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January 6, 1993

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93 JAN 12 AM 8:10  
U.S. Department of Justice

Attn: 8(e) Coordinator

Re: Union Carbide Corporation's TSCA §8(e) Submission of July 21, 1992  
Concerning Triethylene Glycol (CASRN 112-27-6).

Dear Sir or Madam:

As a follow-up to the above-noted submission concerning triethylene glycol (CASRN 112-27-6), Union Carbide Corporation ("Union Carbide") herewith submits the following report.

"Triethylene Glycol: Nine-Day Aerosol Inhalation Study in Rats", Bushy Run Research Center, BRRC Report 91U0027, December 14, 1992 (only the first 72 pages of this report is enclosed; the remainder is available on request).

In the attached report the term "Confidential" may appear. This precautionary statement was for internal use at the time of issuance of this report. Confidentiality is hereby waived for purposes of the needs of the Agency in assessing health and safety information. The Agency is advised, however, that the publication rights to the contained information are the property of Union Carbide.

Please contact the undersigned with questions, if any, at 203/794-5230.

Very truly yours,

William C. Kuryla, Ph.D.  
Associate Director  
Product Safety

WCK/cr  
Attachment

73 pgs.

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## BUSHY RUN RESEARCH CENTER

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### STUDY TITLE

Triethylene Glycol:  
Nine-Day Aerosol Inhalation Study in Rats

### TEST SUBSTANCE

Triethylene Glycol (TEG)

### DATA REQUIREMENT

Not Applicable

### AUTHORS

J. D. Sun and W. J. Kintigh

### STUDY COMPLETION DATE

December 14, 1992

### PERFORMING LABORATORY

Bushy Run Research Center (BRRC)  
Union Carbide Chemicals and  
Plastics Company Inc. (UCC&P)  
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### LABORATORY PROJECT ID

91U0027

### SPONSOR

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Page 1 of 328

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Triethylene Glycol: Nine-Day Aerosol Inhalation Study in Rats

CONFIDENTIALITY STATEMENT

This report is Union Carbide Corporation Business Confidential and is not to be released outside of the Corporation without the written consent of the Sponsor.

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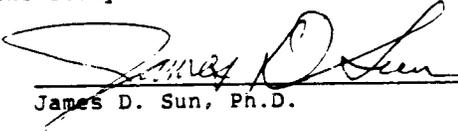
Triethylene Glycol: Nine-Day Aerosol Inhalation Study in Rats

COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

This study meets the requirements of the following Good Laboratory Practice Standards: Toxic Substances Control Act (TSCA), 40 CFR Part 792 with exceptions. The exceptions are:

1. The Study Director had no knowledge of the procedures used for the chemical analyses for interfering contaminants in the water conducted by the supplier, the NUS Corporation, Materials Engineering and Testing Co., and Lancaster Laboratories, Inc. or procedures used for diet analysis by Agway Inc.
2. Test animals for this study arrived before an approved protocol was available. During this interim, however, no critical study data were collected and BRC Standard Operating Procedures for animal receipt and housing were followed. Therefore, this event is not expected to affect the integrity of the study results.

Study Director:

  
James D. Sun, Ph.D.

12-11-92  
Date

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**Triethylene Glycol: Nine-Day Aerosol Inhalation Study in Rats**SUMMARY

Four groups, each consisting of 10 Sprague Dawley® rats per sex, were exposed to an aerosol of triethylene glycol (TEG) (CAS No. 112-27-6) at target concentrations of 0 (control), 500, 2000 and 5000 mg/m<sup>3</sup> for 6 hours per day for 9 exposures during a 2-week period. An additional 5 animals per sex were added to the high exposure concentration and control groups for planned postexposure recovery observations. Control animals were exposed to filtered air only. For the target concentrations of 500, 2000, and 5000 mg/m<sup>3</sup>, mean analytical exposure concentrations (± SD) were determined to be 494 (± 14.2), 2011 (± 94.4) and 4824 (± 182.9) mg/m<sup>3</sup>, respectively. A mean mass median aerodynamic diameter (MMAD) for all 3 exposure groups was 2.48 microns with a mean geometric standard deviation (G<sub>g</sub>) of 1.6. Determinants of toxic effects were clinical observations, ophthalmic examinations, body and organ weights, hematologic and serum clinical chemistry evaluations, urinalysis, and macroscopic and microscopic evaluations.

For all TEG-exposed rats, exposure-related clinical observations occurred. At 4824 mg/m<sup>3</sup>, clinical observations included ataxia, prostration, unkempt fur, labored respiration (males only), ocular discharge, swollen periocular tissue, perinasal and periocular encrustation, and blepharospasm in both sexes unless noted otherwise. At 494 and 2011 mg/m<sup>3</sup>, there were swollen periocular tissues and perinasal encrustations. Statistically significant decreases in body weights and body weight gains were also seen in animals exposed to 4824 mg/m<sup>3</sup> of TEG. At 2011 mg/m<sup>3</sup>, there were statistically significant decreases in body weights in males from Exposure Day 5. Females from the 2011 mg/m<sup>3</sup> exposure concentration group and rats of both sexes from the 494 mg/m<sup>3</sup> exposure concentration group had body weights and body weight gains that were not significantly different from the controls. The most notable gross findings from TEG-exposed rats were unkempt fur, swollen eyelids with periocular and perinasal discharge and crusting, and multifocal or diffuse color change due to congestion and/or hemorrhage of various organs and tissues.

Rats from the 5000 mg/m<sup>3</sup> exposure concentration group all died or were sacrificed in a moribund condition on or before the beginning of Exposure Day 5. Therefore, only limited data were obtained from these animals. In addition to the gross pathology findings noted above, hyperinflation of the lungs (failure of lungs to collapse when the chest cavity was opened) was observed during necropsy in 5 males and 10 females from the 5000 mg/m<sup>3</sup> exposure concentration group. Ocular opacities were also seen in 5 males and 5 females from this exposure group. The most prominent microscopic lesions found in the 5000 mg/m<sup>3</sup> TEG-exposed rats which died or were sacrificed moribund involved congestion and, occasionally, hemorrhage of many organs and tissues. The pituitary, nasal mucosa, brain, and lungs were affected in many of the rats of both sexes. Congestion of the kidneys and hemorrhage of the thymus were also relatively common in the females.

For TEG-exposed rats that survived the exposure regimen, food consumption was statistically significantly increased in an exposure concentration-related fashion for females only at 494 and 2011 mg/m<sup>3</sup>. Water consumption was statistically significantly increased in both sexes at 2011 mg/m<sup>3</sup> and in females at 494 mg/m<sup>3</sup>. The only statistically significant hematological

effects were seen in females from the 2011 mg/m<sup>3</sup> group, and included slight increases in erythrocyte count, and slight decreases in mean corpuscular volume. Notable clinical chemistry findings were increased activities of alanine aminotransferase at 2011 mg/m<sup>3</sup> and alkaline phosphatase at 494 and 2011 mg/m<sup>3</sup>, and slight increases in blood urea nitrogen and inorganic phosphorous in females from the 494 and 2011 mg/m<sup>3</sup> exposure concentration groups. Urinalysis showed statistically significant increases in urine volume and decreased osmolality, pH, and N-acetyl-β-D-glucosaminidase activity at 2011 mg/m<sup>3</sup>, with a trend for changes in these values at 494 mg/m<sup>3</sup>. Absolute liver and kidney weights were increased in females from the 2011 mg/m<sup>3</sup> exposure concentration group and increased relative (to body weight) weights were measured for both organs at 2011 mg/m<sup>3</sup>. There was no histological evidence of liver or kidney injury noted in animals from any exposure concentration group. The only microscopic lesion seen was minimal to mild alveolar histiocytosis, which was in excess of that for the controls at 2011 mg/m<sup>3</sup>, but not at 494 mg/m<sup>3</sup>. The above findings indicate impairment of liver function, but without morphological evidence of organ injury.

This study shows that daily inhalation exposures to TEG aerosol at or above concentrations of 5000 mg/m<sup>3</sup> were fatally toxic to rats within 5 days. Similar exposures for up to 9 days at or below concentrations of 2000 mg/m<sup>3</sup>, however, did not result in life threatening signs of toxic effects. The urinary changes and associated increase in water consumption are consistent with an osmotic diuresis resulting from the excretion of absorbed TEG and its metabolites. There were no consistent findings suggestive of renal injury. The increased serum enzyme activities suggest minimal hepatotoxicity, which, for this study, has a threshold exposure concentration for this toxic response that is near to 494 mg/m<sup>3</sup>.

### OBJECTIVE

The objective of this study was to determine and evaluate the toxic effects in rats which may occur from 9 days of repeated, whole body, inhalation exposure to TEG aerosol.

### BACKGROUND INFORMATION

Triethylene glycol (TEG) is most commonly used as a solvent and plasticizer for the manufacture of vinyl, polyester, and polyurethane resins. Because of its wide use in industry, there is a potential for worker exposure to this compound by inhalation. An acute inhalation toxicology study was previously performed at BRRC (Report No. 53-139) in which Sprague Dawley® albino rats were exposed once to 5200 mg/m<sup>3</sup> of TEG aerosol for 4 hours. Clinical signs observed on the day of exposure included periocular wetness, blepharospasm, wet (oily) fur, and an absence of toe and tail pinch reflexes. During the 14-day recovery period, unkempt fur was the only clinical sign observed. No mortalities occurred during this study and no gross lesions were found in animals sacrificed after the 14-day recovery period. The results from this study indicate that inhaled TEG aerosol has a relatively low acute toxicity and that the LC<sub>50</sub> value for TEG aerosol in Sprague Dawley® rats is greater than 5200 mg/m<sup>3</sup>.

### TARGET CONCENTRATION SELECTION

Target TEG aerosol concentrations of 0 (control), 500, 2000, and 5000 mg/m<sup>3</sup> were selected by the Sponsor based on the results from the acute study.

### MATERIALS AND METHODS

The protocol, any protocol amendments and any protocol deviations (BRRC Project Number 90-22-44008) detailing the design and conduct of this study are presented in Appendix 12.

#### Test Substance

Three 5-gallon containers of TEG, Lot TS-2300128, Tk-706, CAS No. 112-27-6, were received on January 30, 1991, from UCC&P, Texas City, TX, and assigned BRRC Sample No. 54-19 A, B, and C. The test substance was a transparent, white liquid with a mild odor. The test substance was stored under normal conditions and kept in Room 137. The purity of the test substance was determined by the GLP Analytical Skills Center at the UCC&P South Charleston, WV, Technical Center to be approximately 99.9%; their report is included in Appendix 1. A reserve sample was taken and stored in the BRRC Archives. Pertinent chemical and physical properties of TEG are listed in Appendix 1.

#### Animals and Husbandry

Sixty-five male and 65 female Sprague Dawley® rats were received on February 10, 1991, from Harlan Sprague Dawley, Inc. (Indianapolis, IN). They were designated by the supplier to be approximately 34 days old (birth date was recorded as January 7, 1991) and to weigh 100-124 g and 75-99 g for the male and female rats, respectively, upon arrival. The females were nulliparous and non-pregnant.

Animals were housed in Room 154 from arrival to termination of the study except during exposures. Within 2 days of receipt, the animals were examined by the BRRC Clinical Veterinarian, and representative animals were subjected to a pretest health screen including full necropsy and histologic examination of selected tissues including respiratory organs and serum viral antibody analysis. Based on the results of these data, the Clinical Veterinarian indicated that the animals were in good health and suitable for use on this study.

All animals were assigned a unique number and identified by cage tags. Animals considered at risk for tail breakage were also identified by a tail tattooing procedure using Animal Identification and Marking System, AIMS® Inc., Piscataway, NJ. Animals selected for the pretest health screen were identified by toe-clipping procedures after blood collection.

The animals were housed individually in stainless steel, wire-mesh cages (15 cm x 22 cm x 18 cm). DACB® (Deotized Animal Cage Board; Shepherd Specialty Papers, Inc.) was placed under each cage and changed regularly. An automatic timer was set to provide fluorescent lighting for a 12-hour photoperiod starting at 5 a.m. Temperature and relative humidity were recorded continuously (Cole-Parmer Hygrothermograph® Seven-Day Continuous Recorder, Model No. 8368-00, Cole-Parmer Instrument Co., Chicago, IL). Temperature was routinely maintained at 64-79°F; relative humidity was routinely maintained at 40-70%. Any minor exceptions to these specified ranges were noted in the raw data.

Tap water (Municipal Authority of Westmoreland County, Greensburg, PA) was available ad libitum except during exposures. Water was provided by an automatic watering system with demand control valves mounted on each rack, except during the water consumption period. Water analyses were provided by the supplier, the NUS Corporation, Materials Engineering and Testing Co., and Lancaster Laboratories, Inc. at regular intervals. EPA standards for maximum levels of contaminants were not exceeded. Powdered, certified AGWAY® PROLAB® Animal Diet Rat, Mouse, Hamster 3200 (Agway Inc.) was available ad libitum except during exposures. Analyses for chemical composition and possible contaminants of each feed lot were performed by Agway Inc., and the results are located in the BRRC Archives.

#### Animal Acclimation

The acclimation period was 3 weeks for the animals. During this period, the animals were weighed 3 times at scheduled intervals. Detailed clinical observations were conducted in conjunction with body weight measurements. Cage-side animal observations were conducted at least once daily, and an additional mortality check was conducted each day (morning). The animals were examined approximately 2 weeks prior to the initiation of the study by a Clinical Veterinarian. Animals considered unacceptable for the study, based on the clinical signs, ophthalmic examination, body weights, or body weight gains, were rejected. The fate of rejected animals and the reasons for rejection were documented in the study record.

Study Organization

Animals were assigned to 3 exposure groups and a control group using a nonstratified randomization procedure based on body weight. At the time of group assignment, only animals with body weights within two standard deviations of the population mean for each sex were included. On the morning prior to the first exposure, only animals with body weights  $\pm 20\%$  of the mean body weight for each sex were retained for the study. The following table summarizes the organization of the study.

Group	Number of Animals		Target Concentration (mg/m <sup>3</sup> )
	Male	Female	
Control*	15	15	0
Low	10	10	500
Intermediate	10	10	2000
High*	15	15	5000

\*Five animals/sex of the control and high concentration groups were assigned to a 2-week recovery group.

The exposures began on March 4, 1991 (Study Day 1). Animals were exposed for 6 hours per day for 5 consecutive days. After 2 days without exposure, the animals were exposed for an additional 4 consecutive days. The 6-hour exposure period for each exposure day was defined as the time when the aerosol generation system was turned on and subsequently turned off. All surviving animals were sacrificed on March 15, 1991, after a total of 9 exposures.

Administration of Test SubstanceInhalation Chamber Description and Operation

The inhalation chambers (Young & Berthe, Cincinnati, OH) used for this study were located in Room 137. The chambers, constructed from stainless steel with glass windows for animal observation, were rectangular (132 x 85 x 91 cm) in shape with a pyramidal top and bottom. The volume of each chamber was approximately 1330 liters, and the airflow rate was approximately 300 liters/minute (13-14 air changes per hour). A Dwyer Magnehelic® pressure gauge (Dwyer Instruments, Inc., Michigan City, IN) was used to monitor chamber airflow. The theoretically-derived time required for each chamber to reach 99% of the target concentration ( $t_{99}$ ) was calculated to be 20 minutes. Chamber temperature and relative humidity were recorded using a Fisherbrand® dial type thermometer (Fisher Scientific, Pittsburgh, PA) and an Airguide humidity indicator (Airguide Instrument Co., Chicago, IL), respectively. Temperature and relative humidity measurements were recorded approximately 2 times each hour of exposure.

### **Aerosol Generation**

Liquid TEG was metered from a piston pump (RPG-6-1/8" - 500 mg/m<sup>3</sup>; RPG-20-1/4" - 2000 mg/m<sup>3</sup>; RPG-20-3/8" - 5000 mg/m<sup>3</sup>; Fluid Metering, Inc., Oyster Bay, NY) into an atomizer (Spraying Systems Co., Wheaton, IL) fitted with a No. 1850 liquid nozzle and a No. 64 air nozzle. The atomizer was inserted into the top of the inhalation chamber turret where the liquid aerosol was dispersed throughout the chamber & filtered chamber supply air. The operating pressure of the atomizer was 20 psi.

### **Chamber Atmosphere Measurements**

Chamber concentrations of TEG were analyzed by gravimetric methods. Six samples were obtained from the TEG aerosol exposure chambers each day. The sample flowrates were 4.25, 1.81, and 0.81 liters/minute for the 100, 2000, and 5000 mg/m<sup>3</sup> target concentrations, respectively. The sample collection time ranged from 10 to 20 minutes. A glass fiber filter (#7 mm; type A/E, Gelman Instrument Co., Ann Arbor, MI) used to collect the TEG aerosol was connected to a dry gas meter (Rockwell International, Pittsburgh, PA), a critical orifice, and a vacuum pump (Terracon Corp., Waltham, MA). The nominal concentration was calculated by dividing the total amount of TEG used to generate the exposure atmosphere by the total volume of air delivered to each chamber.

The particle size distribution was measured using a TSI Particle Aerodynamic Sizer Model APS 3300 (TSI Incorporated, St. Paul, MN). The dilution ratio was 100:1, and the sample collection time was 30 seconds for all target concentrations. These determinations were made at least 2 times per week per chamber. The data collected were analyzed by the method of Hinds (1982) to obtain the MMAD and the  $\sigma_g$ .

### **Observations and Measurements**

#### ***In-Life Evaluations***

All animals were individually observed for signs of toxic effects except during the exposures. During the exposures, observations were recorded on a group basis. Preceding and following each exposure, observations were recorded for animals exhibiting overt clinical signs. At the time of body weight measurements and just preceding sacrifice, detailed observations were performed on all animals. On nonexposure days, the animals were observed once a day for overt clinical signs and twice a day for mortality.

Body weight data were collected for all animals on the morning prior to initiation of the first exposure (denoted as Day 1 of the study), preceding the second, fifth, sixth, and seventh exposures, and immediately preceding sacrifice.

Food and water consumption measurements were obtained over an approximate 1 hour period following the eighth exposure of male rats and the ninth exposure of female rats (excluding the animals designated for the 2-week recovery period). All animals were housed individually in Nalgene® metabolic cages with stainless steel, wire-mesh bottoms, approximately 20 cm diameter x 11 cm high (Nalge Company, Rochester, NY) during the measurement period.

Prior to the first exposure, the eyes of all rats were examined by a Veterinary Ophthalmologist using indirect ophthalmoscopy following dilation of the pupils with MYDRIACYL® 1% (tropicamide 1.0%) Ophthalmic Solution. Following the ninth exposure, the eyes of all surviving rats (excluding the animals designated for the 2-week recovery period) were again examined by a Veterinary Ophthalmologist by the procedure previously mentioned. A complete description of the ophthalmic examination procedures is included in Appendix 4.

#### *Clinical Pathology Evaluation*

Prior to sacrifice, blood was collected from all rats (excluding animals designated for the 2-week recovery period) for hematology and clinical chemistry determinations. Blood was obtained from the orbital sinuses of methoxyflurane-anesthetized animals. Food was removed from the animal cages prior to the start of the blood collection period, but water was supplied ad libitum.

Following the eighth exposure of male rats and following the ninth exposure of female rats, urine was collected from all surviving rats (excluding animals designated for the 2-week recovery period) while the rats were in the metabolism cages (see Food and Water Consumption). Food and water were available ad libitum. Two or three thymol crystals were added as a preservative to the collection tubes.

The following parameters were measured or calculated:

#### Hematology

hematocrit	mean corpuscular hemoglobin concentration (MCHC)
hemoglobin	total leukocyte count
erythrocyte count	differential leukocyte count
mean corpuscular volume (MCV)	platelet count
mean corpuscular hemoglobin (MCH)	reticulocyte count

#### Clinical Chemistry

glucose	sodium
urea nitrogen	potassium
creatinine	chloride
total protein	aspartate aminotransferase (AST)
albumin	alanine aminotransferase (ALT)
globulin (calculated)	creatine kinase (CK)
total bilirubin	with isoenzymes
direct bilirubin	lactate dehydrogenase (LDH)
indirect bilirubin	with isoenzymes
calcium	gamma-glutamyl transferase (GGT)
phosphorus	sorbitol dehydrogenase (SDH)
	alkaline phosphatase (ALK)

Urinalysis and Urine Chemistry

osmolality	blood
pH	urobilinogen
protein	total volume
glucose	color and appearance
ketones	microscopic elements
bilirubin	N-acetyl-b-D-glucosaminidase (NAG)

The blood smears for the differential leukocyte counts and reticulocyte counts were prepared for all groups, but were evaluated only for the control and highest exposure concentration group that survived the exposure regimen. Details for clinical pathology procedures are included in Appendix 3.

Anatomic Pathology Evaluations

At the end of exposures, all rats (except animals designated for the 2-week recovery period) were anesthetized with methoxyflurane and euthanized by exsanguination via the brachial blood vessels. A complete necropsy was performed on all animals (except animals designated for the 2-week recovery period). The liver, spleen, brain, lungs, kidneys, adrenals, and testes (males) were weighed for all sacrificed animals. The following tissues were collected and saved in 10% neutral buffered formalin:

<u>gross lesions</u>	<u>kidneys</u>
<u>lungs</u>	<u>adrenals</u>
<u>nasal turbinates</u>	testes
(four sections)	ovaries
brain	lymph node
thymus	(submandibular)
<u>trachea</u>	eyes
<u>heart</u>	<u>bladder</u>
<u>larynx</u>	<u>spinal cord</u>
<u>liver</u>	<u>sciatic nerve</u>
spleen	<u>tibial nerve</u>

Tails were also saved for identification purposes. Underlined tissues for 10 rats per sex from the control group and 2000 mg/m<sup>3</sup> exposure concentration group and from all rats (15 per sex) from the 5000 mg/m<sup>3</sup> exposure concentration group were processed histologically and examined microscopically. In addition, the respiratory tract (nasal cavities, trachea, larynx, and lungs) was also examined from the 500 mg/m<sup>3</sup> exposure concentration group rats. Details of the anatomic pathology procedures are included in Appendix 2.

Data Analyses

The data for continuous, parametric variables were intercompared for the exposure and control groups by Levene's test for homogeneity of variances, by analysis of variance, and by t-tests. The t-test was used, if the analysis of variance was significant, to delineate which groups differed from the control group. If Levene's test indicated homogeneous variances, the groups were compared by an analysis of variance for equal variances followed, when appropriate, by pooled variance t-tests. If Levene's test indicated

heterogeneous variances, the groups were compared by an analysis of variance for unequal variance followed, when appropriate, by separate variance t-tests. Frequency data were compared using Fisher's exact tests. All statistical tests, except the frequency comparisons, were performed using BMDP Statistical Software (Dixon, 1990). The frequency data tests are described in Biometry (Sokal and Rohlf, 1981). The probability value of  $p < 0.05$  (two-tailed) was used as the critical level of significance for all tests. Details of the statistical procedures for hematologic and serum clinical chemistry parameters can be found in Appendix 3.

Various models of calculators, computers, and computer programs may have been used to analyze data for this study. Since various models round or truncate numbers differently, values in some tables may differ slightly from those in other tables or from independently calculated data. The integrity of the study and interpretation of the data were unaffected by these differences.

#### RETENTION OF RECORDS

The final report, tissue specimens, nonperishable slides, and all raw data are retained in the Archives of BRRC for future reference.

#### RESULTS AND DISCUSSION

All references of differences in group mean values in the following text refer to comparisons between the exposure group and the control group, unless otherwise noted. Repeated reference to the control will not be made in order to simplify the text.

##### Chamber Atmosphere

Control animals were exposed to filtered air only. For the target concentrations of 500, 2000, and 5000 mg/m<sup>3</sup>, mean gravimetric exposure concentrations ( $\pm$  SD) were determined to be 494 ( $\pm$  14.2), 2011 ( $\pm$  94.4) and 4824 ( $\pm$  182.9) mg/m<sup>3</sup>, respectively. The MMAD for the 500, 2000, and 5000 mg/m<sup>3</sup> exposures was 1.92, 2.57, and 2.94 microns, respectively, with a G<sub>0</sub> of 1.56, 1.65, and 1.70, respectively. Details of these results are presented in Appendix 1.

Among exposure groups, the daily mean chamber temperature and relative humidity ranged from 20.5-24.2°C and 39.9-54.9%, respectively. The chamber temperature and humidity data are presented in Appendix 1.

##### Clinical Observations and Mortality

Tables 1 and 2 present summaries of the clinical observations for male and female rats, respectively. Individual animal clinical observation data are included in Appendix 5.

All rats in the 5000 mg/m<sup>3</sup> exposure group died or were sacrificed in a moribund condition on or before the end of exposure day 5. Exposure-related clinical observations included ataxia, prostration, unkempt fur, labored respiration (males only), ocular discharge, swollen periorcular tissue, perinasal and periorcular encrustation, and blepharospasm in both sexes from the 5000 mg/m<sup>3</sup> exposure concentration group. The only significant signs of toxicity in rats from the 500 and 2000 mg/m<sup>3</sup> exposure concentration groups

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were periocular swelling and perinasal encrustation.

#### Body Weights

Summaries of absolute body weights and body weight gains for males are presented in Tables 3 and 4, respectively. Corresponding values for females are presented in Tables 5 and 6. Individual animal body weight data are included in Appendix 6.

Statistically significant decreases in body weights were seen in male rats exposed to 2000 and 5000 mg/m<sup>3</sup> of TEG aerosol. Significant decreases in body weight gains were also seen in male rats exposed to 5000 mg/m<sup>3</sup> TEG. Female rats also showed statistically significant decreases in body weights and body weight gains, but only in the 5000 mg/m<sup>3</sup> exposure concentration group.

#### Food and Water Consumption

Summaries of food consumption data for males and females are presented in Tables 7 and 8, respectively. Summaries of water consumption data for males and females are presented in Tables 9 and 10, respectively. Individual animal food and water consumption data are included in Appendix 7 and 8, respectively.

Since the highest exposure concentration of TEG (5000 mg/m<sup>3</sup>) killed all the rats before the end of exposures, food and water consumption measurements were obtained only on the remaining exposures group of animals and controls. Statistically significant increases in food consumption were noted for females from the 500 and 2000 mg/m<sup>3</sup> exposure concentration groups, but not in any of the male rats exposed to TEG. Water consumption was significantly increased in females exposed to 500 and 2000 mg/m<sup>3</sup> TEG and in male rats exposed to 2000 mg/m<sup>3</sup> TEG.

#### Ophthalmic Examinations

Details of the results and discussion of the ophthalmic examination are presented in Appendix 4. Individual ophthalmic data are included in Appendix 11.

No ophthalmic lesions that could be attributed to the TEG aerosol exposure were noted in rats that survived the exposure regimen.

#### Clinical Pathology Evaluations

Summaries of hematology measurements are presented in Tables 11 and 12 for males and females sacrificed immediately after the exposure regimen, respectively. Summaries of clinical chemistry measurements are presented in Tables 13 and 14 for males and females, respectively. Summaries of special chemistry determinations for male and female rats are presented in Tables 15 and 16, respectively. Summaries of urine N-acetyl-b-D-glucosaminidase (NAG) determinations for male and female rats are presented in Tables 17 and 18, respectively. Summaries of urinalysis measurements for males and females are presented in Tables 19 and 20, respectively. Individual clinical pathology data are included in Appendix 10. Detailed results and discussion of the clinical pathology findings are included in Appendix 3.

Since all the animals in the 5000 mg/m<sup>3</sup> exposure concentration group died before the end of the exposures, blood samples were only collected from the two remaining exposure groups and control rats. Male rats did not show statistically significant changes in the hematology parameters measured. Female rats in the 2000 mg/m<sup>3</sup> exposure group had a significant increase in total erythrocyte counts with a significant decrease in MCV.

Since all the animals in the 5000 mg/m<sup>3</sup> exposure concentration group died before the end of the exposures, blood samples were only collected from the two remaining exposure groups and control rats. The only statistically significant changes in male rats were an increase in ALT activity and a decrease in serum creatinine in the 2000 mg/m<sup>3</sup> exposure concentration group. Female rats from the 2000 mg/m<sup>3</sup> exposure concentration group showed statistically significant increases in urea nitrogen, ALT, ALK, and inorganic phosphorus and decreases in glucose, creatinine, and chloride. Females from the 500 mg/m<sup>3</sup> exposure concentration group had significant increases in ALK activity, inorganic phosphorus, and total protein.

Since all the animals in the 5000 mg/m<sup>3</sup> exposure concentration group died before the end of the exposures, urine samples were only collected from the 2 remaining exposure groups and control rats. Male rats from the 2000 mg/m<sup>3</sup> exposure concentration group had statistically significant increases in total urine volume and significant decreases in urine osmolality, pH, and NAG activity. However, the decreased NAG activity was probably due to dilution of the enzyme because of the increased urine volume, since the total NAG enzyme excreted was actually slightly elevated in both male and female rats from the 2000 mg/m<sup>3</sup> exposure concentration group. Female rats from the 2000 mg/m<sup>3</sup> exposure concentration group had statistically significant increases in total urine volume, and decreases in pH.

#### Organ Weights, Necropsy Observations, and Microscopic Diagnoses

The mean absolute and relative (as percentages of body and brain weights) organ weights are presented in Tables 21 to 23 for males and Tables 24 to 26 for females sacrificed after the exposure regimen. Summaries of the necropsy findings for males and females sacrificed at the end of the exposure regimen are presented in Tables 27 and 29, respectively. Summaries of the necropsy findings on dead or sacrificed moribund male and female rats are presented in Tables 28 and 30, respectively. Summaries of the histopathology findings are presented in Tables 31 and 32 and Tables 33 and 34 for the males and females, respectively. Individual anatomic pathology data are included in Appendix 9. Detailed results and discussion of the necropsy and histopathology findings are included in Appendix 2.

The only statistically significant changes observed for male rats were increases in liver and kidney weights relative to body weights in the 2000 mg/m<sup>3</sup> or the 500 and 2000 mg/m<sup>3</sup> exposure concentration groups, respectively. Statistically significant changes in female rats included increases in absolute weights and in weights relative to body and brain weights for liver and kidneys from animals in the 2000 mg/m<sup>3</sup> exposure concentration group. Female rats exposed to 2000 mg/m<sup>3</sup> TEG also showed a significant increase in adrenal gland weight relative to brain weight.

The most notable gross findings from TEG-exposed rats for both those

The most notable gross findings from TEG-exposed rats for both those sacrificed and those which died during the study were unkempt fur, swollen eyelids with periocular and perinasal discharge and crusting, and multifocal or diffuse color change due to congestion and/or hemorrhage of various organs and tissues. Hyperinflation of the lungs (failure of lungs to collapse when chest cavity was opened) was observed in 5 males and 10 females from the 5000 mg/m<sup>3</sup> exposure concentration group. Ocular opacities were also seen in 5 males and 5 females from this latter exposure group.

The most prominent microscopic lesions found in the 5000 mg/m<sup>3</sup> TEG-exposed rats which died or were sacrificed moribund involved congestion and, occasionally, hemorrhage of the pituitary, nasal cavities, brain, and lungs of both sexes. Congestion of the kidneys and hemorrhage of the thymus were also relatively common in the females.

The only significant microscopic lesion seen was in female rats sacrificed after the 2000 mg/m<sup>3</sup> exposure regimen and was limited to minimal to mild alveolar histiocytosis. Similar findings were seen in both sexes of rats exposed to 500 mg/m<sup>3</sup> TEG, but these latter findings were not significant.

#### CONCLUSIONS

Exposure of rats to a respirable aerosol of TEG at a mean analytical concentration of 4924 mg/m<sup>3</sup> for 6 hours/day resulted in mortality after 2 to 4 days of exposures. Clinical signs of toxicity at this exposure concentration included ataxia, prostration, unkempt fur, labored breathing (males only), ocular discharge, swollen periocular tissue, perinasal and periocular encrustation, and blepharospasm in both sexes unless otherwise noted. Exposure-related decreases in body weights and body weight gains were also noted for both sexes. Significant increases in food consumption were measured in females, but not male rats, while water consumption increases were noted for both sexes.

No statistically significant differences in hematology parameters were seen in male rats. Female rats from the 2000 mg/m<sup>3</sup> exposure concentration group had statistically significant increases in total erythrocyte counts with a decrease in the MCV value. However, these rats may have had a slight water imbalance, which caused the hemoconcentration of these cells in the peripheral blood. Clinical chemistry findings showed significant increases in ALT in both sexes, indicating a slight exposure-related effect on the liver. Serum ALK was also elevated, suggesting that the liver was injured. However, microscopic evidence of liver damage was not seen. Decreased serum creatinine values in TEG-exposed animals were probably due to the reduced body weight and loss of muscle mass. The phosphorus increase in serum was also attributed to weight loss or possibly fluid loss due to kidney damage. However, there were no other consistent biochemical indications of renal injury. Also, kidney damage was not seen histopathologically. The increased serum protein was not considered to be biologically significant because a similar increase was not seen in the higher exposure group. The decrease in serum chloride was not considered to be biologically significant because the decrease was so small. No conclusion could be made regarding the increased serum glucose, because the rats were not fasted prior to measurements.

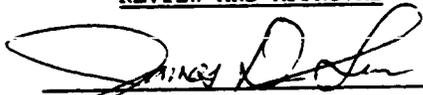
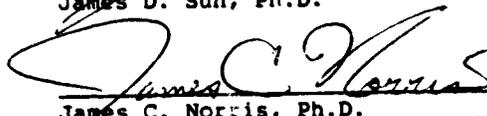
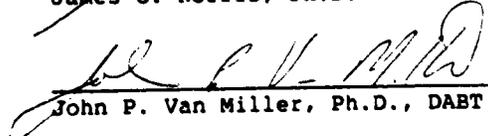
Statistically significant changes were seen in several of the urinalysis measurements (total volume, NAG activity, osmolality, and pH). However, these

data, taken together with the increased water consumption and the lack of microscopic findings in the kidneys, indicate a water overload and dilutional effect of the increased water consumption and urine output instead of a toxic effect on kidneys. This may have been due to an osmotic diuresis resulting from the excretion of absorbed TEG and its metabolites.

In keeping with the clinical pathology and urinalysis findings, significant increases in liver and kidney weights were seen, again suggesting that these organs may be target tissues for TEG exposures. These increases were more evident in females than males. Male rats showed such increases only when expressed as weights relative to body weights. Female rats had significantly increased liver and kidney weights both as absolute weights and as weights relative to body and brain weights. Female rats also had increased adrenal gland weights relative to brain weights. However, histopathological examinations did not find evidence of adrenal gland damage. The only significant microscopic finding in female rats from the 2000 mg/m<sup>3</sup> exposure group was minimal to mild alveolar histiocytosis in the lungs. Similar findings were present in animals from the 500 mg/m<sup>3</sup> exposure concentration group of rats of both sexes, but these were not statistically different from controls.

In conclusion, inhalation exposures to 5000 mg/m<sup>3</sup> of TEG aerosol for 6 hours/day produced 100% mortality within 5 days. At lower exposure concentrations over the course of 9 daily exposures, gross evidence of toxicity included periorcular and perinasal irritation in both sexes exposed to 2000 mg/m<sup>3</sup> and in males at 500 mg/m<sup>3</sup>. The only statistically significant microscopic finding was a minimal to mild increase in alveolar histiocytosis in female rats exposed to 2000 mg/m<sup>3</sup> TEG aerosol. Biochemical findings suggest that the liver may be a target organ for toxicity by repeated inhalation exposure to a high concentration of a respirable aerosol of TEG. Minimal effects (irritation and increased serum ALK activity) were seen at 500 mg/m<sup>3</sup>, the lowest exposure concentration tested in this study.

REVIEW AND APPROVAL

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Project Manager:	 _____ James C. Norris, Ph.D.	12/14/92 _____ Date
Director:	 _____ John P. Van Miller, Ph.D., DABT	12/14/92 _____ Date

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Additional personnel are listed in the raw data.

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TABLE 1  
 TRIETHYLENE GLYCOL: NINE-DAY AEROSOL INHALATION STUDY IN RATS  
 SUMMARY OF CLINICAL OBSERVATIONS<sup>a</sup>

CATEGORY FINDING (LOCATION)	GRADE <sup>b</sup>	TARGET CONCENTRATION (mg/m <sup>3</sup> )			5000 (DAYS)
		0 (DAYS) <sup>c</sup>	500 (DAYS)	2000 (DAYS)	
DEAD					
FOUND DEAD	P	0	0	0	8 ( 3- 5)
SACRIFICED MORIBUND	P	0	0	0	7 ( 3- 5)
SCHEDULED SACRIFICE	P	15 ( 12)	10 ( 12)	10 ( 12)	0
BEHAVIOR/CNS					
ATAXIA	P	0	0	0	8 ( 2- 4)
TREMOR	P	0	0	0	1 ( 3)
PROSTRATION	P	0	0	0	12 ( 2- 5)
BODY					
UNKEMPT	P	0	7 ( 5)	10 ( 2- 12)	15 ( 2- 5)
HUNCHED POSTURE	P	0	0	0	1 ( 2)
CARDIO-PULMONARY					
LABORED RESPIRATION	P	0	0	0	2 ( 5)
GASPING	P	0	0	0	1 ( 3)

<sup>a</sup>Number of animals exhibiting the finding at least once during the study.  
<sup>b</sup>Grades: P = present, 1 = mild, 2 = moderate, 3 = severe.  
<sup>c</sup>Earliest to latest day a finding of the specified grade was observed.

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TABLE 1 (continued)  
 TRIFTHYLENE GLYCOL: NINE-DAY AEROSOL INHALATION STUDY IN RATS  
 SUMMARY OF CLINICAL OBSERVATIONS<sup>a</sup>

CATEGORY FINDING (LOCATION)	GRADE <sup>b</sup>	MALES			
		0 (DAYS) <sup>c</sup>	TARGET CONCENTRATION (mg/m <sup>3</sup> ) 500 (DAYS)	2000 (DAYS)	5000 (DAYS)
EYES/EARS/NOSE					
OCULAR DISCHARGE(EYE-BOTH)	P 0	0	0	0	2 ( 2)
SWOLLEN PERIOCCULAR TISSUE (EYE-BOTH)	P 0	1	2	8	15
(EYE-LEFT)	P 1 ( 8- 9)	1 ( 5)	1 ( 8- 12)	6 ( 5- 12)	15 ( 2- 5)
(EYE-RIGHT)	P 0	0	1 ( 2- 12)	1 ( 5)	0
PERIOCCULAR ENCRUSTATION (EYE-BOTH)	P 0	0	0	0	4
(EYE-LEFT)	P 0	0	0	0	2 ( 2)
(EYE-RIGHT)	P 0	0	0	0	1 ( 2)
PERINASAL ENCRUSTATION	P 3 ( 2- 12)	8 ( 2- 12)	7 ( 2- 12)	1 ( 2)	
BLEPHAROSPASM (EYE-BOTH)	P 0	0	0	2	11
(EYE-LEFT)	P 0	0	0	0	1 ( 2- 5)
(EYE-RIGHT)	P 0	0	0	2 ( 2- 12)	0

<sup>a</sup>Number of animals exhibiting the finding at least once during the study.  
<sup>b</sup>Grades: P = present, 1 = mild, 2 = moderate, 3 = severe.  
<sup>c</sup>Earliest to latest day a finding of the specified grade was observed.