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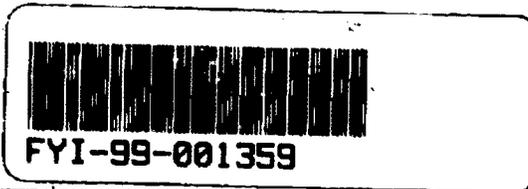
UNION CARBIDE CORPORATION
P. O. Box 670, Bound Brook, NJ 08805-0670

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Attention: 8(e) FYI Coordinator



Dear Sir or Madam:

Union Carbide Corporation, Inc. "Union Carbide" herewith submits the following report concerning isopropoxyethanol (Isopropyl CELLOSOLVE®, CASRN 109-59-1) which EPA may find of interest. Union Carbide does not consider this information to be reportable under the provisions of TSCA Section 8(e).

"Final Report: Developmental Toxicity Evaluation of Inhaled Isopropyl Cellosolve® (Ethylene Glycol Monoisopropyl Ether, EGIE) Vapor in CD® (Sprague Dawley) Rats, Union Carbide Corporation Project Report 96U1661, March 11, 1999.

This study describes a developmental toxicity study of isopropyl CELLOSOLVE® in rats. Groups of 25 timed pregnant Sprague-Dawley rats were exposed by inhalation to isopropyl CELLOSOLVE® vapor at 100, 300, or 600 ppm. Controls were exposed to purified room air. Exposure was for 6 hours per day on gestational days (gd) 6 through 15. There were no treatment-related effects on gestational parameters, including pre- or post-implantation loss, number of live fetuses per litter, fetal sex ratio or the average fetal body weight per litter. The percentage of adversely affected implants per litter, which encompassed resorptions, dead fetuses, and malformed fetuses, was significantly increased at 600 ppm. This increase was observed in the absence of any increased incidences of the component parameters. There was no treatment-related statistically or

*Union Carbide Corporation
June 25, 1999*

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biologically significant changes in the incidences of pooled external, visceral (including craniofacial), skeletal, or total fetal malformations or variations

Thus the conclusion was that exposure to isopropyl CELLUSOLVE™ by inhalation during the major period of organogenesis in Sprague-Dawley rats resulted in maternal toxicity at 300 and 600 ppm, and developmental toxicity at 600 ppm. There was no evidence of teratogenicity at any exposure concentration tested. The no-observable adverse effect level was 100 ppm for maternal toxicity and 300 ppm for developmental toxicity.

Very truly yours,



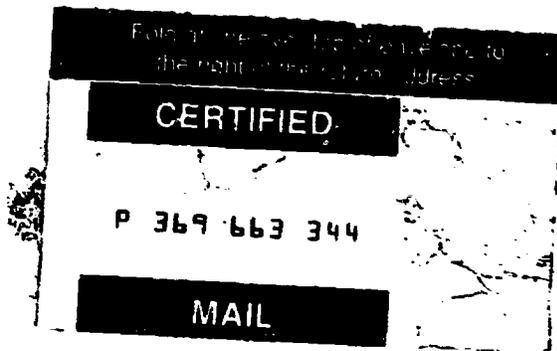
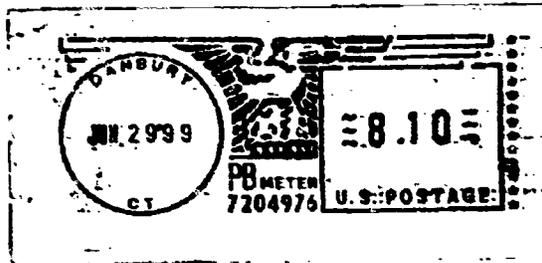
Imogene E. Treble, Ph.D.

Assistant Director

Chemical Control Compliance

Attachment

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TITLE PAGE

FINAL REPORT

TITLE: Developmental Toxicity Evaluation of Inhaled Isopropyl Cellosolve® (Ethylene Glycol Monoisopropyl Ether, EGIE) Vapor in CD² (Sprague-Dawley) Rats

AUTHORS: Rochelle W. Tyl, Ph.D., DABT, RTI
Frank Welsch, DVM, DABT, CIIT
Melissa C. Marr, B.A., LATG, RTI
Christina B. Myers, M.S., RTI

PERFORMING LABORATORIES: Chemical Industry Institute of Toxicology
6 Davis Drive
Post Office Box 12137
Research Triangle Park, NC 27709-2137

Research Triangle Institute
Center for Life Sciences and Toxicology
3040 Cornwallis Road
P. O. Box 12194
Research Triangle Park, NC 27709-2194

SPONSOR: Union Carbide Corporation
Health, Safety and Environment
39 Old Ridgebury Road
Danbury, CT 06817-0001

SPONSOR'S REPRESENTATIVE: Hon-Wing Leung, Ph.D., DABT, CIH
Associate Director of Applied Toxicology
Union Carbide Corporation

STUDY INITIATION DATE: February 26, 1997

IN-LIFE PERFORMANCE DATES: March 10-April 17, 1997

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FINAL REPORT DATE: March 11, 1999

CIIT PROTOCOL NOS.: 97006/96033

RTI PROTOCOL NOS.: RTI-572/RTI-571

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UCC Study No.: 96U1661

Developmental Toxicity Evaluation of Inhaled Isopropyl Cellosolve® (Ethylene Glycol Monoisopropyl Ether, EGIE) Vapor in CD® (Sprague-Dawley) Rats

Statement of Data Confidentiality Claim

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.

Sponsor: Union Carbide Corporation

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SIGNATURE PAGE

CIIT:

Frank Welsch, D.V.M., DABT

Frank Welsch
Study Director

11 March 1999
Date

Fred Miller, Ph.D.

Fred J. Miller
Program Manager

3/11/99
Date

Roger O. McClellan, D.V.M.,
DABT, DABVT

Roger O. McClellan
President

3/11/99
Date

RTI:

Rochelle W. Tyl, Ph.D., DABT

Rochelle W. Tyl
Co-Investigator

3/11/99
Date

F. Ivy Carroll, Ph.D.

F. Ivy Carroll
Vice President, Chemistry and Life
Sciences

3/11/99
Date

CIIT Protocol No. 97006 (Definitive Study)
RTI Protocol No.: RTI-572 (65C-6625-200)

Developmental Toxicity Evaluation of Inhaled Isopropyl Cellosolve®
(Ethylene Glycol Monoisopropyl Ether, EGIE) Vapor
in CD® (Sprague-Dawley) Rats

Sponsor: The Union Carbide Corporation

ABSTRACT

Based on information provided by a preliminary concentration range-finding study, timed-pregnant CD® (Sprague-Dawley) rats were exposed to the test chemical, ethylene glycol monoisopropyl ether (EGIE), as a vapor for approximately six hours per day for ten consecutive days, on gestational days (gd) 6 through 15 at target concentrations of 0, 100, 300 or 600 ppm. There were 25 sperm-positive females per group. Clinical observations were taken daily, except during the exposure period when they were made at least twice daily, immediately before and after each daily exposure. Maternal body weights were taken in the morning on gd 0, 6, 9, 12, 15, 18, and 20. Feed consumption was measured for the intervals gd 0-6, 6-9, 9-12, 12-15, 15-18, and 18-20. At scheduled sacrifice on gd 20 the dams were evaluated for body, liver, spleen, thymus, and gravid uterine weights. Ovarian corpora lutea were counted and the status of uterine implantation sites (*i.e.*, resorptions, dead fetuses, live fetuses) was recorded. All fetuses were dissected from the uterus, counted, weighed, sexed, and examined for external abnormalities. Approximately one-half of the fetuses in each litter were examined for visceral malformations and variations. These fetuses were decapitated and the heads fixed in Bouin's solution; serial free-hand sections of the heads were examined for soft tissue craniofacial malformations and variations. All fetuses in each litter were eviscerated, fixed in alcohol, and stained with alizarin red S/alcian blue. Intact fetuses (approximately one-half per litter, the ones not examined visceraally or decapitated) were examined for skeletal malformations and variations.

Pregnancy rates were high and approximately equivalent across all groups (92.0-100.0%). Six females (two each at 0, 300 and 600 ppm) were not pregnant. No dams died, aborted, delivered early, or were removed from study. All pregnant animals had one or more

live fetuses at sacrifice; the numbers of litters (fetuses) examined were 23 (347), 25 (374), 23 (351), and 23 (334) at 0, 100, 300, and 600 ppm, respectively. Maternal body weights were significantly reduced at 600 ppm on gd 9, 12, and 15, and at 300 ppm on gd 9; maternal weight change was significantly reduced at 300 and 600 ppm for gd 6-9 and at 600 ppm for gd 9-12 and for the exposure period (gd 6-15). Maternal spleen weights, absolute and relative to total body weight, were significantly increased at 600 ppm. Maternal feed consumption in g/day was significantly reduced at 300 and 600 ppm and in g/kg/day at 600 ppm during the exposure period; at 100 ppm, feed consumption in g/kg/day only was significantly reduced early in the exposure period (gd 6-9). Treatment-related clinical observations at 300 and 600 ppm included blood in urine early in the exposure period (gd 6-7) and piloerection at 600 ppm. There were no treatment-related effects on gestational parameters, including pre- or postimplantation loss, number of live fetuses per litter, fetal sex ratio (% males per litter), or on fetal body weight per litter (for sexes pooled and separately). Percent adversely affected implants per litter (which encompassed resorptions, dead fetuses, and malformed fetuses) was significantly increased at 600 ppm in the absence of any increased incidences of the component parameters. There were no treatment-related statistically or biologically significant changes in the incidence of pooled external, visceral (including craniofacial), skeletal, or total fetal malformations or variations in this study.

In conclusion, EGIE administered by inhalation of the vapor during major organogenesis in CD[®] (Sprague-Dawley) rats resulted in maternal toxicity at 300 and 600 ppm, and developmental toxicity at 600 ppm. There was no evidence for teratogenicity at any concentration tested. The "no observable adverse effect level" (NOAEL) for maternal toxicity was at or about 100 ppm and for developmental toxicity was 300 ppm in rats under the conditions of this study.

INTRODUCTION

The present study was designed to evaluate the potential of ethylene glycol mono-isopropyl ether (EGIE) to produce maternal and developmental toxicity (including teratogenicity) when administered by inhalation of the vapor during the period of major organogenesis (gestational days [gd] 6 through 15: a ten-day exposure regimen), for approximately six hours per day, in CD[®] (Sprague-Dawley) rats.

MATERIALS AND METHODS

Test Chemical

Liquid ethylene glycol monoisopropyl ether (EGIE; Company Product Name Isopropyl Cellosolve®, CAS Name 2-Isopropoxyethanol, CAS No. 109-59-1) was sent by Union Carbide (Benelux N.V., Zwijndrecht, Belgium) and received at CIIT on November 8, 1996. The method of synthesis was the responsibility of the Sponsor. The supplier lot number was 96 00054592. It was a colorless liquid with a mild odor. The chemical was received in two five-gallon drums, which were labeled with CIIT barcodes, T00029 and T00030. EGIE was pumped from the drum using a stainless steel air-operated pump into stainless steel reservoirs. The reservoirs were then connected to the generation system. A small sample was withdrawn from the drum prior to being used on the study. The sample was analyzed by NMR and GC-MS for identity and gas chromatography for purity by CIIT. The purity of EGIE was >99.5 (see Appendix I-A for test chemical characterization by the Sponsor and Appendix I-B for CIIT test chemical identity and purity). The EGIE was sampled before, during and after the exposure period. The EGIE remained stable throughout the study.

Generation of Atmospheres

The exposure atmosphere was produced by vaporizing liquid EGIE into air carrier gas in a J-tube and then further diluting and mixing it into the incoming chamber airflow. A liquid metering pump (Fluid Metering, Inc., Oyster Bay, NY) was used to meter liquid EGIE from a stainless steel reservoir into a J-shaped stainless steel tube filled with 6 mm glass beads. The long end was warmed by a heating jacket to aid in the vaporization of the EGIE. The temperature, as measured between the heating jacket and outer J-tube surface reached 125-128°C for the 100 and 300 ppm generators, and 164°C for the 600 ppm generator. Liquid EGIE was pumped into the long end of the J-tube while air flowed into the short end and carried EGIE vapor into the exposure chamber. The generation system was operated by and the exposures controlled by the Andover Infinity Control System (Andover Controls Corporation, Andover, MA).

The system controlled the exposure concentration via a feedback loop. The liquid FMI pump flow rate into the J-tube was the only parameter that was adjusted to control the exposure concentration. Total air flow through the 1-m³ chamber was monitored by measuring the pressure drop across an orifice at the inlet of the chamber and adjustments were made with a previously calibrated 8-m³ exhaust damper control through the Andover Infinity System.

The exposure chambers were provided with air at a flow rate of approximately 12-15 air changes per hour to ensure an adequate oxygen content of at least 19% (which was measured once during the study). The temperature and relative humidity inside the H-1000 chambers were monitored by the Andover system and recorded 6-12 times during the exposure period on each day. The total air flow rate through each chamber was monitored and recorded at least every 30 minute during the exposure. All chambers were maintained at a slightly negative pressure. To the extent possible, the temperatures were maintained between 64 to 79°F, and the relative humidities were maintained between 30 to 70%.

Analyses of Atmospheres

A Hewlett-Packard (HP) 5890 Series II Gas Chromatograph (GC), equipped with a flame ionization detector, HP 3396A, and a VICI Gas Sampling Valve was used to monitor the exposure chamber concentration and room air. Concentrations were measured at the center of each chamber during the exposure. The chamber concentration of the test substance was analyzed one to two times per hour in each chamber during each daily exposure period.

Prior to the start of the range-finding study, each chamber had been checked for uniformity of distribution of test compound by measuring the concentration at nine positions (eight corners and the center) within the chamber. The test material vapor was uniformly distributed. As there were changes neither to the generation system nor to the exposure chambers for the definitive study, the uniformity of distribution was not rechecked prior to this study.

For analysis of chamber concentrations, a sample of the atmosphere was continuously pulled through the sample probe. A stream selector valve was used to conduct the atmosphere from the sample lines one at a time, into the sample loop of the GC. The data from the GC, including time of analysis and concentration, were transmitted from the GC integrator to the Andover Infinity Control System. The gas chromatograph was calibrated using standards prepared by injecting the test material into a Tedlar® bag filled with a known volume of air. The calibrate function was then used on the GC to internally generate the calibration curve. The

estimated limit of detection is approximately 0.02 ppm. Details of the analytical procedures and results are presented in Appendix 1-B.

Chamber Environmental Parameters

Animals were exposed in Hazelton 1m³ H-1000 stainless steel and glass chambers (Lab Products, Inc., Maywood, NJ). As an additional safety factor, the H-1000 chamber was contained within CIIT's permanent 8m³ Hinners-type chambers. The chambers were grounded to prevent electrostatic sparking from igniting the exposure atmosphere of the test material. The generation system was also grounded. Airflow through the 8m³ chambers was controlled by a supply fan, an exhaust fan, and two butterfly dampers. Airflow was monitored by measuring the pressure drop across an orifice in the exhaust line and controlled by the damper in the exhaust duct system. Air was pulled through the H-1000 and from the 8m³ chamber into a manifold connected to the 8m³ chamber exhaust duct. A damper at the opening to the manifold from the 8m³ chamber was fixed in place to proportion air flow between the H-1000 and 8m³ chambers. Air flow through the H-1000 chamber was controlled by the total air flow in the 8m³ chamber.

Airflow in the H-1000 chamber was monitored by measuring the pressure drop across an orifice located at the inlet of each H-1000 chamber. Placement of orifices at the inlet and outlet assured that a slightly negative static pressure was maintained inside the H-1000 chamber. The static pressure differential between the 8m³ chamber and the anteroom was measured with a differential pressure transducer and controlled by the damper in the inlet air duct.

Temperature and relative humidity of the exposure air were measured in the H-1000 chamber using a temperature/relative humidity probe (Omega Engineering, Inc., Stamford, CT) connected to the Andover Infinity Control System. Calibration was performed by comparing the temperature transducer to a reference thermometer. The relative humidity sensor was calibrated by immersion in an atmosphere of known humidity generated from a saturated salt solution.

Anteroom Environmental Parameters

Inhalation exposures were conducted in 1m³ H-1000 inhalation chambers contained inside 8m³ Hinners-type exposure chambers. After the approximately six-hour exposures, the animals were removed to the 8m³ anterooms for overnight housing. The average temperature and relative humidity in the anteroom were recorded by the Andover Infinity Control System for each 30-minute period. A report of the environmental parameters over a 24-hour period,

each 30-minute period. A report of the environmental parameters over a 24-hour period, including the housing period, was printed every day, containing the average, standard deviation, maximum, and minimum values.

Animals and Husbandry

The test animals were Caesarean-originated, Virus Antibody Free (VAF) CD® (SD)BR outbred albino rats supplied by Charles River Laboratories, Inc., Raleigh, NC. At all times, the animals were cared for, handled, and treated in compliance with the NRC Guide (NRC, 1996).

One hundred seventy-five (175) nulliparous female rats and 110 virgin male rats were purchased for the developmental toxicity study. The males were approximately ten weeks old upon arrival at CIIT on March 10, 1997 (date of birth, December 30, 1996). One hundred (100) males were used to generate timed-mated females for this study. Five males were used for Quality Control and five males were used as sentinels. Females were approximately eight weeks old at arrival at CIIT on March 10, 1997 (date of birth, January 13, 1997). Female rats were approximately ten weeks of age and 217.4-299.0 grams in weight on gd 0. One hundred seventy (170) females were required to generate 100 sperm-positive females in four consecutive days; five additional nonpregnant females were used for quality control. One hundred (100) sperm-positive females (25 per group and four groups) are required to supply a minimum of 20 litters per group, which is required by U.S. EPA TSCA Testing Guidelines (U.S. EPA, 1985).

During a 14-day quarantine period, animals were randomly assigned to cages and uniquely identified by eartag. In addition, as each female became sperm positive, she was assigned a dam number. Data generated during the course of this study were tracked by these numbers. Males were housed singly in stainless steel suspended caging. Nonmated females were group housed (maximum three per cage), and mated females were housed singly in plastic shoebox cages on gd 0 until killed, except when in the inhalation chambers. Feed [NIH-07; Zeigler Brothers, Inc., Gardners, PA; Lot Nos. "NIH-07 (41070075), P-1-2-97 NIH-07-P," and "NIH-07 (41070075), P-2-5-97 NIH-07-P"] was available *ad libitum* throughout the study except during the exposure periods. The automatic watering system was used for *ad libitum* supply of water for all males and females during mating, and for all females during quarantine and while in inhalation chambers. The females in shoebox cages were supplied the same water via plastic bottles beginning on gd 0 until killed, except when in inhalation chambers. De-ionized drinking water was supplied by Hydro's Picosystem (Hydro Service and Supplies, Research Triangle Park, NC) filtration system.

Four stainless steel H-1000 chambers with glass doors and windows for animal observations were used. The estimated total volume of the animals did not exceed 5% of the volume of the chambers. Chambers were provided with air at a flow rate of approximately 12-15 air changes each hour to ensure an adequate oxygen content of at least 19% (as measured once during the study). The airflow rate was monitored continuously by the Andover Infinity Direct Digital Control System (DDC; Andover Controls Corp., Andover, MA) by recording the electronic pressure signal with a pressure transducer (Baritron, MKS, Andover, MA) from either side of an orifice at the inlet of the H-1000 and recorded at least every 30 minutes. All chambers were maintained at a slightly negative pressure.

The temperature and relative humidity of the 1 m³ exposure chambers were monitored continuously by the Andover Infinity System by recording the electronic signal from a temperature/relative humidity combination probe (Omega Engineering Inc., Stamford, CT) and recorded approximately 12 times during each exposure period. The temperature and relative humidity of the animal holding areas were monitored continuously and recorded approximately twice an hour. Animal rooms used for this study were maintained on a 12:12 hour light:dark cycle (light phase from 0600-1800 hours). Environmental conditions were continuously monitored during the course of the study by the use of the Andover Infinity Direct Digital Control System (DDC; Andover Controls Corp., Andover, MA). Target conditions for temperature and relative humidity in the anterooms and exposure chambers were 64-79°F and 30-70%, respectively (NIH, 1996). The chamber rooms (anteroom plus exposure chamber) were numbers 304 (control), 302 (100 ppm), 300 (300 ppm), and 298 (600 ppm). The temperature and relative humidity results for the four anterooms and exposure chambers were as follows.

TEXT TABLE A

	1. Anterooms (Exposure Concentrations)			
	304 (control)	302 (100 ppm)	300 (300 ppm)	298 (600 ppm)
Grand Mean Temperature ± SD, °F	65.7 ± 0.2 ^a	67.9 ± 0.1	68.1 ± 0.3	69.0 ± 0.2
Minimum Daily Reading ^b	64.9	67.4	67.2	68.2
Maximum Daily Reading ^b	66.9	69.0	69.2	70.2
Grand Mean Relative Humidity ± SD, %	44.3 ± 2.2 ^a	48.8 ± 2.4	51.3 ± 1.9	47.4 ± 3.3
Minimum Daily Reading ^b	35.7	45.2	41.0	37.0
Maximum Daily Reading ^b	55.7	63.1	60.2	63.5

(continued)

TEXT TABLE A (Continued)

	2. Chambers (Exposure Concentrations)			
	304A (control)	302A (100 ppm)	300A (300 ppm)	298A (600 ppm)
Grand Mean Temperature ± SD, °F	70.4 ± 0.2 ^a	76.1 ± 1.9	76.3 ± 2.9	74.9 ± 1.1
Minimum Daily Reading ^b	68.5	71.9	71.6	72.1
Maximum Daily Reading ^b	70.8	77.8	79.9 ^c	76.4
Grand Mean Relative Humidity ± SD, %	50.0 ± 2.2 ^a	51.6 ± 2.3	46.9 ± 1.2	46.9 ± 2.4
Minimum Daily Reading ^b	45.1	46.2	43.5	41.2
Maximum Daily Reading ^b	61.8	59.4	50.7	52.5

^a Grand mean of the 13 daily means for the chambers and of the 17-18 daily means for the anterooms.

^b Minimum or maximum of 30-minute readings, except for the control chamber where data were recorded once per hour.

^c Out of range (64-79°F).

There were no excursions outside the protocol-mandated range for temperature and relative humidity in the anterooms, based on the 30-minute recordings (see Appendix 1-C). Therefore, husbandry conditions in the anterooms did not affect the design, conduct, or conclusions of this study.

Excursions outside the protocol-mandated range for temperature in the exposure chambers, based on the 30-minute recordings (except for the control chamber, when readings were recorded once per hour), occurred only in chamber 300A when the temperature exceeded the upper bound (79°F) by less than 1°F (up to 79.9°) on five days. Relative humidity stayed within protocol-mandated ranges for 300A, and there were no excursions for temperature or relative humidity in the other chambers (details on excursions are listed in Table 9c, in Appendix 1-C, and are maintained in the study records). The relatively brief and minor excursions outside the protocol-mandated range for temperature in chamber 300A did not affect the design, conduct, or conclusions of this study.

All maternal rats were individually identified by ear tag after arrival at CIIT. In addition, each sperm-positive female received a dam study number. All data generated during the course of this study were tracked by these numbers.

Mating

For breeding, individual females were placed in the home cage of singly-housed males (i.e., one male and one female). On the following morning and each morning thereafter, the

females were examined for the presence of vaginal sperm and/or vaginal or dropped copulation plug. The days on which sperm were found were designated as gd 0 (Hafez, 1970). Sperm-positive females were individually housed until scheduled sacrifice on gd 20. Sperm-negative females were retained in the same male's cage and checked for sperm on successive mornings until insemination occurred. When sufficient sperm-positive females were generated (100), remaining sperm-negative females were euthanized by carbon dioxide asphyxiation and discarded or transferred to other projects, according to CIIT Standard Operating Procedures, with the fate of all animals documented in the study records.

Study Design and Treatment

The study was conducted with three treatment groups and an air (vehicle control) group, each comprised of 25 sperm-positive rats. The dates of performance were as follows: the animals were paired on March 24, 1997; gd 0 dates were March 25-28, 1997; exposure dates for gd 6 through 15 were March 31 through April 12, 1997. Necropsy dates (gd 20) at RTI were April 14 through 17, 1997.

The target exposure concentrations were 0, 100, 300, and 600 ppm. The rationale for choosing these exposure concentrations was based on a range-finding study in pregnant rats performed at CIIT and RTI (Appendix IV) which employed exposure concentrations of 0, 100, 300, and 600 ppm. With a small number of dams per group, 600 and 300 ppm resulted in demonstrable maternal toxicity and possible (not statistically significant) developmental toxicity, and 100 ppm resulted in minimal maternal toxicity and no developmental toxicity. The highest exposure concentration level, 600 ppm, was therefore chosen to induce overt maternal toxicity. The low exposure concentration, 100 ppm, was selected to be a maternal and developmental No Observable Adverse Effect Level (NOAEL). The mid exposure concentration was between the high and low exposure concentrations, 300 ppm, to allow evaluation of concentration-response relationships were such to occur. See Text Table B for summarization of study design and target exposure concentrations.

Sperm-positive female rats (dams) were assigned to treatment groups by a stratified randomization method designed to provide uniform mean body weights across concentration groups on gd 0 at the initiation of the study. On gd 0, maternal body weights ranged from 217.4 - 299.0 g. Sperm-positive females were exposed to EGIE vapor, approximately six hours per day from gd 6 through gd 15, at target concentrations of 0, 100, 300 or 600 ppm.

TEXT TABLE B

DEVELOPMENTAL TOXICITY STUDY						
Group Number	Rx Code	Color Code	Number of Animals Assigned to Study Groups			
			Number of Animals Exposed	No. of Days of Exposure	Exposure Period (gd)	Target Exposure Concentration (ppm)
1	04542	Green	25	10	6 through 15	0
2	21999	Yellow	25	10	6 through 15	100
3	10992	Red	25	10	6 through 15	300
4	71060	Blue	25	10	6 through 15	600

For each daily exposure, females were transferred into inhalation cage units and the cage units were moved into the appropriate chambers for exposure. Following each daily exposure, females were transferred back to home caging for residence and access to feed overnight. Maternal animals were weighed in the morning on gd 0, 6, 9, 12, 15, 18, and 20. Clinical observations of all animals were made at least once daily on gd 0-5 (prior to exposure period) and on gd 16-20 (after the exposure period), and at least twice daily, prior to and immediately after each daily exposure period and throughout the exposure period (gd 6 through gd 15). Maternal feed consumption was evaluated for gd 0-6, 6-9, 9-12, 12-15, 15-18, and 18-20.

No maternal animals died or were sacrificed moribund during the course of the study. No maternal animals showed signs of abortion or premature delivery.

On gd 20, approximately one to one and a half days before expected parturition, maternal animals were transported to RTI from CIIT and were sacrificed by asphyxiation with CO₂, thoracic and abdominal cavities and organs examined, and their pregnancy status was confirmed by uterine examination. Uteri which presented no visible implantation sites were stained with ammonium sulfide (10%) in order to visualize any implantation sites which may have undergone very early resorption (Safewski, 1964). At sacrifice, the body, liver, spleen, thymus, and uterus of each sperm-positive female were weighed. For all pregnant dams, ovarian corpora lutea were counted, and gravid uterine contents (*i.e.*, number of implantation sites, resorptions, dead fetuses, live fetuses) were recorded. Live fetuses were dissected from the uterus and immediately placed on a moist paper towel over a tray of ice, a procedure which induces anesthesia by lowering the core body temperature below 25°C (Lumb and Jones, 1973; Blair, 1979). All live fetuses were weighed, sexed, and examined for external morphological abnormalities, including cleft palate. Approximately half of the live fetuses per litter were examined for visceral malformations and had their sex confirmed using a fresh tissue dissection method (Staples, 1974; Stuckhardt and Poppe, 1984). These fetuses were decapitated prior to

dissection, and the heads were fixed in Bouin's solution for free-hand sectioning and examination (Wilson, 1965). All fetal carcasses were eviscerated (with sex confirmed internally for those fetuses not scheduled for visceral examination), macerated, and stained with alcian blue/alizarin red S, and half (intact fetuses) per litter were examined for skeletal malformations and variations (Marr *et al.*, 1988). After examination, all maternal and fetal organs and maternal carcasses were destroyed by incineration. Fetal carcasses were stored in glycerol:70% ethanol (1:1) following examination of skeletal structures or for those not examined skeletally; fetal head sections were stored in 70% ethanol solution after examination.

Statistics

The unit of comparison was the pregnant female or the litter. Quantitative continuous data (*e.g.*, maternal body weights, maternal organ weights, fetal body weights, feed consumption, etc.) were compared among the three treatment groups against the one air only control group by the use of Bartlett's test for homogeneity of variances. If Bartlett's test indicated lack of homogeneity of variances (*i.e.*, $p < 0.001$), then nonparametric statistical tests were employed for the continuous variables (Winer, 1962; see below). If Bartlett's test indicated homogeneous variances (*i.e.*, $p > 0.001$), then parametric statistical tests were employed for the continuous variables. Parametric statistical procedures which were applied to selected measures from this developmental toxicity study were as follows. Appropriate General Linear Models (GLM) procedures (SAS Institute Inc., 1989a,b; 1990a,b,c; 1996; 1997) were used for the Analyses of Variance (ANOVA). Prior to GLM analysis, an arcsine-square root transformation was performed on all litter-derived percentage data (Snedecor and Cochran, 1967) to allow use of parametric methods. For these litter-derived percentage data, the ANOVA was weighted according to litter size. GLM analysis was used to determine the significance of the dosage-response relationship (Test for Linear Trend), and to determine whether significant dosage effects had occurred for selected measures (ANOVA). When a significant ($p < 0.05$) main effect for dosage occurred, Dunnett's Multiple Comparison Test (Dunnett, 1955; 1964) was used to compare each EGIE-exposed group to the control group for that measure. A one-tailed test (*i.e.*, Dunnett's Test) was used for all pairwise differences from the vehicle control group except that a two-tailed test was used for maternal body and organ weight parameters, maternal feed consumption, fetal body weight, and percent males per litter. Nonparametric tests which were used on continuous data which did not have homogenous variances included the Kruskal-Wallis Test to determine if significant differences were present among the groups, followed by the Mann-Whitney U test for pairwise differences from the

Kruskal-Wallis test was significant (Siegel, 1956). Jonckheere's test for k independent samples (Jonckheere, 1954) was used to identify significant dose-response trends for nonparametric continuous data. Nominal scale measures were analyzed by Chi-Square Test for Independence for differences among treatment groups, and by the Cochran-Armitage Test for Linear Trend on Proportions (Cochran, 1954; Armitage, 1955; Agresti, 1990). When Chi-Square revealed significant ($p < 0.05$) differences among groups, then a two-tailed Fisher's Exact Probability Test, with appropriate adjustments for multiple comparisons, was used for pairwise differences between each EGIE-exposed group and the control group (Snedecor and Cochran, 1967). A test for statistical outliers (SAS; 1990b) was performed on maternal body weights and feed consumption (in g/day). If examination of pertinent study data did not provide a plausible biologically-sound reason for inclusion of the data flagged as "outlier," the data were excluded from summarization and analysis and were designated as outliers. If feed consumption data in g/day were negative for a given dam and period, they were designated "unrealistic" and excluded from summarization and analysis. If feed consumption data for a given observational interval (e.g., gd 6-9, 9-12, or 12-15 during the treatment period) were designated outliers or unrealistic, then summarized data encompassing this period (e.g., exposure period, gd 6-15) also did not include this value.

Personnel

The evaluation of EGIE for developmental toxicity in CD[®] (Sprague-Dawley) rats was conducted at The Chemical Industry Institute of Toxicology (CIIT) and Research Triangle Institute (RTI), Research Triangle Park, NC, under contract to The Union Carbide Corporation, Danbury, CT. Dr. Hon-Wing Leung, of the Union Carbide Corporation, was the Sponsor's Representative. The CIIT and RTI personnel indicated below contributed to the completion of this study.

Study Director: Dr. Frank Welsch, D.V.M., DABT, CIIT

Co-Investigator: Dr. Rochelle W. Tyl, Ph.D., DABT, RTI

CIIT Personnel:

Animal Research Facility Veterinarian: Dr. Jeffrey I. Everitt, D.V.M., ACLAM, DACVP

Animal Research Facility Supervisor: Mr. Paul W. Ross, B.S., LATG

Inhalation Facility: Dr. Owen R. Moss, Ph.D.

Inhalation Technical Advisor: Dr. Brian Wong, Ph.D.

Inhalation Exposure Unit Supervisor: Mr. Arden James, B.A.

Inhalation Lead Technician: Ms. Marianne W. Marshall, B.S.
Analytical Chemistry: Mr. Max Turner, B.S.
Research Associate: Ms. Barbara Elswick, B.S.
Quality Assurance: Ms. Patricia O'Brien Pomerleau, M.S.

RTI Personnel:

Animal Research Facility Veterinarian: Dr. Donald B. Feldman, D.V.M., ACLAM
Veterinary Pathologist: Dr. John C. Seely, D.V.M., ACVP (PATHCO, Inc.)
Reproductive and Developmental
Laboratory Supervisor: Ms. Melissa C. Marr, B.A., LATG
Data Specialist: Ms. Christina B. Myers, M.S.
Biologists: Ms. Frieda S. Gerling
Ms. Vickie I. Wilson
Biological Laboratory Assistants: Ms. Lawson B. Pelletier, RVMT, LAT
Ms. Mal-Selika Perry, RVMT
Quality Assurance Unit Manager: Ms. Stephanie M. Taulbee, M.S.P.H.
(through 9/30/98)
Mr. David L. Brodish, M.A. (from 10/1/98)
Quality Assurance Unit Specialists: Ms. Celia D. Keller, M.S.
Ms. Patricia D. Hall
Mr. Stanley Sherrill, B.S.
Ms. Mary E. Parker, B.A.

The final report was prepared by Dr. R.W. Tyl, with assistance from Ms. C.B. Myers and Ms. F.S. Gerling on data compilation and statistical analyses and from Dr. Frank Welsch (CIIT), Ms. M.C. Marr (RTI) and Ms. B. Elswick (CIIT). The individual scientist reports were prepared and signed by the author(s).

The protocol and one amendment detailing the design and conduct of the study are presented in Appendix V. The protocol was signed by the Study Director on February 26, 1997.

Historical Control Dataset

A historical control summary dataset for developmental toxicity studies with the CD[®] (Sprague-Dawley) rat at RTI is presented in Appendix III.

Storage of Records

All original data sheets for the present study are stored in the CIIT archives, along with all biological samples collected during the course of the study, which remain the responsibility of CIIT. Work sheets and computer printouts, which were generated in the statistical analysis of data, are stored in the CIIT Archives for a period of ten years; material will then be transferred

to the Sponsor's archives. Copies of this report are filed with the CIIT and RTI Archives as well as with Union Carbide Corporation, Danbury, CT.

Compliance

The study was performed in compliance with the Toxic Substances Control Act (TSCA), Test Guidelines Section 798.4900 (U.S. EPA, 1985, 1987). All records, data, and reports will be maintained in storage in the CIIT archives as specified in the TSCA Good Laboratory Practice (GLP) Standards (U.S. EPA, 1989) or for as long as the quality of the preparation affords evaluation, whichever is less. GLP compliance for test chemical analyses was the responsibility of the Sponsor, Supplier and CIIT.

The toxicology laboratories at RTI are operated in compliance with TSCA GLP Standards (U.S. EPA, 1989). The CIIT Animal Research Facility is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC), International. This study was conducted in compliance with the TSCA GLP regulations and AAALAC accreditation standards.

RESULTS

Test Atmospheres

The target concentrations were 0, 100, 300, and 600 ppm. The grand mean actual chamber concentrations (ACC) and standard deviations were 99.5 ± 1.2 , 299.8 ± 1.7 , and 599.5 ± 2.0 ppm for the low, mid, and high concentrations, respectively, calculated as a grand mean from individual daily mean values for each of the 13 exposure days. The grand mean ACC for the control chamber was 0.0 ± 0.0 ppm; the estimated limit of detection was 0.02 ppm. The grand mean nominal chamber concentrations (NCC) were 97.5, 289.5, and 552.4 ppm for the low, mid and high concentrations, respectively. The grand mean of the ratio of the actual chamber concentrations, compared with the nominal chamber concentrations (RAN), were 102, 104, and 109% for the low, mid, and high concentrations, respectively. The grand mean of the ratio of the actual chamber concentrations, compared with the target concentrations (RAT), were 99.5, 99.9, and 99.9% for the low, mid, and high concentrations, respectively. In the H-1000 exposure chambers, the grand mean temperature \pm standard deviation (SD) for the chambers containing control, low, mid, and high concentrations were 70.4 ± 0.2 , 76.1 ± 1.9 , 76.3 ± 2.9 , and 74.9 ± 1.1 °F, respectively. In the H-1000 exposure chambers, the grand mean relative humidity (RH) \pm SD standard deviation for the control, low, mid, and high concentrations were 50.0 ± 2.2 , 51.6 ± 2.3 , 46.9 ± 1.2 , and 46.9 ± 2.4 %, respectively. Anteroom grand mean (\pm SD) were 65.7 ± 0.2 , 67.9 ± 0.1 , 68.1 ± 0.3 , and 69.0 ± 0.2 , and grand mean RH (\pm SD) were 44.3 ± 2.2 , 48.8 ± 2.4 , 51.3 ± 1.8 , and 47.4 ± 3.3 %, for the control, low, mid, and high concentrations. See Summary Table 1 and Appendix 1-B for details.

Maternal Toxicity

Pregnancy rates were high and approximately equivalent across all groups (92.0-100.0%) (Table 2). Six females (two each at 0, 300, and 6000 ppm) were nonpregnant in the study. No dams died, aborted, delivered early, or were removed from study. All pregnant dams had one or more live fetuses at scheduled sacrifice. The numbers of litters (and fetuses) evaluated were 23 (347) at 0 ppm, 25 (374) at 100 ppm, 23 (351) at 300 ppm, and 23 (334) at 600 ppm. All subsequent summary tables include data only from confirmed pregnant females. Data collected from nonpregnant females are retained in the study records.

Maternal body weights were equivalent across all groups on gd 0 and 6 prior to the start of the exposure period. On gd 9 (the first weigh date during the exposure period), mean maternal body weights were statistically significantly reduced at 300 and 600 ppm. Maternal

body weights were also reduced at 600 ppm for gd 12 and 15 (during the exposure period). Maternal body weights were statistically equivalent across all groups for gd 18 and 20 (in-life and at sacrifice). Maternal weight change was significantly reduced for gd 6-9 (first interval of the exposure period) at 300 and 600 ppm. Maternal weight change was also significantly reduced at 600 ppm for gd 9-12 and gd 6-15 (exposure period). There were no differences among groups for maternal weight change for gd 15-20 (post-exposure period), gd 0-20 (gestational period), maternal weight change corrected for the weight of the gravid uterus, gravid uterine weight, or for absolute and relative maternal liver weight. Maternal spleen weights, absolute and relative to terminal body weight, were significantly increased at 600 ppm. Maternal absolute thymus weight was significantly reduced at 300 ppm but not at 600 ppm, and maternal relative thymus weight was unchanged across groups (Table 2). Individual maternal body and organ weights are presented in Appendix II.

Maternal clinical observations are presented in Table 3. Treatment-related clinical signs included blood (confirmed by Chemstrip®) in bedding, on tail and fur after exposures on gd 6 and 7 at 300 and 600 ppm with a concentration-related incidence, and more severe on gd 6. General clinical observations (not assigned to specific dams) also indicated blood in catch pans (under the cages in the cage racks in the inhalation chamber and immediately after exposure) at 300 and 600 ppm on March 31-April 3, 1997, which corresponded to the first through the last gd 6 (four mating days were required to generate 100 timed-mated females) and possibly through gd 9 (last date corresponds to gd 9 for dams with the earliest gd 6 date). Rust-colored fur on head and neck (probably from chromodacryorrhea from the Harderian glands behind the eyes groomed onto the head and/or neck) was also observed at 300 and 600 ppm on gd 7-12, also on gd 15 on the neck at 600 ppm, and at 0 ppm on gd 9 and 13. Piloerection was observed at 600 ppm on gd 7-13 and 16 (1-14 dams) and at 300 ppm on gd 9-13, and 15 (1-4 dams). Clinical weight loss (≥ 5.0 g within a weigh period) was observed in ten dams at 600 ppm, three dams at 300 ppm, and one dam at 100 ppm on gd 9 (for interval gd 6-9), and in one control dam on gd 12 (for interval gd 9-12). No other observations appeared treatment related. At scheduled necropsy on gd 20, one dam at 300 ppm exhibited pale kidneys, which was not considered treatment related (based on incidence and no such finding at 600 ppm) (Table 3). Individual maternal clinical observations and necropsy findings are presented in Appendix II.

Maternal feed consumption, expressed as g/day and g/kg body weight/day, is presented in Table 4. Maternal feed consumption for gd 0-6 prior to the exposure period was equivalent across all groups (as g/day or g/kg/day). Maternal feed consumption in g/day was significantly reduced at 300 and 600 ppm for gd 6-9 and 6-15 (exposure period). At 100 ppm, feed

consumption as g/day was unaffected. When the data were expressed as g/kg/day, maternal feed consumption at 600 ppm was reduced for gd 6-9 and 6-15. At 300 ppm, feed consumption as g/kg/day was significantly reduced only for gd 6-9 and significantly increased for gd 12-15. At 100 ppm, maternal feed consumption as g/kg/day was significantly reduced only for gd 6-9 (Table 4). Individual maternal feed consumption data are presented in Appendix II.

Developmental Toxicity

Results of the uterine examination are presented in Table 5. There were no significant effects of treatment on the following gestational parameters, including number of ovarian corpora lutea, total number of uterine implantation sites, pre- or postimplantation loss, number of live fetuses per litter, and sex ratio (% male fetuses) per litter. The value for percent adversely affected implants per litter (which encompasses resorptions plus late fetal deaths, termed nonlive, plus malformed fetuses) was significantly ($p < 0.05$) increased at 600 ppm, with no significant changes to the incidences of the component parameters, *i.e.*, no significant changes to the incidences of resorptions, of late fetal deaths (none were observed in this study), or of incidences of malformations (see Table 6). Fetal body weight per litter, when calculated as all fetuses, or males or females separately, was also unaffected by exposure (Table 5).

There were no treatment-related changes in the incidence of pooled external, visceral, skeletal, or total malformations or variations by litter or by fetus per litter in this study (Table 6). Listing of fetal findings by defect type is presented in Table 7. Three fetuses, one each at 100, 300, and 600 ppm, exhibited external malformations. The fetus at 600 ppm (dam no. 5, fetus no. 3, male) exhibited cleft palate. The fetus at 300 ppm (dam no. 90, fetus no. 9, male) exhibited three external malformations: cleft palate, anasarca (whole body edema) and micromelia (short limbs). The fetus at 100 ppm (dam no. 58, fetus no. 13, male) exhibited short, thread-like tail. Fetal visceral malformations were almost exclusively limited to hydronephrosis and hydroureter distributed across all groups, a very common finding in term rodent fetuses (see Appendix III for the RTI historical control data set for CD[®] rat fetuses), and one fetus in one litter at 0 ppm (dam no. 23, fetus no. 3, female) with kidneys fused with one ureter. Only one fetal skeletal malformation was observed; one fetus (in one litter) at 300 ppm (dam no. 90, fetus no. 9, male; the same fetus with multiple external malformations), exhibited cartilage of sternum split (present in the historical control dataset, Appendix III). Fetal external variations were limited to one fetus at 0 ppm (dam no. 80, fetus no. 11, female) with a hematoma on the neck. Fetal visceral variations were distributed across all groups with no

treatment- or exposure-related pattern; they included predominantly enlarged lateral ventricles of the cerebrum, and distended ureters, both common findings in term fetuses (Appendix III). Fetal skeletal variations included misaligned sternbrae and changes in cartilage and bone in the thoracic centra, and predominantly extra rib (full or rudimentary) on Lumbar I, and short rib XIII, common fetal findings, across all groups examined. All uterine and fetal individual data are presented in Appendix II. All fetal findings judged common or typical to this species and strain are also present in published historical control databases (e.g., Woo and Hoar, 1979; Charles River, 1988).

DISCUSSION

The present study has shown that ethylene glycol monoisopropyl ether (EGIE), administered by inhalation of the vapor from gd 6 through 15, approximately six hours/day, in CD® (Sprague-Dawley) rats, resulted in maternal toxicity at 300 and 600 ppm, specifically reductions in body weight, weight gain, and in feed consumption and treatment-related clinical signs of toxicity and increased absolute and relative spleen weights at 600 ppm. There was no evidence for maternal toxicity at 100 ppm, except for reduced feed consumption as g/kg/day (but not as g/day) for gd 6-9 (first interval of the exposure period). There were clear indications of maternal accommodation to the top two exposure concentrations, as evidenced by diminution in the incidence of clinical signs such as blood in the urine, which was observed only on gd 6 and 7 after exposures, and piloerection. The maternal bleeding early in the exposure period, essentially only post-exposure on gd 6-7, is consistent with findings in CD® (Sprague-Dawley) rat dams exposed to ethylene glycol monopropyl ether (EGPE) by inhalation (Krasavage and Katz, 1985), and in Fischer 344 rat dams exposed to ethylene glycol monobutyl ether (EGBE) by inhalation (Tyl *et al.*, 1984). The "blood" represents hematuria (erythrocytes in urine) and/or hemoglobinuria ("naked" hemoglobin in urine from lysed erythrocytes) and was observed with inhaled EGPE in pregnant CD® rats, with inhaled EGBE in pregnant Fischer 344 rats (see above) and with inhaled Isopropyl Cellosolve® in Wistar rats (males and females) in a 28-day study (Arts *et al.*, 1992). EGBE did not affect maternal erythrocyte fragility (Tyl *et al.*, 1984). Spleen weights were also increased and blood parameters were altered in these studies, consistent with a macrocytic hemolytic anemia. In the study with EGPE, 200 ppm and above resulted in maternal toxicity but no teratogenicity or "significant embryo/fetotoxicity" although skeletal variations (e.g., effects on ossification and increased extra rudimentary ribs) were increased; 100 ppm was a NOAEL for both dams and conceptuses. In the study with EGBE, 100 ppm and above resulted in maternal and embryo/fetal toxicity, including a decreased number of viable implantations per litter (but no effects on fetal malformations in rats); 50 ppm was a NOAEL for both dams and conceptuses (Tyl *et al.*, 1984). In the study with EGIE, the hemolytic anemia was transient at 100 ppm (as it was in the present study), and the adult NOAEL was established at 30 ppm (Arts *et al.*, 1992). Therefore, the maternal observations in this study are consistent with effects observed in the range-finding study, and with effects previously observed with EGBE and with EGIE in different rat strains, and with EGPE in the same strain.

Developmental toxicity was present at 600 ppm, expressed only as a significant increase in adversely affected implants per litter. However, there were no significant increases to the components of this "umbrella" term, namely resorptions, dead fetuses (none were observed), or malformed fetuses. There was no evidence of treatment-related teratogenicity at any exposure concentration evaluated. There were no significant embryo/fetal effects observed at 300 or 100 ppm. All of the fetal malformation and variation findings in this study were those commonly observed in historical control CD[®] rat fetuses in the performing laboratory (RTI; Appendix III) and in published control databases (e.g., Woo and Hoar, 1979; Charles River, 1988). The absence of any treatment-related increased incidences in fetal malformations or variations in this study is consistent with the results observed with EGPE, which also did not elicit teratogenicity in CD[®] rats (Krasavage and Katz, 1985) and with EGBE for teratogenicity in both Fischer 344 rats and New Zealand White rabbits (Tyl *et al.*, 1984). The embryotoxicity previously observed with EGBE (Tyl *et al.*, 1984) included increased resorptions in rats at 100 and 200 ppm. In the present study, there were no significant changes in post-implantation losses at any exposure concentration. It is important to note that EGIE has a three-carbon branched side chain (isopropyl), EGPE has a three-carbon straight side chain (propyl), and EGBE has a four-carbon side chain (butyl), and the one- and two-carbon side chain (methyl and ethyl) glycol ethers are known teratogens with induced malformations similar to the ones observed in one fetus at 300 ppm (split sternum) in the present study. In addition, although the EGBE study was performed in a different rat strain, the Fischer 344 versus the CD[®] (Sprague-Dawley) in the present study, the EGPE study was performed in the same rat strain as in the present study. Therefore, there is a clear SAR (Structure-Activity Relationship) for developmental toxicity, including teratogenicity, with the length of the carbon side chain in the ethylene glycol-based glycol ethers. The present study has confirmed that the propyl (EGPE) versus isopropyl (EGIE) isomer as the side chain results in comparable effects on dams and conceptuses in the same rat strain as EGBE, and as EGIE in a different rat strain.

CONCLUSIONS

Therefore, the "no observable adverse effect level" (NOAEL) was at or about 100 ppm for maternal toxicity, and at 300 ppm for developmental toxicity in rats under the conditions of this study.

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Table 1. Exposure Chamber Parameters

Parameter	Target EGIE Concentration, ppm			
	0	100	300	600
Analytical Chamber Concentration, ppm	0.0 ^a ± 0.0	99.5 ± 1.2	299.8 ± 1.7	599.5 ± 2.0
Ratio of Analytical to Target Concentration, %	NA ^b	100	100	100
Nominal Chamber Concentration, ppm	NA	97.5	289.5	552.4
Ratio of Analytical to Nominal Concentration, %	NA	102	104	109
Chamber Airflow, L/ min	237.5 ^a ± 0.7	220.0 ± 2.8	234.9 ± 0.5	248.5 ± 1.2
Chamber Temperature, °F	70.4 ^a ± 0.2	76.1 ± 1.9	76.3 ± 2.9	74.9 ± 1.1
Chamber Relative Humidity, %	50.0 ^a ± 2.2	51.6 ± 2.3	46.9 ± 1.2	46.9 ± 2.4
Anteroom Temperature, °F	65.7 ± 0.2 ^{a,c}	67.9 ± 0.1	68.1 ± 0.3	69.0 ± 0.2
Anteroom Relative Humidity, %	44.3 ± 2.2 ^{a,c}	48.8 ± 2.4	51.3 ± 1.9	47.4 ± 3.3

^a Data are presented as grand mean of daily means ± standard deviation, n=13 exposure days (to accommodate a ten-day exposure regimen for each study female; study females were bred over four days).

^b NA = not applicable; estimated limit of detection is about 0.02 ppm.

^c Anteroom temperature and relative humidity were monitored, controlled and recorded during the times the animals were housed in the anterooms prior to, in between, and after the exposures, n=17-18 days.

Table 2. Summary and Statistical Analysis of Maternal Body Weights, Weight Gains, Organ Weights and Relative Organ Weights (page 1 of 3)

	Isopropyl Cellosolve® (ppm, inhalation)			
	0	100	300	600
SUBJECTS (No. Dams)				
No. on Study	25	25	25	25
No. Removed	0	0	0	0
No. Dead or Euthanized	0	0	0	0
No. Nonpregnant on Gestational Day 20	2	0	2	2
No. (%) Pregnant on Gestational Day 20	23 (92.0)	25 (100.0)	23 (92.0)	23 (92.0)
Maternal Body Weight (gd 0) (g) ^a				
	253.2 ± 3.3 N=23	251.3 ± 2.8 N=25	249.4 ± 2.8 N=23	249.7 ± 2.6 N=23
Maternal Body Weight (gd 6) (g) ^a				
	287.5 ± 3.8 N=23	289.6 ± 3.0 N=25	282.3 ± 3.6 N=23	284.3 ± 2.9 N=23
Maternal Body Weight (gd 9) (g) ^a				
	299.8 ††† ± 3.9 \$\$\$ N=23	298.3 ± 3.4 N=25	285.8 * ± 3.7 N=23	278.5 ** ± 4.1 N=23
Maternal Body Weight (gd 12) (g) ^a				
	314.9 † ± 4.2 \$\$ N=23	312.5 ± 3.4 N=25	303.3 ± 3.7 N=23	299.0 * ± 3.9 N=23
Maternal Body Weight (gd 15) (g) ^a				
	335.6 † ± 4.6 \$\$ N=23	333.0 ± 3.7 N=25	324.5 ± 4.1 N=23	319.6 * ± 4.2 N=23
Maternal Body Weight (gd 18) (g) ^a				
	372.8 ± 5.3 \$ N=23	369.9 ± 4.5 N=25	363.6 ± 4.8 N=23	358.4 ± 4.9 N=23
Maternal Body Weight (gd 20) (g) ^a				
	404.9 ± 5.7 N=23	402.6 ± 5.1 N=25	397.5 ± 5.1 N=23	392.1 ± 6.3 N=23
Maternal Body Weight (gd 20 at sacrifice) (g) ^a				
	391.7 ± 5.0 N=23	390.9 ± 4.8 N=25	386.2 ± 4.8 N=23	381.6 ± 6.0 N=23

(continued)

Table 2. Summary and Statistical Analysis of Maternal Body Weights, Weight Gains, Organ Weights and Relative Organ Weights (page 2 of 3)

	Isopropyl Cellosolve® (ppm, inhalation)			
	0	100	300	600
Maternal Body Weight Change (gd 0 to 6) (g) ^a	34.3 ± 1.4 N=23	38.3 ± 1.7 N=25	32.9 ± 2.1 N=23	34.7 ± 1.6 N=23
Maternal Body Weight Change (gd 6 to 9) (g) ^a	12.4 ††† ± 1.2 §§§ N=23	8.7 ± 2.1 N=25	3.5 ** ± 2.0 N=23	-5.9 ** ± 2.6 N=23
Maternal Body Weight Change (gd 9 to 12) (g) ^a	15.0 †† ± 1.7 §§§ N=23	14.1 ± 1.2 N=25	17.6 ± 1.2 N=23	20.6 * ± 1.5 N=23
Maternal Body Weight Change (gd 12 to 15) (g) ^a	20.7 ± 1.3 N=23	20.5 ± 0.9 N=25	21.1 ± 1.2 N=23	20.6 ± 1.5 N=23
Maternal Body Weight Change (gd 15 to 18) (g) ^a	37.2 ± 1.1 N=23	36.9 ± 1.2 N=25	39.1 ± 1.4 N=23	38.8 ± 1.7 N=23
Maternal Body Weight Change (gd 18 to 20) (g) ^a	32.2 ± 1.3 N=23	32.7 ± 1.3 N=25	33.9 ± 1.2 N=23	33.7 ± 1.8 N=23
Maternal Body Weight Change (gd 6 to 15) (g) ^a	48.1 ††† ± 2.1 §§§ N=23	43.4 ± 1.6 N=25	42.2 ± 2.1 N=23	35.3 ** ± 2.1 N=23
Maternal Body Weight Change (gd 15 to 20) (g) ^a	69.4 ± 1.8 N=23	69.6 ± 2.2 N=25	73.0 ± 1.7 N=23	72.5 ± 3.2 N=23
Maternal Body Weight Change (gestation) (g) ^a	138.5 ± 2.9 N=23	139.6 ± 3.6 N=25	136.8 ± 3.6 N=23	132.0 ± 4.3 N=23
Maternal Body Weight Change (corrected) (g) ^{a,b}	55.62 ± 2.00 N=23	57.03 ± 2.63 N=25	51.51 ± 2.96 N=23	51.95 ± 1.71 N=23

(continued)

Table 2. Summary and Statistical Analysis of Maternal Body Weights, Weight Gains, Organ Weights and Relative Organ Weights (page 3 of 3)

	Isopropyl Cellosolve® (ppm, inhalation)			
	0	100	300	600
Gravid Uterine Weight (g) ^a	82.88 ± 2.13 N=23	82.59 ± 2.48 N=25	85.31 ± 1.97 N=23	80.04 ± 4.00 N=23
Absolute Maternal Liver Weight (g) ^a	17.48 ± 0.34 N=23	17.58 ± 0.32 N=25	17.41 ± 0.37 N=23	17.69 ± 0.34 N=23
Relative Maternal Liver Weight (% sacrifice weight) ^a	4.47 ± 0.07 N=23	4.50 ± 0.06 N=25	4.51 ± 0.07 N=23	4.64 ± 0.06 N=23
Absolute Maternal Spleen Weight (g) ^a	0.727 ††† ± 0.021 \$\$\$ N=23	0.728 ± 0.024 N=25	0.792 ± 0.022 N=23	0.918 ** ± 0.036 N=23
Relative Maternal Spleen Weight (% sacrifice weight) ^a	0.185 ††† ± 0.005 \$\$\$ N=23	0.186 ± 0.005 N=25	0.205 ± 0.005 N=23	0.241 ** ± 0.009 N=23
Absolute Maternal Thymus Weight (g) ^a	0.456 ‡ ± 0.017 N=23	0.432 ± 0.016 N=25	0.391 * ± 0.013 N=23	0.440 ± 0.015 N=23
Relative Maternal Thymus Weight (% sacrifice weight) ^a	0.117 ± 0.004 N=23	0.110 ± 0.004 N=25	0.102 ± 0.004 N=23	0.116 ± 0.006 N=23

^aIncludes all pregnant dams until they were sacrificed on gestational day 20. Reported as the mean ± S.E.M.;
gd=gestational day.

^bWeight change during gestation minus gravid uterine weight.

‡p<0.05; ANOVA Test.

††p<0.01; ANOVA Test.

†††p<0.001; ANOVA Test.

\$p<0.05; Test for Linear Trend.

\$\$p<0.01; Test for Linear Trend.

\$\$\$p<0.001; Test for Linear Trend.

*p<0.05; Dunnett's Test

**p<0.01; Dunnett's Test

Table 3. Summary of Clinical Observations and Necropsy Findings (page 1 of 3)

Day ^a	Observation ^b	Isopropyl Cellosolve [®] (ppm, inhaled)			
		0	100	300	600
0	Swollen digits on rear foot				1
1	Swollen digits on rear foot				1
2	Cut on upper lip				1
	Swollen digits rear foot				1
3	Cut on upper lip, healing				1
	Swollen digits rear foot				1
4	Swollen digits rear foot				1
5	Swollen digits rear foot				1
6	Alopecia: limb(s)		1		
	multiple areas		1		
	Blood: in bedding			10	11
	on tail			7	10
	on tail and bedding			2	2
	on tail and fur			1	
	Swollen digits rear foot				1
7	Alopecia: limb(s)		1		
	multiple areas		1		
	Blood tinged bedding			4	5
	Fur: rust colored on head			8	15
	Piloerection				9
	Swollen digits rear foot				1
8	Alopecia: limb(s)	1	1		
	multiple areas		1		
	Fur: rust colored on head			8	13
	Piloerection				14
	Swollen digits rear foot				1
9	Alopecia: limb(s)	1	1		
	multiple areas		1		
	Chromodacryorrhea		1		
	Feces: soft			1	
	Fur: rust colored on head	1		1	10
	Malocclusion ^c		1		
	Piloerection			4	10
	Swollen digits rear foot ^c				1
	Weight loss ^d : 32.37 g		1		
	11.45 - 19.80 g			3	
5.44 - 34.92 g				10	
10	Alopecia: limb(s)	1	1		1
	multiple areas		1		
	Chromodacryorrhea		1		
	Fur: rust colored on head			4	7
	Piloerection			3	5

(continued)

Table 3. Summary of Clinical Observations and Necropsy Findings (page 2 of 3)

Day	Observation	Isopropyl Cellosolve [®] (ppm, inhaled)			
		0	100	300	600
11	Alopecia: limb(s)	1	1		1
	multiple areas		1		
	Chromodacryorrhea		1		
	Fur: rust colored on head			1	2
	Piloerection			3	3
12	Alopecia: limb(s)	1	1		1
	multiple areas		1		
	Fur: rust colored on head	1		1	1
	Piloerection			1	2
	Weight loss ^c : 5.11 g	1			
13	Alopecia: limb(s)	1	1		1
	multiple areas		1		
	Fur: rust colored on head	1			
	Piloerection			2	1
14	Alopecia: limb(s)	1	1		1
	multiple areas		1		
15	Alopecia: abdomen		1		
	limb(s)	1	1		1
	multiple areas		1		
	Fur: rust colored on neck				1
	Piloerection			1	
16	Alopecia: abdomen		1		
	limb(s)	1	1		1
	multiple areas		1		
	Piloerection				1
17	Alopecia: abdomen		1		
	limb(s)	1	1		1
	multiple areas		1		
18	Alopecia: abdomen		1		
	limb(s)	1	1	1	1
	multiple areas		1		
19	Alopecia: abdomen		1		
	limb(s)	1	1	1	1
	multiple areas		1		
20	Alopecia: abdomen		1		
	limb(s)	1	1	1	1
	multiple areas		1		

(continued)

Table 3. Summary of Clinical Observations and Necropsy Findings (page 3 of 3)

NECROPSY FINDINGS FOR SCHEDULED DEATHS

Day	Finding	Isopropyl Cellosolve [®] (ppm, inhaled)			
		0	100	300	600
20	Kidney(s): pale, bilateral			1	

^aGestational day.

^bClinical observations are tabulated once per day per animal.

^cNo further notation made unless a change occurs.

^dClinical weight loss is weight loss \geq 5.0 grams in any one weigh period.

Table 4. Summary and Statistical Analysis of the Maternal Feed Consumption (page 1 of 3)

	Isopropyl Cellosolve® (ppm, inhalation)			
	0	100	300	600
No. Dams	23	25	23	23
Maternal Feed Consumption (gd 0 to 6) (g/day) ^a				
	27.0	27.2	26.8	27.4
	± 0.6	± 0.5	± 0.4	± 0.5
	N=23	N=25	N=23	N=23
Maternal Feed Consumption (gd 6 to 9) (g/day) ^a				
	26.0 †††	24.8	19.7 **	16.5 **
	± 0.6 \$\$\$	± 0.5	± 0.8	± 1.1
	N=23	N=25	N=23	N=23
Maternal Feed Consumption (gd 9 to 12) (g/day) ^a				
	24.8 ‡	23.3	24.6	23.1
	± 0.7	± 0.4	± 0.4	± 0.5
	N=23	N=25	N=23	N=23
Maternal Feed Consumption (gd 12 to 15) (g/day) ^a				
	25.9	26.3	26.8	25.9
	± 0.7	± 0.6	± 0.5	± 0.5
	N=23	N=25	N=23	N=23
Maternal Feed Consumption (gd 15 to 18) (g/day) ^a				
	27.6	27.1	27.6	26.9
	± 0.7	± 0.6	± 0.8	± 0.6
	N=23	N=25	N=23	N=23
Maternal Feed Consumption (gd 18 to 20) (g/day) ^a				
	28.1	28.0	28.9	28.1
	± 0.7	± 0.7	± 0.7	± 0.5
	N=23	N=25	N=23	N=23
Maternal Feed Consumption (gd 6 to 15) (g/day) ^a				
	25.6 †††	24.8	23.7 *	21.8 **
	± 0.6 \$\$\$	± 0.4	± 0.4	± 0.5
	N=23	N=25	N=23	N=23
Maternal Feed Consumption (gd 15 to 20) (g/day) ^a				
	27.8	27.4	28.1	27.4
	± 0.7	± 0.6	± 0.7	± 0.5
	N=23	N=25	N=23	N=23
Maternal Feed Consumption (gd 0 to 20) (g/day) ^a				
	26.5	26.2	25.7	24.9
	± 0.5 \$\$	± 0.4	± 0.4	± 0.4
	N=23	N=25	N=23	N=23

(continued)

Table 4. Summary and Statistical Analysis of the Maternal Feed Consumption (page 2 of 3)

	Isopropyl Cellosolve® (ppm, inhalation)			
	0	100	300	600
Maternal Feed Consumption (gd 0 to 6) (g/kg/day) ^a	99.9 ± 1.7 N=23	100.7 ± 1.6 N=25	100.8 ± 1.2 N=23	102.7 ± 1.5 N=23
Maternal Feed Consumption (gd 6 to 9) (g/kg/day) ^a	88.6 ^{††††} ± 1.9 ^{††††} N=23	84.5 [□] ± 1.3 N=25	69.2 ^{□□} ± 2.5 N=23	58.1 ^{□□} ± 3.6 N=23
Maternal Feed Consumption (gd 9 to 12) (g/kg/day) ^a	80.4 ^{††} ± 1.6 N=23	76.5 ± 1.1 N=25	83.7 ± 1.3 N=23	80.1 ± 1.2 N=23
Maternal Feed Consumption (gd 12 to 15) (g/kg/day) ^a	79.6 [†] ± 1.3 [§] N=23	81.3 ± 1.6 N=25	85.5 [*] ± 1.2 N=23	83.7 ± 1.5 N=23
Maternal Feed Consumption (gd 15 to 18) (g/kg/day) ^a	77.8 ± 1.2 N=23	77.0 ± 1.3 N=25	80.2 ± 1.9 N=23	79.5 ± 1.5 N=23
Maternal Feed Consumption (gd 18 to 20) (g/kg/day) ^a	72.0 ± 1.0 N=23	72.5 ± 1.7 N=25	75.0 ± 1.5 N=23	74.8 ± 1.1 N=23
Maternal Feed Consumption (gd 6 to 15) (g/kg/day) ^a	82.5 ^{†††} ± 1.5 ^{§§§} N=23	80.4 ± 1.0 N=25	79.3 ± 0.9 N=23	73.8 ^{**} ± 1.3 N=23
Maternal Feed Consumption (gd 15 to 20) (g/kg/day) ^a	74.7 ± 1.0 N=23	74.5 ± 1.3 N=25	77.7 ± 1.4 N=23	76.8 ± 1.1 N=23
Maternal Feed Consumption (gd 0 to 20) (g/kg/day) ^a	81.8 ± 1.0 N=23	81.2 ± 1.0 N=25	81.7 ± 0.9 N=23	79.9 ± 0.7 N=23

(continued)

Table 4. Summary and Statistical Analysis of the Maternal Feed Consumption (page 3 of 3)

^aIncludes all pregnant dams until they were sacrificed on gestational day 20. Reported as the mean \pm S.E.M.;
gd=gestational day.

#Bartlett's test for homogeneity of variances was significant ($p < 0.001$) or could not be done because there was
zero variance in one or more groups, therefore nonparametric statistical procedures were employed.

† $p < 0.05$; ANOVA Test.

‡ $p < 0.01$; ANOVA Test.

‡‡ $p < 0.001$; ANOVA Test.

\$ $p < 0.05$; Test for Linear Trend.

\$\$ $p < 0.01$; Test for Linear Trend.

\$\$\$ $p < 0.001$; Test for Linear Trend.

* $p < 0.05$; Dunnett's Test.

** $p < 0.01$; Dunnett's Test.

††† $p < 0.001$; Kruskal-Wallis Test.

‡‡‡ $p < 0.001$; Jonckheere's Test.

□ $p < 0.05$; Mann-Whitney U Test.

□□ $p < 0.01$; Mann-Whitney U Test.

Table 5. Summary and Statistical Analysis of Uterine Contents, Live Fetal Sex and Live Fetal Weight
(page 1 of 3)

	Isopropyl Cellosolve® (ppm, inhalation)			
	0	100	300	600
ALL LITTERS^a	23	25	23	23
No. Corpora Lutea per Dam^b				
#	16.83 ± 0.27 N=23	16.52 ± 0.39 N=25	16.57 ± 0.39 N=23	16.35 ± 0.72 N=23
No. Implantation Sites per Litter^b				
#	15.52 ± 0.33 N=23	15.72 ± 0.48 N=25	15.61 ± 0.37 N=23	15.30 ± 0.75 N=23
Percent Preimplantation Loss per Litter^b				
	7.67 ± 1.54 N=23	5.60 ± 1.69 N=25	5.59 ± 1.29 N=23	8.37 ± 2.90 N=23
No. Resorptions per Litter^b				
	0.43 ± 0.15 N=23	0.76 ± 0.22 N=25	0.35 ± 0.15 N=23	0.78 ± 0.23 N=23
Percent Resorptions per Litter^b				
	2.92 ± 1.02 N=23	4.46 ± 1.28 N=25	2.17 ± 0.90 N=23	4.89 ± 1.41 N=23
No. Litters with Resorptions	8	13	5	10
% Litters with Resorptions	34.78	52.00	21.74	43.48
No. Late Fetal Deaths per Litter^b				
	0.00 ± 0.00 N=23	0.00 ± 0.00 N=25	0.00 ± 0.00 N=23	0.00 ± 0.00 N=23
Percent Late Fetal Deaths per Litter^b				
#	0.00 ± 0.00 N=23	0.00 ± 0.00 N=25	0.00 ± 0.00 N=23	0.00 ± 0.00 N=23
No. Litters with Late Fetal Deaths	0	0	0	0
% Litters with Late Fetal Deaths	0.00	0.00	0.00	0.00

(continues)

Table 5. Summary and Statistical Analysis of Uterine Contents, Live Fetal Sex and Live Fetal Weight
(page 2 of 3)

	Isopropyl Cellosolve® (ppm, inhalation)			
	0	100	300	600
No. Nonlive Implants per Litter ^{b,c}	0.43 ± 0.15 N=23	0.76 ± 0.22 N=25	0.35 ± 0.15 N=23	0.78 ± 0.23 N=23
Percent Nonlive Implants per Litter ^{b,c}	2.92 ± 1.02 N=23	4.46 ± 1.28 N=25	2.17 ± 0.90 N=23	4.89 ± 1.41 N=23
No. Litters with Nonlive Implants ^c	8	13	5	10
% Litters with Nonlive Implants ^c	34.78	52.00	21.74	43.48
No. Adversely Affected Implants per Litter ^{b,d}	0.57 ± 0.19 N=23	0.96 ± 0.20 N=25	0.61 ± 0.20 N=23	1.22 ± 0.23 N=23
Percent Adversely Affected Implants per Litter ^{b,d}	3.77 ‡ ± 1.25 N=23	5.80 ± 1.20 N=25	3.90 ± 1.27 N=23	7.56 * ± 1.46 N=23
No. Litters with Adversely Affected Implants ^d	9	18	8	15
% Litters with Adversely Affected Implants ^d	39.13 £	72.00	34.78	65.22
LIVE LITTERS^e	23	25	23	23
No. Live Fetuses per Litter ^b	15.09 ± 0.39 N=23	14.96 ± 0.44 N=25	15.26 ± 0.36 N=23	14.52 ± 0.73 N=23
Percent Male Fetuses per Litter ^b	47.51 ‡ ± 3.02 N=23	50.60 ± 2.33 N=25	56.28 ± 2.84 N=23	44.37 ± 2.86 N=23
No. Male Fetuses per Litter ^b	7.09 ± 0.42 N=23	7.68 ± 0.41 N=25	8.61 ± 0.48 N=23	6.70 ± 0.46 N=23

(continued)

Table 5. Summary and Statistical Analysis of Uterine Contents, Live Fetal Sex and Live Fetal Weight
(page 3 of 3)

	Isopropyl Cellosolve® (ppm, inhalation)			
	0	100	300	600
No. Female Fetuses per Litter^b	8.00 ± 0.52 N=23	7.28 ± 0.33 N=25	6.65 ± 0.43 N=23	7.83 ± 0.51 N=23
Average Fetal Body Weight (g) per Litter^b	3.509 ± 0.048 N=23	3.517 ± 0.066 N=25	3.524 ± 0.054 N=23	3.452 ± 0.075 N=23
Average Male Fetal Body Weight (g) per Litter^b	3.611 ± 0.052 N=23	3.619 ± 0.071 N=25	3.606 ± 0.055 N=23	3.516 ± 0.076 N=22 ^f
Average Female Fetal Body Weight (g) per Litter^b	3.424 ± 0.050 N=23	3.409 ± 0.063 N=25	3.407 ± 0.057 N=23	3.370 ± 0.075 N=23

Repeated Measures for Average Fetal Body Weight per Litter:

Bartlett's (p=0.2469); DOSE (p=0.9184); SEX (p≤0.0001); DOSEXSEX (p=0.8502).

^aIncludes all dams pregnant at terminal sacrifice on gestational day 20; litter size = no. implantation sites per dam.

^bReported as the mean ± S.E.M.

^cNonlive = late fetal deaths plus resorptions.

^dAdversely affected = nonlive plus malformed

^eIncludes only dams with live fetuses; litter size = no. live fetuses per dam.

^fOne litter had only female fetuses.

[#]Bartlett's test for homogeneity of variances was significant (p<0.001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed.

[‡]p<0.05; ANOVA Test.

^{*}p<0.05; Dunnett's Test.

[£]p<0.05; Chi-Square Test.

Table 6. Summary and Statistical Analysis of Malformations and Variations (page 1 of 4)

	Isopropyl Cellosolve® (ppm, inhalation)			
	0	100	300	600
No. Fetuses Examined ^a	347	374	351	334
No. Litters Examined ^b	23	25	23	23
No. Fetuses with External Malformations ^c	0	1	1	1
% Fetuses with External Malformations ^c	0.00	0.27	0.28	0.30
No. Litters with External Malformations ^d	0	1	1	1
% Litters with External Malformations ^d	0.00	4.00	4.35	4.35
No. Fetuses with Visceral Malformations ^c	3	4	5	9
% Fetuses with Visceral Malformations ^c	1.71	2.16	2.86	5.33
No. Litters with Visceral Malformations ^d	2	4	4	5
% Litters with Visceral Malformations ^d	8.70	16.00	17.39	21.74
No. Fetuses with Skeletal Malformations ^c	0	0	1	0
% Fetuses with Skeletal Malformations ^c	0.00	0.00	0.57	0.00
No. Litters with Skeletal Malformations ^d	0	0	1	0
% Litters with Skeletal Malformations ^d	0.00	0.00	4.35	0.00

(continued)

Table 6. Summary and Statistical Analysis of Malformations and Variations (page 2 of 4)

	Isopropyl Cellosolve® (ppm, inhalation)			
	0	100	300	600
No. Fetuses with Malformations per Litter^{C,e}	0.13 ± 0.10 N=23	0.20 ± 0.08 N=25	0.26 ± 0.11 N=23	0.43 ± 0.18 N=23
No. Male Fetuses with Malformations per Litter^{C,e}	0.09 ± 0.09 N=23	0.20 ± 0.08 N=25	0.22 ± 0.11 N=23	0.23 ± 0.11 N=22 ^f
No. Female Fetuses with Malformations per Litter^{C,e}	0.04 ± 0.04 N=23	0.00 ± 0.00 N=25	0.04 ± 0.04 N=23	0.22 ± 0.11 N=23
Percent Fetuses with Malformations per Litter^{C,e}	0.89 ± 0.67 N=23	1.34 ± 0.55 N=25	1.80 ± 0.79 N=23	2.69 ± 1.09 N=23
Percent Male Fetuses with Malformations per Litter^{C,e}	2.90 ± 2.90 N=23	2.57 ± 1.08 N=25	2.68 ± 1.35 N=23	2.68 ± 1.31 N=22 ^f
Percent Female Fetuses with Malformations per Litter^{C,e}	# 0.43 ± 0.43 N=23	0.00 ± 0.00 N=25	0.54 ± 0.54 N=23	2.46 ± 1.19 N=23
Repeated Measures for Percent Fetuses with Malformations per Litter: Bartlett's (9); DOSE (p=0.5821); SEX (p=0.0393); DOSEXSEX (p=0.5510).				
No. Fetuses with Malformations^C	3	5	6	10
% Fetuses with Malformations^C	0.86	1.34	1.71	2.99
No. Litters with Malformations^d	2	5	5	6
% Litters with Malformations^d	8.70	20.00	21.74	26.09

(continued)

Table 6. Summary and Statistical Analysis of Malformations and Variations (page 3 of 4)

	Isopropyl Cellosolve [®] (ppm, inhalation)			
	0	100	300	600
No. Fetuses with External Variations^c	1	0	0	0
% Fetuses with External Variations^c	0.29	0.00	0.00	0.00
No. Litters with External Variations^d	1	0	0	0
% Litters with External Variations^d	4.35	0.00	0.00	0.00
No. Fetuses with Visceral Variations^c	35	42	43	53
% Fetuses with Visceral Variations^c	20.00	22.70	24.57	31.36
No. Litters with Visceral Variations^d	17	17	19	20
% Litters with Visceral Variations^d	73.91	68.00	82.61	86.96
No. Fetuses with Skeletal Variations^c	12	12	7	7
% Fetuses with Skeletal Variations^c	6.98	6.35	3.98	4.22
No. Litters with Skeletal Variations^d	8	8	7	5
% Litters with Skeletal Variations^d	34.78	32.00	30.43	21.74
No. Fetuses with Variations per Litter^{c,e}	2.09 ± 0.35 N=23	2.16 ± 0.38 N=25	2.17 ± 0.26 N=23	2.61 ± 0.37 N=23
No. Male Fetuses with Variations per Litter^{c,e}	1.04 ± 0.20 N=23	1.28 ± 0.25 N=25	1.43 ± 0.23 N=23	1.23 ± 0.28 N=22 ^f
No. Female Fetuses with Variations per Litter^{c,e}	1.04 ± 0.23 N=23	0.88 ± 0.25 N=25	0.74 ± 0.14 N=23	1.43 ± 0.23 N=23

(continued)

Table 6. Summary and Statistical Analysis of Malformations and Variations (page 4 of 4)

	Isopropyl Cellosolve® (ppm, inhalation)			
	0	100	300	600
Percent Fetuses with Variations per Litter ^{c,e}	13.91 ± 2.30 N=23	14.09 ± 2.29 N=25	14.37 ± 1.79 N=23	17.19 ± 2.33 N=23
Percent Male Fetuses with Variations per Litter ^{c,e}	14.86 ± 2.91 N=23	15.84 ± 2.96 N=25	16.82 ± 3.03 N=23	16.11 ± 3.28 N=22 ^f
Percent Female Fetuses with Variations per Litter ^{c,e}	13.14 ± 2.97 N=23	11.38 ± 2.81 N=25	12.02 ± 2.55 N=23	18.61 ± 3.30 N=23
Repeated Measures for Percent Fetuses with Variations per Litter: Bartlett's (p=0.9991); DOSE (p=0.7622); SEX (p=0.3195); DOSExSEX (p=0.2862).				
No. Fetuses with Variations ^c	48	54	50	60
% Fetuses with Variations ^c	13.83	14.44	14.25	17.96
No. Litters with Variations ^d	18	20	21	21
% Litters with Variations ^d	78.26	80.00	91.30	91.30

^aOnly live fetuses were examined for malformations and variations.

^bIncludes only litters with live fetuses.

^cFetuses with one or more malformations or variations.

^dLitters with one or more fetuses with malformations or variations.

^eReported as the mean ± S.E.M.

^fOne litter had only female fetuses.

^gZero variance in one or more groups - test not done.

[#]Bartlett's test for homogeneity of variances was significant (p<0.001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed.

Table 7. Summary of Morphological Abnormalities in CD Rat Fetuses: Listing by Defect Type^a (page 1 of 3)

	Isopropyl Cellosolve [®] (ppm, inhalation)			
	0	100	300	600
ANY MALFORMATIONS				
Total No. of Fetuses Examined for Any Malformations ^b	347	374	351	334
No. of Fetuses with Any Malformations ^c	3	5	6	10
% Fetuses with Any Malformations	0.9%	1.3%	1.7%	3.0%
Total No. of Litters Examined for Any Malformations ^d	23	25	23	23
No. of Litters with Any Malformations ^e	2	5	5	6
% Litters with Any Malformations	8.7%	20.0%	21.7%	26.1%
EXTERNAL MALFORMATIONS				
Total No. of Fetuses Examined for External Malformations ^b	347	374	351	334
No. of Fetuses with External Malformations ^c	0	1	1	1
% Fetuses with External Malformations	0.0%	0.3%	0.3%	0.3%
Total No. of Litters Examined for External Malformations ^d	23	25	23	23
No. of Litters with External Malformations ^e	0	1	1	1
% Litters with External Malformations	0.0%	4.0%	4.3%	4.3%
Cleft Palate			1(1)	1(1)
Anasarca			1(1)	
Micromelia			1(1)	
Short Thread Like Tail		1(1)		
VISCERAL MALFORMATIONS				
Total No. of Fetuses Examined for Visceral Malformations ^b	175	185	175	169
No. of Fetuses with Visceral Malformations ^c	3	4	5	9
% Fetuses with Visceral Malformations	1.7%	2.2%	2.9%	5.3%
Total No. of Litters Examined for Visceral Malformations ^d	23	25	23	23
No. of Litters with Visceral Malformations ^e	2	4	4	5
% Litters with Visceral Malformations	8.7%	16.0%	17.4%	21.7%
Kidneys Fused with One Ureter	1(1)			
Hydronephrosis: Bilateral				3(3)
Left				
Right		1(1)		
Hydroureter: Bilateral	1(1)		1(1)	5(4)
Left	1(1)	1(1)	2(2)	3(3)
Right		1(1)	2(2)	1(1)
Right	1(1)	1(1)		1(1)
SKELETAL MALFORMATIONS				
Total No. of Fetuses Examined for Skeletal Malformations ^b	172	189	176	166
No. of Fetuses with Skeletal Malformations ^c	0	0	1	0
% Fetuses with Skeletal Malformations	0.0%	0.0%	0.6%	0.0%
Total No. of Litters Examined for Skeletal Malformations ^d	23	25	23	23
No. of Litters with Skeletal Malformations ^e	0	0	1	0
% Litters with Skeletal Malformations	0.0%	0.0%	4.3%	0.0%
Cartilage of Sternum Split			1(1)	

(continued)

Table 7. Summary of Morphological Abnormalities in CD Rat Fetuses: Listing by Defect Type^a (page 2 of 3)

	Isopropyl Cellosolve [®] (ppm, inhalation)			
	0	100	300	600
ANY VARIATIONS				
Total No. of Fetuses Examined for Any Variations ^b	347	374	351	334
No. of Fetuses with Any Variations ^c	48	54	50	60
% Fetuses with Any Variations	13.8%	14.4%	14.2%	18.0%
Total No. of Litters Examined for Any Variations ^d	23	25	23	23
No. of Litters with Any Variations ^e	18	20	21	21
% Litters with Any Variations	78.3%	80.0%	91.3%	91.3%
EXTERNAL VARIATIONS				
Total No. of Fetuses Examined for External Variations ^b	347	374	351	334
No. of Fetuses with External Variations ^c	1	0	0	0
% Fetuses with External Variations	0.3%	0.0%	0.0%	0.0%
Total No. of Litters Examined for External Variations ^d	23	25	23	23
No. of Litters with External Variations ^e	1	0	0	0
% Litters with External Variations	4.3%	0.0%	0.0%	0.0%
Hematoma: Neck			1(1)	
VISCERAL VARIATIONS				
Total No. of Fetuses Examined for Visceral Variations ^b	175	185	175	169
No. of Fetuses with Visceral Variations ^c	35	42	43	53
% Fetuses with Visceral Variations	20.0%	22.7%	24.6%	31.4%
Total No. of Litters Examined for Visceral Variations ^d	23	25	23	23
No. of Litters with Visceral Variations ^e	17	17	19	20
% Litters with Visceral Variations	73.9%	68.0%	82.6%	87.0%
Enlarged Lateral Ventricle (Full): Bilateral	1(1)	2(2)	2(1)	8(6)
Left	2(2)	2(2)	3(3)	
Right	2(2)	2(2)		2(2)
Enlarged Lateral Ventricle (Half): Bilateral	12(9)	14(7)	12(8)	16(10)
Left	6(6)	8(6)	4(3)	8(6)
Right	5(5)	6(5)	5(4)	2(1)
Agenesis of the Innominate Artery	2(2)			
Distended Ureter: Bilateral	7(6)	6(6)	9(7)	12(8)
Left	1(1)	5(5)	3(2)	2(2)
Right	1(1)	2(2)	7(6)	6(6)
Displaced Ovary: Bilateral	1(1)			

(continued)

Table 7. Summary of Morphological Abnormalities in CD Rat Fetuses: Listing by Defect Type^a (page 3 of 3)

	Isopropyl Cellosolve [®] (ppm, inhalation)			
	0	100	300	600
SKELETAL VARIATIONS				
Total No. of Fetuses Examined for Skeletal Variations ^b	172	189	176	166
No. of Fetuses with Skeletal Variations ^c	12	12	7	7
% Fetuses with Skeletal Variations	7.0%	6.3%	4.0%	4.2%
Total No. of Litters Examined for Skeletal Variations ^d	23	25	23	23
No. of Litters with Skeletal Variations ^e	8	8	7	5
% Litters with Skeletal Variations	34.8%	32.0%	30.4%	21.7%
Misaligned Sternebrae	1(1)	1(1)		1(1)
Rib on Lumbar I: Bilateral Full	1(1)			
Bilateral Rudimentary	1(1)		1(1)	
Left Rudimentary	1(1)	1(1)	1(1)	
Right Rudimentary	2(1)	2(1)		1(1)
Short Rib: XIII		2(1)		1(1)
Normal Cartilage, Bipartite Ossification Center, Thoracic Centrum	3(3)	2(2)	2(2)	
Dumbbell Cartilage, Normal Ossification Center, Thoracic Centrum			1(1)	
Dumbbell Cartilage, Dumbbell Ossification Center, Thoracic Centrum	3(2)	3(3)		3(2)
Dumbbell Cartilage, Bipartite Ossification Center, Thoracic Centrum	2(2)	1(1)	2(2)	1(1)

^aA single fetus may be represented more than once in listing individual defects. Data are presented as the number of fetuses (number of litters).

^bOnly live fetuses were examined.

^cFetuses with one or more malformations/variations

^dIncludes only litters with live fetuses.

^eLitters with one or more malformed/variant fetuses.

GLP COMPLIANCE STATEMENT

This study was performed in compliance with the Good Laboratory Practices (GLP) Standards promulgated by the U.S. Environmental Protection Agency, Toxic Substances Control Act (TSCA), Final Rule, *Federal Register* 54, 34034-34050, August 17, 1989, the Good Laboratory Practice regulations as set forth in the Code of Federal Regulations (40 CFR 792). The raw data have been reviewed and the evaluation of the test article as presented herein represents an appropriate conclusion within the context of the study design and evaluation criteria.

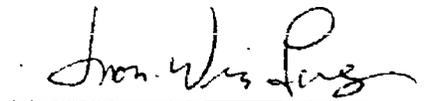
All test and control results in this report are supported by an experimental data record, and this record has been reviewed. Ethylene glycol monoisopropyl ether (EGIE), the test article of the present study, was supplied by the Sponsor and characterized by the Sponsor. All raw data, documentation, records, protocols, and the Final Report generated as a result of this study will be archived in the CIIT Secure Archives.



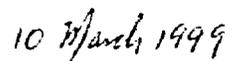
Frank Welsch, DVM, DABT
Study Director
Chemical Industry Institute of Toxicology



Date



Hon-Wing Leung, Ph.D., DABT, CIH
Associate Director of Applied Toxicology
Union Carbide Corporation
Sponsor's Representative



Date

97006/572

LABORATORY QA STATEMENT
(RTI and CIIT)

QUALITY ASSURANCE UNIT INSPECTION AND REPORTING DATES

Study Title: Developmental Toxicity Evaluation of Inhaled Isopropyl Cellosolve® (Ethylene Glycol Monoisopropyl Ether, EGIE) Vapor in CD® (Sprague-Dawley) Rats

CIIT Protocol No.: 97006
RTI Master Protocol No.: RTI-572

Study Director: Frank Welsch, D.V.M., DABT, CIIT
Co-Investigator: Rochelle W. Tyl, Ph.D., DABT, RTI

RTI Project No.: 65C-6625-200
RTI Study Code: RI 97-EGIE
UCC Study No.: 96U1661

Sponsor: Union Carbide Corporation

<u>Phase(s)</u>	<u>Quality Assurance Unit (QAU) inspection Date(s)</u>	<u>Date of QAU Report to Study Director</u>	<u>Date of QAU Report to Management</u>
<u>Protocol Review</u>	<u>02/25/97</u>	<u>02/25/97</u>	<u>02/25/97</u>
<u>Pre-Experimental Period</u>	<u>03/10-11/97</u>	<u>03/11/97</u>	<u>03/11/97</u>
<u>Experimental Period</u>	<u>03/26/97</u>	<u>03/26/97</u>	<u>03/26/97</u>
<u>Experimental Period</u>	<u>04/01/97</u>	<u>04/01/97</u>	<u>04/01/97</u>
<u>Experimental Period</u>	<u>04/14/97</u>	<u>04/14/97</u>	<u>04/14/97</u>
<u>Protocol Amendment</u>	<u>04/25/97</u>	<u>04/25/97</u>	<u>04/25/97</u>
<u>Experimental Period</u>	<u>04/11/97 and 04/30/97</u>	<u>04/30/97</u>	<u>04/30/97</u>
<u>Raw Data/Draft Final Report</u>	<u>8/29/97, 9/12/97, 9/19/97, 09/24-26/97, 09/29-30/97 and 10/2/97</u>	<u>10/08/97</u>	<u>10/08/97</u>
<u>Raw Data/Draft Final Report</u>	<u>07/97</u>	<u>10/09/97</u>	<u>10/09/97</u>

97006/572

LABORATORY QA STATEMENT
(RTI and CIIT)

QUALITY ASSURANCE UNIT INSPECTION AND REPORTING DATES

Study Title: Developmental Toxicity Evaluation of Inhaled Isopropyl Cellosolve® (Ethylene Glycol Monoisopropyl Ether, EGIE) Vapor in CD® (Sprague-Dawley) Rats

CIIT Protocol No.: 97006

Study Director: Frank Welsch, D.V.M., DABT, CIIT

RTI Master Protocol No.: RTI-572

Co-Investigator: Rochelle W. Tyl, Ph.D., DABT, RTI

RTI Project No.: 65C-6625-200

RTI Study Code: Rt 97-EGIE

UCC Study No.: 96U1661

Sponsor: Union Carbide Corporation

<u>Phase(s)</u>	<u>Quality Assurance Unit (QAU) Inspection Date(s)</u>	<u>Date of QAU Report to Study Director</u>	<u>Date of QAU Report to Management</u>
<u>Raw Data/Draft Final Report</u>	<u>03/04-05/99</u>	<u>03/09/99</u>	<u>03/09/99</u>
<u>Final Report</u>	<u>03/10/99</u>	<u>03/10/99</u>	<u>03/10/99</u>

Phase inspections, raw data and final report reviews were performed by the CIIT and/or the RTI Quality Assurance Unit in accordance with the U.S. Environmental Protection Agency's Toxic Substances Control Act (TSCA) (40 CFR Part 792). The dates of the QAU inspections and dates results were reported to the Study Director and Management are noted in the above list.

The Quality Assurance Unit at CIIT and RTI has reviewed the final report to help assure that the report describes the methods and that the reported results reflect the raw data.

Patricia O'Brien Pomerleau 11 March 1999
 Patricia O'Brien Pomerleau, M.S. Date
 Quality Assurance Manager, CIIT

David L. Brodish 11 March 1999
 David L. Brodish, M.A. Date
 Quality Assurance Manager, RTI

APPENDIX I

Test Material Characterization and Generation
and Analyses of Test Atmospheres

Part A

Union Carbide Corporation (UCC)

1. Analysis of Isopropyl Glycol Ether
2. Isopropyl CELLOSOLVE® GLP
Analytical Characterization

Parts B, C, and D

Chemical Industry Institute of Toxicology (CIIT)

Part B: Test Substance Identity and Purity Report

Part C: Definitive Study Inhalation Report

Part D: Range-Finding Study Inhalation Report