	0 ppm	6 hours	301 - 305 Male 316 - 320 Female	*	5 Male & 5 Female
Test 1	1750 ppm	6 hours	306 - 315 Male 321 - 330 Female	*	10 Male & 10 Female
Control 2	0 ppm	4 hours	331 - 333 Male 347 - 349 Female	334 - 338 Male 350 - 354 Female	8 Male & 8 Female
Test 2	1500 ppm	4 hours	339 - 341 Male 355 - 357 Female	342 - 346 Male 358 - 362 Female	8 Male & 8 Female
Control 3	0 ppm	4 hours	371 - 373 Male 387 - 389 Female	374 - 378 Male 390 - 394 Female	8 Male & 8 Female
Test 3	300 ppm	4 hours	379 - 381 Male 395 - 397 Female	382 - 386 Male 398 - 402 Female	8 Male & 8 Female

* Due to mortality observed for Test 1 animals, all surviving animals from Control and Test 1 were euthanatized on Day 1.

Animals received single 4- or 6-hour exposures. Surviving animals were euthanatized and necropsied on Day 1 or 14 as indicated above.

Body Weight Determinations

Body weights were measured on Days 0 (pre-exposure), 7 or 8, and 14.

Clinical Observations

Rats visible through chamber windows were observed for clinical signs during exposure. Tapping sounds were made on the outside of the chamber with a key or other metal object to assess the animals' activity level. Animals were removed from their cages and examined before and after exposure and on each subsequent morning. Cageside observations were conducted on subsequent workday afternoons. Observations included, but were not limited to, examination of the hair, skin, eyes, mucous membranes, motor activity, feces, urine, respiratory system, circulatory system, autonomic nervous system, central nervous system, and behavior patterns.

Experimental Design, continued

Necropsy

Animals were anesthetized with Metofane™, exsanguinated by severing the posterior vena cava prior, and subjected to a necropsy and gross examination. The following tissues were fixed in 10% buffered formalin: nasal passages, liver, kidneys, spleen, and gross lesions.

Histopathology

All tissues were embedded in paraffin, sectioned at 5 μ m, and stained with hematoxylin and eosin (H&E) stains. The nasal passages were decalcified prior to being embedded and sectioned. All tissues collected were examined for histopathology.

Data Storage

The final report, tissues, paraffin blocks, slides, data sheets, all nonperishable raw data, and an aliquot of the test substance have been stored in the testing facility archive managed under GLP-mandated conditions.

Calculations and Statistical Procedures

Mean values were calculated for chamber temperature, chamber relative humidity, and body weight. Body weight data were evaluated using the following computer-generated statistical tests: Bartlett's test ($p \leq 0.01$), one-way analysis of variance (ANOVA) ($p \leq 0.05$), and Dunnett's t-test ($p \leq 0.05$) to indicate statistical significance. When the variances of the means were not considered equal by the Bartlett's test ($p \leq 0.01$), the data were evaluated using a Kruskal-Wallis H-test and Mann-Whitney U-test.

Protocol and Standard Operating Procedure Deviations

Spleens were collected at necropsy from all Test 1 and Control 1 animals. Body weights were determined on Day 8 instead of Day 7 for the Test 2 and Control 2 animals. The relative humidity in the animal room was deviated to 72 and 74% on two days for the Test/Control 2 and 3 animals. These deviations did not affect the outcome of the study.

For the Test 1 animals, the oxygen content in the chamber dropped to less than 19% for approximately 3 hours during the exposure. The reduced oxygen concentration may have had an effect on the respiratory pattern for these animals.

Subsequent to the conduction of the study, it was determined that the total volume of the chamber was ~590 L instead of 420 L. The air flow in the chamber was maintained to provide at least 12 air changes per hour for a 420 L chamber. However, based upon a chamber volume of 590 L, there were 9 to 12 air changes per hour. The lower number of air changes per hour may have contributed to the reduced oxygen concentration.

There were no SOP deviations and no other protocol deviations during the study.

RESULTS

Exposure Conditions

Exposure data are summarized on page 29. The time-weighted average analytical concentrations for Test 1, 2, and 3, respectively, were 1892, 1697, and 368 ppm; these concentrations were 8, 13, and 23% above the target concentrations of 1750, 1500, and 300 ppm, respectively. Nominal concentrations were 1940, 1604, and 332 ppm for the same groups; these concentrations were within 11% of the target concentrations. No test substance was detected in the control chambers. The chamber temperatures and relative humidity inside the chamber during exposure were 22.4 - 24.0°C and 35.0 - 65.0%, respectively.

During the Test 1 exposure, the oxygen level was determined to be 17.5%. The nitrogen flow rate was lowered and the oxygen level increased to at least 19.0%. The oxygen concentration was as low as 17.5% for no more than 3 hours during this exposure. The oxygen level within the chambers was at least 19.0% throughout the Control 1, 2, and 3 and Test 2 and 3 exposures.

Mortality

For the Test 1 animals, 7/10 male and 10/10 female rats died by the morning following the exposure. For the Test 2 group, 3/5 male and 4/5 female rats were found dead from 2 to 8 days following exposure. No mortality was observed for the Test 3 group or for any control groups.

Clinical Observations

Clinical signs observed during exposure are summarized on page 30 followed by summaries of clinical examinations prior to and following exposure. Each clinical sign observed during the exposure period is listed for each group, as is each clinical sign observed before or after exposure. Individual animal data are presented in the Appendix.

During exposure to all concentrations of the test substance, general activity was reduced. The severity of the reduced activity was concentration dependent. Additionally, the Test 1 group had rapid, shallow respiration during the second and third exposure hours and labored breathing during the fourth through sixth exposure hours with a slower rate of breathing during the sixth hour.

Immediately following exposure, the Test 1 animals had moderate to severe reductions in activity level and deep, rapid respiration. Additionally, one or two animals had porphyrin discharges around the nose or eyes, excessive tearing, and/or hypothermia. The following morning, similar signs were observed with all surviving Test 1 male rats exhibiting moderate to severe reductions in activity level, deep and rapid respiration, and hypothermia; one male rat also had porphyrin discharge around the eyes. Due to the high mortality observed within 24 hours of exposure

(17/20 Test 1 animals), all surviving animals (Test 1 and Control 1) were euthanatized and necropsied on Day 1.

Immediately following the exposure, most Test 2 animals had reduced activity levels (minimal to moderate severity) and/or abnormal gaits (hypotonic gait, splayed walking, and/or knuckling over). By the morning following the exposure, the same signs were observed for all Test 2 animals but with greater severity of reduced activity level (minor to severe). For the animals which survived, abnormal gaits were observed through Day 2 and reduced activity levels were observed through Day 3 (2 male rats) or 4 (one female rat). One male rat (#343) and one female rat (#361) exhibited head shaking motions on Day 2 only. One male rat (#345) appeared normal by Day 6; the other surviving male rat and female rat appeared normal by Day 9. For animals which died, abnormal gaits were observed until the animal became prostrate or until the animal died. One male rat (#344) and one female rat (#362) exhibited head shaking motions between Days 2-7 and on Day 3, respectively. Two male rats (#342 and #346) and one female rat (#362) had tremors during the 24 - 48 hours prior to death on Days 3 or 4. Additionally, animals had porphyrin discharges around the nose or eyes, excessive tearing, partially closed eyes, dehydration, decreased fecal volume, softened feces, inguinal haircoat wet with urine and/or stained with feces, and/or unkempt haircoats.

Immediately following exposure, a single Test 3 male rat a reduced activity level (minimal severity); all other Test 3 animals appeared normal. By three hours post-exposure and for the remainder of the study, all Test 3 animals appeared normal.

Body Weight

Body weights are presented as mean and standard deviation on pages 47 (male) and 48 (female). Individual animal data are presented in the Appendix. For the Test 2 group, all surviving animals lost weight or had reduced weight gain during the first week when compared to the concurrent control group. During the second week, the Test 2 group appeared to recover, gaining weight at a rate similar to that of the Control 2 group. For the Test 3 group, mean body weights were comparable to those of the Control 3 group throughout the study.

Gross Pathology

No exposure-related changes were detected on gross examination of male or female rats exposed to the test substance. Incidental findings are described below.

For the Test 1 animals, lesions that were considered secondary to stress consisted of reduced size of the spleens (6/10 male and 7/10 female rats). Incidental findings included red (1/10 male rats) or focal red (3/10 male and 1/10 female rats) discoloration of the lungs, distention of the stomach with feed (8/10 male and 6/10 female rats), distention of the urinary bladder with urine (5/10 male and 5/10 female rats), red discoloration of the urinary bladder (4/10 male and 1/10 female rats), red discoloration of the urine in the urinary bladder (4/10 male and 4/10 female

rats), thymic hemorrhage (1/10 male and 2/10 female rats), edema of the pancreas (1/10 male rats), porphyrin ocular discharge (1/10 male rats), and torsion of the caudate lobe of the liver (1/10 male rats).

For the Test 2 animals, lesions that were considered secondary to stress consisted of reduced size of the spleens (2/3 male and 3/3 female rats necropsied on Day 1 and 3 female rats necropsied on Days 2 to 4) and reduced size of the thymus (1 male and 1 female rat necropsied on Days 8 and 4, respectively). Incidental findings for animals necropsied on Day 1 consisted of focal red discoloration of the lungs (1/3 male rats), bilateral hydronephrosis of the kidneys (1/3 male rats), pallor of the liver (3/3 male and 3/3 female rats), and the accumulation of mucus in the cecum (1/3 male rats). Incidental findings for animals which died consisted of hemorrhage in the glandular gastric mucosa and pallor of the liver (1 male rat necropsied on Day 4), and focal red discoloration of the lungs (1 male rat necropsied on Day 8). Incidental findings for animals necropsied on Day 14 consisted of raised white nodules in the liver (1/2 male and 1/1 female rats), adhesion of the liver lobes to each other (1/2 male rats), an adhesion of the liver to the stomach (1/2 male rats), enlarged spleens (1/2 male and 1/1 female rats), and thickened splenic capsule (1/2 male and 1/1 female), an adhesion of the splenic capsule to adjoining adipose tissue (1/1 female rats), a dry porphyrin ocular discharge (1/1 female rats), thymic hemorrhage (1/1 female rats), and an accumulation of mucus in the duodenum (1/1 female rats).

For the Test 3 animals, incidental findings consisted of a thickened splenic capsule (1/5 male rats necropsied on Day 14).

Histopathology

Exposure-related lesions were observed for Test 1 and Test 2 animals only, and were restricted to the liver. Liver lesions consisted of minor to moderate eosinophilic cytoplasmic changes in hepatocytes (10/10 male and 7/10 female Test 1 rats and 7/8 male and 7/8 female Test 2 rats), and minor to moderate hypertrophy of hepatocytes (1/2 male Test 2 rats necropsied on Day 14 and 1/2 female Test 2 rats necropsied on Day 2). These lesions are typically associated with induction of enzyme synthesis. The study pathologist considered these lesions to be an adaptive response. There was no apparent difference between Day 1 and Day 14 in the severity or incidence of the lesion.

For the Test 1 animals, lesions that were considered secondary to stress consisted of atrophy of the lymphatic follicles in the spleen (10/10 male and 10/10 female rats) and focal necrosis of the lymphatic follicles in the spleen, (10/10 male and 5/10 female rats). For the Test 2 animals, lesions that were considered secondary to stress consisted of atrophy of the lymphatic follicles in the spleen (3/3 male and 3/3 female rats necropsied on Day 1; 3/3 male and 4/4 female rats necropsied on Days 2-8; and in 1/2 male and 1/1 female rats necropsied on Day 14) and atrophy of the thymus (1 male and 1 female rat necropsied on Days 8 and 4, respectively).

Incidental findings for Test 1 animals included hemorrhage in the lungs (4/4 male and 1/1 female rats), focal necrosis of the liver (1/10 male rats), chronic focal inflammations of the liver (1/10 male and 3/10 female rats), hemorrhage in the mucosa (3/10 female rats) or submucosa of the urinary bladder (4/10 male and 1/10 female rats), inter- and perilobular edema of the pancreas (1/10 male rats), unilateral (1/10 male rats) or bilateral (3/10 male rats) hydronephrosis of the kidneys, minimal tubular mineralization in the kidneys (4/10 female rats), a kidney cyst (1/10 male rats), and thymic hemorrhage (2/10 female rats). Incidental findings for Test 2 animals included hemorrhage in the lungs (2/8 male rats), increased extramedullary hematopoiesis in the spleen (1/8 male and 1/8 female rats), diffuse fibrosis of the splenic capsule (1/8 male and 1/8 female rats), cytoplasmic vacuolization in hepatocytes (5/8 male and 8/8 female rats), chronic focal inflammations of the liver (1/8 male and 1/8 female rats), liver abscesses (1/8 male and 1/8 female rats), unilateral (1/8 male rats) or bilateral (1/8 male rats) hydronephrosis of the kidneys, a kidney cyst (1/8 male rats), and thymic hemorrhage (1/8 female rats). For the Test 3 animals, incidental findings included cytoplasmic vacuolizations in hepatocytes (8/8 male and 8/8 female rats), chronic focal inflammations of the liver (2/8 male and 1/8 female rats), unilateral (1/8 male and 1/8 female rats) or bilateral (1/8 male rats) hydronephrosis of the kidneys, tubular mineralizations in the kidneys (6/8 female rats), kidney cysts (3/8 male rats), and kidney scarring (1/8 male rats).

For details of the gross pathology and histopathology examinations, see the pathologist's report beginning on page 49.

DISCUSSION

The irritation potential of the test substance to the respiratory tract is not clear. Exposure of animals to high concentrations did not result in increased ocular or nasal secretions that typically occur during exposure to known sensory or respiratory irritants (Alarie, 1973). On the other hand, there were changes in the respiratory pattern which are characteristic of sensory irritation associated with exposure to aldehydes such as formaldehyde (Chang *et al.*, 1981); Test 1 animals exhibited altered respiratory patterns during exposure. However, the changes in respiratory pattern may not have been due to irritation by the test substance. Chang *et al.* (1981) reported that rats did not alter their respiratory rate as readily as did mice exposed to the same concentration of irritant. In addition, an oxygen concentration of approximately 17.5% for the three hours of exposure may have had an effect on respiratory pattern for the Test 1 animals. Once oxygen levels were restored to adequate levels, the respiratory pattern changed again. Therefore, altered respiratory pattern for Test 1 animals may have been a physiological response to reduced oxygen levels; no changes in respiratory pattern were observed for Test 2 animals. There was also no indication of irritation of the upper respiratory tract such as has been described for formaldehyde, acetaldehyde, and acrolein (Cassee *et al.*, 1996), although nasal lesions associated with those chemicals were observed after three days of exposure and not after a single exposure (Cassee *et al.*, 1996). Thus, it is difficult to draw conclusions concerning the irritation potential of the test substance.

Exposure did result in acute central nervous system clinical signs in Test 2 animals that survived exposure. These signs consisted of head-shaking motions and abnormal gaits which included hypotonic gait, splayed walking, and/or knuckling over of toes. Although tremors were seen in three animals, they occurred within 24-48 hours of death, and are considered to reflect a moribund condition. Because gait abnormalities were observed in animals that survived exposure and were observed for several days after exposure, these signs may reflect possible neurotoxic potential by the test substance. No signs of neurotoxicity were noted in Test 3 animals.

Exposure-related liver lesions consisted of eosinophilic cytoplasmic changes in hepatocytes and hypertrophy of hepatocytes. These lesions have been associated with induction of enzyme synthesis (Greaves and Faccini, 1992) which is considered to be an adaptive response to treatment. There was no apparent difference between Day 1 and Day 14 in the severity or incidence of the lesion. Thus, the significance of the lesions is not clear. Lesions that were considered secondary to stress for Test 1 animals consisted of atrophy and focal necrosis of the lymphatic follicles in the spleen and for Test 2 animals consisted of atrophy of the lymphatic follicles in the spleen and atrophy of the thymus. Stress has been shown to cause reduced thymus and spleen weights in mice (Azoulay-Dupuis, *et al.*, 1987). The cytoplasmic vacuolization observed in the hepatocytes of the Test 2 and 3 animals was not considered to be substance-related since the incidence and severity was similar in the control animals.

CONCLUSION

No clear signs of nasal or respiratory irritation were observed at any exposure level. There were signs of acute central nervous system effects in animals exposed to 1697 ppm, but not to 368 ppm. Adaptive lesions in the liver reflective of increased enzyme synthesis were observed in animals exposed to 1697 and 1892 ppm, but not to 368 ppm. LC_{50} values were calculated by plotting the percent mortality (probability scale) versus the exposure concentration (log scale). Due to the unequal group size and the change in length of exposure, the LC_{50} values were calculated using the 1697 and 368 ppm (4-hour exposure) groups only. The 4-hour LC_{50} values for male and female rats were 1525 ppm and 1275 ppm, respectively. When the mortality data for male and female rats were combined, the 4-hour LC_{50} was 1395 ppm.

REFERENCES

- Alarie, Y. (1973). Sensory irritation of airborne chemicals. *Crit. Rev. Toxicol.* **2**, 299-363.
- Azoulay-Dupuis, E., Bouley, G., Moreau, J., Muffat-Joly, M., and Pocidalo, J.J. (1987). Evidence for Humoral Immunodepression in NO₂-Exposed Mice: Influence of Feed-Restriction and Stress. *Environ. Res.* **42**, 446-454.
- Cassee, F.R., Grotten, J.P., and Feron, V.J. (1996). Changes in the nasal epithelium of rats exposed by inhalation to mixtures of formaldehyde, acetaldehyde, and acrolein. *Fundam. Appl. Toxicol.* **29**, 208-218.
- Chang, J.C.F., Steinhagen, W.H., and Barrow, C.S. (1981). Effect of Single or Repeated Formaldehyde Exposure on Minute Volume of B6C3F1 Mice and F-344 Rats. *Toxicol Appl. Pharmacol.* **61**, 451-459.
- Greaves, P., and Faccini, J.M. (1992). *Rat Histopathology*. Elsevier, London.

Summary of Exposure Conditions

Group		Control 1	Test 1	Control 2	Test 2	Control 3	Test 3
Target Concentration (ppm)		0	1750	0	1500	0	300
Number Of Exposures		1	1	1	1	1	1
Length Of Exposure (hours)		6	6	4	4	4	4
Time Weighted Average Exposure Concentration (ppm)		0	1892	0	1697	0	368
Nominal Concentration (ppm)		0	1940	0	1604	0	332
Temperature (°C)	Mean	23.1	23.3	23.5	23.1	23.2	22.9
	SD	0.2	0.3	0.5	0.3	0.4	0.2
	n	12	12	8	8	8	8
Relative Humidity (%)	Mean	48.1	48.5	38.1	53.6	50.3	62.0
	SD	0.8	2.1	3.6	1.4	3.0	1.5
	n	12	12	8	8	8	8
AIRFLOW (Lpm)	Mean	85.5	90.8	93.1	95.3	96.2	113.1
	SD	1.8	2.8	1.5	2.3	2.6	4.2
	n	13	13	9	9	9	9

Summary of During Exposure Clinical Signs

	Hour of Onset	Last Hour of Observation	Number of Rats Displaying Sign	Maximum Daily Severity
Control 1				
Normal	1	6	5/5 M & 5/5 F	--
Test 1				
Normal	1	1	10/10 M & 10/10 F	--
Reduced Activity	2	6	10/10 M & 10/10 F	4.00
Rapid, Shallow Respiration	2	3	10/10 M & 10/10 F	4.00
Labored Breathing (Deeper than Controls)	4	6	10/10 M & 10/10 F	3.00
Respiration Rate Slower Than Normal	6	6	10/10 M & 10/10 F	3.00
Control 2				
Normal	1	4	8/8 M & 8/8 F	--
Test 2				
Reduced Activity	1	4	8/8 M & 8/8 F	4.00
Control 3				
Normal	1	4	8/8 M & 8/8 F	--
Test 3				
Normal	1	1	8/8 M & 8/8 F	--
Reduced Activity	2	4	8/8 M & 8/8 F	2.00

Severities: 1 = Minimal, 2 = Minor, 3 = Moderate, 4 = Severe

GROUPED SUMMARY OF CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - A.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
Control 1				
* NORMAL	5			301-305
INDUCED DEATH,METOFANE,EXSANGUINATION	5	1.	0.	301-305
Test 1				
GENERAL ACTIVITY DEPRESSED	3	1.	0.	307,314,315
HYPOTHERMIA	3	1.	0.	307,314,315
SPONTANEOUS DEATH	7	1.	0.	306,308-313
INDUCED DEATH,METOFANE,EXSANGUINATION	3	1.	0.	307,314,315
RESPIRATORY TRACT DYSPNEA	3	1.	0.	307,314,315
EYES PORPHYRIN TEARS	1	1.	0.	307

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - P.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED

Control 1				

* NORMAL	5			301-305
Test 1				

GENERAL ACTIVITY DEPRESSED	10	0.	0.	306-315
HYPOTHERMIA	1	0.	0.	311
RESPIRATORY TRACT DYSPNEA	10	0.	0.	306-315
EYES PORPHYRIN TEARS	1	0.	0.	312

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - A.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED

Control 1				

* NORMAL	5			316-320
INDUCED DEATH, METOFANE, EXSANGUINATION	5	1.	0.	316-320
Test 1				

SPONTANEOUS DEATH	10	1.	0.	321-330

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - P.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED

Control 1				

* NORMAL	5			316-320
Test 1				

GENERAL ACTIVITY DEPRESSED	10	0.	0.	321-330
RESPIRATORY TRACT DYSPNEA	9	0.	0.	321,323-330
EYES				
PORPHYRIN TEARS	1	0.	0.	326
EXCESSIVE TEARING	1	0.	0.	329
NOSE				
PORPHYRIN NASAL DISCHARGE	1	0.	0.	329

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - A.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED

Control 2				

* NORMAL	8			331-338
INDUCED DEATH, METOFANE, EXSANGUINATION	8	9.	7.	331-338

Test 2				

GENERAL ACTIVITY DEPRESSED	8	1.	0.	339-346
GAIT DISTURBANCE	8	1.	0.	339-346
DEHYDRATION	8	1.	0.	339-346
HYPOTHERMIA	5	2.	0.	342-346
TREMOR	1	2.	0.	346
SPONTANEOUS DEATH	3	5.	3.	342,344,346
INDUCED DEATH, METOFANE, EXSANGUINATION	5	6.	7.	339-341,343,345
FECES				
DECREASED VOLUME	8	1.	0.	339-346
SOFTENED	4	2.	2.	341, 343-345
DIARRHEA	1	2.	0.	346
SMALL	3	6.	0.	343-345
NOSE				
PORPHYRIN NASAL DISCHARGE	3	1.	1.	340, 344-345
EYES				
EXCESSIVE TEARING	4	3.	3.	340, 342,344,346
PORPHYRIN TEARS	4	3.	1.	342-345
DRIED PORPHYRIN DISCHARGE	1	2.	0.	345
PARTIALLY OPEN	2	4.	1.	342,344
HAIR OF INGUINAL REGION				
DISCOLORATION, BROWN	4	3.	2.	342-344,346
HAIRCOAT-DRY URINE STAIN	4	4.	2.	342-345
HAIRCOAT-WET BY URINE	2	3.	1.	344,346
HAIR, PERIORAL				
DISCOLORATION, RED	1	4.	0.	344
HAIR				
PILOERECTION	2	6.	0.	343-344
HAIR, PERIANAL				
DISCOLORATION, BROWN	1	6.	0.	344

KEY: *-INDICATES ANIMALS SHOWING CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - POST DOSE

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
Control 2				
* NORMAL	8			331-338
Test 2				
GENERAL ACTIVITY DEPRESSED	7	0.	0.	339-344,346
GAIT DISTURBANCE	6	0.	0.	340-342,344-346

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - P.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED

Control 2				

* NORMAL	8			331-338
Test 2				

GENERAL ACTIVITY DEPRESSED	8	0.	0.	339-346
GAIT DISTURBANCE	8	0.	0.	339-346
DEHYDRATION	5	1.	0.	342-346
HYPOTHERMIA	4	2.	1.	342-344,346
TREMOR	2	2.	0.	342,346
NOSE				
PORPHYRIN NASAL DISCHARGE	2	1.	1.	342,344
FECES				
DECREASED VOLUME	5	1.	0.	342-346
SOFTENED	2	4.	4.	344,346
DIARRHEA	1	2.	0.	344
HAIR OF INGUINAL REGION				
DISCOLORATION, BROWN	3	2.	1.	342,344,346
HAIRCOAT-WET BY URINE	2	4.	4.	344-345
HAIRCOAT-DRY URINE STAIN	5	3.	2.	342-346
EYES				
PORPHYRIN TEARS	3	2.	1.	343-345
PARTIALLY OPEN	2	5.	2.	342,344
EXCESSIVE TEARING	1	7.	0.	344
HAIR				
PILOERECTION	2	6.	0.	343-344
HAIR, PERIANAL				
DISCOLORATION, BROWN	1	6.	0.	344

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - A.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
Control 2				
* NORMAL	8			347-354
INDUCED DEATH, METOFANE, EXSANGUINATION	8	9.	7.	347-354
Test 2				
GENERAL ACTIVITY DEPRESSED	8	1.	0.	355-362
GAIT DISTURBANCE	8	1.	0.	355-362
DEHYDRATION	8	1.	0.	355-362
HYPOTHERMIA	5	2.	0.	358-362
SPONTANEOUS DEATH	2	4.	1.	359, 362
INDUCED DEATH, METOFANE, EXSANGUINATION	4	4.	7.	355-357, 361
FECES				
DECREASED VOLUME	8	1.	0.	355-362
SOFTENED	2	1.	0.	357, 361
SMALL	1	6.	0.	361
EYES				
EXCESSIVE TEARING	6	2.	1.	355-356, 358-360, 362
PORPHYRIN TEARS	3	2.	1.	357, 361-362
DRIED PORPHYRIN DISCHARGE	1	2.	0.	362
PARTIALLY OPEN	1	3.	0.	362
HAIR OF INGUINAL REGION				
HAIRCOAT-WET BY URINE	6	1.	0.	355-356, 359-362
DISCOLORATION, BROWN	1	1.	0.	361
HAIRCOAT-DRY URINE STAIN	1	2.	0.	361
HAIR				
UNKEMPT HAIRCOAT	1	1.	0.	360
PILOERECTION	1	6.	0.	361
RIGHT EYE				
EXCESSIVE TEARING	1	1.	0.	361
LEFT EYE				
EXCESSIVE TEARING	1	1.	0.	362
RESPIRATORY TRACT				
DYSPNEA	2	2.	0.	359-360
NOSE				
PORPHYRIN NASAL DISCHARGE	2	3.	0.	361-362
HAIR, PERIORAL				
DISCOLORATION, RED	1	4.	0.	361

KEY: *-INDICATES ANIMALS SHOWING CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - POST DOSE

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED

Control 2				

* NORMAL	8			347-354

Test 2				

GENERAL ACTIVITY DEPRESSED	8	0.	0.	355-362
GAIT DISTURBANCE	8	0.	0.	355-362

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - P.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
Control 2				
* NORMAL	8			347-354
Test 2				
GENERAL ACTIVITY DEPRESSED	8	0.	0.	355-362
GAIT DISTURBANCE	8	0.	0.	355-362
DEHYDRATION	5	1.	0.	358-362
SPONTANEOUS DEATH	2	2.	0.	358,360
HYPOTHERMIA	3	2.	0.	359,361-362
TREMOR	1	2.	0.	362
FECES DECREASED VOLUME	5	1.	0.	358-362
LEFT EYE EXCESSIVE TEARING	1	1.	0.	359
EYES EXCESSIVE TEARING	3	2.	1.	359-360,362
PORPHYRIN TEARS	2	2.	0.	361-362
PARTIALLY OPEN	1	3.	0.	362
HAIR OF INGUINAL REGION HAIRCOAT-WET BY URINE	2	2.	1.	361-362
HAIRCOAT-DRY URINE STAIN	2	2.	0.	359,361
DISCOLORATION,BROWN	1	2.	0.	362
NOSE PORPHYRIN NASAL DISCHARGE	2	2.	0.	361-362
HAIR, PERIORAL DISCOLORATION,RED	2	3.	0.	361-362
HAIR PILOERECTION	1	6.	0.	361

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - A.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
Control 3				
* NORMAL	8			371-378
INDUCED DEATH, METOFANE, EXSANGUINATION	8	9.	7.	371-378
Test 3				
* NORMAL	8			379-386
INDUCED DEATH, METOFANE, EXSANGUINATION	8	9.	7.	379-386

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - POST DOSE

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
Control 3				
* NORMAL	8			371-378
Test 3				
* NORMAL	7			379-385
GENERAL ACTIVITY DEPRESSED	1	0.	0.	386

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - P.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
Control 3				
* NORMAL	8			371-378
Test 3				
* NORMAL	8			379-386

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - A.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED

Control 3				

* NORMAL	8			387-394
INDUCED DEATH, METOFANE, EXSANGUINATION	8	9.	7.	387-394
Test 3				

* NORMAL	8			395-402
INDUCED DEATH, METOFANE, EXSANGUINATION	8	9.	7.	395-402

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - POST DOSE

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED

Control 3				

* NORMAL	8			387-394
Test 3				

* NORMAL	8			395-402

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - P.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
Control 3				
* NORMAL	8			387-394
Test 3				
* NORMAL	8			395-402

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

MEAN FOR BODY WEIGHT (GRAMS) - MALE RATS

		Control 1	Test 1
WEEK #	1		
DAY	0	264.7 11.5 5	263.7 14.6 10
		Control 2	Test 2
WEEK #	1		
DAY	0	203.1 3.9 8	199.7 7.1 8
WEEK #	2		
DAY	8	261.3 7.3 5	189.3 17.4 2
DAY	14	318.0 11.7 5	253.1 * 6.0 2
		Control 3	Test 3
WEEK #	1		
DAY	0	221.1 8.6 8	225.4 6.2 8
DAY	7	283.9 15.7 5	291.4 4.3 5
WEEK #	2		
DAY	14	332.6 23.8 5	350.3 8.8 5

KEY: DATA REPORTED AS MEAN, STANDARD DEVIATION, AND NUMBER PER GROUP

* - STATISTICALLY DIFFERENT FROM CONTROLS ($P \leq 0.05$).

MEAN FOR BODY WEIGHT (GRAMS) - FEMALE RATS

WEEK #	DAY	Control 1	Test 1
1	0	209.8	207.2
		13.4	6.0
		5	10

WEEK #	DAY	Control 2	Test 2
1	0	178.6	179.6
		2.0	5.9
		8	8
2	^a 8	209.0	179.2
		8.0	0.0
		5	1
	^a 14	242.6	241.4
		17.4	0.0
		5	1

WEEK #	DAY	Control 3	Test 3
1	0	190.6	189.6
		4.4	8.0
		8	8
	7	214.0	223.5
		10.8	16.0
		5	5
2	14	236.8	250.5
		11.6	18.0
		5	5

KEY: DATA REPORTED AS MEAN, STANDARD DEVIATION, AND NUMBER PER GROUP

^a - STATISTICAL ANALYSIS WERE NOT PERFORMED DUE TO THE NUMBER PER GROUP FOR TEST 2.

PATHOLOGY REPORT

CYCLOPROPANECARBOXALDEHYDE

SYNONYM: CPCA

AN ACUTE INHALATION TOXICITY STUDY IN THE RAT

HAEL No: 96-0212 EAN 023931

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LABORATORY PROJECT ID

960212I1

REPORT COMPLETION DATE

October 2, 1996

INTRODUCTION

The purpose of this study was to determine LC₅₀ value and inhalation toxicity of the test substance in the rat following a single inhalation exposure.

The animals were exposed to vapor concentrations of 0 or 1750 ppm for 6 hours or to 0, 300, or 1500 ppm for 4 hours. Each exposure concentration and time period had its own control group. This report covers the results of the necropsy and histopathology examinations conducted during this study.

The cause of death for rats which died after exposure to the test substance was not determined.

METHODS:

Necropsy

Animals were anesthetized with Metofane® and exsanguinated by severing the posterior vena cava. Necropsies were conducted according to pathology SOP No. TP 180.

Trimming procedures, fixation, and staining

Nasal passages, liver, kidneys, spleen, and selected gross lesions were fixed by immersion in 10 percent neutral-buffered formalin for at least 48 hours prior to further processing. Trimming procedures were conducted according to pathology SOP No. TP 210 which specifies the following procedures for the nasal passages and lungs. The nasal cavity was sectioned transversely at four levels according to the scheme described by Young (1981). Level I is taken posterior to the upper incisor teeth. This level is lined entirely with respiratory epithelium, with the exception of the ventral meatus which is lined with squamous epithelium. Level II is taken through the incisive papilla. At this level, the dorsal meatus is covered with olfactory epithelium while the remainder of the nasal cavity is lined by respiratory epithelium. Level III is taken at the second palatal ridge and contains the ethmoid turbinates. The majority of the mucosa is olfactory epithelium, with the exception of the nasopharyngeal duct area which is covered with respiratory epithelium. Level IV is taken at the middle of the first upper molar teeth and is deep into the blind end of the ethmoid recess. This area is almost entirely lined by olfactory epithelium. Sections of the lungs consisted of a longitudinal sample through each lobe, so as to include as much of the tracheobronchial tree as possible. The section containing the most tracheobronchial tree was selected for paraffin embedment. After dehydration, clearing, and embedding, all tissue blocks were labeled. Tissue blocks were sectioned at 5 micrometers and mounted on standard glass slides. Tissues were stained with hematoxylin and eosin (H & E) stains. Microscopic lesions were graded on a scale of minimal (1), minor (2), moderate (3), and severe (4).

RESULTS

GROSS PATHOLOGY:

SIX-HOUR EXPOSURE, 1- AND 14 -DAY OBSERVATION PERIOD GROUPS:

Two out of five male rats and all five female rats from the 1750 ppm exposure group that were scheduled to be euthanatized on Day 14 died on Day 1. Three surviving male rats from this group and all corresponding control rats were euthanatized on Day 1. The interpretation of the results for both groups is summarized together.

Male Rats - 1750 ppm exposure group: No exposure-related changes were observed.

Lesions that were considered secondary to stress consisted of minimal to moderate reduction in the size of the spleen (6/10).

Incidental findings included minimal or minor focal red discoloration (3/10) or minor red discoloration of the lungs (1/10), distention of the stomach with feed (8/10), moderate or severe distention of the urinary bladder with urine (5/10), minimal to severe red discoloration of the urinary bladder (4/10), severe red discoloration of the urine in the urinary bladder (4/10), moderate edema of the pancreas (1/10), minimal porphyrin tearing (1/10), torsion of the caudate lobe of the liver (1/10), and moderate thymus hemorrhage (1/10). Seven rats died on Day 1 and the remaining three rats were euthanatized on Day 1.

Male Rats - 0 ppm exposure group: All rats (R 301-305) survived the 1-day observation period. No incidental findings were observed.

Female Rats - 1750 ppm exposure group: No exposure-related changes were observed.

Lesions that were considered secondary to stress consisted of minor or moderate reduction in the size of the spleen (7/10).

Incidental findings included minor red discoloration of the lungs (1/10), distention of the stomach with feed (6/10), moderate red discoloration of the urinary bladder (1/10), minor or moderate red discoloration of the urine in the urinary bladder (4/10), minimal to moderate distention of the urinary bladder with urine (5/10), and minor thymus hemorrhage (2/10). No rats died on Day 1.

Female Rats - 0 ppm exposure group: All rats (R 316-320) survived the 1-day observation period. No incidental findings were observed.

FOUR HOUR EXPOSURE, 1-DAY OBSERVATION PERIOD GROUPS:

Male Rats - 1500 ppm exposure group: No exposure-related changes were observed in Rats 339, 340, and 341. All rats survived the 1-day observation period.

Lesions that were considered secondary to stress consisted of minimal reduction in the size of the spleen (2/3).

Incidental findings included minimal focal red discoloration of the lungs (1/3), minimal accumulation of mucus in the cecum (1/3), minor bilateral hydronephrosis of the kidneys (1/3), and minor pallor of the liver (3/3).

Male Rats - 0 ppm: All rats (R 331, 332, and 333) survived the 1-day observation period.

Incidental findings included minor unilateral hydronephrosis of the kidneys (1/3).

Female Rats - 1500 ppm exposure group: No exposure-related changes were observed in Rats 355, 356, and 357. All rats survived the 1-day observation period.

Lesions that were considered secondary to stress consisted of minor reduction in the size of the spleen (3/3).

Incidental findings consisted of minor pallor of the liver (3/3).

Female Rats - 0 ppm exposure group: All rats (R 347, 348, and 349) survived the 1-day observation period. No incidental findings were observed.

Male Rats - 300 ppm exposure group: No exposure-related changes were observed in Rats 379, 380, and 381. All rats survived the 1-day observation period. No incidental findings were observed.

Male Rats - 0 ppm exposure group: All rats (R 371, 372, and 373) survived the 1-day observation period. No incidental findings were observed.

Female Rats - 300 ppm exposure group: No exposure-related changes were observed. All rats (R 395, 396, and 397) survived the 1-day observation period. No incidental findings were observed.

Female Rats - 0 ppm exposure group: All rats (R 387, 388, and 389) survived the 1-day observation period. No incidental findings were observed.

FOUR HOUR EXPOSURE, 14-DAY OBSERVATION PERIOD GROUPS:

Male Rats - 1500 ppm exposure group: No exposure-related changes were observed either in Rats 342, 344, and 346 that died on Days 4, 8, and 3, respectively, or in Rats 343 and 345 that survived the 14-day observation period.

Lesions that were considered secondary to stress consisted of severely reduced size of the thymus (1/5).

Incidental findings included minor focal red discoloration of the lungs (1/5), minimal hemorrhage in the glandular gastric mucosa (1/5), minimal pallor of the liver (1/5), moderately raised white nodules in the liver (1/5), adhesion of the liver lobes to each other (1/5), adhesion of the liver to the stomach (1/5), minimally enlarged spleen (1/5), and minimally thickened splenic capsule (1/5).

The carcasses of Rats 342, 344, and 346 showed minimal autolysis.

Male Rats - 0 ppm exposure group: All rats (R 334-338) survived the 14-day observation period. No incidental findings were observed.

Female Rats - 1500 ppm exposure group: No exposure-related changes were observed either in Rats 358, 359, 360, and 362 that died on Days 2, 3, 2, and 4, respectively, or in Rat 361 that survived the 14-day observation period.

Lesions that were considered secondary to stress included minor reduction in the size of the thymus (1/5) and minor or moderate reduction in the size of the spleen (3/5).

Incidental findings included minor focal white discoloration of the liver (1/5), minimally enlarged spleen (1/5), minimally thickened splenic capsule (1/5), adhesion of the splenic capsule to adjoining adipose tissue (1/5), moderate dry porphyrin ocular discharge (1/5), minor thymic hemorrhage (1/5), and excessive accumulation of mucus in the duodenum (1/5).

The carcass of Rat 362 showed minor autolysis.

Female Rats - 0 ppm exposure group: All rats (R 350-354) survived the 14-day observation period. No incidental findings were observed.

Male Rats - 300 ppm exposure group: No exposure-related changes were observed. All rats (R 382-386) survived the 14-day observation period.

Incidental findings consisted of slightly thickened splenic capsule (1/5).

Male Rats - 0 ppm exposure group: All rats (R 374-378) survived the 14-day observation period. No incidental findings were observed.

Female Rats - 300 ppm exposure group: No exposure-related changes were observed. All rats (R 398-402) survived the 14-day observation period. No incidental findings were observed.

Female Rats - 0 ppm exposure group: All rats (R 390-394) survived the 14-day observation period. No incidental findings were observed.

HISTOPATHOLOGY:

SIX-HOUR EXPOSURE, 1- AND 14-DAY OBSERVATION PERIOD GROUPS:

Male Rats - 1750 ppm exposure group: Exposure-related changes were observed in the liver.

Liver changes included moderate eosinophilic cytoplasmic change in hepatocytes (10/10).

Lesions that were considered secondary to stress included minor atrophy (10/10) and minimal focal necrosis of the lymphatic follicles in the spleen (10/10).

Incidental findings included minimal or minor hemorrhage in the lungs (4/4), moderate thymus hemorrhage (1/1), minimal focal necrosis of the liver (1/10), minimal chronic focal inflammation of the liver (1/10), minor or moderate hemorrhage in the submucosa of the urinary bladder (4/4), moderate inter- and perilobular edema of the pancreas (1/1), minor unilateral (1/10) or minimal bilateral (3/10) hydronephrosis of the kidneys, and kidney cyst (1/10).

Male Rats - 0 ppm exposure group: Incidental findings included minimal chronic focal inflammation of the liver (4/5), minor cytoplasmic vacuolization in hepatocytes (5/5), minimal bilateral hydronephrosis of the kidneys (2/5), and kidney cyst (1/5).

Female Rats - 1750 ppm exposure group: Exposure-related changes were observed in the liver.

The liver showed minor (1/10) or moderate (6/10) eosinophilic cytoplasmic change in hepatocytes.

Lesions that were considered secondary to stress included minor atrophy (10/10) and minimal focal necrosis (5/10) of the lymphatic follicles in the spleen.

Incidental findings included minor hemorrhage in the lungs (1/1), minimal chronic focal inflammation of the liver (3/10), minimal tubular mineralizations in the kidneys (4/10), minimal hemorrhage in the mucosa (3/4) or submucosa (1/4) of the urinary bladder, and minimal or minor thymus hemorrhage (2/2).

Female Rats - 0 ppm: Incidental findings included minimal chronic focal inflammation of the liver (1/5), minor cytoplasmic vacuolization in hepatocytes (5/5), minor unilateral hydronephrosis of the kidneys (1/5), minimal tubular mineralizations in the kidneys (2/5), and kidney scar (1/5).

FOUR-HOUR EXPOSURE, 1-DAY OBSERVATION PERIODS:

Male Rats - 1500 ppm exposure group: Exposure-related changes were observed in the liver.

The liver changes consisted of moderate eosinophilic cytoplasmic change in hepatocytes (3/3).

Lesions that were considered secondary to stress consisted of minor atrophy of the lymphatic follicles (3/3) in the spleen.

Incidental findings included minimal hemorrhage in the lungs (1/1), minimal or minor cytoplasmic vacuolization in hepatocytes (2/3), and minor unilateral hydronephrosis of the kidneys (1/3).

Male Rats - 0 ppm exposure group: Incidental findings included minimal or minor cytoplasmic vacuolization in hepatocytes (3/3) and minor bilateral hydronephrosis of the kidneys (1/3).

Female Rats - 1500 ppm exposure group: Exposure-related changes were observed in the liver.

Liver changes included minor or moderate eosinophilic cytoplasmic change in hepatocytes (2/3).

Lesions that were considered secondary to stress consisted of minor atrophy of the lymphatic follicles (3/3) in the spleen.

Incidental findings consisted of minimal or minor cytoplasmic vacuolization in hepatocytes (3/3).

Female Rats - 0 ppm exposure group: Incidental findings included minimal chronic focal inflammation of the liver (2/3) and minimal or minor cytoplasmic vacuolization in hepatocytes (3/3).

Male Rats - 300 ppm exposure group: No exposure-related changes were observed. Incidental findings included minor cytoplasmic vacuolization in hepatocytes (3/3), kidney cysts (2/3), and kidney scar (1/3).

Male Rats - 0 ppm exposure group: Incidental findings included minor cytoplasmic vacuolization in hepatocytes (3/3), minimal unilateral hydronephrosis of the kidneys (1/3), and kidney cyst (1/3).

Female Rats - 300 ppm exposure group: No exposure-related changes were observed. Incidental findings included minimal chronic focal inflammation of the liver (1/3), minimal or minor cytoplasmic vacuolization in hepatocytes (3/3), minimal unilateral hydronephrosis of the kidneys (1/3), and minimal tubular mineralizations in the kidneys (2/3).

Female Rats - 0 ppm exposure group: Incidental findings included minimal chronic focal inflammation of the liver (3/3), minimal cytoplasmic vacuolization in hepatocytes (3/3), minimal tubular mineralizations in the kidneys (2/3), kidney cyst (1/3), and kidney scar (1/3).

FOUR HOUR EXPOSURE, 14-DAY OBSERVATION PERIOD GROUPS:

Male Rats - 1500 ppm exposure group: Exposure-related changes were observed in the liver

The liver changes included moderate eosinophilic cytoplasmic change (4/5) and moderate hypertrophy (1/5) of hepatocytes.

Lesions that were considered secondary to stress included severe atrophy of the thymus (1/1) and minimal to moderate atrophy of the lymphatic follicles (4/5) in the spleen.

Incidental findings included minor hemorrhage in the lungs (1/1), minimal chronic focal inflammation of the liver (1/5), liver abscesses (1/5), minimal to moderate cytoplasmic vacuolization in hepatocytes (3/5), minor bilateral hydronephrosis of the kidneys (1/3), kidney cyst (1/3), moderately increased extramedullary hematopoiesis in the spleen (1/5), and minor diffuse fibrosis of the splenic capsule (1/5).

Male Rats - 0 ppm exposure group: Incidental findings included minimal or minor cytoplasmic vacuolization in hepatocytes (5/5) and minimal unilateral hydronephrosis of the kidneys (1/5).

Female Rats -1500 ppm exposure group: Exposure-related changes were observed in the liver

Liver changes included minor or moderate eosinophilic cytoplasmic change (5/5) and minor hypertrophy (1/5) of hepatocytes.

Lesions that were considered secondary to stress included severe atrophy of the thymus (1/1) and minor or moderate atrophy of the lymphatic follicles in the spleen (5/5).

Incidental findings included minor thymic hemorrhage (1/1), minimal chronic focal inflammation of the liver (1/5), liver abscesses (1/5), minimal to moderate cytoplasmic vacuolization in hepatocytes (5/5), moderately increased extramedullary hematopoiesis in the spleen (1/5), and minor diffuse fibrosis of the splenic capsule (1/5).

Female Rats - 0 ppm exposure group: Incidental findings included minimal chronic focal inflammation of the liver (3/5), minimal or minor cytoplasmic vacuolization in hepatocytes (5/5), kidney cyst (1/5), and minimal tubular mineralizations in the kidneys (2/5).

Male Rats - 300 ppm exposure group: No exposure-related changes were observed. Incidental findings included minimal chronic focal inflammation of the liver (2/5), minimal or minor cytoplasmic vacuolization in hepatocytes (5/5), minimal bilateral (1/5) and minor unilateral hydronephrosis of the kidneys (1/5), and kidney cyst (1/5).

Male Rats - 0 ppm exposure group: Incidental findings included minimal chronic focal inflammation of the liver (1/5), minimal or minor cytoplasmic vacuolization in hepatocytes (5/5), minimal unilateral hydronephrosis of the kidneys (1/5), and kidney scar (1/5).

Female Rats - 300 ppm exposure group: No exposure-related changes were observed. Incidental findings included minimal or minor cytoplasmic vacuolization in hepatocytes (5/5) and minimal tubular mineralizations in the kidneys (4/5).

Female Rats - 0 ppm exposure group: Incidental findings included minimal chronic focal inflammation of the liver (4/5), minimal or minor cytoplasmic vacuolization in hepatocytes (5/5), minor unilateral hydronephrosis of the kidneys (1/5), and minimal tubular mineralizations in the kidneys (2/5).

COMMENTS:

The control rats of both sexes had no significant lesions. The changes observed in the tissues and organs of the control rats on this study are commonly observed in this age and strain of rat.

Microscopic lesions which have been associated with the treatment were found in the liver.

The incidence of eosinophilic cytoplasmic change of hepatocytes was 10/10 for male rats and 7/10 for female rats from the 1750 ppm exposure group, and 7/8 for both male and female rats from the 1500 ppm exposure group. The affected hepatocytes showed dispersed basophilic

clumps of rough endoplasmic reticulum, and cytoplasm had assumed a granular eosinophilic appearance which sometimes had the appearance of "ground glass." In single male and female rats from the 1500 ppm exposure group the centrilobular hepatocytes were enlarged (hypertrophy). Increased cytoplasmic eosinophilia and hypertrophy of hepatocytes, as seen in this study, most often represent adaptive changes which would be expected to be reversible on cessation of exposure.

Lesions that were considered secondary to stress included thymus atrophy and atrophy and necrosis of the lymphatic follicles in the spleen.

Severe thymus atrophy was observed in two rats from the 1500 ppm exposure group. The affected thymuses showed totally depleted outer zones with only sparse identifiable cortical lymphocytes. Grossly, this lesion was characterized as minor or severe reduction in the size of the thymus. This type of lesion is probably induced by stress and is most likely mediated by glucocorticosteroid release from the adrenal cortex.

Splenic lesions included atrophy and necrosis of the lymphatic follicles. The incidences of minimal to moderate atrophy was 0, 0, 7, and 10 for male rats and 0, 0, 8, and 10 for female rats from the 0, 300, 1500, and 1750 ppm groups, respectively. A typical lesion was characterized by lymphocyte depletion in the periarteriolar lymphoid sheaths and marginal zones of the spleen. Grossly, this lesion was characterized as minimal to moderate reduction in the size of the spleen. The incidences of minimal necrosis of the lymphocytes in the lymphatic follicles were 0, 0, 0, and 10 for male rats and 0, 0, 0, and 5 for female rats from the 0, 300, 1500, and 1750 ppm groups, respectively. A typical lesion was characterized by small areas containing necrotic lymphocytes in the periarteriolar sheaths and marginal zones of the spleen. Atrophy and necrosis of the lymphatic follicles are probably induced by stress and are most likely mediated by glucocorticosteroid release from the adrenal cortex.

Incidental findings were observed in the lungs, thymus, spleen, liver, urinary bladder, and pancreas.

Minimal to minor lung hemorrhage was the only lung lesion observed in 4/10 male and 1/10 female rats from the 1750 ppm exposure groups and in 2/8 male rats from the 1500 ppm exposure group. Grossly, this lesion was characterized as red or focal red discoloration of the lungs. "As a single lung lesion, pulmonary hemorrhage is rarely induced by drugs or toxins and is usually only observed as a terminal event in acute inhalation studies" (Whimster and de Poitiers, 1982).

Minimal to moderate thymus hemorrhage was observed in Rats 306, 322, and 325 from the 1750 ppm exposure group and in Rat 362 from the 1500 ppm exposure group. Hemorrhagic foci in the thymus included large numbers of extravascular erythrocytes in medulla and/or cortex. Thymus hemorrhage is considered either an agonal process or a dissection artifact.

Minimal focal necrosis of the liver was observed in Rat 312 (1750 ppm). This lesion was characterized by a well-defined focus of necrotic hepatocytes without inflammation or regeneration. Although not observed in the concurrent control rats, this lesion is occasionally observed in untreated control rats.

Multiple liver abscesses were observed in Rats 343 and 361 (1500 ppm). Grossly, these lesions were characterized as moderately raised white nodules in the liver. An abscess is a cavity formed by necrosis of tissues and accumulation of acute inflammatory cells that is walled off by fibrosis. Abscesses develop when invading bacteria are contained by the inflammatory response of the host. In the absence of concurrent degenerative changes in the liver, and considering the likely bacterial origin of the lesions, low incidence, and lack of dose-response relationship, the liver abscesses observed in Rats 343 and 361 were considered incidental and not related to exposure to the test substance.

Chronic focal inflammation of the liver and cytoplasmic vacuolization in hepatocytes were more frequent in control group rats than in exposed rats on this study. The foci of chronic inflammation were routinely distributed throughout the liver and were characterized by small accumulations of predominantly mononuclear cells. On gross observation, cytoplasmic vacuolization in hepatocytes was characterized as pallor of the liver. Cytoplasmic vacuolization in hepatocytes was characterized by the presence of large membrane-bound vacuoles. These vacuoles may have contained lipids; however, the unambiguous determination of vacuolar lipid content depends on avoiding embedment procedures that extract lipid and on the use of special stains.

Moderate increase in extramedullary hematopoiesis in the spleen and minor diffuse fibrosis of the splenic capsule were observed in Rats 343 and 361 (1500 ppm). Both lesions were considered secondary to liver abscesses. Increase in extramedullary hematopoiesis of the spleen was probably due to increased demand for polymorphonuclear leukocytes that were accumulating in the liver abscesses. Diffuse fibrosis of the splenic capsule was also considered secondary to liver abscesses, because inflammatory lesions of the splenic capsule usually originate by extension from adjacent abdominal organs.

The following types of kidney lesions were observed: a) congenital (hydronephrosis and congenital cortical cysts); b) degenerative (renal tubule mineralization); and c) inflammatory (scars).

- a) Hydronephrosis was more frequent in control group rats than in exposed rats on this study. This lesion was characterized by dilation of the renal pelvis, with excavation of the renal medulla, reduction in the length of the collecting tubules, and absence of an inflammatory response. In the absence of obstruction of the lower urinary tract, this lesion was considered to be congenital. Solitary cortical cysts were more frequent in control group rats than in exposed rats. This lesion could be acquired or congenital. Acquired cortical cysts are formed from dilated tubules and are secondary to chronic progressive nephrosis. In the absence of chronic progressive nephrosis, cortical cysts observed in rats on this study were considered to be congenital. Congenital cortical cysts were lined by a flattened epithelium and contained proteinaceous fluid.
- b) Tubular mineralizations were more frequent in control group female rats than in exposed female rats on this study. This lesion was characterized by tiny lamellated concretions or microliths located in the lumen of the renal tubules. Only a few of the microliths were intracellular. The microliths were not associated with evidence of cell degeneration.
- c) Kidney scars were present in control Rats 319, 379, and 389. This type of lesion is characterized by pale fibroblastic tissue that is shrunken and sharply demarcated from the surrounding normal kidney structures.

Minimal to moderate hemorrhage in the mucosa or submucosa of the urinary bladder was observed in rats from the 1750 ppm exposure group (Rats 308, 310, 311, 312, 323, 325, 326, and 329). Affected mucosa or submucosa of the urinary bladder contained a variable number of fresh extravascular erythrocytes. All affected rats died spontaneously and the majority of their urinary bladders was distended with red urine. It is the study's pathologist's opinion that this lesion is agonal and not related to exposure.

Moderate peri- and interlobular edema was observed in the pancreas of Rat 315 (1750 ppm). The cause for this lesion was not determined.

CONCLUSIONS

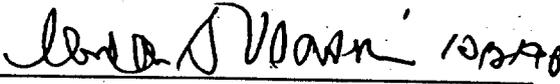
Single exposure to 1750 or 1500 ppm of the test substance resulted in eosinophilic cytoplasmic change and hypertrophy of hepatocytes. Minimal or minor lung hemorrhage is not considered exposure-related since it is rarely induced by drugs or toxins, and is usually only observed as a terminal event in acute inhalation studies. Atrophy of the splenic lymphatic follicles and thymus were considered to be secondary to stress.

No exposure-related changes were observed in rats of either sex exposed to 300 ppm of the test substance.

REFERENCES:

Whimster, W. F. and de Poitiers, W.: The lung. In Riddell, R. H. (ed.) Pathology of Drug-Induced and Toxic Diseases, pp 167-200. New York: Churchill Livingstone 1982.

Young, J. T.: Histopathologic examination of the rat nasal cavity. Fundam. Appl. Toxicol. 1:309-312, 1981.

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 10/2/96

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10/02/96

SUMMARY GROSS PATHOLOGY INCIDENCE TABLE - MALE RATS

GROUP	Control 1	Test1
DAYS ON TEST	1	1
NASAL PASSAGES	5	10
TRACHEA	5	10
LUNGS	5	10
DISCOLORATION, FOCAL RED	0	3
DISCOLORATION, RED	0	1
LARYNX	5	10
HEART	5	10
ESOPHAGUS	5	10
STOMACH	5	10
GASTRIC CONTENTS INCREASED	0	8
DUODENUM	5	10
JEJUNUM	5	10
ILEUM	5	10
CECUM	5	10
COLON	5	10
URINARY BLADDER	5	10
DISTENTION	0	5
DISCOLORATION, RED	0	4
URINE	5	10
DISCOLORATION, RED	0	4
PITUITARY GLAND	5	10
PANCREAS, NOS	5	10
EDEMA	0	1
THYROID GLANDS	5	10
PARATHYROID GLANDS	5	10
MESENTERIC LYMPH NODES	5	10
BONE MARROW	5	10
BRAIN	5	10
EYES	5	10
PORPHYRIN TEARS	0	1
SKIN, NOS	5	10
SALIVARY GLANDS	5	10
KIDNEYS	5	10

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS,
THE NUMBER OF TISSUES WITH EACH ABNORMALITY

SUMMARY GROSS PATHOLOGY INCIDENCE TABLE - MALE RATS

GROUP	Control 1	Test 1
DAYS ON TEST	1	1
LIVER	5	10
CAUDATE LOBE OF LIVER TORSION	0	1
THYMUS	5	10
HEMORRHAGE	0	1
ADRENALS	5	10
SPLEEN	5	10
SMALL	0	6
EPIDIDYMIDES	5	10
ACCESSORY SEX ORGANS (MALE)	5	10
TESTES	5	10

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS,
THE NUMBER OF TISSUES WITH EACH ABNORMALITY

SUMMARY CROSS PATHOLOGY INCIDENCE TABLE - FEMALE RATS

GROUP	Control 1	Test 1
DAYS ON TEST	1	1
NASAL PASSAGES	5	10
TRACHEA	5	10
LUNGS	5	10
DISCOLORATION, FOCAL RED	0	1
LARYNX	5	10
HEART	5	10
ESOPHAGUS	5	10
STOMACH	5	10
GASTRIC CONTENTS INCREASED	0	6
DUODENUM	5	10
JEJUNUM	5	10
ILEUM	5	10
CECUM	5	10
COLON	5	10
URINARY BLADDER	5	10
DISTENTION	0	5
DISCOLORATION, RED	0	1
URINE		
DISCOLORATION, RED	0	4
PITUITARY GLAND	5	10
PANCREAS, NOS	5	10
THYROID GLANDS	5	10
PARATHYROID GLANDS	5	10
MESENTERIC LYMPH NODES	5	10
BONE MARROW	5	10
BRAIN	5	10
EYES	5	10
SKIN, NOS	5	10
SALIVARY GLANDS	5	10
KIDNEYS	5	10
LIVER	5	10
THYMUS	5	10
HEMORRHAGE	0	2

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS,
THE NUMBER OF TISSUES WITH EACH ABNORMALITY

SUMMARY GROSS PATHOLOGY INCIDENCE TABLE - FEMALE RATS

GROUP	Control 1	Test 1
DAYS ON TEST	1	1
ADRENALS	5	10
SPLEEN	5	10
SMALL	0	7
OVARIES	5	10
FALLOPIAN TUBES	5	10
UTERUS	5	10
VAGINA	5	10

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS,
THE NUMBER OF TISSUES WITH EACH ABNORMALITY

SUMMARY GROSS PATHOLOGY INCIDENCE TABLE - MALE RATS

GROUP	Control 2	Control 2	Test 2	Test 2
DAYS ON TEST	1	14	1	14
NASAL PASSAGES	3	5	3	5
TRACHEA	3	5	3	5
LUNGS	3	5	3	5
DISCOLORATION, FOCAL RED	0	0	1	1
LARYNX	3	5	3	5
HEART	3	5	3	5
ESOPHAGUS	3	5	3	5
STOMACH	3	5	3	5
AUTOLYSIS	0	0	0	1
STOMACH, NON-GLANDULAR HEMORRHAGE	0	0	0	1
DUODENUM	3	5	3	5
AUTOLYSIS	0	0	0	2
DISTENTION	0	0	0	1
JEJUNUM	3	5	3	5
AUTOLYSIS	0	0	0	2
DISTENTION	0	0	0	1
ILEUM	3	5	3	5
AUTOLYSIS	0	0	0	2
DISTENTION	0	0	0	1
CECUM	3	5	3	5
AUTOLYSIS	0	0	0	2
INTESTINAL CONTENTS INCREASED	0	0	1	0
COLON	3	5	3	5
AUTOLYSIS	0	0	0	2
URINARY BLADDER	3	5	3	5
PITUITARY GLAND	3	5	3	5
PANCREAS, NOS	3	5	3	5
THYROID GLANDS	3	5	3	5
PARATHYROID GLANDS	3	5	3	5
MESENTERIC LYMPH NODES	3	5	3	5
BONE MARROW	3	5	3	5
BRAIN	3	5	3	5
EYES	3	5	3	5
SKIN, NOS	3	5	3	5
SALIVARY GLANDS	3	5	3	5

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS,
THE NUMBER OF TISSUES WITH EACH ABNORMALITY

SUMMARY GROSS PATHOLOGY INCIDENCE TABLE - MALE RATS

GROUP	Control 2	Control 2	Test 2	Test 2
DAYS ON TEST	1	.14	1	14
KIDNEYS	3	5	3	5
HYDRONEPHROSIS, UNILATERAL	1	0	0	0
HYDRONEPHROSIS	0	0	1	0
AUTOLYSIS	0	0	0	1
LIVER	3	5	3	5
PALLOR	0	0	3	1
AUTOLYSIS	0	0	0	1
ADHESION	0	0	0	1
DISCOLORATION, FOCAL WHITE	0	0	0	1
THYMUS	3	5	3	5
SMALL	0	0	0	1
ADRENALS	3	5	3	5
SPLEEN	3	5	3	5
SMALL	0	0	2	2
AUTOLYSIS	0	0	0	1
SPLENIC CAPSULE				
THICKENED	0	0	0	1
ENLARGED,NOS	0	0	0	1
EPIDIDYMIDES	3	5	3	5
ACCESSORY SEX ORGANS (MALE)	3	5	3	5
TESTES	3	5	3	5
RECTUM	0	0	0	1
AUTOLYSIS	0	0	0	1
BODY AS A WHOLE, NOS	0	0	0	1
AUTOLYSIS	0	0	0	1

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS, THE NUMBER OF TISSUES WITH EACH ABNORMALITY

SUMMARY GROSS PATHOLOGY INCIDENCE TABLE - FEMALE RATS

GROUP	Control 2	Control 2	Test 2	Test 2
DAYS ON TEST	1	14	1	14
NASAL PASSAGES	3	5	3	5
TRACHEA	3	5	3	5
LUNGS	3	5	3	5
LARYNX	3	5	3	5
HEART	3	5	3	5
ESOPHAGUS	3	5	3	5
STOMACH	3	5	3	5
DUODENUM	3	5	3	5
INTESTINAL CONTENTS INCREASED	0	0	0	1
JEJUNUM	3	5	3	5
ILEUM	3	5	3	5
CECUM	3	5	3	5
COLON	3	5	3	5
URINARY BLADDER	3	5	3	5
PITUITARY GLAND	3	5	3	5
PANCREAS, NOS	3	5	3	5
THYROID GLANDS	3	5	3	5
PARATHYROID GLANDS	3	5	3	5
MESENTERIC LYMPH NODES	3	5	3	5
BONE MARROW	3	5	3	5
BRAIN	3	5	3	5
EYES	3	5	3	5
DRIED PORPHYRIN DISCHARGE	0	0	0	1
SKIN, NOS	3	5	3	5
SALIVARY GLANDS	3	5	3	5
KIDNEYS	3	5	3	5
LIVER	3	5	3	5
PALLOR	0	0	3	0
DISCOLORATION, FOCAL WHITE	0	0	0	1
THYMUS	3	5	3	5
SMALL	0	0	0	1
HEMORRHAGE	0	0	0	1
ADRENALS	3	5	3	5

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS,
THE NUMBER OF TISSUES WITH EACH ABNORMALITY

SUMMARY GROSS PATHOLOGY INCIDENCE TABLE - FEMALE RATS

GROUP	Control 2	Control 2	Test 2	Test 2
DAYS ON TEST	1	14	1	14
SPLEEN	3	5	3	5
SMALL	0	0	3	3
ENLARGED,NOS	0	0	0	1
SPLENIC CAPSULE				
THICKENED	0	0	0	1
ADHESION	0	0	0	1
OVARIES	3	5	3	5
FALLOPIAN TUBES	3	5	3	5
UTERUS	3	5	3	5
VAGINA	3	5	3	5
HAIR	0	0	0	1
HAIR OF INGUINAL REGION				
HAIRCOAT-DRY URINE STAIN	0	0	0	1
DISCOLORATION,BROWN	0	0	0	1
HAIR, PERIORAL				
DISCOLORATION,RED	0	0	0	1
BODY AS A WHOLE, NOS	0	0	0	1
AUTOLYSIS	0	0	0	1

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS,
 THE NUMBER OF TISSUES WITH EACH ABNORMALITY

SUMMARY GROSS PATHOLOGY INCIDENCE TABLE - MALE RATS

GROUP	Control 3	Control 3	Test 3	Test 3
DAYS ON TEST	1	14	1	14
NASAL PASSAGES	3	5	3	5
TRACHEA	3	5	3	5
LUNGS	3	5	3	5
LARYNX	3	5	3	5
HEART	3	5	3	5
ESOPHAGUS	3	5	3	5
STOMACH	3	5	3	5
DUODENUM	3	5	3	5
JEJUNUM	3	5	3	5
ILEUM	3	5	3	5
CECUM	3	5	3	5
COLON	3	5	3	5
URINARY BLADDER	3	5	3	5
PITUITARY GLAND	3	5	3	5
PANCREAS, NOS	3	5	3	5
THYROID GLANDS	3	5	3	5
PARATHYROID GLANDS	3	5	3	5
MESENTERIC LYMPH NODES	3	5	3	5
BONE MARROW	3	5	3	5
BRAIN	3	5	3	5
EYES	3	5	3	5
SKIN, NOS	3	5	3	5
SALIVARY GLANDS	3	5	3	5
KIDNEYS	3	5	3	5
LIVER	3	5	3	5
THYMUS	3	5	3	5
ADRENALS	3	5	3	5
SPLEEN	3	5	3	5
SPLENIC CAPSULE THICKENED	0	0	0	1
EPIDIDYMIDES	3	5	3	5

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS,
THE NUMBER OF TISSUES WITH EACH ABNORMALITY

SUMMARY GROSS PATHOLOGY INCIDENCE TABLE - MALE RATS

GROUP	Control 3	Control 3	Test 3	Test 3
DAYS ON TEST	1	14	1	14
ACCESSORY SEX ORGANS (MALE)	3	5	3	5
TESTES	3	5	3	5

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS,
THE NUMBER OF TISSUES WITH EACH ABNORMALITY

SUMMARY GROSS PATHOLOGY INCIDENCE TABLE - FEMALE RATS

GROUP	Control 3	Control 3	Test 3	Test 3
DAYS ON TEST	1	14	1	14
NASAL PASSAGES	3	5	3	5
TRACHEA	3	5	3	5
LUNGS	3	5	3	5
LARYNX	3	5	3	5
HEART	3	5	3	5
ESOPHAGUS	3	5	3	5
STOMACH	3	5	3	5
DUODENUM	3	5	3	5
JEJUNUM	3	5	3	5
ILEUM	3	5	3	5
CECUM	3	5	3	5
COLON	3	5	3	5
URINARY BLADDER	3	5	3	5
PITUITARY GLAND	3	5	3	5
PANCREAS, NOS	3	5	3	5
THYROID GLANDS	3	5	3	5
PARATHYROID GLANDS	3	5	3	5
MESENTERIC LYMPH NODES	3	5	3	5
BONE MARROW	3	5	3	5
BRAIN	3	5	3	5
EYES	3	5	3	5
SKIN, NOS	3	5	3	5
SALIVARY GLANDS	3	5	3	5
KIDNEYS	3	5	3	5
LIVER	3	5	3	5
THYMUS	3	5	3	5
ADRENALS	3	5	3	5
SPLEEN	3	5	3	5
OVARIES	3	5	3	5
FALLOPIAN TUBES	3	5	3	5

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS, THE NUMBER OF TISSUES WITH EACH ABNORMALITY

SUMMARY GROSS PATHOLOGY INCIDENCE TABLE - FEMALE RATS

GROUP	Control 3	Control 3	Test 3	Test 3
DAYS ON TEST	1	14	1	14
UTERUS	3	5	3	5
VAGINA	3	5	3	5

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS,
THE NUMBER OF TISSUES WITH EACH ABNORMALITY

SUMMARY HISTOPATHOLOGY INCIDENCE TABLE - MALE RATS

GROUP	Control 1	Test 1
DAYS ON TEST	1	1
NASAL PASSAGES	5	10
AUTOLYSIS	0	8
LIVER	5	10
INFLAMMATION, CHRONIC FOCAL	4	1
NECROSIS, FOCAL	0	1
HEPATOCTYTE		
CYTOPLASMIC VACUOLIZATION	5	0
EOSINOPHILIC CYTOPLASMIC CHANGE	0	10
KIDNEYS	5	10
HYDRONEPHROSIS, BILATERAL	2	3
CYST	1	1
AUTOLYSIS	0	8
HYDRONEPHROSIS, UNILATERAL	0	1
LUNGS	0	4
HEMORRHAGE	0	4
THYMUS	0	1
HEMORRHAGE	0	1
URINARY BLADDER	0	4
SUBMUCOSA		
HEMORRHAGE	0	4
SPLEEN	5	10
SPLENIC LYMPHATIC FOLLICLE		
ATROPHY	0	10
NECROSIS, FOCAL	0	10
PANCREAS, NOS	0	1
EDEMA	0	1

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS, THE NUMBER OF TISSUES WITH EACH ABNORMALITY

SUMMARY HISTOPATHOLOGY INCIDENCE TABLE - FEMALE RATS

GROUP	Control 1	Test 1
DAYS ON TEST	1	1
NASAL PASSAGES	5	9
AUTOLYSIS	0	9
LIVER	5	10
INFLAMMATION, CHRONIC FOCAL HEPATOCTYE	1	3
CYTOPLASMIC VACUOLIZATION	5	0
EOSINOPHILIC CYTOPLASMIC CHANGE	0	7
KIDNEYS	5	10
HYDRONEPHROSIS, UNILATERAL	1	0
AUTOLYSIS	0	10
CYST	0	1
RENAL TUBULE MINERALIZATION	2	4
SCAR	1	0
LUNGS	0	1
HEMORRHAGE	0	1
THYMUS	0	2
HEMORRHAGE	0	2
URINARY BLADDER	0	4
MUCOSA HEMORRHAGE	0	3
SUBMUCOSA HEMORRHAGE	0	1
SPLEEN	5	10
SPLENIC LYMPHATIC FOLLICLE ATROPHY	0	10
NECROSIS, FOCAL	0	5
TRACHEA	0	1
AUTOLYSIS	0	1

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS,
THE NUMBER OF TISSUES WITH EACH ABNORMALITY

SUMMARY HISTOPATHOLOGY INCIDENCE TABLE - MALE RATS

GROUP	Control 2	Control 2	Test 2	Test 2
DAYS ON TEST	1	3,4,8,14	1	2,3,4,14
NASAL PASSAGES	3	5	3	5
AUTOLYSIS	0	0	0	2
LIVER	3	5	3	5
ABSCESS	0	0	0	1
INFLAMMATION, CHRONIC FOCAL	0	0	0	1
HEPATOCTE				
CYTOPLASMIC VACUOLIZATION	3	5	2	3
EOSINOPHILIC CYTOPLASMIC CHANGE	0	0	3	4
HYPERTROPHY	0	0	0	1
AUTOLYSIS	0	0	0	1
KIDNEYS	3	5	3	3
HYDRONEPHROSIS, BILATERAL	1	0	0	1
HYDRONEPHROSIS, UNILATERAL	0	1	1	0
AUTOLYSIS	0	0	0	2
CYST	0	0	0	1
SPLEEN	3	5	3	5
SPLENIC LYMPHATIC FOLLICLE				
ATROPHY	0	0	3	4
SPLENIC CAPSULE				
FIBROSIS, DIFFUSE	0	0	0	1
SPLENIC RED PULP				
HEMATOPOIESIS (EXTRAMEDULLARY)	0	0	0	1
LUNGS	0	0	1	1
HEMORRHAGE	0	0	1	1
STOMACH	0	0	0	1
THYMUS	0	0	0	1
ATROPHY	0	0	0	1

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS, THE NUMBER OF TISSUES WITH EACH ABNORMALITY

SUMMARY HISTOPATHOLOGY INCIDENCE TABLE - FEMALE RATS

GROUP	Control 2	Control 2	Test 2	Test 2
	1	3,4,8,14	1	2,3,4,14
DAYS ON TEST				
NASAL PASSAGES	3	5	3	5
AUTOLYSIS	0	0	0	2
LIVER	3	5	3	5
INFLAMMATION, CHRONIC FOCAL	2	3	0	1
ABSCESS	0	0	0	1
AUTOLYSIS	0	0	0	1
HEPATOCTYTE				
CYTOPLASMIC VACUOLIZATION	3	5	3	5
EOSINOPHILIC CYTOPLASMIC CHANGE	0	0	2	5
HYPERTROPHY	0	0	0	1
KIDNEYS	3	5	3	5
CYST	0	1	1	0
AUTOLYSIS	0	0	0	3
RENAL TUBULE				
MINERALIZATION	0	2	0	0
SPLEEN	3	5	3	5
SPLENIC LYMPHATIC FOLLICLE				
ATROPHY	0	0	3	5
SPLENIC CAPSULE				
FIBROSIS, DIFFUSE	0	0	0	1
SPLENIC RED PULP				
HEMATOPOIESIS (EXTRAMEDULLARY)	0	0	0	1
THYMUS	0	0	0	1
ATROPHY	0	0	0	1
HEMORRHAGE	0	0	0	1

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS, THE NUMBER OF TISSUES WITH EACH ABNORMALITY

SUMMARY HISTOPATHOLOGY INCIDENCE TABLE - MALE RATS

GROUP	Control 3	Control 3	Test 3	Test 3
DAYS ON TEST	1	14	1	14
NASAL PASSAGES	3	5	3	5
LIVER	3	5	3	5
INFLAMMATION, CHRONIC FOCAL	0	1	0	2
HEPATOCTE				
CYTOPLASMIC VACUOLIZATION	3	5	3	5
KIDNEYS	3	5	3	5
CYST	1	0	2	1
HYDRONEPHROSIS, UNILATERAL	1	1	0	1
SCAR	0	1	1	0
HYDRONEPHROSIS, BILATERAL	0	0	0	1
SPLEEN	3	5	3	5

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS, THE NUMBER OF TISSUES WITH EACH ABNORMALITY

SUMMARY HISTOPATHOLOGY INCIDENCE TABLE - FEMALE RATS

GROUP	Control 3	Control 3	Test 3	Test 3
DAYS ON TEST	1	14	1	14
NASAL PASSAGES	3	5	3	5
LIVER	3	5	3	5
INFLAMMATION, CHRONIC FOCAL HEPATOCTE	3	4	1	0
CYTOPLASMIC VACUOLIZATION	3	5	3	5
KIDNEYS	3	5	3	5
CYST	1	0	0	0
SCAR	1	0	0	0
HYDRONEPHROSIS, UNILATERAL	0	1	1	0
RENAL TUBULE MINERALIZATION	2	2	2	4
SPLEEN	3	5	3	5

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS,
 THE NUMBER OF TISSUES WITH EACH ABNORMALITY

APPENDIX

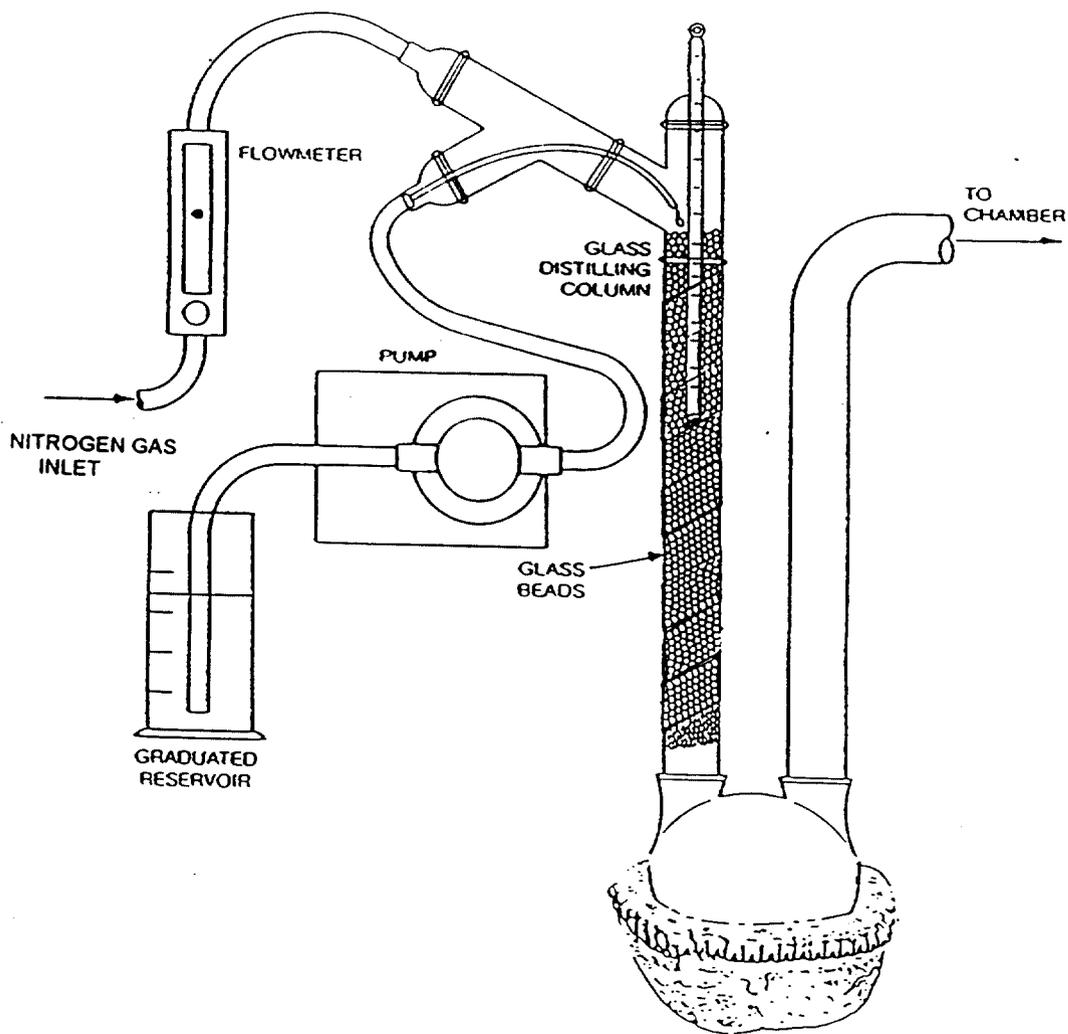
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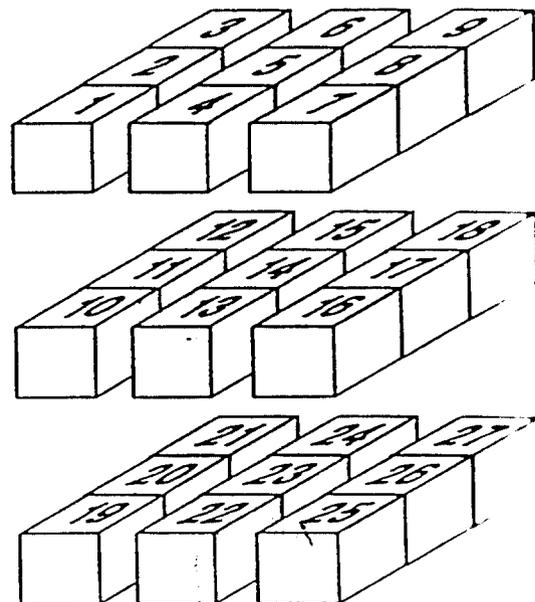
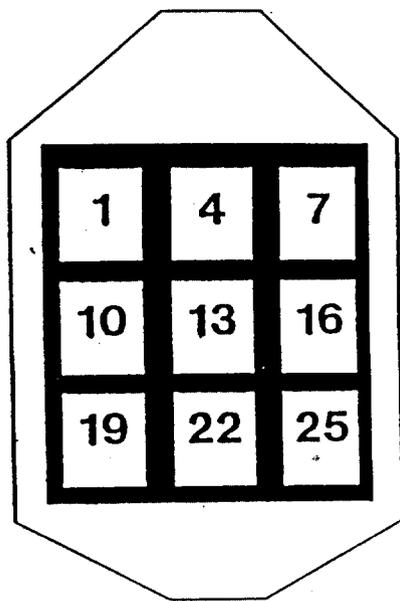
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Diagram of Exposure System



Exploded View of Chamber



Clinical Signs During Exposure

Male Rats

Control 1 Rat No. 301 - 305		1 Hour	2 Hours	Observation After			
				3 Hours	4 Hours	5 Hours	6 Hours
Normal	Incidence	5/5	5/5	5/5	5/5	5/5	5/5

Test 2 Rat No. 306 - 315		1 Hour	2 Hours	Observation After			
				3 Hours	4 Hours	5 Hours	6 Hours
Normal	Incidence	10/10					
Reduced Activity	Incidence		10/10	10/10	10/10	10/10	10/10
	Severity		2	4	4	4	4
Rapid, Shallow Respiration	Incidence		10/10	10/10			
	Severity		3	4			
Labored Breathing (Deeper than controls)	Incidence				10/10	10/10	10/10
	Severity				2	2	3
Respiration Rate Slower than Normal	Incidence						10/10
	Severity						3

Female Rats

Control 1 Rat No. 316-320		1 Hour	2 Hours	Observation After			
				3 Hours	4 Hours	5 Hours	6 Hours
Normal	Incidence	5/5	5/5	5/5	5/5	5/5	5/5

Test 1 Rat No. 321-330		1 Hour	2 Hours	Observation After			
				3 Hours	4 Hours	5 Hours	6 Hours
Normal	Incidence	10/10					
Reduced Activity	Incidence		10/10	10/10	10/10	10/10	10/10
	Severity		2	4	4	4	4
Rapid, Shallow Respiration	Incidence		10/10	10/10			
	Severity		3	4			
Labored Breathing (Deeper than controls)	Incidence				10/10	10/10	10/10
	Severity				2	2	3
Respiration Rate Slower than Normal	Incidence						10/10
	Severity						3

Severities: 1 = Minimal, 2 = Minor, 3 = Moderate, and 4 = Severe.

Clinical Signs During Exposure

Male Rats

Control 2 Rat No. 331-338		1 Hour	Observation After		
			2 Hours	3 Hours	4 Hours
Normal	Incidence	8/8	8/8	8/8	8/8

Test 2 Rat No. 339-346		1 Hour	Observation After		
			2 Hours	3 Hours	4 Hours
Normal	Incidence				
Reduced Activity	Incidence	7/8	8/8	8/8	8/8
	Severity	1	1	4	4
Reduced Activity	Incidence	1/8 [342]			
	Severity	2			

Female Rats

Control 2 Rat No. 347-354		1 Hour	Observation After		
			2 Hours	3 Hours	4 Hours
Normal	Incidence	8/8	8/8	8/8	8/8

Test 2 Rat No. 355-362		1 Hour	Observation After		
			2 Hours	3 Hours	4 Hours
Normal	Incidence				
Reduced Activity	Incidence	8/8	8/8	7/8	8/8
	Severity	1	1	4	4
Reduced Activity	Incidence			1/8 [359]	
	Severity			3	

Severities: 1 = Minimal, 2 = Minor, 3 = Moderate, and 4 = Severe.

If the incidence was less than all the animals in the group, then the animal numbers are shown in brackets.

Clinical Signs During Exposure

Male Rats

Control 3 Rat No. 371-378		1 Hour	Observation After		
			2 Hours	3 Hours	4 Hours
Normal	Incidence	8/8	8/8	8/8	8/8

Test 3 Rat No. 379-386		1 Hour	Observation After		
			2 Hours	3 Hours	4 Hours
Normal	Incidence	8/8			
Reduced Activity	Incidence		8/8	8/8	8/8
	Severity		1	1	2

Female Rats

Control 3 Rat No. 387-394		1 Hour	Observation After		
			2 Hours	3 Hours	4 Hours
Normal	Incidence	8/8	8/8	8/8	8/8

Test 3 Rat No. 395-402		1 Hour	Observation After		
			2 Hours	3 Hours	4 Hours
Normal	Incidence	8/8			
Reduced Activity	Incidence		8/8	8/8	8/8
	Severity		1	1	2

Severities: 1 = Minimal, 2 = Minor, 3 = Moderate, and 4 = Severe.

INDIVIDUAL ANIMAL CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - A.M.

Control 1

	ANIMAL #	301	302	303	304	305
DAY # 0						
CLINICAL EXAMINATION, NORMAL		N	N	N	N	N
DAY # 1						
CLINICAL EXAMINATION, NORMAL		N	N	N	N	N
INDUCED DEATH, METOFANE, EXSANGUINATION		P	P	P	P	P

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT.

INDIVIDUAL ANIMAL CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - A.M.

Test 1

	ANIMAL #	306	307	308	309	310	311	312	313	314	315
DAY # 0											
CLINICAL EXAMINATION, NORMAL		N	N	N	N	N	N	N	N	N	N
DAY # 1											
* GENERAL ACTIVITY DEPRESSED			3							4	3
HYPOTHERMIA			1							2	1
SPONTANEOUS DEATH		P		P	P	P	P	P	P		
INDUCED DEATH, METOFANE, EXSANGUINATION			P							P	P
RESPIRATORY TRACT											
* DYSPNEA			3							3	3
EYES											
PORPHYRIN TEARS			1								

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
 P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT.

TRIAGE of 8(e) Submissions

Date sent to triage: _____

NON-CAP

CAP

Submission number: 13873A

TSCA Inventory: Y N D

STUDY TYPE (circle appropriate):

Ernest Falke (E605C)

ATOX

SBTOX

SEN

CARC

Gordon Cash (E425)

ECO

AQUATO

Katherine Anitole (E613B)

RTOX/DTOX

Daljit Sawhney (E611A)

CTOX

STOX

Deborah Norris (E606)

NEUR

Elizabeth Margosches (E613C)

EPI

Michael Cimino (E611D)

GTOX

Leonard Keifer (E611C)

Metabolism/Pharmacokinetics

OTHER: _____

NOTES:

CECATS TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA: 0197-
 Submission # SEHO: 13873
 TYPE: (NT) SUPP FLWP
 SUBMITTER NAME: Eastman Chemical Company

SEQ. A

INFORMATION REQUESTED: FLWP DATE:
 0301 NO INFO REQUESTED
 0302 INFO REQUESTED (TECH)
 0303 INFO REQUESTED (VOL ACTIONS)
 0304 INFO REQUESTED (REPORTING RATIONALE)
 DISPOSITION:
 0305 REFER TO CHEMICAL SCREENING
 0306 CAP NOTICE

VOLUNTARY ACTIONS:
 0401 REACTION REPORTED
 0402 STUDY'S PLANNED DURING MEAT
 0403 MUTAGENICITY IN MURKIN 10/11/84
 0404 LABELING (TEAM 1.3)
 0405 PROCESSING/IMP. CHANGES
 0406 APP. USE DISCONTINUED
 0407 PRODUCTION DISCONTINUED
 0408 CONFIDENTIAL

SUB. DATE: 1-29-97
 OTS DATE: NS
 CRAD DATE: 3/27/97
 CHEMICAL NAME: Cyclohexanecarboxaldehyde
 CAS# 1489-69-6

INFORMATION TYPE:	L.F.C.	INFORMATION TYPE:	L.F.C.	INFORMATION TYPE:	L.F.C.	P.F.C.
0201 ONCO (HUMAN)	01 02 04	0216 EPICLIN	01 02 04	0241 IMMUNO (ANIMAL)	01 02 04	01 02 04
0202 ONCO (ANIMAL)	01 02 04	0217 HUMAN EXPOS (PROD CONTAM)	01 02 04	0242 IMMUNO (HUMAN)	01 02 04	01 02 04
0203 CELL TRANS (IN VITRO)	01 02 04	0218 HUMAN EXPOS (ACCIDENTAL)	01 02 04	0243 CHEMOPHYS PROP	01 02 04	01 02 04
0204 MUTA (IN VITRO)	01 02 04	0219 HUMAN EXPOS (MONITORING)	01 02 04	0244 CLASTO (IN VITRO)	01 02 04	01 02 04
0205 MUTA (IN VIVO)	01 02 04	0220 BIOAQUA TOX	01 02 04	0245 CLASTO (ANIMAL)	01 02 04	01 02 04
0206 REPRO/TERATO (HUMAN)	01 02 04	0221 ENV. OCCURRENCE	01 02 04	0246 CLASTO (HUMAN)	01 02 04	01 02 04
0207 REPRO/TERATO (ANIMAL)	01 02 04	0222 EMER INCI OF ENV CONTAM	01 02 04	0247 DNA DAMAGE/REPAIR	01 02 04	01 02 04
0208 NEURO (HUMAN)	01 02 04	0223 RESPONSE REQUEST DELAY	01 02 04	0248 PRODUCE/PROC	01 02 04	01 02 04
0209 NEURO (ANIMAL)	01 02 04	0224 PRODUCE/CHEM ID	01 02 04	0251 MSDS	01 02 04	01 02 04
0210 ACUTE TOX. (HUMAN)	01 02 04	0225 REPORTING RATIONALE	01 02 04	0299 OTHER	01 02 04	01 02 04
0211 CHR. TOX. (HUMAN)	01 02 04	0226 CONFIDENTIAL	01 02 04			
0212 ACUTE TOX. (ANIMAL)	01 02 04	0227 ALLERG (HUMAN)	01 02 04			
0213 SUB ACUTE TOX (ANIMAL)	01 02 04	0228 ALLERG (ANIMAL)	01 02 04			
0214 SUB CHRONIC TOX (ANIMAL)	01 02 04	0229 METAPHARMACO (ANIMAL)	01 02 04			
0215 CHRONIC TOX (ANIMAL)	01 02 04	0240 METAPHARMACO (HUMAN)	01 02 04			

IMAGE DATE: NON-CELL INVENTORY
 YES
 NO
 IN ITAMIN

CAS# R
 YES (DROP/PREFER)
 NO (CONTINUE)
 LEFT R

TOXICOLOGICAL CONCERN:
 LOW
 MED
 HIGH

STATUS: R.A.T.

PRODUCTION:

1-19-97

CYCLOPROPANECARBOXALDEHYDE

1489-69-6

M - 6 Hrs
"13873A"=*M*"="SPRAGUE-DAWLEY RATS WERE EXPOSED BY INHALATION TO 0 (5/SEX) OR 1892 PPM (10/SEX) OF CYCLOPROPANECARBOXALDEHYDE (CAS# 1489-69-6) FOR 6 HOURS. SEVEN MALES AND ALL 10 FEMALES DIED IN TREATED GROUP. CLINICAL SIGNS OF TOXICITY INCLUDED REDUCED ACTIVITY, RAPID AND SHALLOW RESPIRATION, LABORED BREATHING, AND SLOWED BREATHING PRIOR TO DEATH. EXPOSURE RELATED LESIONS CONSISTED OF EOSINOPHILIC CYTOPLASMIC CHANGES AND HYPERTROPHY OF HEPATOCYTES.

M - 4 Hrs
RATS (8/SEX/GROUP) WERE ALSO EXPOSED BY INHALATION TO 0, 368, OR 1697 PPM FOR 4 HOURS. THE 4 HOUR LC50 FOR MALES AND FEMALES WAS 1395 PPM. CLINICAL SIGNS OF TOXICITY INCLUDED REDUCED ACTIVITY, WEIGHT LOSS, REDUCED WEIGHT GAIN, ABNORMAL GAIT, PORPHYRIN DISCHARGES AROUND THE NOSE OR EYES, EXCESSIVE TEARING, PARTIALLY CLOSED EYES, DEHYDRATION, DECREASED FECAL VOLUME, SOFTENED FECES, URINE AND FECES STAINED INGUINAL COATS, AND/OR UNKEMPT HAIRCOATS. EXPOSURE RELATED LESIONS CONSISTED OF EOSINOPHILIC CYTOPLASMIC CHANGES AND HYPERTROPHY OF HEPATOCYTES."