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HEALTH, SAFETY AND ENVIRONMENTAL AFFAIRS

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Attn: Section 8(e) Coordinator (CAP Agreement)

Re: CAP Agreement Identification No. 8ECAP-0110

Dear Sir or Madam:

Union Carbide Corporation ("Union Carbide") herewith submits the following report pursuant to the terms of the TSCA §8(e) Compliance Audit Program and Union Carbide's CAP Agreement dated August 14, 1991 (8ECAP-0110). This report describes a mice developmental study with triethylene glycol (CASRN 112-27-6).

"Developmental toxicity Study of Triethylene Glycol Administered by Gavage to CD®-1 Mice", Bushy Run Research Center, Project Report 53-65, November 16, 1990.

A complete summary of this report is attached.

Previous TSCA Section 8(e) or "FYI" Submission(s) related to this substance are:

(none)

Previous PMN submissions related to this substance are: (none)

39 OLD RIDGEBURY ROAD, DANBURY, CT 06817-0001

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This information is submitted in light of EPA's current guidance. Union Carbide does not necessarily agree that this information reasonably supports the conclusion that the subject chemical presents a substantial risk of injury to health or the environment.

In the attached report the term "BUSINESS CONFIDENTIAL" is entered on the first page. This precautionary statement was for internal use at the time of issuance of the 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.

Yours truly,

William C. Kuryla, Ph.D.
Assistant Director
Product Safety
(203/794-5230)

WCK/cr
Attachment (3 copies of cover letter, summary, and report)

trieg

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SUMMARY

53-65

Developmental Toxicity Study of Triethylene Glycol Administered by Gavage to CD®-1 Mice

Sponsor: Industrial Chemicals Division
Union Carbide Chemicals and
Plastics Company Inc.

* * * * *

ABSTRACT

Timed-pregnant CD®-1 mice were exposed to triethylene glycol (CAS No. 112-27-6) by gavage on gestational days (gd) 6 through 15 at doses of 0.0, 0.5, 5.0 or 10.0 ml/kg/day, 30 plug-positive females per group. As the test chemical was dosed "neat" (undiluted), the dose volume employed was based on the dose selected for each group and the individual animals' most recent body weight. Vehicle control animals were dosed with deionized water at a volume equivalent to the top dose volume (10.0 ml/kg/day). Clinical observations were taken daily and maternal body weights were measured on gd 0, 6, 9, 12, 15 and 18. Food and water consumption was measured throughout gestation (gd 0-18). At scheduled sacrifice on gd 18, the dams were evaluated for body weight, liver weight, kidney (2) weight, gravid uterine weight and status of implantation sites (i.e. resorptions, dead fetuses, live fetuses). Maternal kidneys were retained in fixative and fixed kidneys from high dose and control groups were examined microscopically. Live fetuses were dissected from the uterus, counted, weighed, sexed and examined for external abnormalities. All live fetuses in each litter were examined for visceral malformations and variations. Approximately one-half of the live fetuses in each litter were then 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 (50% intact, 50% decapitated) in each litter were eviscerated, fixed in alcohol, stained with alizarin red S and examined for skeletal malformations and variations.

There were no treatment-related maternal deaths. No dams aborted. One female, at 10.0 ml/kg/day, delivered early. One dam each at 0.0, 0.5 and 10.0 ml/kg/day, and two dams at 5.0 ml/kg/day contained uteri with nonviable

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UNION CARBIDE

BUSHY RUN RESEARCH CENTER

6702 Mellon Road, Export, Pennsylvania 15632-8902

Telephone (412) 733-5200
Telecopier (412) 733-4804

PROJECT REPORT 53-65

TITLE: Developmental Toxicity Study of Triethylene Glycol Administered by Gavage to CD®-1 Mice

AUTHOR: T. L. Neeper-Bradley

SPONSOR: Industrial Chemicals Division
Union Carbide Chemicals and
Plastics Company Inc.
39 Old Ridgebury Road
Danbury, CT 06817-0001

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DATE: November 16, 1990

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BUSHY RUN RESEARCH CENTER

5702 Mellon Road, Export, Pennsylvania 15632-8902

Telephone (412) 733-5200
Telecopier (412) 733-4804

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Developmental Toxicity Study of Triethylene Glycol Administered by Gavage to CD®-1 Mice

Sponsor: Industrial Chemicals Division
Union Carbide Chemicals and
Plastics Company Inc.

* * * * *

ABSTRACT

Timed-pregnant CD®-1 mice were exposed to triethylene glycol (CAS No. 112-27-6) by gavage on gestational days (gd) 6 through 15 at doses of 0.0, 0.5, 5.0 or 10.0 ml/kg/day, 30 plug-positive females per group. As the test chemical was dosed "neat" (undiluted), the dose volume employed was based on the dose selected for each group and the individual animals' most recent body weight. Vehicle control animals were dosed with deionized water at a volume equivalent to the top dose volume (10.0 ml/kg/day). Clinical observations were taken daily and maternal body weights were measured on gd 0, 6, 9, 12, 15 and 18. Food and water consumption was measured throughout gestation (gd 0-18). At scheduled sacrifice on gd 18, the dams were evaluated for body weight, liver weight, kidney (2) weight, gravid uterine weight and status of implantation sites (i.e. resorptions, dead fetuses, live fetuses). Maternal kidneys were retained in fixative and fixed kidneys from high dose and control groups were examined microscopically. Live fetuses were dissected from the uterus, counted, weighed, sexed and examined for external abnormalities. All live fetuses in each litter were examined for visceral malformations and variations. Approximately one-half of the live fetuses in each litter were then 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 (50% intact, 50% decapitated) in each litter were eviscerated, fixed in alcohol, stained with alizarin red S and examined for skeletal malformations and variations.

There were no treatment-related maternal deaths. No dams aborted. One female, at 10.0 ml/kg/day, delivered early. One dam each at 0.0, 0.5 and 10.0 ml/kg/day, and two dams at 5.0 ml/kg/day contained uteri with nonviable

implants only. A total of 25-28 live litters were examined in each dose group. Maternal gestational body weights and weight gains were equivalent across dose groups. Food and water consumption were statistically equivalent across dose groups as well. Treatment-related clinical signs were observed only at 10.0 ml/kg/day and included hypoactivity and audible and rapid respiration. At scheduled sacrifice on gd 18, maternal body weight (corrected for gravid uterine weight), gestational weight gain (corrected) and liver weight (relative or absolute) from treated dams were equivalent across dose groups. Relative (but not absolute) kidney weights were significantly increased at 10.0 ml/kg/day. Gestational parameters, including number of ovarian corpora lutea, total, viable and nonviable implantations per litter, and sex ratio were unaffected by treatment. Fetal body weights per litter (all fetuses, males or females) were significantly reduced at 5.0 and 10.0 ml/kg/day.

There were no statistically significant increases in the incidences of malformations (individual, pooled external, visceral, skeletal or total) in any treatment group relative to controls. There were no treatment-related differences among groups for individual external or visceral variations or for pooled external, visceral, skeletal or total variations. Six (6) individual skeletal variations (cervical centra #1, #2, #3 and/or #4 poorly ossified, reduced number of caudal segments, poorly ossified frontal bone, poorly ossified supraoccipital, some proximal phalanges of the hindlimb unossified and some proximal phalanges of the hindlimb poorly ossified) exhibited increased incidences at 10.0 ml/kg/day. The incidences of poorly ossified frontal and supraoccipital bones were also significantly increased at 5.0 ml/kg/day. There were no significantly increased incidences of skeletal variations at 0.5 ml/kg/day.

In conclusion, exposure of pregnant CD®-1 mice to triethylene glycol by gavage at 0.5, 5.0 and 10.0 ml/kg/day during organogenesis resulted in evidence of slight maternal toxicity at 10.0 ml/kg/day and consistent evidence of developmental delay at 5.0 and 10.0 ml/kg/day. No significant embryotoxicity or teratogenicity was observed at any dosage employed, including those which produced maternal toxicity. The "no observable effect level" (NOEL) for maternal toxicity was 5.0 ml/kg/day, and the NOEL for developmental toxicity was 0.5 ml/kg/day.

OBJECTIVES

The present study was designed to evaluate the potential of triethylene glycol to produce maternal and developmental toxicity (including teratogenicity) when administered by gavage (oral intubation) during organogenesis in CD®-1 mice.

MATERIALS AND METHODS

Test Chemical, Dosage Formulations and Analyses

The test chemical, triethylene glycol (TEG; glycol-bis(hydroxyethyl)ether; ethanol, 2,2'[1,2-ethanediylbis(oxy)] bis-; CAS No. 112-27-6), bearing the identification TANK 9502 PC-88505, was received in two one-gallon sealed plastic bottles from Union Carbide Corporation, Texas City, TX, on September 29, 1988. The shipment was assigned the Bushy Run Research Center (BRRC) Sample Nos. 51-438 A and B. The material was a clear, nonviscous liquid. The accompanying analytical sheet indicated a purity of 99.9%. Test chemical characterization performed at Union Carbide Corporations' Technical Skills Center, South Charleston, WV indicated a test chemical purity of greater than 99% TEG as measured by capillary GC and GC/MS. (See Appendix 7 for details.)

Since the test chemical was administered undiluted, no homogeneity, stability or dose-level verification analyses were performed at BRRC.

Animals and Animal Husbandry

Two hundred six (206) virgin male and virgin female [CR1:CD®-1(ICR)BR] outbred albino mice referred to as the CD®-1 mouse were received from Charles River Breeding Laboratories, Inc., Kingston, NY, on April 24, 1989. Males' and females' date of birth was March 13, 1989; animals were 42 days old upon arrival with males weighing approximately 25-30 g and females' approximately 23-25 g. Animals were housed in stainless steel wire-mesh cages (23.5 cm x 20.0 cm x 18 cm high) in animal rooms 107 (from April 25 to April 28, 1989) and 147 (from April 28-June 2, 1989). During the two-week quarantine period females and males were housed one to three per cage per sex and representative animals were subjected to fecal sampling, histologic examination of selected organs and to serum viral antibody examination. Quality control results indicated that the animals were suitable for use. Food (Prolab Certified Ground Rodent Chow® RMH-3200, Batch Nos. DEC 20 88 W2 and FEB 8 89 W2, Agway, Inc., St. Marys, OH) and water (Municipal Authority of Westmoreland County, Greensburg, PA) were available ad libitum. Females were maintained on water bottles with stainless steel sipper tubes to allow water consumption measurements. All animals were assigned a unique number and were identified by a system of toe clipping and ear notching.

Deotized Animal Cage Board® (Shepherd Specialty Papers, Inc., Kalamazoo, MI) was placed beneath the cages and changed frequently. Animals were kept on a 12-hour photoperiod and room temperatures and humidity were recorded continuously (Cole-Parmer Hygrothermograph® Seven-Day Continuous Recorder, Model #8368-00, Cole-Parmer Instrument Company, Chicago, IL). Throughout the study, temperature was maintained at 68-72°F except for a brief (less than 15 minutes) spike at 72-74°F. Relative humidity was maintained at 40-60% except for four brief spikes (three at 60-62% and one at 68-83.5%). There were also several excursions, totalling 55 hours, during which the humidity ranged from 34-40%.

Mice were mated 1:1 (one male:one female) in stainless steel wire-mesh cages (23.5 cm x 20.0 cm x 18 cm high) and the paperboard beneath the cages was checked daily for dropped copulation plugs (Hafez, 1970). Each male was used only once in this study. Successfully mated (plug-positive) females were housed singly in animal room 147 for the duration of the study. The day a dropped copulation plug was found was designated gestational day (gd) 0 (Hafez, 1970). Thirty (30) plug-positive females were assigned to each experimental

group by a randomization procedure stratified by body weight such that all groups were equivalent in both mean body weight and body weight range on gd 0; mean body weights were 26.55-26.61 grams on gd 0. The mating period for these animals was May 11-15, 1989; gd 0 was May 12 through May 15, 1989).

Treatment

Timed-pregnant CD®-1 dams were dosed daily with undiluted TEG or vehicle alone on gd 6 through 15. All treatments were administered by gavage using a 18 gauge stainless steel dosing tube 1.5 inches long (Perfektum®, Popper and Sons, Inc., New Hyde Park, NY) attached to a 50 or 1000 µl glass tuberculin syringe (Becton-Dickinson), depending on the dose level. The dose volume was based on the dose group and the individual animals' most recent body weight. The doses employed were 0.0, 0.5, 5.0 or 10.0 ml/kg/day based on results from a dose range-finding study also performed on timed-pregnant CD®-1 mice (Appendix 5). Vehicle control animals were dosed with deionized (Millipore®) water (CAS No. 7732-18-5) at the top dose volume (10.0 ml/kg/day).

All females on study were weighed on gd 0, 6 (prior to onset of dosing), 9, 12, 15 (during the dosing period) and 18. Food and water consumption were measured at three-day intervals throughout gestation (gd 0-18). All females were examined daily for clinical signs of toxicity. The treatment period for all study females was gd 6 through 15, May 18 through May 30, 1989.

Thoracolaparotomy and Maternal and Fetal Examinations

All surviving study females were sacrificed on gd 18 by carbon dioxide asphyxiation. The sacrifice period was May 30 through June 2, 1989. The maternal body cavities were opened by midline thoracolaparotomy. The gravid uterus, ovaries (including corpora lutea), cervix, vagina and abdominal and thoracic cavities were examined grossly. Ovarian corpora lutea of pregnancy were counted. Maternal liver and uterine weights were determined. Maternal kidneys (2) were also weighed, and then bisected (left longitudinally, right transversely) and fixed in buffered neutral 10% formalin for possible subsequent histopathologic examination (kidneys from high-dose and control group dams were subsequently examined by light microscopy). The uterus was externally examined for signs of hemorrhage, removed from the abdominal cavity and dissected longitudinally to expose the contents. All live and dead fetuses and resorption sites were noted and recorded. Uteri from females that appeared nongravid were placed in a 10% ammonium sulfide solution for detection of early resorptions (Salewski, 1964).

All live fetuses were weighed and sexed. All fetuses were examined for external variations and malformations including cleft palate. All live fetuses in each litter were examined for thoracic and abdominal visceral abnormalities by modification of methods described by Staples (1974). One-half of the live fetuses (even-numbered fetuses from litters with an even number of live fetuses, odd-numbered fetuses from litters with an odd number of live fetuses) in each litter were decapitated and their heads were fixed in Bouin's solution for examination of craniofacial structures by sectioning methods modified from Wilson (1965; 1973). All fetuses (50% intact, 50% decapitated) in each litter were eviscerated, fixed in ethanol, processed for skeletal staining with alizarin red S (Crary, 1962; Peltzer and Schardein, 1966), and examined for skeletal malformations and variations.

Statistical Analyses

The unit of comparison was the pregnant female or the litter (Weil, 1970). Results of the quantitative continuous variables (e.g., maternal body weights, organ weights, etc.) were intercompared for the three TEG-exposed groups and the vehicle control group by use of Levene's test for equal variances (Levene, 1960), analysis of variance (ANOVA), and t-tests with Bonferroni probabilities for pairwise comparisons. When Levene's test indicated homogeneous variances and the ANOVA was significant, the pooled t-test was used. When Levene's test indicated heterogeneous variances, all groups were compared by an ANOVA for unequal variances (Brown and Forsythe, 1974) followed, when necessary, by the separate variance t-test.

Nonparametric data obtained following laparohysterectomy were statistically treated using the Kruskal-Wallis test (Sokal and Rohlf, 1969) followed by the Mann-Whitney U test (Sokal and Rohlf, 1969) when appropriate. Incidence data were compared using Fisher's Exact Test (Sokal and Rohlf, 1969). For all statistical tests, the probability value of $p <$ of 0.05 (two-tailed) was used as the critical level of for significance.

Personnel

The evaluation of triethylene glycol for developmental toxicity in CD® (Sprague-Dawley) rats was conducted at Bushy Run Research Center (BRRC), Export, PA under contract to the Sponsor Representative. The BRRC personnel indicated below contributed to the completion of this study.

Dr. R. W. Tyl served as Study Director until June 9, 1989; Dr. T. L. Neeper-Bradley served as Study Director from June 9, 1989 until completion of the Final Report. Developmental toxicology personnel included R. R. Altman, T. R. Brownfield, B. L. Butler, M. A. Copeman, D. L. Fait, L. C. Fisher, L. J. Fosnight, M. F. Kubena (Study Leader for the definitive and range-finding studies) and D. J. Tarasi. The attending veterinarian and pathologist was Dr. P. E. Losco. Analytical personnel included Dr. J. P. Van Miller and M. A. Vrbanic. Quality Assurance personnel included L. J. Calisti, J. R. Bernard, J. H. Coleman and B. E. Thomas. Animal care personnel included A. Chiaramonte, P. E. Biondo, G. W. Klingensmith, Jr., L. E. Lipko and T. D. Schwartz.

The final report was prepared by Dr. T. L. Neeper-Bradley with assistance from L. C. Fisher and M. F. Kubena on data compilation and statistical analyses.

The protocol and five (5) amendments detailing the design and conduct of the study are presented in Appendix 5.

Storage of Records

All original data sheets for the present study are stored in the BRRC Archives along with all biological samples collected during the course of the study which remain the responsibility of BRRC. Work sheets and computer printouts which were generated in the statistical analysis of data are stored in the BRRC Archives. Copies of this report will be filed with the BRRC Archives as well as with Union Carbide Chemicals and Plastics Company Inc., Danbury, CT.

Compliance

All records, data and reports will be maintained in storage for ten (10) years or for as long as the quality of the preparation affords evaluation, whichever is less. This study was performed according to Environmental Protection Agency (EPA) Good Laboratory Practices (EPA, 1983) and EPA TSCA Testing Guidelines (1985; 1987).

RESULTS

The distribution and fate of all plug-positive rats on study are presented in Table 1. No females aborted or died prior to scheduled sacrifice. One female, at 10.0 ml/kg/day, delivered early (on gd 18), was euthanized, and removed from study. Her data were eliminated from the summarized results. Pregnancy rate was equivalent for all dose groups, ranging from 90.0 to 96.7%. One female each at 0.0, 1.0 and 10.0 ml/kg/day and two females at 5.0 ml/kg/day contained only nonviable implants (early or late resorptions or dead fetuses) at scheduled sacrifice. A total of 25 to 28 litters containing one or more live fetuses were examined in each group.

Periodic maternal body weights and body weight changes (Table 2) were statistically equivalent across treatment groups. No apparent trends (nonstatistically significant reductions) were observed at any exposure level.

Clinical observations of the dams were recorded daily (Table 3). There were no statistically significant treatment-related clinical signs of toxicity. However, treatment-associated clinical signs were observed in two dams at 10.0 ml/kg/day. These included hypoactivity in both dams, and audible and rapid respiration in one dam.

Food consumption during gestation, expressed as grams/dam/day (Table 4) was statistically equivalent among groups. Water consumption (Table 5) was also equivalent among groups. Individual maternal in-life data are presented in Appendix 1.

There were no treatment-related necropsy findings of the dams at scheduled sacrifice on gd 18 (Table 6). At 0.5 (but not 5.0 and 10.0) ml/kg/day dams exhibited a statistically increased incidence of cystic ovaries. Findings at 10.0 ml/kg/day involved two dams, one exhibiting small kidneys and one exhibiting clotted blood and color change in a single amniotic sac. These findings were not considered to be treatment-related. There were no treatment-related differences in maternal terminal body weight (Table 7). While not statistically significant, gravid uterine weight appeared reduced at 5.0 and 10.0 ml/kg/day. Corrected terminal body weight (body weight at sacrifice minus gravid uterine weight), corrected body weight change (gestational weight gain minus gravid uterine weight), liver weight (absolute and relative to corrected body weight) and absolute kidney weight were unaffected by treatment. Relative kidney weight was significantly increased at 10.0 ml/kg/day (Table 7). Microscopic evaluation of maternal kidneys from the 0.0 and 10.0 ml/kg/day groups revealed no treatment-related histological changes. Histological evaluation of maternal kidneys from high dose and control dams are presented in Appendix 3.

Gestational parameters are presented in Table 8. There was no effect of treatment on the number of ovarian corpora lutea, total, viable or nonviable (early and late resorptions and dead fetuses) implantations per litter or on sex ratio (percent males). Percent preimplantation and postimplantation losses were equivalent across groups. Individual maternal necropsy and laparotomy data are presented in Appendix 2.

Fetal body weights (all fetuses, male or female) per litter were significantly reduced at 5.0 and 10.0 ml/kg/day. Fetal body weights per litter at 0.5 ml/kg/day were equivalent to control values.

The results of fetal external, visceral and skeletal evaluations are summarized in Table 9 for malformations and Table 10 for variations. There were no statistical differences in the incidences of any individual malformations (Table 9). There were no significant differences in malformations by category (external, visceral including craniofacial or skeletal) or of total malformations among all groups.

There were no significant differences among groups in the incidence of individual fetal external or visceral variations. A total of 78 different types of individual fetal skeletal variations were observed. Of these, six (6) findings, cervical centra #1, #2, #3 and/or #4 poorly ossified, reduced number of caudal segments, poorly ossified frontal bone, poorly ossified supraoccipital bone, some proximal phalanges of the hindlimb poorly ossified and some proximal phalanges of the hindlimb unossified, exhibited significantly increased incidences at 10.0 ml/kg/day when compared to the control group. There were also a statistically significant increases in the incidences of poorly ossified supraoccipital and frontal at 5.0 ml/kg/day. There were no statistically increased individual skeletal variations at 0.5 ml/kg/day. There were no treatment-related increases in the incidence of variations by category (external, visceral or skeletal) or of total variations (Table 10). (Fetal body weights and malformations and variations by individual fetuses and litters are presented in Appendix 4.)

DISCUSSION

Triethylene glycol, administered by gavage during organogenesis in CD®-1 mice, produced indications of slight maternal toxicity, including clinical signs of toxicity and increased relative kidney weight, at 10.0 ml/kg/day. Slightly reduced gravid uterine weights observed at 5.0 and 10.0 ml/kg/day were consistent with developmental delay observed in fetuses at 5.0 and 10.0 ml/kg/day. Fetotoxicity/developmental delay was evidenced by reduced fetal body weights and consistent findings of reduced ossification in several skeletal districts at 10.0 ml/kg/day and in the head region at 5.0 ml ml/kg/day.

In this study the "no observable effect level" (NOEL) for maternal toxicity was 5.0 ml/kg/day, and the NOEL for developmental toxicity was 0.5 ml/kg/day.

CONCLUSIONS

Administration of triethylene glycol by gavage to pregnant CD®-1 mice during organogenesis at 0.0, 0.5, 5.0 or 10.0 ml/kg/day resulted in maternal toxicity at 10.0 ml/kg/day and fetotoxicity at 10.0 and 5.0 ml/kg/day. The A/D ratio (the ratio of the adult lowest observable effect level to the developmental lowest observable effect level) is greater than 1 indicating preferential susceptibility of the developing mouse fetus to triethylene glycol under the conditions of this study.

Reviewed and Approved by:

T.L. Neeper-Bradley 11-16-90
T. L. Neeper-Bradley, Ph.D. Date
Study Director

J. P. Van Miller 11-16-90
J. P. Van Miller, Ph.D., DABT Date
Assistant Director

F. P. Frank 11/16/90
F. P. Frank, Ph.D. Date
Director

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TABLE 1
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE

SUMMARY OF DISTRIBUTION AND FATE[a]

GROUP (ML/KG/DAY):	0.0	0.5	5.0	10.0
FEMALES ON STUDY	30	30	30	30
FEMALES THAT DIED	0 0.0	0 0.0	0 0.0	0 0.0
PREGNANT	0 0.0	0 0.0	0 0.0	0 0.0
FEMALES THAT ABORTED	0 0.0	0 0.0	0 0.0	0 0.0
FEMALES THAT DELIVERED	0 0.0	0 0.0	0 0.0	1 3.3
FEMALES REMOVED FROM STUDY	0 0.0	0 0.0	0 0.0	0 0.0
FEMALES EXAMINED AT LAPAROTOMY	30 100.0	30 100.0	30 100.0	29 96.7
NONPREGNANT	2 6.7	1 3.3	2 6.7	3 10.3
PREGNANT	28 93.3	29 96.7	28 93.3	26 89.7
FEMALES WITH NON-VIABLE IMPLANTS ONLY	1 3.6	1 3.4	2 7.1	1 3.8
FEMALES WITH VIABLE FETUSES	27 96.4	28 96.6	26 92.9	25 96.2
FEMALES THAT WERE PREGNANT	28 93.3	29 96.7	28 93.3	27 90.0

[a] For all parameters, the data are presented as the number of dams on top and the percentage beneath.

Table 2
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE
SUMMARY OF GESTATIONAL BODY WEIGHT AND WEIGHT CHANGE (GRAMS)

FEMALES

GROUP: ML/KG/DAY	0.0	0.5	5.0	10.0
GESTATIONAL BODY WEIGHTS (g)				
DAY 0				
MEAN	26.58	26.58	26.95	26.61
S.D.	1.334	1.405	1.311	1.235
N	26	29	26	26
DAY 6				
MEAN	30.36	29.95	30.73	30.85
S.D.	1.737	1.744	1.477	1.602
N	26	29	26	26
DAY 9				
MEAN	33.02	33.22	33.16	33.26
S.D.	2.006	2.125	2.105	2.386
N	26	29	26	26
DAY 12				
MEAN	38.09	38.03	38.49	38.21
S.D.	3.454	3.162	3.252	3.741
N	26	29	26	26
DAY 15				
MEAN	46.80	46.21	45.49	45.13
S.D.	5.337	4.793	5.405	5.042
N	26	29	26	26
DAY 18				
MEAN	57.46	56.21	54.90	54.20
S.D.	8.031	7.090	8.801	7.464
N	26	29	26	26
GESTATIONAL BODY WEIGHT CHANGES (g)				
DAY 0 TO 6 (PRETREATMENT)				
MEAN	3.78	3.38	4.18	4.24
S.D.	0.954	1.554	1.029	0.867
N	26	29	26	26
DAY 6 TO 9				
MEAN	2.67	3.26	2.43	2.41
S.D.	0.823	1.500	1.572	1.310
N	26	29	26	26
DAY 9 TO 12				
MEAN	5.07	5.01	5.34	4.95
S.D.	1.742	1.667	1.616	1.828
N	26	29	26	26
DAY 12 TO 15				
MEAN	7.91	7.38	7.00	6.91
S.D.	2.055	2.026	2.492	1.780
N	26	29	26	26
DAY 15 TO 18 (POST-TREATMENT)				
MEAN	10.66	9.99	9.40	9.06
S.D.	2.876	2.477	3.600	2.611
N	26	29	26	26
DAY 6 TO 15 (TREATMENT)				
MEAN	16.46	16.26	14.77	14.26
S.D.	4.362	4.546	5.232	4.171
N	26	29	26	26
DAY 0 TO 18 (GESTATION)				
MEAN	30.90	29.63	28.35	27.59
S.D.	7.468	6.584	8.444	6.941
N	26	29	26	26

None significantly different from control group

TABLE 3
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE

INCIDENCE OF CLINICAL OBSERVATIONS BY GESTATION DAY
FEMALES

CATEGORY	FINDING (LOCATION)	GESTATIONAL DAYS	ML/KG/DAY 0.0	0.5	5.0	10.0
NORMAL						
	NO SIGNIFICANT CLINICAL OBSERVATIONS					
		0- 5	28	29	28	26
		6- 15	28	29	28	26
		16- 18	28	29	28	26
DEAD						
	SCHEDULED SACRIFICE					
		16- 18	28	29	28	26
BEHAVIOR/CNS						
	HYPOACTIVE					
		6- 15	0	0	0	2
CARDIO-PULMONARY						
	AUDIBLE RESPIRATION					
		6- 15	0	0	0	1
	RAPID RESPIRATION					
		6- 15	0	0	0	1

None significantly different from control group

Table 4
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE
SUMMARY OF GESTATIONAL FOOD CONSUMPTION (GRAMS/ANIMAL/DAY)

FEMALES

GROUP: ML/KG/DAY	0.0	0.5	5.0	10.0
DAY 0 TO 3				
MEAN	7.91	8.01	7.07	6.84
S.D.	2.407	4.413	1.095	1.417
N	28	29	28	26
DAY 3 TO 6				
MEAN	9.40	9.67	8.97	9.65
S.D.	2.613	2.099	1.797	2.066
N	28	29	28	26
DAY 6 TO 9				
MEAN	10.37	10.62	9.23	8.92
S.D.	2.080	2.427	2.420	2.058
N	28	29	28	26
DAY 9 TO 12				
MEAN	9.59	10.48	9.69	9.44
S.D.	1.082	1.994	2.211	2.060
N	28	29	28	26
DAY 12 TO 15				
MEAN	10.66	11.02	10.77	10.35
S.D.	1.071	1.782	2.098	2.564
N	28	29	28	26
DAY 15 TO 18 (POST-TREATMENT)				
MEAN	10.79	11.61	11.41	10.67
S.D.	1.200	2.267	2.196	1.881
N	28	29	28	26
DAY 0 TO 6 (PRETREATMENT)				
MEAN	8.65	8.84	8.02	8.25
S.D.	2.243	2.549	1.204	1.402
N	28	29	28	26
DAY 6 TO 15 (TREATMENT)				
MEAN	10.21	10.71	9.90	9.57
S.D.	1.770	1.652	1.999	1.965
N	28	29	28	26
DAY 15 TO 18 (POST-TREATMENT)				
MEAN	10.79	11.61	11.41	10.67
S.D.	1.200	2.267	2.196	1.881
N	28	29	28	26

None significantly different from control group

Table 5
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE
SUMMARY OF GESTATIONAL WATER CONSUMPTION (GRAMS/ANIMAL/DAY)

FEMALES

GROUP: ML/KG/DAY	0.0	0.5	5.0	10.0
DAY 0 TO 3				
MEAN	10.26	10.21	10.80	10.89
S.D.	2.987	1.928	1.781	1.906
N	28	29	28	26
DAY 3 TO 6				
MEAN	12.63	13.29	13.86	13.82
S.D.	3.647	3.705	2.504	2.418
N	28	29	28	26
DAY 6 TO 9				
MEAN	14.77	13.80	16.02	16.64
S.D.	7.404	3.300	6.177	3.732
N	28	29	28	26
DAY 9 TO 12				
MEAN	13.81	14.27	16.60	15.60
S.D.	8.601	4.793	5.904	2.413
N	28	29	28	26
DAY 12 TO 15				
MEAN	15.65	15.48	17.03	16.55
S.D.	8.036	4.669	4.153	4.024
N	28	29	28	26
DAY 15 TO 18 (POST-TREATMENT)				
MEAN	14.42	13.47	13.22	13.23
S.D.	8.700	3.790	2.626	2.712
N	28	29	28	26
DAY 0 TO 6 (PRETREATMENT)				
MEAN	11.45	11.75	12.33	12.36
S.D.	2.341	2.703	1.918	2.044
N	28	29	28	26
DAY 6 TO 15 (TREATMENT)				
MEAN	14.74	14.51	16.55	16.26
S.D.	5.890	3.566	4.223	2.708
N	28	29	28	26
DAY 15 TO 18 (POST-TREATMENT)				
MEAN	14.42	13.47	13.22	13.23
S.D.	8.700	3.790	2.626	2.712
N	28	29	28	26

None significantly different from control group

TABLE 6
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE

SUMMARY OF NECROPSY OBSERVATIONS

ALL PREGNANT FEMALES SACRIFICED AT SCHEDULED LAPAROTOMY

GROUP: ML/KG/DAY	0.0	0.5	5.0	10.0
NUMBER OF ANIMALS IN DOSE GROUP	30	30	30	30
NUMBER OF ANIMALS SACRIFICED	28	29	28	28
OVARIES				
CYST	2	10*	8	8
UTERUS				
BEGAN TO DELIVER	1	1	2	0
AMNIOTIC SACS				
COILED STRUCTURE OF CLOTTED BLOOD	0	0	0	1
COLOR CHANGE	0	0	0	1
CONTAINS BLOOD (BY HEMASTIX)	0	1	0	0
KIDNEYS				
SMALLER THAN NORMAL IN SIZE	0	0	0	1

* Significantly different from control group ($p < 0.05$).

Table 7
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE
SUMMARY OF MATERNAL ORGAN WEIGHTS (GRAMS)

	FEMALES			
GROUP: ML/KG/DAY	0.0	0.5	5.0	10.0
INITIAL BODY WEIGHT (g)				
MEAN	26.58	26.58	26.55	26.61
S.D.	1.334	1.405	1.311	1.235
N	28	29	28	26
BODY WEIGHT AT SACRIFICE (g)				
MEAN	57.48	56.21	54.90	54.20
S.D.	8.031	7.090	8.801	7.464
N	28	29	28	26
GRAVID UTERINE WEIGHT (g)				
MEAN	20.729	20.303	19.631	18.562
S.D.	6.0556	4.8997	6.0572	4.9796
N	28	29	28	26
CORRECTED BODY WEIGHT (g)[a]				
MEAN	36.75	35.90	35.27	35.64
S.D.	2.605	3.189	3.363	3.332
N	28	29	28	26
CORRECTED WEIGHT CHANGE (g)[b]				
MEAN	10.17	9.33	8.72	9.03
S.D.	2.079	2.551	2.894	2.696
N	28	29	28	26
LIVER WEIGHT (g)				
MEAN	2.952	2.835	2.801	2.840
S.D.	0.3632	0.4161	0.5216	0.4440
N	28	29	28	26
KIDNEY WEIGHT (g)				
MEAN	0.476	0.473	0.476	0.493
S.D.	0.0446	0.0577	0.0493	0.0696
N	28	29	28	26
RELATIVE LIVER WEIGHT (%)[c]				
MEAN	8.013	7.873	7.883	7.929
S.D.	0.6681	0.7096	1.0163	0.7116
N	28	29	28	26
RELATIVE KIDNEY WEIGHT (%)[c]				
MEAN	1.297	1.319	1.353	1.384*
S.D.	0.1094	0.1290	0.1032	0.1435
N	28	29	28	26

* Significantly different from control group ($p < .05$)
[a] Corrected body weight = body weight at sacrifice minus gravid uterine weight.
[b] Corrected weight change = corrected body weight minus initial body weight.
[c] Value is a percentage of corrected body weight.

Table 8
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE
SUMMARY OF GESTATIONAL PARAMETERS

FEMALES

GROUP: ML/KG/DAY	0.0	0.5	5.0	10.0
CORPORA LUTEA[a]				
MEAN	13.0	13.0	12.9	12.7
S.D.	2.92	1.95	3.19	1.97
N	28	28	27	25
TOTAL IMPLANTS				
MEAN	12.2	12.2	12.4	12.0
S.D.	3.50	2.51	3.20	2.07
N	28	29	28	26
PERCENT PREIMPLANTATION LOSS[b]				
MEAN	10.8	5.1	4.7	7.2
S.D.	19.48	7.79	7.06	9.93
N	28	29	28	26
VIABLE IMPLANTS				
MEAN	11.1	10.9	11.1	10.9
S.D.	3.82	2.74	3.59	3.05
N	28	29	28	26
NON-VIABLE IMPLANTS				
MEAN	1.1	1.3	1.3	1.2
S.D.	1.60	1.37	0.94	2.36
N	28	29	28	26
EARLY RESORPTIONS				
MEAN	0.7	1.1	0.9	1.0
S.D.	0.67	1.14	0.83	2.38
N	28	29	28	26
LATE RESORPTIONS				
MEAN	0.1	0.0	0.2	0.1
S.D.	0.45	0.19	0.48	0.27
N	28	29	28	26
DEAD FETUSES				
MEAN	0.3	0.2	0.2	0.1
S.D.	1.16	0.47	0.42	0.27
N	28	29	28	26
PERCENT LIVE FETUSES				
MEAN	86.9	86.9	83.9	90.4
S.D.	21.99	19.73	24.77	19.64
N	28	29	28	26
SEX RATIO (% MALE FETUSES)				
MEAN	51.2	44.4	49.4	49.5
S.D.	16.86	13.24	15.55	14.29
N	27	28	26	25
FETAL BODY WEIGHTS PER LITTER (GRAMS)				
ALL FETUSES				
MEAN	1.429	1.416	1.350*	1.303**
S.D.	0.1152	0.0973	0.0662	0.0979
N	27	28	26	25
MALE FETUSES				
MEAN	1.483	1.442	1.384*	1.332**
S.D.	0.1144	0.1157	0.0742	0.1060
N	27	28	26	25
FEMALE FETUSES				
MEAN	1.381	1.395	1.321*	1.271**
S.D.	0.1184	0.0924	0.0657	0.1019
N	27	28	26	25

* Significantly different from control group ($p < .05$)
** Significantly different from control group ($p < .01$)
[a] Females with no visible corpora lutea are not included in the mean.
[b] Percent preimplantation loss=[(corpora lutea - total implants)/corpora lutea] X 100.

TABLE 9
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE

SUMMARY OF MALFORMATIONS IN FETUSES AND LITTERS[a]

GROUP: ML/KG/DAY	FETUSES 0.0	0.5	5.0	10.0	LITTERS 0.0	0.5	5.0	10.0
NUMBER EXAMINED EXTERNALLY[b]	310	316	310	283	27	28	26	25
CLUBBED LIMB(S)	4	4	1	0	4	3	1	0
	1.3	1.3	0.3	0.0	14.8	10.7	3.8	0.0
EXENCEPHALY - EYE CLOSED	0	1	0	0	0	1	0	0
	0.0	0.3	0.0	0.0	0.0	3.6	0.0	0.0
LOW SET EAR(S)	0	1	0	0	0	1	0	0
	0.0	0.3	0.0	0.0	0.0	3.6	0.0	0.0
PROTRUDING TONGUE	0	1	0	0	0	1	0	0
	0.0	0.3	0.0	0.0	0.0	3.6	0.0	0.0
CLEFT PALATE	1	1	1	0	1	1	1	0
	0.3	0.3	0.3	0.0	3.7	3.6	3.8	0.0
OPEN EYE(S)	0	0	0	1	0	0	0	1
	0.0	0.0	0.0	0.4	0.0	0.0	0.0	4.0

None significantly different from control (0.0 ML/KG/DAY)
See footnotes on last page of table.

TABLE 9
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE

SUMMARY OF MALFORMATIONS IN FETUSES AND LITTERS[B]

GROUP: ML/KG/DAY	FETUSES 0.0	0.5	5.0	10.0	LITTERS 0.0	0.5	5.0	10.0
NUMBER EXAMINED VISCERALLY[C]	310	316	310	283	27	28	26	25
CLEFT PALATE	1	0	0	0	1	0	0	0
	0.3	0.0	0.0	0.0	3.7	0.0	0.0	0.0
LATERAL VENTRICLE DILATED - TISSUE DEPRESSED	5	5	2	4	5	4	2	3
	1.6	1.6	0.6	1.4	18.5	14.3	7.7	12.0

None significantly different from control (0.0 ML/KG/DAY)
See footnotes on last page of table.

TABLE 9
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE

SUMMARY OF MALFORMATIONS IN FETUSES AND LITTERS[a]

	FETUSES				LITTERS			
GROUP: ML/KG/DAY	0.0	0.5	5.0	10.0	0.0	0.5	5.0	10.0
NUMBER EXAMINED SKELETALLY[d]	310	316	310	283	27	28	26	25
THORACIC ARCHES FUSED	0 0.0	0 0.0	0 0.0	5 1.8	0 0.0	0 0.0	0 0.0	1 4.0
EXTRA THORACIC ARCH (NOT 14TH)	0 0.0	0 0.0	0 0.0	1 0.4	0 0.0	0 0.0	0 0.0	1 4.0
THORACIC ARCHES MISSING	0 0.0	0 0.0	0 0.0	1 0.4	0 0.0	0 0.0	0 0.0	1 4.0
LUMBAR ARCH(ES) #6 MISSING	1 0.3	0 0.0	2 0.6	5 1.8	1 3.7	0 0.0	1 3.8	4 16.0
LUMBAR CENTRUM #6 MISSING	1 0.3	0 0.0	2 0.6	5 1.8	1 3.7	0 0.0	1 3.8	4 16.0
LUMBAR ARCHES FUSED	0 0.0	1 0.3	0 0.0	0 0.0	0 0.0	1 3.6	0 0.0	0 0.0
RIBS FORKED	0 0.0	0 0.0	0 0.0	3 1.1	0 0.0	0 0.0	0 0.0	1 4.0
RIBS MISSING	1 0.3	0 0.0	0 0.0	3 1.1	1 3.7	0 0.0	0 0.0	1 4.0
RIBS FUSED	0 0.0	0 0.0	0 0.0	4 1.4	0 0.0	0 0.0	0 0.0	1 4.0
EXTRA RIB (NOT 14TH)	0 0.0	0 0.0	0 0.0	1 0.4	0 0.0	0 0.0	0 0.0	1 4.0
FRONTAL BONE - MISSING	0 0.0	1 0.3	0 0.0	0 0.0	0 0.0	1 3.6	0 0.0	0 0.0
PARIETAL BONE - MISSING	0 0.0	1 0.3	0 0.0	0 0.0	0 0.0	1 3.6	0 0.0	0 0.0

None significantly different from control (0.0 ML/KG/DAY)
See footnotes on last page of table.

TABLE 9
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE

SUMMARY OF MALFORMATIONS IN FETUSES AND LITTERS[a]

GROUP: ML/KG/DAY	FETUSES 0.0	0.5	5.0	10.0	LITTERS 0.0	0.5	5.0	10.0
NUMBER EXAMINED SKELETALLY[d]	310	316	310	283	27	28	26	25
INTERPARIETAL - MISSING	0 0.0	1 0.3	0 0.0	0 0.0	0 0.0	1 3.6	0 0.0	0 0.0
SUPRAOCCIPITAL - MISSING	0 0.0	1 0.3	0 0.0	0 0.0	0 0.0	1 3.6	0 0.0	0 0.0
EXTRA STERNEBRA BETWEEN STERNEBRAE	1 0.3	0 0.0	0 0.0	0 0.0	1 3.7	0 0.0	0 0.0	0 0.0
EXTRA STERNEBRA BETWEEN STERNEBRAE BILOBED	1 0.3	0 0.0	0 0.0	0 0.0	1 3.7	0 0.0	0 0.0	0 0.0

None significantly different from control (0.0 ML/KG/DAY)
See footnotes on last page of table.

TABLE 9
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE

SUMMARY OF MALFORMATIONS IN FETUSES AND LITTERS[a]

	FETUSES				LITTERS			
GROUP: ML/KG/DAY	0.0	0.5	5.0	10.0	0.0	0.5	5.0	10.0
TOTAL MALFORMATIONS								
NUMBER WITH EXTERNAL MALFORMATIONS	5	5	2	1	5	4	2	1
PERCENT WITH EXTERNAL MALFORMATIONS	1.6	1.6	0.6	0.4	18.5	14.3	7.7	4.0
NUMBER WITH SOFT TISSUE MALFORMATIONS	6	5	2	4	6	4	2	3
PERCENT WITH SOFT TISSUE MALFORMATIONS	1.9	1.6	0.6	1.4	22.2	14.3	7.7	12.0
NUMBER WITH SKELETAL MALFORMATIONS	3	2	2	10	3	2	1	4
PERCENT WITH SKELETAL MALFORMATIONS	1.0	0.6	0.6	3.5	11.1	7.1	3.8	16.0
TOTAL NUMBER WITH MALFORMATIONS	13	10	6	15	12	7	5	6
TOTAL PERCENT WITH MALFORMATIONS	4.2	3.2	1.9	5.3	44.4	25.0	19.2	24.0

None significantly different from control (0.0 ML/KG/DAY)

[a] For all findings, the number (of fetuses affected or litters with one or more affected fetuses) is presented on top and the percentage of the total (fetuses or litters) examined is presented beneath. A single fetus may be represented more than once in listing individual defects. Only live fetuses were examined.

[b] All fetuses were examined externally.

[c] All fetuses were examined viscerally (Staples, 1974), and approximately 50% of each litter were examined for soft tissue craniofacial defects (Wilson, 1965; van Julsingha and Bennett, 1977).

[d] All fetuses were examined for skeletal defects after staining with Alizarin Red S.

TABLE 10
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE

SUMMARY OF VARIATIONS IN FETUSES AND LITTERS[a]

GROUP: ML/KG/DAY	FETUSES 0.0	FETUSES 0.5	FETUSES 5.0	FETUSES 10.0	LITTERS 0.0	LITTERS 0.5	LITTERS 5.0	LITTERS 10.0
NUMBER EXAMINED EXTERNALLY[b]	310	316	310	283	27	28	26	25
ECCHYMOSIS - EXTREMITIES	2 0.6	3 0.9	1 0.3	3 1.1	2 7.4	3 10.7	1 3.8	3 12.0
ECCHYMOSIS - HEAD	1 0.3	1 0.3	1 0.3	1 0.4	1 3.7	1 3.6	1 3.8	1 4.0

None significantly different from control (0.0 ML/KG/DAY)
See footnotes on last page of table.

TABLE 10
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE

SUMMARY OF VARIATIONS IN FETUSES AND LITTERS[a]

GROUP: ML/KG/DAY	FETUSES 0.0	FETUSES 0.5	FETUSES 5.0	FETUSES 10.0	LITTERS 0.0	LITTERS 0.5	LITTERS 5.0	LITTERS 10.0
NUMBER EXAMINED VISCERALLY[c]	310	316	310	283	27	28	26	25
LATERAL VENTRICLE DILATED - NO DEPRESSION	4 1.3	9 2.8	4 1.3	7 2.5	4 14.8	9 32.1	4 15.4	4 16.0
BROWN MATERIAL AMONG BRAIN TISSUE OF HINDBRAIN	0 0.0	0 0.0	1 0.3	0 0.0	0 0.0	0 0.0	1 3.8	0 0.0
BROWN MATERIAL BETWEEN CRANIUM AND SKIN	3 1.0	1 0.3	1 0.3	2 0.7	3 11.1	1 3.6	1 3.8	2 8.0
BROWN DISCOLORATION WITHIN BRAIN SECTIONS	1 0.3	0 0.0	0 0.0	0 0.0	1 3.7	0 0.0	0 0.0	0 0.0
FETAL ATELECTASIS	95 30.6	58 18.4	76 24.5	84 29.7	18 66.7	13 46.4	18 69.2	21 84.0
PARTIAL FETAL ATELECTASIS	118 38.1	103 32.6	106 34.2	124 43.8	27 100.0	26 92.9	23 88.5	24 96.0
LIVER FOCI	0 0.0	0 0.0	1 0.3	0 0.0	0 0.0	0 0.0	1 3.8	0 0.0
SPLEEN PALE	0 0.0	1 0.3	0 0.0	0 0.0	0 0.0	1 3.6	0 0.0	0 0.0
STOMACH EMPTY	4 1.3	1 0.3	4 1.3	2 0.7	3 11.1	1 3.6	4 15.4	2 8.0
DILATED RENAL PELVIS - UNILATERAL	0 0.0	0 0.0	0 0.0	2 0.7	0 0.0	0 0.0	0 0.0	2 8.0
DILATED RENAL PELVIS - BILATERAL	3 1.0	0 0.0	0 0.0	0 0.0	2 7.4	0 0.0	0 0.0	0 0.0
KIDNEY SMALL	0 0.0	0 0.0	0 0.0	1 0.4	0 0.0	0 0.0	0 0.0	1 4.0

None significantly different from control (0.0 ML/KG/DAY)
See footnotes on last page of table.

TABLE 19
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE

SUMMARY OF VARIATIONS IN FETUSES AND LITTERS[a]

GROUP: ML/KG/DAY	FETUSES 0.0	0.5	5.0	10.0	LITTERS 0.0	0.5	5.0	10.0
NUMBER EXAMINED VISCERALLY[c]	310	316	310	283	27	28	26	25
KIDNEY HIGHLY VASCULARIZED	1 0.3	0 0.0	0 0.0	0 0.0	1 3.7	0 0.0	0 0.0	0 0.0
KIDNEY DISCOLORED	0 0.0	1 0.3	1 0.3	0 0.0	0 0.0	1 3.6	1 3.8	0 0.0
DILATED URETER - UNILATERAL	0 0.0	0 0.0	1 0.3	0 0.0	0 0.0	0 0.0	1 3.8	0 0.0
CLOTTED BLOOD IN INTESTINAL MESENTERY	0 0.0	0 0.0	0 0.0	1 0.4	0 0.0	0 0.0	0 0.0	1 4.0

None significantly different from control (0.0 ML/KG/DAY)
See footnotes on last page of table.

TABLE 10
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE

SUMMARY OF VARIATIONS IN FETUSES AND LITTERS[a]

GROUP: ML/KG/DAY	FETUSES 0.0	0.5	5.0	10.0	LITTERS 0.0	0.5	5.0	10.0
NUMBER EXAMINED SKELETALLY[d]	310	316	310	283	27	28	26	25
CERVICAL CENTRA #1,#2,#3 AND/OR #4 POORLY OSSIFIED	7 2.3	9 2.8	14 4.5	26 9.2	6 22.2	7 25.0	9 34.6	14* 56.0
CERVICAL CENTRA #1,#2,#3 AND/OR #4 UNOSSIFIED	2 0.6	5 1.6	3 1.0	9 3.2	2 7.4	5 17.9	2 7.7	5 20.0
CERVICAL CENTRUM #5 POORLY OSSIFIED	4 1.3	5 1.6	4 1.3	11 3.9	4 14.8	4 14.3	4 15.4	7 28.0
CERVICAL CENTRUM #5 UNOSSIFIED	1 0.3	3 0.9	3 1.0	6 2.1	1 3.7	3 10.7	3 11.5	4 16.0
CERVICAL CENTRUM #6 POORLY OSSIFIED	4 1.3	3 0.9	7 2.3	11 3.9	4 14.8	2 7.1	5 19.2	8 32.0
CERVICAL CENTRUM #6 UNOSSIFIED	0 0.0	4 1.3	1 0.3	7 2.5	0 0.0	4 14.3	1 3.8	4 16.0
CERVICAL CENTRUM #7 POORLY OSSIFIED	3 1.0	6 1.9	5 1.6	9 3.2	3 11.1	4 14.3	3 11.5	6 24.0
CERVICAL CENTRUM #7 UNOSSIFIED	0 0.0	1 0.3	2 0.6	5 1.8	0 0.0	1 3.6	2 7.7	3 12.0
ANTERIOR ARCH OF THE ATLAS POORLY OSSIFIED	2 0.6	6 1.9	6 1.9	7 2.5	2 7.4	4 14.3	5 19.2	3 12.0
BONE ISLAND - CERVICAL ARCH(ES) #7	0 0.0	0 0.0	1 0.3	0 0.0	0 0.0	0 0.0	1 3.8	0 0.0
THORACIC CENTRUM #1 POORLY OSSIFIED	2 0.6	7 2.2	6 1.9	14 4.9	2 7.4	5 17.9	4 15.4	7 28.0
EXTRA #14 THORACIC CENTRUM AND ARCHES	1 0.3	1 0.3	1 0.3	1 0.4	1 3.7	1 3.6	1 3.8	1 4.0

*= significantly different from control (0.0 ML/KG/DAY) at .05 level using two-tailed Fisher's exact test.
See footnotes on last page of table.

TABLE 10
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE
SUMMARY OF VARIATIONS IN FETUSES AND LITTERS[a]

GROUP: ML/KG/DAY	FETUSES 0.0	0.5	5.0	10.0	LITTERS 0.0	0.5	5.0	10.0
NUMBER EXAMINED SKELETALLY[d]	310	315	319	283	27	28	26	25
THORACIC CENTRUM #2 POORLY OSSIFIED	0 0.0	0 0.0	1 0.3	6 2.1	0 0.0	0 0.0	1 3.8	1 4.0
THORACIC CENTRUM #3 POORLY OSSIFIED	0 0.0	0 0.0	0 0.0	3 1.1	0 0.0	0 0.0	0 0.0	1 4.0
THORACIC CENTRUM #4 POORLY OSSIFIED	0 0.0	0 0.0	0 0.0	4 1.4	0 0.0	0 0.0	0 0.0	1 4.0
THORACIC CENTRUM #6 POORLY OSSIFIED	0 0.0	0 0.0	0 0.0	6 2.1	0 0.0	0 0.0	0 0.0	1 4.0
THORACIC CENTRUM #7 POORLY OSSIFIED	0 0.0	0 0.0	0 0.0	3 1.1	0 0.0	0 0.0	0 0.0	1 4.0
THORACIC CENTRUM #8 POORLY OSSIFIED	0 0.0	0 0.0	0 0.0	4 1.4	0 0.0	0 0.0	0 0.0	1 4.0
THORACIC CENTRUM #9 POORLY OSSIFIED	0 0.0	0 0.0	0 0.0	4 1.4	0 0.0	0 0.0	0 0.0	1 4.0
THORACIC CENTRUM #10 POORLY OSSIFIED	0 0.0	0 0.0	0 0.0	3 1.1	0 0.0	0 0.0	0 0.0	1 4.0
THORACIC CENTRUM #5 POORLY OSSIFIED	0 0.0	0 0.0	0 0.0	3 1.1	0 0.0	0 0.0	0 0.0	1 4.0
THORACIC CENTRUM #1 UNOSSIFIED	0 0.0	0 0.0	0 0.0	3 1.1	0 0.0	0 0.0	0 0.0	1 4.0
THORACIC CENTRUM #11 POORLY OSSIFIED	0 0.0	0 0.0	0 0.0	2 0.7	0 0.0	0 0.0	0 0.0	1 4.0
THORACIC CENTRUM #12 POORLY OSSIFIED	0 0.0	0 0.0	0 0.0	1 0.4	0 0.0	0 0.0	0 0.0	1 4.0

None significantly different from control (0.0 ML/KG/DAY)
See footnotes on last page of table.

TABLE 10
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE

SUMMARY OF VARIATIONS IN FETUSES AND LITTERS[a]

GROUP: ML/KG/DAY	FETUSES 0.0	FETUSES 0.5	FETUSES 5.0	FETUSES 10.0	LITTERS 0.0	LITTERS 0.5	LITTERS 5.0	LITTERS 10.0
NUMBER EXAMINED SKELETALLY[d]	310	316	310	283	27	28	26	25
THORACIC CENTRUM #12 SPLIT	0 0.0	0 0.0	0 0.0	1 0.4	0 0.0	0 0.0	0 0.0	1 4.0
LUMBAR CENTRUM #5 POORLY OSSIFIED	0 0.0	0 0.0	0 0.0	2 0.7	0 0.0	0 0.0	0 0.0	1 4.0
REDUCED NUMBER OF CAUDAL SEGMENTS (5 OR LESS)	11 3.5	22 7.0	24 7.7	46 16.3	5 18.5	8 28.6	12 46.2	14* 56.0
BONE ISLAND - ON THORACIC ARCH #14 - UNILATERAL	1 0.3	1 0.3	0 0.0	0 0.0	1 3.7	1 3.6	0 0.0	0 0.0
RUDIMENTARY RIB #14 - FIRST LUMBAR ARCH - UNILATERAL	16 5.2	14 4.4	10 3.2	6 2.1	9 33.3	12 42.9	6 23.1	4 16.0
RUDIMENTARY RIB #14 - FIRST LUMBAR ARCH - BILATERAL	5 1.6	6 1.9	5 1.6	0 0.0	5 18.5	4 14.3	4 15.4	0 0.0
EXTRA RIB #14 - FIRST LUMBAR ARCH - UNILATERAL	15 4.8	18 5.7	9 2.9	16 5.7	7 25.9	12 42.9	8 30.8	9 36.0
EXTRA RIB #14 - FIRST LUMBAR ARCH - BILATERAL	14 4.5	15 4.7	29 9.4	41 14.5	7 25.9	9 32.1	7 26.9	11 44.0
EXTRA RIB #14 - ON THORACIC ARCH #14 - UNILATERAL	0 0.0	0 0.0	1 0.3	0 0.0	0 0.0	0 0.0	1 3.8	0 0.0
EXTRA RIB #14 - ON THORACIC ARCH #14 - BILATERAL	0 0.0	0 0.0	0 0.0	1 0.4	0 0.0	0 0.0	0 0.0	1 4.0
BONE ISLAND - FIRST LUMBAR ARCH - UNILATERAL	1 0.3	2 0.6	0 0.0	1 0.4	1 3.7	2 7.1	0 0.0	1 4.0
FRONTAL BONE - POORLY OSSIFIED	36 11.6	48 15.2	60 19.4	67 23.7	13 48.1	20 71.4	21* 80.8	22** 88.0

*= significantly different from control (0.0 ML/KG/DAY) at .05 level using two-tailed Fisher's exact test.
**= significantly different from control (0.0 ML/KG/DAY) at .01 level using two-tailed Fisher's exact test.
See footnotes on last page of table.

TABLE 10
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE

SUMMARY OF VARIATIONS IN FETUSES AND LITTERS®

GROUP: ML/KG/DAY	FETUSES 0.0	0.5	5.0	10.0	LITTERS 0.0	0.5	5.0	10.0
NUMBER EXAMINED SKELETALLY®	310	318	310	283	27	28	26	25
PARIETAL - POORLY OSSIFIED	1 0.3	0 0.0	0 0.0	0 0.0	1 3.7	0 0.0	0 0.0	0 0.0
SUPRAOCCIPITAL - POORLY OSSIFIED	45 14.5	54 17.1	83 26.8	85 30.0	17 63.0	20 71.4	24* 92.3	23* 92.0
HYOID - POORLY OSSIFIED	0 0.0	0 0.0	0 0.0	1 0.4	0 0.0	0 0.0	0 0.0	1 4.0
SUPRAOCCIPITAL SPLIT	0 0.0	0 0.0	0 0.0	1 0.4	0 0.0	0 0.0	0 0.0	1 4.0
SUPRAOCCIPITAL BILOBED	1 0.3	0 0.0	0 0.0	1 0.4	1 3.7	0 0.0	0 0.0	1 4.0
FRONTAL FONTANEL ENLARGED	0 0.0	2 0.6	0 0.0	0 0.0	0 0.0	1 3.6	0 0.0	0 0.0
SUPRAOCCIPITAL BILOBED	0 0.0	0 0.0	0 0.0	1 0.4	0 0.0	0 0.0	0 0.0	1 4.0
SOME INTER. PHALANGES (FORELIMB) POORLY OSSIFIED	61 19.7	66 20.9	69 22.3	76 26.9	23 85.2	24 85.7	23 88.5	22 88.0
SOME INTER. PHALANGES (FORELIMB) UNOSSIFIED	255 82.3	251 79.4	259 83.5	224 79.2	26 96.3	28 100.0	26 100.0	25 100.0
MAJORITY INTER. PHALANGES (FORELIMB) UNOSSIFIED	12 3.9	20 6.3	12 3.9	19 6.7	8 29.6	11 39.3	8 30.8	11 44.0
ALL INTER. PHALANGES (FORELIMB) UNOSSIFIED	21 6.8	29 9.2	22 7.1	34 12.0	10 37.0	10 35.7	13 50.0	15 60.0
SOME INTER. PHALANGES (HINDLIMB) POORLY OSSIFIED	71 22.9	68 21.5	54 17.4	43 15.2	22 81.5	23 82.1	23 88.5	17 68.0

*= significantly different from control (0.0 ML/KG/DAY) at .05 level using two-tailed Fisher's exact test.
See footnotes on last page of table.

TABLE 10
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE

SUMMARY OF VARIATIONS IN FETUSES AND LITTERS[a]

GROUP: ML/KG/DAY	FETUSES 0.0	0.5	5.0	10.0	LITTERS 0.0	0.5	5.0	10.0
NUMBER EXAMINED SKELETALLY[d]	310	316	310	283	27	28	26	25
MAJORITY INTER. PHALANGES (HINDLIMB) POORLY OSSIFIED	2 0.6	2 0.6	4 1.3	1 0.4	2 7.4	2 7.1	4 15.4	1 4.0
SOME INTER. PHALANGES (HINDLIMB) UNOSSIFIED	186 60.0	163 51.6	130 41.9	75 26.5	25 92.6	26 92.9	24 92.3	20 80.0
MAJORITY INTER. PHALANGES (HINDLIMB) UNOSSIFIED	30 9.7	22 7.0	25 8.1	29 10.2	17 63.0	15 53.6	13 50.0	12 48.0
ALL INTER.PHALANGES (HINDLIMB) UNOSSIFIED	83 26.8	119 37.7	151 48.7	176 62.2	22 81.5	23 82.1	23 88.5	25 100.0
SOME PROXIMAL PHALANGES (HINDLIMB) UNOSSIFIED	17 5.5	32 10.1	31 10.0	63 22.3	11 40.7	14 50.0	13 50.0	19* 76.0
SOME PROXIMAL PHALANGES (HINDLIMB) POORLY OSSIFIED	18 5.8	23 7.3	35 11.3	47 16.6	11 40.7	9 32.1	18 69.2	18* 72.0
SOME PROXIMAL PHALANGES (FORELIMB) UNOSSIFIED	6 1.9	10 3.2	7 2.3	5 1.8	5 18.5	5 17.9	6 23.1	5 20.0
SOME PROXIMAL PHALANGES (FORELIMB) POORLY OSSIFIED	1 0.3	1 0.3	3 1.0	6 2.1	1 3.7	1 3.6	3 11.5	5 20.0
ALL PROXIMAL PHALANGES (FORELIMB) UNOSSIFIED	0 0.0	1 0.3	0 0.0	0 0.0	0 0.0	1 3.6	0 0.0	0 0.0
SOME METATARSALS (HINDLIMB) UNOSSIFIED	0 0.0	1 0.3	0 0.0	0 0.0	0 0.0	1 3.6	0 0.0	0 0.0
MAJORITY PROXIMAL PHALANGES (HINDLIMB) UNOSSIFIED	0 0.0	1 0.3	0 0.0	0 0.0	0 0.0	1 3.6	0 0.0	0 0.0
ALL PROXIMAL PHALANGES (HINDLIMB) UNOSSIFIED	1 0.3	2 0.6	3 1.0	1 0.4	1 3.7	2 7.1	3 11.5	1 4.0

*= significantly different from control (0.0 ML/KG/DAY) at .05 level using two-tailed Fisher's exact test.
See footnotes on last page of table.

TABLE 10
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE
SUMMARY OF VARIATIONS IN FETUSES AND LITTERS®

GROUP: ML/KG/DAY	FETUSES 0.0	FETUSES 0.5	FETUSES 5.0	FETUSES 10.0	LITTERS 0.0	LITTERS 0.5	LITTERS 5.0	LITTERS 10.0
NUMBER EXAMINED SKELETALLY[d]	310	316	310	283	27	28	26	25
MAJORITY PROXIMAL PHALANGES (FORELIMB) UNOSSIFIED	1 0.3	1 0.3	0 0.0	0 0.0	1 3.7	1 3.6	0 0.0	0 0.0
STERNEBRA #1 POORLY OSSIFIED	1 0.3	0 0.0	1 0.3	6 2.1	1 3.7	0 0.0	1 3.8	4 16.0
STERNEBRA #2 POORLY OSSIFIED	4 1.3	4 1.3	4 1.3	7 2.5	3 11.1	4 14.3	3 11.5	3 12.0
STERNEBRA #3 POORLY OSSIFIED	9 2.9	6 1.9	11 3.5	11 3.9	5 18.5	4 14.3	9 34.6	7 28.0
STERNEBRA #4 POORLY OSSIFIED	25 8.1	43 13.6	59 19.0	40 14.1	14 51.9	18 64.3	24** 92.3	17 68.0
STERNEBRA #5 POORLY OSSIFIED	245 79.0	259 82.0	241 77.7	240 84.8	27 100.0	28 100.0	26 100.0	25 100.0
STERNEBRA #6 POORLY OSSIFIED	50 16.1	93 29.4	75 24.2	116 41.0	16 59.3	19 67.9	20 76.9	21 84.0
STERNEBRA #5 BILOBED	40 12.9	34 10.8	44 14.2	27 9.5	18 66.7	16 57.1	18 69.2	14 56.0
STERNEBRA #5 SPLIT	4 1.3	4 1.3	9 2.9	4 1.4	4 14.8	2 7.1	7 26.9	4 16.0
STERNEBRAE FUSED	5 1.6	2 0.6	7 2.3	6 2.1	5 18.5	2 7.1	5 19.2	5 20.0
EXTRA OSSIFICATION SITE BETWEEN STERNEBRAE	3 1.0	1 0.3	4 1.3	10 3.5	3 11.1	1 3.6	4 15.4	6 24.0
STERNEBRA #3 BILOBED	0 0.0	1 0.3	2 0.6	3 1.1	0 0.0	1 3.6	2 7.7	2 8.0

**= significantly different from control (0.0 ML/KG/DAY) at .01 level using two-tailed Fisher's exact test.
See footnotes on last page of table.

TABLE 10
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE

SUMMARY OF VARIATIONS IN FETUSES AND LITTERS[a]

GROUP: ML/KG/DAY	FETUSES 0.0	0.5	5.0	10.0	LITTERS 0.0	0.5	5.0	10.0
NUMBER EXAMINED SKELETALLY[d]	310	316	310	283	27	28	26	25
STERNEBRA #5 UNOSSIFIED	0 0.0	0 0.0	0 0.0	2 0.7	0 0.0	0 0.0	0 0.0	2 8.0
STERNEBRA #4 BILOBED	4 1.3	5 1.6	4 1.3	4 1.4	4 14.8	4 14.3	4 15.4	4 16.0
STERNEBRAE #2 SPLIT	0 0.0	0 0.0	0 0.0	1 0.4	0 0.0	0 0.0	0 0.0	1 4.0
STERNEBRA #2 BILOBED	1 0.3	1 0.3	2 0.6	1 0.4	1 3.7	1 3.6	2 7.7	1 4.0
STERNEBRA #6 SPLIT	0 0.0	0 0.0	1 0.3	0 0.0	0 0.0	0 0.0	1 3.8	0 0.0

None significantly different from control (0.0 ML/KG/DAY)
See footnotes on last page of table.

TABLE 10
DEVELOPMENTAL TOXICITY STUDY OF TRIETHYLENE GLYCOL ADMINISTERED
BY GAVAGE TO CD®-1 MICE

SUMMARY OF VARIATIONS IN FETUSES AND LITTERS[a]

	FETUSES				LITTERS			
GROUP: ML/KG/DAY	0.0	0.5	5.0	10.0	0.0	0.5	5.0	10.0
TOTAL VARIATIONS								
NUMBER WITH EXTERNAL VARIATIONS	3	4	2	4	3	4	2	4
PERCENT WITH EXTERNAL VARIATIONS	1.0	1.3	0.6	1.4	11.1	14.3	7.7	16.0
NUMBER WITH SOFT TISSUE VARIATIONS	217	166	184	210	27	28	24	25
PERCENT WITH SOFT TISSUE VARIATIONS	70.0	52.5	59.4	74.2	100.0	100.0	92.3	100.0
NUMBER WITH SKELETAL VARIATIONS	310	315	310	283	27	28	26	25
PERCENT WITH SKELETAL VARIATIONS	100.0	99.7	100.0	100.0	100.0	100.0	100.0	100.0
TOTAL NUMBER WITH VARIATIONS	310	315	310	283	27	28	26	25
TOTAL PERCENT WITH VARIATIONS	100.0	99.7	100.0	100.0	100.0	100.0	100.0	100.0

None significantly different from control (0.0 ML/KG/DAY)

[a] For all findings, the number (of fetuses affected or litters with one or more affected fetuses) is presented on top and the percentage of the total (fetuses or litters) examined is presented beneath. A single fetus may be represented more than once in listing individual defects. Only live fetuses were examined.

[b] All fetuses were examined externally.

[c] All fetuses were examined viscerally (Staples, 1974), and approximately 50% of each litter were examined for soft tissue craniofacial defects (Wilson, 1965; van Julsingha and Bennett, 1977).

[d] All fetuses were examined for skeletal defects after staining with Alizarin Red S.

BUSHY RUN RESEARCH CENTER
6702 Mellon Road, Export, Pennsylvania 15632-8902
Telephone (412) 733-5200
Telecopier (412) 733-4804

GOOD LABORATORY PRACTICES COMPLIANCE

The portions of this study conducted at the Bushy Run Research Center were in full compliance with the Good Laboratory Practices (GLP) Standards promulgated by the U. S. Environmental Protection Agency Toxic Substances Control [40 CFR Part 792].

Prepared by:

T.L. Neeper-Bradley 11-6-90
T. L. Neeper-Bradley, Ph.D. Date
Study Director

PATH/tjs/1817P-3
08-13-90

BUSHY RUN RESEARCH CENTER
6702 Mellon Road, Export, Pennsylvania 15632-8902
Telephone (412) 733-5200
Telecopier (412) 733-4804

Quality Assurance Unit Study Inspection Summary

Test Substance: Triethylene Glycol

Study: Developmental Toxicity Evaluation of the Test Substance Administered by Gavage to CD®-1 Mice

Study Director: T. L. Neeper-Bradley, Ph.D.

The Quality Assurance Unit of BRRC conducted the inspections listed below and reported the results to the study director and to management on the dates indicated. It is the practice of this Quality Assurance Unit to report the results of each inspection to both the study director and management.

Inspection Date	Inspection Type	Date QAU Report Issued To Study Director	Date QAU Report Issued To Management
8-30 to 9-2-88	Protocol (Range-Finding)	9-2-88	9-6-88
8-31 to 9-2-88	Protocol	9-2-88	9-6-88
10-4-88	Protocol Amendment #1 (Range-Finding)	10-4-88	10-5-88
11-16-88	Event-Animal Receipt (Range-Finding)	11-16-88	12-14-88
12-2-88	Protocol Amendment #2 (Range-Finding)	12-2-88	12-9-88
12-14-88	Event-Sacrifice (Range-Finding)	12-14-88	1-24-89
1-6-89	Protocol Amendment #3 (Range-Finding)	1-9-89	1-10-89
1-23-89	Protocol Amendment #1	1-25-89	2-14-89
2-13-89	Event-Sacrifice (Range-Finding)	2-15-89	3-28-89
3-23-89	Protocol Amendment #2	3-23-89	4-3-89

Inspection Date	Inspection Type	Date QAU Report Issued To Study Director	Date QAU Report Issued To Management
4-19-89	Protocol Amendment #3	4-19-89	5-1-89
4-25-89	Event-Animal Receipt	4-25-89	6-7-89
5-19-89	Event-Dosing	5-22-89	6-7-89
5-30-89	Event-Sacrifice	5-30-89	7-31-89
7-13-89	Protocol Amendment #4 (Range-Finding)	7-19-89	7-24-89
7-13-89	Protocol Amendment #4	7-19-89	7-24-89
11-20 to 11-22-89	Raw Data and Report (Range-Finding)	11-22-89	11-16-90
11-22 to 12-4-89	Raw Data and Report	12-11-89	11-16-90
3-22-90 to 4-2-90	Anatomic Pathology Raw Data and Report	4-2-90	11-16-90
5-14-90	Protocol Amendment #5	5-15-90	5-29-90
11-15-90	Archives	11-15-90	11-16-90

Linda J. Calisti 11/16/90

Linda J. Calisti, Manager Date
Good Laboratory Practices/Quality Assurance

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Place Syracuse New York
(City) (State)

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