PDCN:8895CCCC0185

ORIGINAL (B)

DuPont Specialty Chemicals
1007 Market Street
Wilmington, DE 19898

DuPont Specialty Chemicals

8EHQ-95-13401
SP001 06/22/95

8EHQ-0695-13401 June 15, 1995

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

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Document Processing Center (7407)
Attention: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, DC 20460-0001

Contains No CBI

Dear Sir/Madam:

Re: 8EHQ-0395-13401

With reference to your request of April 24, 1995 addressed to C. F. Reinhardt on the subject TSCA 8(e) notification, attached is a copy of the final report from the pilot development toxicity study conducted on 70% Glycolic acid solution (technical grade) which gave rise to the 8(e) notification.

The study on completion confirmed the preliminary findings of evidence of maternal and developmental toxicity at 500 and 1000 mg/kg/day and no evidence of maternal or developmental toxicity at the two lower doses tested (125 or 250 mg/kg/day). The maternal and developmental No-Observed-Adverse-Effect Level (NOAEL) thus was 250 mg/kg/day. On the basis of these pilot study results we conclude that 70% aqueous glycolic acid solution (technical grade) is not a developmental toxin because it is not uniquely toxic to the rat conceptus.

Nevertheless, DuPont has initiated additional studies to validate this conclusion beginning with a study to establish the time course for induction of metabolic acidosis in pregnant rats after an oral gavage dose of either glycolic acid or another reference acid. Assuming acidosis is detected we shall conduct a dose response test with both glycolic and the reference acid. Studies will also be initiated to determine whether acidosis can occur in pregnant female rats through dermal exposure and if this is found the dose-response relationship will be established.

Following completion of these studies a definitive developmental toxicity study in rats, using EPA/OECD protocols and following GLP requirements, is planned.

RECEIVED 7/5/95

Besides notification to EPA, the results of the pilot study have been communicated to customers, employees and to the Cosmetics, Toiletries and Fragrance Association (CTFA).

The MSDS has been revised; a copy is attached.

Finally, considering the nature of the findings and the NOAEL it was decided that the existing safe exposure limit (DuPont's Acceptable Exposure Limit) of 10 mg/m3, 8- and 12-hr. TWA, did not need revision. However, this decision will be revisited as additional toxicity data become available.

You may contact me on 302/774-6467 if there are any questions.

Yours truly,

K. D. Dastur
Manager, Product Toxicology
and Chemical Regulations

DuPont HLR 96-95

Contains No CBI

Study Title

Pilot Developmental Toxicity of 70% Glycolic Acid Technical Solution in Rats

Laboratory Project ID

Haskell Laboratory Report No. 96-95

Data Requirements

U.S. EPA Pesticide Assessment Guidelines
Subdivision F, 83-3

OECD Guidelines for Testing of Chemicals
Section 4, No. 414

MAFF Testing Guidelines for Toxicology Studies
NohSan 59, No. 4200

Guideline Directive

Commission Directive 87/302/EEC (OJ No.L133 31.5.88)

Author

Susan M. Munley, M.A.

Study Completed on

June 2, 1995

Performing Laboratory

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

Medical Research Project No. 10042-001

PILOT DEVELOPMENTAL TOXICITY STUDY OF 70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

This page reserved for specific country requirements.

PILOT DEVELOPMENTAL TOXICITY STUDY OF 70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study was conducted in compliance with EPA FIFRA (40 CFR 160) and EPA TSCA (40 CFR 792) Good Laboratory Practice Standards, OECD Principles of Good Laboratory Practice (C(81)30(Final), Annex 2), and MAFF Japan Good Laboratory Practice Standards (59 NohSan No. 3850) except for the deviations documented and explained below.

1. Samples from the first batch of dosing solutions were shipped to the Sponsor's laboratory in Belle, West Virginia, for concentration analyses. These analyses were not conducted in compliance with GLPs since this laboratory is not a GLP laboratory. This deviation did not affect the validity or integrity of the study; these analyses were done this way because the analytical method was unavailable at Haskell Laboratory at the outset of the study. The method was subsequently developed and samples from all batches of dosing solutions were analyzed accordingly. The results of all analyses are contained in this report.

Submitter: E. I. du Pont de Nemours and Company

Sponsor: DuPont Specialty Chemicals
E. I. du Pont de Nemours and Company

Date

Study Director: Susan M. Munley 6/2/95

Susan M. Munley, M.A.
Toxicologist
Developmental and
Reproductive Toxicology

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

FLAGGING OF STUDIES FOR POTENTIAL ADVERSE EFFECTS

I have applied the criteria of 40 CFR 158.34 for flagging studies for potential adverse effects to the results of the attached study. This study neither meets nor exceeds any of the applicable criteria.

Date

Study Director: Susan M. Munley 6/2/95

Susan M. Munley, M.A.
Toxicologist
Developmental and
Reproductive Toxicology

PILOT DEVELOPMENTAL TOXICITY STUDY OF 70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

GENERAL INFORMATION

Material Tested:	Acetic acid, hydroxy-
Structure:	$HOCH_2COOH$
Synonyms and Codes:	Glycolic acid (70% Solution Technical) Glycolic acid Hydroxyacetic acid Hydroxyethanoic acid Oxyethanoic Acid HAA
C.A.S. Registry No:	79-14-1
Haskell No.:	20895
Purity:	70% 71.17% (typical analysis from routine 1994 production)
Physical State:	Clear liquid
Major impurities:	Formic acid (0.32%) Sulfates (128 ppm) Sodium (3.4 ppm) Iron (6.2 ppm) Chlorides (1 ppm) Ammonia (80.8 ppm) Diglycolic acid (0.97%) Methoxyacetic acid (1.53%)
Stability:	Stable according to analyses.
Sponsor:	DuPont Specialty Chemicals E. I. du Pont de Nemours and Company
Study Initiated/Completed:	December 30, 1994 / June 2, 1995
Experiment Initiated/Completed:	January 3, 1995 (first day of dosing) / May 25, 1995 (last fetal evaluation)

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PILOT DEVELOPMENTAL TOXICITY STUDY OF 70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

Summary:

Glycolic acid (70% technical solution) was administered by gavage to groups of 8 Crl:CD®BR female rats on days 7-21 of gestation at dose levels of 0, 125, 250, 500, or 1000 mg/kg/day.

Maternal toxicity was demonstrated at 500 and 1000 mg/kg/day. At 1000 mg/kg/day, maternal effects included mortality, significantly reduced maternal body weights, weight changes, and food consumption. Dose-related increases of the following clinical observations were observed: abnormal gait/mobility, lung noise, salivation, stained and wet fur. At 500 mg/kg/day, similar, yet markedly less severe evidence of maternal toxicity was demonstrated. There was a slight but significant reduction in maternal weight gain. The incidences of lung noise and wet fur were significantly increased as well.

Developmental toxicity was evident at 500 and 1000 mg/kg/day. At 1000 mg/kg/day, mean fetal weight was significantly reduced. Embryolethality was significantly increased and among the surviving fetuses, malformations and variations were significantly increased. At 500 mg/kg/day, the significant reduction in fetal weight persisted as did the increase in fetal variations.

No evidence of either maternal or developmental toxicity was detected at 250 or 125 mg/kg/day. Thus, the maternal and developmental no-observed-adverse-effect level (NOAEL) was 250 mg/kg/day. Therefore, the results of this preliminary study suggest that glycolic acid (70% technical solution) is not likely to be uniquely toxic to the rat conceptus.

PILOT DEVELOPMENTAL TOXICITY STUDY OF 70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

Report Prepared by: Amy L. Williamson 6/1/95

Amy L. Williamson
Secretary
Developmental and
Reproductive Toxicology

Susan M. Munley for Bernice Dewberry Street 6/1/95

Bernice Dewberry Street
Toxicology Associate
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Reviewed and Approved by: Mark E. Hurtt 6/1/95

Mark E. Hurtt, Ph.D.
Senior Research Toxicologist
Developmental and
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Authored, Reviewed, and Approved for Issue: Susan M. Munley 6/2/95

Susan M. Munley, M.A.
Study Director
Toxicologist
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QUALITY ASSURANCE DOCUMENTATION

(H-20895)

Dates of Inspection:

Conduct - 1/4,5,16,19,20,23,26/95; 2/2,20/95

Records, Report(s) - 4/25-27/95; 5/1,15-19,22,24-26/95; 5/31/95-6/1/95

Date(s) Findings Reported to:

Study Director - 4/27/95; 5/15,26/95; 6/1/95

Management - 5/15/95; 6/1/95

Reported by: Donna R Holt 6/2/95

Donna R. Holt
Quality Assurance Auditor

Date

PILOT DEVELOPMENTAL TOXICITY STUDY OF 70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

STUDY PERSONNEL

The following individuals participated in the conduct of the in-life portions of the study, maternal postmortem and fetal examinations, and/or in the preparation or review of the final report:

Study Director: Susan M. Munley, M.A.

Management: Mark E. Hurtt, Ph.D.

Primary Technician: Bernice Dewberry Street, B.S.

Laboratory Technicians: Sandra E. Doughty, A.A.S.
Cindy H. Hahn, B.A.
Mary Ann Jacobs, B.A.
Kim H. Kreckmann, B.S.
Richard P. Mathena, Jr.
Ronald L. Poore
Deborah L. Tyler

Secretary: Amy L. Williamson

The following individuals were responsible for the analysis of dosing solutions:

Chemistry Associate: Janet C. Maslanka, B.S.

Chemist: Charlotte H. Lattin, B.S.

The following individuals were responsible for the conduct and reporting of clinical pathology evaluations:

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

Pathology Associate: Cheryl L. Samson, A.A.S.

The health status of the animals on study was assessed by the attending laboratory veterinarian, Charles E. Cover, V.M.D.

INTRODUCTION

The purpose of this study was to evaluate the developmental toxicity of glycolic acid (70% technical solution), administered by gavage to pregnant rats from the time of implantation to the end of gestation.

This study conforms to applicable Good Laboratory Practice Standards[1-3] except for the deviation noted on the compliance page.

MATERIALS AND METHODS

A. Animals

On October 18, 1994, 50 nulliparous female Crl:CD®BR rats were received from Charles River Breeding Laboratories, Inc., Raleigh, North Carolina. They were approximately 63 days old on the date of arrival. On the following day, body weights ranged from 177.9 to 223.0 grams. Males used for breeding were approximately 77 days old when they arrived on September 27, 1994. Body weights on the following day ranged from 329.5 to 371.7 grams. Each rat was identified by a unique number recorded on its cage card, as well as by a tail tattoo with the last three digits of that number.

The rat was selected to provide data in a rodent species. The Crl:CD®BR strain was chosen because historical control data are available from the literature, the supplier, and previous studies at Haskell Laboratory.

B. Animal Husbandry

1. Caging: The rats were housed individually in suspended, wire-mesh, stainless steel cages. Nesting material was not provided because the dams were euthanized prior to expected parturition.

2. Food: The rats were provided Purina® Certified Rodent Chow® #5002 (Meal) ad libitum.

3. Water: The rats were supplied with tap water from the Wilmington Suburban Water Corporation (WSWC) ad libitum.

4. Environmental Conditions: The animal room was maintained on a 12-hour light/dark cycle (fluorescent light) and targeted at a temperature of 23 ± 2°C and a relative humidity of 50 ± 10%. Occasional excursions outside the target ranges were minor and did not affect the study.

5. Animal Quality Monitoring: Haskell Laboratory has an animal quality monitoring program. The following procedures are performed periodically:

- Water samples are analyzed for total bacterial counts, and the presence of coliforms, lead, and other contaminants.

- Food samples are analyzed for the presence of bacteria and fungi.
- Samples from freshly washed cages and cage racks are analyzed to assure adequate sanitation by the cagewashers.

Haskell Laboratory uses certified animal food. The food is guaranteed by the manufacturer to meet specified nutritional requirements and to be free of a list of specified contaminants.

The animal quality monitoring program is administered by the Laboratory Animal Veterinarian. Data are maintained separately from study records and will not be included in the final report.

6. Quarantine: All animals were quarantined for at least 6 days, and then released for the study by the Laboratory Animal Veterinarian.

C. Experimental Design

The experimental design is shown below:

Group	Dose[a] (mg/kg/day)	Concentration (mg/mL)	No. Mated Females[b]
I	0[c]	0.0	8
II	125	12.5	8
III	250	25.0	8
IV	500	50.0	8
V	1000	100.0	8

[a] Glycolic Acid (70% technical solution) administered once daily, by gavage, on Days 7-21 of gestation, at a dosage volume of 10 mL/kg
[b] Copulation confirmed
[c] Vehicle only (deionized or commercially-supplied water)

D. Selection of Dose Levels

The 70% technical solution of glycolic acid is slightly acutely toxic; the rat LD50 is 4240 mg/kg.[4] Other than this acute data, there was little or no data available regarding either the effects of repeated oral dosing with glycolic acid or its potential developmental toxicity. Therefore, rangefinding work was initiated to enable dose selection for the current study. Three pregnant rats were dosed over Days 7-21G with 1000 mg/kg/day 70% glycolic acid technical solution dissolved in deionized water. All three rats gained weight over the course of the dosing period. After anywhere from three to seven doses, observations of lung noise (rales) and salivation were recorded for all three rats. The salivation episodes all occurred immediately after the animal had been dosed. The lung noises

often occurred just after dosing but many of these persisted into the afternoon or to the next day. At necropsy, one dam had a white mucoidal substance in her stomach; the other two females appeared normal. All three dams were pregnant; the litters were of a normal size and the fetuses appeared normal, but the mean fetal weight, which was 2.6 grams, appeared to be much lower than expected based on a general historical mean of approximately 5 grams. Based on these data, the dose levels outlined above were selected for the present study.

E. Preparation, Administration, and Analyses of Test Solutions

Stock solutions (100 mg/mL) of the test material in either house deionized water or commercially supplied water (OmniSolv water, HPLC grade, Lots 34220 (8/95 expiration date) and 34271, (9/95 expiration date), EM Science, Gibbstown, New Jersey) were prepared weekly during the study. The first set of dosing solutions were made using house deionized water and subsequent sets of solutions were prepared using commercially-supplied water. This change was made to ensure that the pH of the vehicle was tightly controlled. The stock solution was used as the high dose level solution and was further diluted to make the lower dose level solutions (50, 25, and 12.5 mg/mL). The first set of dosing solutions were stored at room temperature. Subsequent sets of dosing solutions were stored in the refrigerator and were only out for about one hour each day for the actual dosing.

Glycolic acid (70% technical solution) was administered by gavage because the oral route is a potential route of accidental human exposure. The dose volume was 10 mL/kg and individual dosages were based on the most recently recorded body weights.

The first set of dosing solutions were made with house deionized water. At the start of the study, the analytical method was unavailable at Haskell Laboratory. To ensure that the dosing solutions were at or near targeted concentrations as near to the start of the study as possible, it was necessary to send samples out to be analyzed. Duplicate samples of each dose level solution were shipped to Robert Schacht, 901 West DuPont Avenue, Belle, West Virginia 25015, for concentration verification analyses. After one week, additional samples were taken from each dosing solution for submission to the Analytical Group of Environmental Sciences (ES) at Haskell Laboratory for concentration verification analyses. These additional samples were taken to ensure the seven-day stability of the dosing solutions. These samples were frozen until the analytical method was developed at Haskell Laboratory.

Subsequent sets of dosing solutions were made with the commercially-supplied water. Fresh samples were taken from the second set of dosing solutions. Seven- and eleven-day stability samples were taken from the third and final set of dosing solutions. All of these samples were submitted to the Analytical Group of Environmental Sciences (ES). These samples were analyzed shortly after submission or frozen until analyses could be conducted.

F. Experimental Procedures

1. Mating: Females were cohabited with males (1:1) until copulation was confirmed by the presence of a copulation plug in the vagina or on the cageboard. Checks for copulation plugs were made each morning; the day copulation was confirmed was designated as Day 1 of gestation (Day 1G). Mating began on December 27, 1994, with Day 1G occurring from December 28-30, 1994 and January 2-3, 1995. Females with confirmed copulation on those dates were assigned to 5 breeding lots, A through E, respectively.

2. Assignment to Groups/Control of Bias: Before dosing began, females selected for the study that copulated during the first week of mating were ranked by their body weights on Day 1G and randomly assigned to control or experimental groups. Females selected from the second week of mating were similarly assigned. The randomization resulted in a distribution in which the mean body weights for all groups were not statistically different ($p=0.9777$). In addition to random assignment to groups, bias was controlled by coding all females prior to scheduled sacrifice. They remained coded during the collection of the postmortem and fetal data.

3. Observations: Observations for morbidity and mortality were made daily. Females were weighed on Days 1 and 7-22G. Food was weighed on Days 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, and 22G, and individual clinical signs were recorded each morning on Days 1-22G and each afternoon on Days 7-21G (the dosing period).

4. Euthanasia and Postmortem Examinations: Females were euthanized on Day 22G by carbon dioxide asphyxiation, and the organs of the thoracic and abdominal cavities were examined for gross pathologic changes. The uterus was removed, weighed, and opened. The types of implants (live and dead fetuses, and resorptions) were counted and their relative positions were recorded. Then, the empty uterus was weighed. The ovaries were removed and the corpora lutea were counted and recorded. The uterus of each apparently nonpregnant rat was opened and stained with ammonium sulfide[5] to detect very early resorptions; data collected from those animals were used only to determine the incidence of pregnancy and the number of females with total resorptions.

   Live fetuses were weighed, sexed, and examined for external alterations. To identify stunted fetuses for each litter, the maximum stunted weight (MSW) was calculated by subtracting the lightest weight from the total weight, dividing by the remaining number of fetuses, and multiplying by 0.666. A fetus weighing less than or equal to the MSW was considered stunted. If the lightest fetus was determined to be stunted, the procedure was repeated until all remaining fetal weights were in excess of the MSW. The first live fetus and thereafter every other fetus in each litter was decapitated and examined for visceral alterations[6] and the sex verified. Retarded renal development was classified using the schema of Woo and Hoar.[7] The heads were fixed in Bouin's fluid and examined.[8] All stunted and externally malformed fetuses were also

examined for visceral alterations; a decision to do a head examination was made on an individual basis. The remaining fetuses were euthanized by an intraperitoneal injection of sodium pentobarbital (Arpro Pharmaceuticals, Arcadia, CA, 91006). All fetuses were fixed in 70% ethanol, eviscerated (if not done earlier during visceral examination), macerated in 1% aqueous potassium hydroxide solution, stained with alizarin red S, and examined for skeletal alterations.

5. Clinical Pathology: Blood samples were collected from all rats on the study on January 16, 1995. Approximately 0.5 mL of blood was drawn from the lateral tail vein of each rat. The whole blood samples were submitted to the Clinical Pathology group at Haskell Laboratory. Serum was prepared and analyzed to determine the acid-base status of the animals. Details regarding the methods and results are provided in the clinical pathology report.

6. Statistical Evaluation: Sequential trend testing was applied to the developmental toxicity data for each parameter as tabulated below. If a significant dose-response was detected, data from the top dose group was excluded and the test repeated until no significant trend was detected. For litter parameters, the proportion of affected fetuses per litter or the litter mean was the experimental unit for statistical evaluation.[9] The level of significance selected was $p \leq 0.05$.

Parameter	Trend Test
Maternal weight Maternal weight changes Maternal food consumption	Linear contrast of means from ANOVA[10]
Live fetuses Dead fetuses Resorptions Nidations Corpora lutea Incidence of fetal alterations	Jonckheere's test[11]
Incidence of pregnancy Clinical observations Maternal mortality Females with total resorptions Early deliveries	Cochran-Armitage test[10]
Fetal weight (Covariates: litter size, sex ratio) Sex ratio (Covariate: litter size)	Linear contrast of least square means from ANCOVA[12]

Where the data were tied and the standard large sample version of Jonckheere's test was not applicable, exact p values were calculated using permutation methodology.[13]

use of the words "significant" or "significantly" in this report indicates atistically significant difference between the control and the experimental ps.

Archiving

Raw data and the final report are stored in the archives of Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Delaware, or at the DuPont Records Management Center, Wilmington, Delaware. All skeletal, head, and selected visceral preparations are stored at Haskell Laboratory and will be retained as long as the material permits proper evaluation.

SULTS

Analyses of Solutions (Appendices B.1. and B.2.)

The nominal concentrations of glycolic acid (70% technical solution) in the test solutions submitted for analysis were 0, 12.5, 25.0, 50.0, and 100.0 mg/mL, representing daily dose levels of 0, 125, 250, 500, and 1000 mg/kg, respectively. Measured results for all samples indicated that the test substance was at expected levels (± 15% of nominal) and was stable for up to 11 days at all storage conditions. Glycolic acid (70% technical solution) was not detected in the 0 mg/mL control formulations.

As stated earlier, sets of samples from the first batch of dosing solutions were shipped to the Belle plant for concentration analyses because the analytical method was unavailable at Haskell Laboratory at the start of the study. The results of these analyses indicated that the test substance was at expected levels, ranging from 86.4 to 99.6% of nominal concentrations.

3. Maternal Findings

1. Mortality

There was one dose-related death in the 1000 mg/kg/day group. This animal was sacrificed in extremis on Day 14G after clinical signs including abnormal gait, lethargy, and moribund condition were observed. Postmortem findings included ulcerations in the gastric mucosa. The intestines were empty and distended with air; and kidney coloring was mottled. In addition, one rat from the 1000 mg/kg/day group was accidentally killed (gavage trauma) on Day 10G.

2. Body Weight Changes (Table 1, Appendices C, D, and E)

Maternal body weights and weight changes were reduced at 1000 mg/kg/day. Statistically significant reductions in body weight changes were observed over Days 7-9, 11-13, 17-19, 21-22, and 7-22G. Weight changes calculated using the adjusted final body weight (final body weight minus the

products of conception) were also significantly reduced (Days 7-22 and 1-22G). Maternal body weights were significantly reduced (88% of control) on Day 22G.

At 500 mg/kg/day, maternal weight changes were significantly reduced over Days 21-22G. No other body weight effects were observed at this dose level. Body weights and weight changes were unaffected at 250 and 125 mg/kg/day.

3. Food Consumption (Table 2, Appendix F)

Maternal food consumption was significantly reduced at 1000 mg/kg/day over Days 9-11, 11-13, 13-15, and 7-22G. Maternal food consumption was unaffected at dose levels of 500 mg/kg/day and lower.

4. Clinical Observations (Table 3, Appendix G)

At 1000 mg/kg/day, there were significantly increased incidences of abnormal gait/mobility and stained and wet fur. In addition, the incidence of salivation was significantly increased. The occurrences of salivation were transient in nature; in general, the rats began salivating minutes after having been dosed and were no longer salivating about four hours after dosing when afternoon clinical observations were recorded. Lung noises were recorded for almost all of the animals in the 1000 mg/kg/day group; the animals were wheezing. In some cases, the lung noises persisted into the afternoon and to the next day.

At 500 mg/kg/day, similar lung noises were recorded for two of eight animals; this increase was significant. The incidence of wet fur (chin) was significantly increased as well.

5. Postmortem Findings (Appendix H)

Except for the postmortem observations for the animal that was sacrificed in extremis previously described, no other compound-related increases in the incidence of any postmortem finding were observed.

6. Clinical Pathology (Appendix L)

There were no statistically significant or toxicologically important effects on the clinical chemistry parameters measured. Under the conditions of this study there was no evidence that glycolic acid (70% technical solution) changed the acid-base status of the rats.

The anticipated acid-base alteration due to glycolic acid (70% technical solution) administration was metabolic acidosis. Lack of evidence for metabolic acidosis in this study may have been related to the time of sample collection which was approximately 22 hours after having been dosed. It is possible that the rats in this study had compensated for metabolic acidosis which may have occurred in the first few hours after glycolic acid (70% technical solution) administration.

C. Reproductive Effects (Table 4, Appendix I)

There were no dose-related effects on reproductive outcome parameters (dams with total resorptions, mean corpora lutea, mean number of implantations, litter size or sex ratio).

D. Fetal Findings

1. Mortality (Table 4, Appendix I)

The incidence of early resorptions was significantly increased at 1000 mg/kg/day.

2. Body Weight (Table 4, Appendices I and K)

Mean fetal weight was significantly reduced at 1000 and 500 mg/kg/day.

3. Malformations (Table 5, Appendix K)

The incidence of specific malformations was increased only at 1000 mg/kg/day. These malformations were gastroschisis, hydrocephaly, fused ribs, fused vertebra(e), and hemivertebra(e). No other compound-related malformations were evident.

4. Variations (Table 6, Appendix K)

The incidence of specific variations was increased at 500 and 1000 mg/kg/day. The incidence of misaligned sternebra(e) was significantly increased at 1000 mg/kg/day, as was the incidence of retarded vertebral and sternebral ossification. The incidence of retarded sternebral ossification was significantly increased at 500 mg/kg/day as well.

CONCLUSION

Under the conditions of this pilot study, significant maternal and developmental toxicity was observed at 500 and 1000 mg/kg/day. The maternal and developmental no-observed-adverse-effect level (NOAEL) was 250 mg/kg/day. Thus, the results of this preliminary study suggest that glycolic acid (70% technical solution) is not likely to be uniquely toxic to the rat conceptus.

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PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

TABLE 1

MEAN MATERNAL BODY WEIGHT CHANGES (grams)[a]

GROUP	DAILY DOSE (mg/kg)	N	DAYS OF GESTATION 1-7	7-9	9-11	11-13	13-15	15-17	17-19
I	0	7	30.5	4.0	8.2	6.5	7.0	16.4	25.6
II	125	6	28.6	3.5	6.9	7.8	8.0	15.9	26.8
III	250	8	27.1	3.8	6.9	12.2	5.9	13.5	23.5
IV	500	5	28.1	-0.7	6.8	4.1	10.8	19.1	19.9
V	1000	6	27.7	-3.6*	4.2	-7.0*	10.0	11.4	18.4*

GROUP	DAILY DOSE (mg/kg)	N	DAYS OF GESTATION 19-21	21-22	7-22	1-22[b]	7-22[b]
I	0	7	29.3	19.7	116.8	55.7	25.2
II	125	6	30.0	20.3	119.1	55.8	27.2
III	250	8	28.8	17.7	112.3	48.1	21.0
IV	500	5	32.9	12.5*	105.4	46.6	18.5
V	1000	6	23.0	15.6*	72.0*	34.7*	7.0*

[a] Data from females that died prior to scheduled sacrifice or that were not pregnant were excluded. Individual data, standard deviations, and standard errors are presented in Appendices C (body weight changes), D (body weights), and E (maternal adjusted body weights and weight changes).

[b] Weight changes calculated using the adjusted final body weight (final body weight minus the products of conception).

* Significant trend (linear contrast of means from ANOVA); $p \leq 0.05$.

PILOT DEVELOPMENTAL TOXICITY STUDY OF
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TABLE 2

MEAN MATERNAL FOOD CONSUMPTION (grams)[a]

GROUP	DAILY DOSE (mg/kg)	N	DAYS OF GESTATION 1-7	7-9	9-11	11-13	13-15	15-17	17-19
I	0	7	20.9	20.4	20.4	20.6	21.6	21.8	23.3
II	125	6	21.7	21.2	21.7	21.1	22.3	22.2	23.6
III	250	8	20.6	21.0	20.7	22.3	21.6	22.1	23.2
IV	500	5	20.9	19.1	19.7	17.7	20.5	22.3	24.1
V	1000	6	21.2	18.7	16.4*	11.8*	15.9*	19.0	21.7

GROUP	DAILY DOSE (mg/kg)	N	DAYS OF GESTATION 19-21	21-22	7-22
I	0	7	23.6	22.4	21.7
II	125	6	24.1	24.4	22.6
III	250	8	23.0	23.6	22.1
IV	500	5	23.5	20.7	21.0
V	1000	6	20.9	21.4	18.0*

[a] Data from females that died prior to scheduled sacrifice or that were not pregnant were excluded. Individual data, standard deviations, and standard errors are presented in Appendix F.

* Significant trend (linear contrast of means from ANOVA); $p \leq 0.05$.

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TABLE 3

CLINICAL OBSERVATIONS[a]

DAY OF GESTATION	OBSERVATION	GROUP: I	II	III	IV	V
	DOSE (mg/kg): 0	125	250	500	1000
1-6	No. Examined	8	8	8	8	8
	No. Affected	2	0	1	1	1
	Alopecia	1	0	1	1	1
	Stained fur, perinasal area	1	0	0	0	0
	Teeth broken or chipped	0	0	1	0	0
7-22	No. Examined	8	8	8	8	8
	No. Affected	1	1	1	6	8
	Abnormal gait or mobility	0	0	0	0	2*
	Alopecia	1	1	1	2	1
	Lethargy	0	0	0	0	1
	Lung noise	0	0	0	2*	7*
	Moribund	0	0	0	0	1
	Pallor	0	0	0	0	1
	Salivation	0	0	0	0	4*
	Stained fur, inguinal area	0	0	0	0	1
	Stained fur, mouth	0	0	0	0	2*
	Stained fur, perinasal area	0	0	0	0	1
	Stained fur, perineum	0	0	0	0	2*
	Stained fur, perioral area	0	0	0	0	1
	Teeth broken or chipped	0	0	1	0	0
	Wet fur, chin	0	0	0	4*	6*
	Wet fur, inguinal area	0	0	0	0	1
	Wet fur, perinasal area	0	0	0	0	3*
	Wet fur, perineum	0	0	0	0	1
	Wet fur, perioral area	0	0	0	0	1

[a] Individual clinical observations are presented in Appendix G.

* Significant trend (Cochran-Armitage test); $p \leq 0.05$.

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TABLE 4

REPRODUCTIVE OUTCOME[a]

GROUP:		I	II	III	IV	V
DOSE (mg/kg):		0	125	250	500	1000
No. Mated		8	8	8	8	8
No. Pregnant		7	6	8	5	7
No. Sacrificed in extremis		0	0	0	0	1
No. Accidentally Killed		0	0	0	0	1
No. with Total Resorptions		0	0	0	0	0
No. Litters		7	6	8	5	6
Means Per Litter						
Corpora Lutea		15.7	16.3	16.6	15.0	16.3
Nidations		15.0	15.2	15.9	14.6	13.8
Resorptions:	Total	0.4	0.7	0.4	0.8	1.5*
	Early	0.4	0.7	0.3	0.6	1.5*
	Late	0.0	0.0	0.1	0.2	0.0
Dead Fetuses		0.0	0.0	0.0	0.0	0.0
Live Fetuses[b]	Total	14.6	14.5	15.3	13.8	12.3
	Males	6.9	6.3	7.3	5.8	6.3
	Females	7.7	8.2	8.0	8.0	6.0
Mean Fetal Weight (grams)		4.86	4.80	4.62	4.42**	3.99**
Sex Ratio[c]		0.46	0.43	0.48	0.43	0.49

[a] Individual data, standard deviations, and standard errors are presented in Appendix I. Individual fetal weights are presented in Appendix K.
[b] Statistical analyses are only conducted on the mean total number of live fetuses per litter. The mean numbers of males and females are presented for information only.
[c] No. male fetuses/total no. fetuses per litter.
* Significant trend (Jonckheere's test); $p \leq 0.05$.
** Significant trend (linear contrast of least square means from ANCOVA); $p \leq 0.05$.

Note: The pregnancy rate data, adult mortality data, and the total resorption data were statistically analyzed (Cochran-Armitage test); $p \leq 0.05$.

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TABLE 5

INCIDENCE OF FETAL MALFORMATIONS[a]

GROUP:	I	II	III	IV	V
DOSE (mg/kg):	0	125	250	500	1000
EXTERNAL					
No. Examined	102[7][b]	87[6]	122[8]	69[5]	74[6]
No. Affected	0[0]	0[0]	0[0]	0[0]	2[2]
Abdomen - Gastroschisis	...[c]	...	...	...	2(2)*
VISCERAL					
No. Examined	52[7]	45[6]	63[8]	35[5]	38[6]
No. Affected	0[0]	0[0]	0[0]	0[0]	2[2]
Heart &/or Greater Vessels -	...	...	...	...	1(1)
Septal Defect	...	...	...	...	1(1)
Intestine - Gastroschisis					
HEAD					
No. Examined	52[7]	45[6]	63[8]	35[5]	38[6]
No. Affected	0[0]	0[0]	0[0]	1[1]	4[2]
Brain - Hydrocephaly	...	...	...	1(1)	4(2)*
SKELETAL					
No. Examined	102[7]	87[6]	122[8]	69[5]	74[6]
No. Affected	5[3]	0[0]	0[0]	0[0]	22[4]
Rib					2(2)
- Absent	3(2)	...	...	...	17(3)*
- Fused	...	...	...	...	
Vertebra					1(1)
- Absent	1(1)	...	...	...	10(3)*
- Fused	1(1)	...	...	...	18(4)*
- Hemi	3(1)	...	...	...	1(1)
- Malformation - only 5 cervical vertebra on the left side	...	...	...	...	

[a] Individual fetal alterations are presented in Appendix K.
[b] Data are presented as No. Fetuses [No. Litters] or No. Fetuses (No. Litters).
[c] For ease of reading, zeros have been replaced with ellipses for the listed malformations.
* Significant trend (Jonckheere's test); $p \leq 0.05$

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TABLE 6

INCIDENCE OF FETAL VARIATIONS[a]

GROUP:	I	II	III	IV	V
DOSE (mg/kg):	0	125	250	500	1000
DEVELOPMENTAL VARIATIONS					
EXTERNAL					
No. Examined	102[7][b]	87[6]	122[8]	69[5]	74[6]
No. Affected	0[0]	0[0]	0[0]	0[0]	0[0]
VISCERAL					
No. Examined	52[7]	45[6]	63[8]	35[5]	38[6]
No. Affected	0[0]	0[0]	0[0]	0[0]	0[0]
HEAD					
No. Examined	52[7]	45[6]	63[8]	35[5]	38[6]
No. Affected	0[0]	0[0]	0[0]	0[0]	0[0]
SKELETAL					
No. Examined	102[7]	87[6]	122[8]	69[5]	74[6]
No. Affected	7[2]	2[1]	9[5]	1[1]	8[3]
Rib					
- Rudimentary	2(1)	...[c]	...	...	...
- Rudimentary Cervical	5(1)	1(1)	8(4)	...	...
Sternebra					
- Fused	...	...	...	...	2(1)
- Misaligned	1(1)	1(1)	1(1)	1(1)	6(3)*
VARIATIONS DUE TO RETARDED DEVELOPMENT					
EXTERNAL					
No. Examined	102[7]	87[6]	122[8]	69[5]	74[6]
No. Affected	0[0]	0[0]	0[0]	0[0]	0[0]

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TABLE 6 (CONT.)

INCIDENCE OF FETAL VARIATIONS[a]

GROUP:	I	II	III	IV	V
DOSE (mg/kg):	0	125	250	500	1000
VARIATIONS DUE TO RETARDED DEVELOPMENT (CONT.)					
VISCERAL					
No. Examined	51[7]	45[6]	63[8]	35[5]	38[6]
No. Affected	1[1]	6[3]	4[3]	1[1]	4[2]
Heart &/or Greater Vessels - Patent Ductus Arteriosis	...	1(1)	2(2)	...	4(2)
Kidney - Small Papilla - Size 2	1(1)	5(2)	2(2)	1(1)	...
HEAD					
No. Examined	49[7]	45[6]	63[8]	35[5]	38[6]
No. Affected	0[0]	0[0]	0[0]	0[0]	0[0]
SKELETAL					
No. Examined	102[7]	87[6]	122[8]	69[5]	74[6]
No. Affected	54[7]	25[4]	58[8]	53[5]	47[5]
Skull - Retarded Ossification	10(3)	6(3)	2(2)	4(2)	15(4)
Sternebra - Retarded Ossification	10(5)	8(3)	33(6)	30(5)*	35(5)*
Vertebra - Retarded Ossification	46(7)	13(4)	34(7)	43(5)	45(5)*

[a] Individual fetal alterations are presented in Appendix K.

[b] Data are presented as No. Fetuses [No. Litters] or No. Fetuses (No. Litters). Malformed fetuses are included in the counts of fetuses examined, but excluded from the number affected.

[c] For ease of reading, zeros have been replaced with ellipses for the listed malformations.

* Significant trend (Jonckheere's test); $p \leq 0.05$.

PILOT DEVELOPMENTAL TOXICITY STUDY OF
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APPENDIX A

PILOT DEVELOPMENTAL TOXICITY STUDY OF GLYCOLIC ACID IN RATS

MEDICAL RESEARCH PROJECT NUMBER 10042-001

TEST CODE NUMBER 840

PROTOCOL

Stine-Haskell Animal Welfare Committee No. DGRT 6GP

LOPMENTAL TOXICITY STUDY OF
ACID TECHNICAL SOLUTION IN RATS

APPENDIX A (CONT.)

is to evaluate the developmental toxicity of glycolic
age to pregnant rats from the time of implantation to

y DuPont Specialty Chemicals, E. I. du Pont de Nemours
Virginia, and will be conducted at Haskell Laboratory
rial Medicine, E. I. du Pont de Nemours and Company,

he test substance will be referred to either as
y the Haskell Sample Number, 20895, in this protocol
ecords. It was supplied as a 70% aqueous solution.

er: 79-14-1

t room temperature.

ed water

Crl:CD®BR rats

tion: The rat was selected for this study because it is
ies for developmental toxicity testing. The Crl:CD®BR
n because extensive background information is available
ure, the supplier, and previous studies with other
skell Laboratory. This strain is also considered suitable
liness and incidence of spontaneous disease.

s River Laboratories, Inc., Kingston, New York

0 Nulliparous females, approximately 63 days old, were
ober 18, 1994. On the day after arrival, they ranged in
.9 to 223.0 grams. Males to be used for breeding will be
ich were approximately 77 days old on September 27, 1994,
ch these animals were received. On the day after arrival,
anged in weight from 329.5 to 371.7 grams.

: Each rat was identified by a unique number recorded on
as well as by a tail tattoo with the last three digits of

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX A (CONT.)

C. Husbandry

1. Environmental conditions: Animal rooms will be maintained at a targeted temperature of 23°C ±2°C and a targeted relative humidity of 50% ±10%. Animal rooms will be artificially illuminated (fluorescent light) on a 12-hour light/dark cycle (approximately 0600-1800 hours).

2. Caging: Animals will be housed individually in suspended, wire-mesh, stainless steel cages. Nesting material will not be provided because the dams will be euthanized prior to parturition.

3. Feed: Purina® Certified Rodent Chow® #5002 (Meal) will be available ad libitum.

4. Water: Water from the Wilmington Suburban Water Corporation (WSWC) will be available ad libitum.

5. Animal quality monitoring: Haskell Laboratory has an animal quality monitoring program. The following procedures are performed periodically:

   - Water samples are analyzed for total bacterial counts, and the presence of coliforms, lead, and other contaminants.
   - Feed samples are analyzed for the presence of bacteria and fungi.
   - Samples from freshly washed cages and cage racks are analyzed to assure adequate sanitation by the cagewashers.

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

   The animal quality monitoring program is administered by the laboratory animal veterinarian. Data are maintained separately from study records and will not be included in the final report.

6. Quarantine: Rats were quarantined for 24 days, and then were released for the study upon approval of the Laboratory Veterinarian.

PILOT DEVELOPMENTAL TOXICITY STUDY OF
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APPENDIX A (CONT.)

D. Experimental Design

The experimental design is shown below:

Group	Dose[a] (mg/kg/day)	Concentration (mg/mL)	Mated Females[b]
I	0[c]	0.0	8
II	125	12.5	8
III	250	25.0	8
IV	500	50.0	8
V	1000	100.0	8

[a] Glycolic acid, administered once daily, by gavage, on Days 7-21 of gestation, at a dosage volume of 10 mL/kg
[b] Copulation confirmed
[c] Vehicle only

E. Selection of Dose Levels

The 70% aqueous solution of glycolic acid is slightly acutely toxic; the rat LD50 is 4240 mg/kg.[1] Other than this acute data, there was little or no data available regarding either the effects of repeated oral dosing with glycolic acid or its potential developmental toxicity. Therefore, rangefinding work was initiated to enable dose selection for the current study. Three pregnant rats were dosed over Days 7-21G with 1000 mg/kg/day 70% glycolic acid solution dissolved in deionized water. The resulting concentration was just less than 7% glycolic acid. The pH of the dosing solution was 2.0. All three rats gained weight over the course of the dosing period. After anywhere from three to seven doses, observations of lung noise (rales) and salivation were recorded for all three rats. The salivation episodes all occurred immediately after the animal had been dosed. The lung noises often occurred just after dosing but many of these persisted into the afternoon or to the next day. At necropsy, one dam had a white mucoidal substance in her stomach; the other two females appeared normal. All three dams were pregnant; the litters were of a normal size and the fetuses appeared normal but the mean fetal weight, which was 2.6 grams, appeared to be much lower than expected based on a general historical mean of approximately 5 grams. Based on these data, the dose levels outlined above were selected for the present study.

F. Mating

Each female will be individually housed with a male. Copulation will be verified each morning by detection of a copulation plug in the vagina or on the cageboard. The day copulation is confirmed is defined as Day 1 of gestation (Day 1G).

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APPENDIX A (CONT.)

G. Randomization

Before dosing begins, females selected for the study that copulated during the first week of mating will be ranked by their body weights on Day 1G and randomly assigned to control or experimental groups. The randomization should result in a distribution in which the mean body weights for all groups are not statistically different ($p>0.05$). Dams that lose excessive weight or that are ill prior to the start of dosing will be removed from the study and replaced, if possible.

H. Preparation, Administration, and Analysis of Test Formulations

1. Preparation: A stock formulation (100 mg/mL) of the test material in the vehicle will be prepared once prior to the onset of the dosing period. This stock solution will serve as the high dose level solution and will be further diluted to make the lower dose level solutions (50, 25, and 12.5 mg/mL). The details regarding formulation preparation will be documented in the study records.

2. Administration: Glycolic acid will be administered by gavage because the oral route is a potential route of accidental human exposure. The volume administered will be based on the most recent body weight.

3. Analysis: Duplicate samples (~100 mL each) of each dose level formulation will be shipped to Robert Schacht, 901 West DuPont Avenue, Belle, West Virginia 25015, for concentration verification analyses. Additional samples will be taken from each dosing formulation for submission to the Analytical Group of Environmental Sciences (ES) at Haskell Laboratory for concentration verification analyses. These samples will be stored at room temperature until analyses can be conducted. The analytical method used will be documented in the ES study records.

I. Safety Precautions and Disposal of Waste Material

The 70% solution of glycolic acid is corrosive and has a pH of less than 1. Avoid breathing mist. Do not get in eyes, on skin or on clothing. Wash thoroughly after handling. Good housekeeping procedures will be practiced to avoid potential health hazards and contamination of formulation facilities. To prevent skin contact, gloves will be worn when handling either the test substance or test formulations. In addition, the test substance will be handled in a chemical hood. Dosing formulations will be prepared in properly ventilated areas. Animal carcasses, feces, and unused dosing formulations will be incinerated.

J. Animal Euthanasia

1. Adults: Females will be euthanized by carbon dioxide inhalation.

2. Fetuses: Fetuses will be decapitated before proceeding with visceral examinations; those to be viscerally examined without decapitation will

be injected with sodium pentobarbital. All other fetuses also will be injected with sodium pentobarbital before fixation.

K. Parameters to be Studied

1. In-life Observations of Females

a. Body weight: Body weight will be recorded within one day of arrival, twice more during the first week to provide data for quarantine release, weekly before the study begins, and in the morning of Days 1, 7-22 of gestation.

b. Feed consumption: Individual feeder weights will be measured each morning on Days 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21 and 22 of gestation.

c. Clinical Signs: Clinical signs will be recorded with body weights before the study begins, each morning on Days 1-22 of gestation, and each afternoon on Days 7-21. Clinical signs observed at other times will be recorded by exception.

2. Postmortem Observations of Females Dying Prior to Scheduled Euthanasia

a. External and Visceral Observations: A gross external and visceral examination will be performed within 24 hours after the female is found dead. Dead animals will be refrigerated until autopsied.

b. Implantation Sites: Pregnancy status will be determined by the presence or absence of implantation sites. Corpora lutea and implantation sites will be counted. If possible, the implantation sites will be counted and classified as apparently alive or resorbing at the time of the dam's death.

3. Postmortem Observations of Dams Delivering Early

a. Dam Observations: Dams that deliver before scheduled euthanasia will be euthanized within 24 hours of detection and a gross external and internal examination will be performed. Lesions noted will be retained only if further examination is necessary (at the discretion of the study director or a designee). Corpora lutea and implantation sites will be counted.

b. Fetal Observations: Fetuses remaining in the uterus and those delivered early will be examined to the extent possible, but the collected data will be excluded from all calculations performed for live fetuses.

4. Postmortem Observations of Females Surviving to Scheduled Euthanasia (Day 22 of Gestation)

a. External Appearance: The female will be examined immediately after euthanasia.

b. Viscera: Viscera will be examined grossly immediately after euthanasia. Lesions noted will be retained only if further examination is necessary (at the discretion of the study director or a designee).

c. Uterine Weight: The intact and the empty uterus of each dam having at least one viable fetus will be weighed to permit calculation of maternal body weight adjusted to exclude the products of conception.

d. Corpora Lutea: The count for each ovary of females with viable fetuses will be recorded.

e. Implantation Sites: For each female with visible implantation sites, the types of implants (live and dead fetuses, and resorptions) and their relative positions will be recorded. The uterus of each apparently "nonpregnant" female will be stained with ammonium sulfide[2] to detect very early resorptions; counts will be recorded and each resorption will be classified as definite or questionable. Data from females determined to be pregnant by staining will be used only to calculate the incidence of pregnancy and the number of females with total resorptions.

5. Fetuses of Females Surviving to Scheduled Euthanasia

a. Number, Location, Sex, and Condition: These parameters will be recorded for each fetus.

b. Fetal Weight: The body weight of each fetus will be recorded.

c. External Alterations: The alterations detected for each live fetus will be recorded.

d. Soft Tissue Alterations: For each litter, the first live fetus and every other live fetus thereafter will be examined for visceral alterations.[3] In addition, all live fetuses with malformations visible at external examination and all stunted fetuses will be examined for soft tissue alterations; decapitation of these fetuses will be at the discretion of the study director or a designee.

e. Head Alterations: After fixation in Bouin's fixative, the heads of decapitated fetuses will be examined and alterations will be recorded. Examinations will be based on the method of Barrow and Taylor.[4]

f. Skeletal Alterations: After alcohol fixation, the alizarin-stained skeletons will be examined and skeletal alterations will be recorded for all live fetuses, excluding the fetal heads fixed in formalin.

g. Dead Fetuses: Those fetuses classified as dead will be examined externally, viscerally and skeletally for alterations that obviously preceded death and are not attributable to developmental retardation. Data for these fetuses will be excluded from all calculations performed for live fetuses.

h. Retention of Tissues: Fetal organs or tissues will be retained if

PILOT DEVELOPMENTAL TOXICITY STUDY OF
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APPENDIX A (CONT.)

deemed necessary for obtaining a definitive diagnosis. Bilateral organs will be retained when only one is affected. Sufficient tissues from control fetuses will be fixed to provide comparison with suspect tissues, if needed; tissues will be discarded if not needed.

L. Control of Bias

In addition to random assignment to groups, all females will be coded before scheduled euthanasia and will remain coded during the collection of postmortem and fetal data.

M. Statistics

Sequential trend testing will be applied to the data for each parameter as tabulated below. If a significant dose-response is detected, data from the top dose group will be excluded and the test repeated until no significant trend is detected. For litter parameters, the proportion of affected fetuses per litter or the litter mean will be used as the experimental unit for statistical evaluation.[5] The level of significance selected is $p \leq 0.05$. Additional statistical tests may be used, and other parameters analyzed, if deemed necessary.

Where the data are tied and the standard large sample version of Jonckheere's test is not applicable, exact p values will be calculated using permutation methodology.[6]

Parameter	Trend Test
Maternal weight Maternal weight changes Maternal feed consumption	Linear contrast of means from ANOVA[7]
Live fetuses Dead fetuses Resorptions Implantations Corpora lutea Incidence of fetal alterations	Jonckheere's test[8]
Incidence of pregnancy Clinical observations Maternal mortality Females with total resorptions Early deliveries	Cochran-Armitage test[7]
Fetal weight (Covariates: litter size, sex ratio) Sex ratio (Covariate: litter size)	Linear contrast of least square means from ANCOVA[9]

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APPENDIX A (CONT.)

N. Absorption of Test and Control Substances

Determination of the degree of absorption of the test and control substances by the test system is not necessary to achieve the objectives of the study.

O. Records Maintenance and Specimen Retention

When the study is completed and the final report is issued, the raw data and the final report will be forwarded to the archives of Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Delaware, and will be maintained there or at the DuPont Records Management Center, Wilmington, Delaware.

All skeletal, head and selected visceral specimens, as well as histologic preparations, will be stored at Haskell Laboratory and will be retained for as long as the quality of the material affords proper evaluation.

CRITICAL DATES

Study Start (first Day 7G): January 3, 1995
Completion (last date of data collection): February 17,1994 (approximate)
Final Report: March, 1995

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APPENDIX A (CONT.)

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APPENDIX A (CONT.)

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MEDICAL RESEARCH PROJECT NUMBER MR-10042-001

PROTOCOL

Date

Prepared by: Smm for Bernice Dewberry Street 12/30/94
Bernice Dewberry Street, B.S.
Toxicology Associate
Developmental and
Reproductive Toxicology

Susan M. Munley 12/30/94
Susan M. Munley, M.A.
Study Director
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Approved by: Mark E. Hurtt 12/30/94
Mark E. Hurtt, Ph.D.
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cc: L. B. Biegel
K. H. Kreckmann
C. M. Lattin
J. C. Maslanka
R. J. Schacht

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX A (CONT.)

PILOT DEVELOPMENTAL TOXICITY STUDY OF GLYCOLIC ACID IN RATS

MEDICAL RESEARCH PROJECT NUMBER 10042-001

TEST CODE NUMBER 840

PROTOCOL AMENDMENT 1

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX A (CONT.)

MATERIALS AND METHODS

Change:

A. Test Substance

4. Vehicle: Deionized water

To:

A. Test Substance

4. Vehicle: Deionized water will be used for the first batch of dosing formulations. Commercially-supplied water (OmniSolv water, HPLC grade, Lot 34271, 9/95 expiration date, EM Science, Gibbstown, New Jersey) will be used for subsequent mixes.

Reason for change:

The commercially-supplied water will present less variability than the local deionized water with respect to such things as bacterial content and pH.

Change:

H. Preparation, Administration, and Analysis of Test Formulations

1. Preparation: A stock formulation (100 mg/mL) of the test material in the vehicle will be prepared once prior to the onset of the dosing period. This stock solution will serve as the high dose level solution and will be further diluted to make the lower dose level solutions (50, 25, and 12.5 mg/mL). The details regarding formulation preparation will be documented in the study records.

2. Administration: Glycolic acid will be administered by gavage because the oral route is a potential route of accidental human exposure. The volume administered will be based on the most recent body weight.

3. Analysis: Duplicate samples (~100 mL each) of each dose level formulation will be shipped to Robert Schacht, 901 West DuPont Avenue, Belle, West Virginia 25015, for concentration verification analyses. Additional samples will be taken from each dosing formulation for submission to the Analytical Group of Environmental Sciences (ES) at Haskell Laboratory for concentration verification analyses. These samples will be stored at room temperature until analyses can be conducted. The analytical method used will be documented in the ES study records.

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX A (CONT.)

To:

H. Preparation, Administration, and Analysis of Test Formulations

1. Preparation: A stock formulation (100 mg/mL) of the test material in the vehicle will be prepared once prior to the onset of the dosing period and weekly thereafter. This stock solution will serve as the high dose level solution and will be further diluted to make the lower dose level solutions (50, 25, and 12.5 mg/mL). The details regarding formulation preparation will be documented in the study records.

2. Administration: Glycolic acid will be administered by gavage because the oral route is a potential route of accidental human exposure. The volume administered will be based on the most recent body weight.

3. Analysis: From the first set of dosing formulations, duplicate samples (~100 mL each) of each dose level formulation will be shipped to Robert Schacht, 901 West DuPont Avenue, Belle, West Virginia 25015, for concentration verification analyses. Additional samples will be taken from each of these dosing formulations for submission to the Analytical Group of Environmental Sciences (ES) at Haskell Laboratory for concentration verification analyses. At Haskell Laboratory, these samples will be stored at room temperature for one week and then frozen until analyses can be conducted. These analyses will address seven-day stability. From subsequent formulating times, fresh and seven-day stability samples will be taken and submitted to the Analytical Group of ES. The samples will be frozen unless they are analyzed shortly after submission. The analytical method used will be documented in the ES study records.

Reason for change:

The preparation and analyses sections were revised to reflect that dosing formulations will now be prepared weekly and that each batch will be analyzed for concentration both at the time of preparation and again seven days later.

Date

Susan M. Munley Jan. 9, 1994

Susan M. Munley, M.A.
Study Director
Developmental and
Reproductive Toxicology

cc: L. B. Biegel
P. J. Chapman
S. E. Doughty
M. E. Hurtt
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PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX A (CONT.)

PILOT DEVELOPMENTAL TOXICITY STUDY OF GLYCOLIC ACID IN RATS

MEDICAL RESEARCH PROJECT NUMBER 10042-001

TEST CODE NUMBER 840

PROTOCOL AMENDMENT #2

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX A (CONT.)

MATERIALS AND METHODS

Add the following section:

P. Blood Collection

On January 16, 1995, blood samples will be collected from all of the rats on study. Approximately 0.5 mL of blood will be drawn from the lateral tail vein of each rat. The rats will be bled in a random order. Details regarding the materials and documentation of the bleeding will be provided in the study records. After all the rats are bled, the whole blood samples will be submitted to personnel from the Clinical Pathology group at Haskell Laboratory. Serum will be prepared and analyzed by the Clinical Pathology group. The measurements recorded will enable assessment of the acid-base status of the dams. Details regarding serum preparation and method of analysis will be provided in the study records.

Reason for change:

Since glycolic acid is highly acidic, it has the potential to cause metabolic acidosis. These additional procedures have been included to determine if the dose levels on this study are sufficient to induce this state.

Date

Susan M. Munley 1/13/95

Susan M. Munley, M.A
Study Director
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cc: L. B. Biegel
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PILOT DEVELOPMENTAL TOXICITY STUDY OF 70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX A (CONT.)

PILOT DEVELOPMENTAL TOXICITY STUDY OF GLYCOLIC ACID IN RATS

MEDICAL RESEARCH PROJECT NUMBER 10042-001

TEST CODE NUMBER 840

PROTOCOL AMENDMENT 3

Protocol amendment 1 was inadvertently dated January 9, 1994. It should have actually been dated January 9, 1995.

Date

Susan M. Munley — Jan 19, 1995

Susan M. Munley, M.A.
Study Director
Developmental and
Reproductive Toxicology

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX A (CONT.)

PILOT DEVELOPMENTAL TOXICITY STUDY OF GLYCOLIC ACID IN RATS

MEDICAL RESEARCH PROJECT NUMBER 10042-001

TEST CODE NUMBER 840

PROTOCOL AMENDMENT 4

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX A (CONT.)

MATERIALS AND METHODS

Change the following section which was amended once in Protocol Amendment 1:

H. Preparation, Administration, and Analysis of Test Formulations

3. Analysis: Duplicate samples (~100 mL each) of each dose level formulation will be shipped to Robert Schacht, 901 West DuPont Avenue, Belle, West Virginia 25015, for concentration verification analyses. Additional samples will be taken from each dosing formulation for submission to the Analytical Group of Environmental Sciences (ES) at Haskell Laboratory for concentration verification analyses. These samples will be stored at room temperature until analyses can be conducted. The analytical method used will be documented in the ES study records.

H. Preparation, Administration, and Analysis of Test Formulations

3. Analysis: From the first set of dosing formulations (vehicle: deionized water), duplicate samples (~100 mL each) of each dose level formulation will be shipped to Robert Schacht, 901 West DuPont Avenue, Belle, West Virginia 25015, for concentration verification analyses.

After one week, samples will be taken from the first set of formulations and submitted to the Analytical Group of Environmental Sciences (ES) at Haskell Laboratory for additional concentration verification analyses. All formulations were stored in the refrigerator and were only removed for a short time each day for the purpose of dosing. These analyses will address seven-day stability.

From the second formulating time (vehicle: commercially-supplied water), fresh samples will be taken and submitted to the Analytical Group of ES.

From the third and final formulating time (vehicle: commercially supplied water), 7-day and 11-day stability samples will be taken from the formulations.

All samples will be frozen until they are analyzed. The analytical method used will be documented in the ES study records.

Reason for change:

The analysis sections was revised to specify which particular samples (fresh, 7-day stability, or 11-day stability) were to be taken at each separate formulation time. The stability samples are designed to assure that the formulations were stable for 7 to 11 days after preparation. These times cover the maximum length of time that any of the formulations will be used for dosing. In addition, this revision indicates that the formulations should be stored in the refrigerator when not in use.

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX A (CONT.)

K. Parameters to be Studied

5. Fetuses of Females Surviving to Scheduled Euthanasia

Change:

f. Skeletal Alterations: After alcohol fixation, the alizarin-stained skeletons will be examined and skeletal alterations will be recorded for all live fetuses, excluding the fetal heads fixed in formalin.

To:

f. Skeletal Alterations: After alcohol fixation, the alizarin-stained skeletons will be examined and skeletal alterations will be recorded for all live fetuses, excluding the fetal heads fixed in Bouin's fixative.

Reason for change:

Fetal heads will be fixed in Bouin's fixative rather than formalin.

Date

Susan M. Munley — Jan. 23, 1995

Susan M. Munley, M.A.
Study Director
Developmental and
Reproductive Toxicology

cc: P. J. Chapman
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C. M. Lattin
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B. D. Street

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX A (CONT.)

PILOT DEVELOPMENTAL TOXICITY STUDY OF GLYCOLIC ACID IN RATS

MEDICAL RESEARCH PROJECT NUMBER 10042-001

TEST CODE NUMBER 840

PROTOCOL AMENDMENT 5

Change:

O. Records Maintenance and Specimen Retention

When the study is completed and the final report is issued, the raw data and the final report will be forwarded to the archives of Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Delaware, and will be maintained there or at the DuPont Records Management Center, Wilmington, Delaware.

All skeletal, head and selected visceral specimens, as well as histologic preparations, will be stored at Haskell Laboratory and will be retained for as long as the quality of the material affords proper evaluation.

To:

O. Records, Sample, and Specimen Retention

All original records will be retained at Haskell Laboratory or at the Records Management Center, E. I. du Pont de Nemours and Company, Wilmington, Delaware. A portion of test sample will be collected for archive purposes prior to the outset of the study and retained at Haskell Laboratory. All skeletal, head and selected visceral specimens, as well as histologic preparations, will be stored at Haskell Laboratory and will be retained for as long as the quality of the material affords proper evaluation.

Reason for change:

This section of the protocol was revised to more accurately reflect record, test sample, and specimen retention procedures.

Susan M. Munley 2-23-95

Susan M. Munley Date
Study Director
Developmental and
Reproductive Toxicology

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX A (CONT.)

PILOT DEVELOPMENTAL TOXICITY STUDY OF GLYCOLIC ACID IN RATS

MEDICAL RESEARCH PROJECT NUMBER 10042-001

TEST CODE NUMBER 840

PROTOCOL AMENDMENT 6

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX A (CONT.)

MATERIALS AND METHODS

Change the following section which was amended once in Protocol Amendment 1 and again in Protocol Amendment 4:

H. Preparation, Administration, and Analysis of Test Formulations

3. Analysis: From the first set of dosing formulations (vehicle: deionized water), duplicate samples (~100 mL each) of each dose level formulation will be shipped to Robert Schacht, 901 West DuPont Avenue, Belle, West Virginia 25015, for concentration verification analyses.

   After one week, samples will be taken from the first set of formulations and submitted to the Analytical Group of Environmental Sciences (ES) at Haskell Laboratory for additional concentration verification analyses. All formulations were stored in the refrigerator and were only removed for a short time each day for the purpose of dosing. These analyses will address seven-day stability.

   From the second formulating time (vehicle: commercially-supplied water), fresh samples will be taken and submitted to the Analytical Group of ES.

   From the third and final formulating time (vehicle: commercially supplied water), 7-day and 11-day stability samples will be taken from the formulations.

   All samples will be frozen until they are analyzed. The analytical method used will be documented in the ES study records.

To:

H. Preparation, Administration, and Analysis of Test Formulations

3. Analysis: From the first set of dosing formulations (vehicle: deionized water), duplicate samples (~100 mL each) of each dose level formulation will be shipped to Robert Schacht, 901 West DuPont Avenue, Belle, West Virginia 25015, for concentration verification analyses.

   After one week, samples will be taken from the first set of formulations and submitted to the Analytical Group of Environmental Sciences (ES) at Haskell Laboratory for additional concentration verification analyses. These analyses will address seven-day stability.

   From the second formulating time (vehicle: commercially-supplied water), fresh samples will be taken and submitted to the Analytical Group of ES.

   From the third and final formulating time (vehicle: commercially supplied water), 7-day and 11-day stability samples will be taken from the formulations.

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX A (CONT.)

The first batch of formulations (vehicle: deionized water) were stored at room temperature. Subsequent batches (vehicle: commercially-supplied water) were stored in the refrigerator and were only removed for a short time each day for the purpose of dosing.

All samples will be frozen until they are analyzed. The analytical method used will be documented in the ES study records.

Reason for change:

This section was revised to indicate that the first batch of dosing formulations were stored at room temperature while the subsequent batches were refrigerated except during dosing.

Date

Susan M. Munley

Susan M. Munley, M.A.
Study Director
Developmental and
Reproductive Toxicology

May 16, 1995

cc: P. J. Chapman
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PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX A (CONT.)

PILOT DEVELOPMENTAL TOXICITY STUDY OF GLYCOLIC ACID IN RATS

MEDICAL RESEARCH PROJECT NUMBER 10042-001

TEST CODE NUMBER 840

PROTOCOL AMENDMENT 7

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX A (CONT.)

MATERIALS AND METHODS

K. Parameters to be Studied

4. Postmortem Observations of Females Surviving to Scheduled Euthanasia (Day 22 of Gestation)

Change:

e. Implantation Sites: For each female with visible implantation sites, the types of implants (live and dead fetuses, and resorptions) and their relative positions will be recorded. The uterus of each apparently "nonpregnant" female will be stained with ammonium sulfide[2] to detect very early resorptions; counts will be recorded and each resorption will be classified as definite or questionable. Data from females determined to be pregnant by staining will be used only to calculate the incidence of pregnancy and the number of females with total resorptions.

To:

e. Implantation Sites: For each female with visible implantation sites, the types of implants (live and dead fetuses, and resorptions) and their relative positions will be recorded. The uterus of each apparently "nonpregnant" female will be stained with ammonium sulfide[2] to detect very early resorptions. Data from females determined to be pregnant by staining will be used only to calculate the incidence of pregnancy and the number of females with total resorptions.

Reason for change:

When early resorptions are detected using ammonium sulfide stain, the resorptions are considered definite. Thus, "definite" or "questionable" classifications are not necessary.

Date

Susan M. Munley 5-25-95

Susan M. Munley, M.A.
Study Director
Developmental and
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cc: P. J. Chapman
S. E. Doughty
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C. M. Lattin
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PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX A (CONT.)

PILOT DEVELOPMENTAL TOXICITY STUDY OF GLYCOLIC ACID IN RATS

MEDICAL RESEARCH PROJECT NUMBER 10042-001

TEST CODE NUMBER 840

PROTOCOL AMENDMENT 8

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX A (CONT.)

MATERIALS AND METHODS

B. Animals

Change:

3. Source: Charles River Laboratories, Inc., Kingston, New York

To:

3. Source: Charles River Laboratories, Inc., Raleigh, North Carolina

Reason for change:

The location of the breeder was inadvertently listed as Kingston, New York, when it was actually Raleigh, North Carolina.

Date

Susan M. Munley 5-30-95

Susan M. Munley, M.A.
Study Director
Developmental and
Reproductive Toxicology

cc: P. J. Chapman
S. E. Doughty
M. E. Hurtt
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B. D. Street

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX B.1

PILOT DEVELOPMENTAL TOXICITY STUDY OF GLYCOLIC ACID IN RATS

ANALYSIS OF GLYCOLIC ACID IN DOSING FORMULATIONS

Medical Research Project Number:	10042-001
Haskell Sample Number:	20895
Analytical Report Number:	HA-95-029

SUMMARY

Glycolic acid as used in this report refers to the active ingredient (a.i.) in a 70% glycolic acid aqueous solution.

Formulations at concentrations of 0, 12.5, 25, 50, and 100 mg/mL of glycolic acid were prepared December 29, 1994, January 5, and January 12, 1995. The samples prepared December 29, 1994, were stored at room temperature for 7 days and submitted for stability analysis. Samples prepared January 5, 1995, were submitted for concentration verification. Samples prepared January 12, 1995, were stored refrigerated for 7 or 11 days and submitted for stability analysis.

Concentrations of glycolic acid in dosing formulations were determined by titration with a standard base solution and quantitated as the free acid.

Measured results for all samples indicated that the test substance was at expected levels (± 15 % of nominal) and was stable for all storage conditions.

Glycolic acid was not detected in the 0 mg/mL control formulations.

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX B.1 (CONT.)

ANALYSIS OF GLYCOLIC ACID IN DOSING FORMULATIONS

HA-95-029p2

METHODS

DOSING SAMPLE ANALYSIS

Analysis of glycolic acid in dosing formulations was conducted according to the following method.

Aliquots of the supplied dosing samples were pipetted into a beaker containing phenyl violet indicator/ice slurry. The volume of the aliquots varied based on the concentration of the supplied dosing samples. They were targeted to 50 or 100 mg of glycolic acid for each titration. The aliquots were titrated with a standardized volumetric sodium hydroxide solution (0.2519N- Baker Chemical) to the free acid equivalence point of the 70% glycolic acid.

All glycolic acid samples submitted for analysis were stored frozen and brought to room temperature before analysis.

TITRATION EQUIPMENT AND REAGENTS

Burette:	Kimax 10 mL micro burette, needle tip
Pipettes:	Volumetric; 1, 2, and 4 mL
Reagents:	Water; cracked ice
Titrant:	0.25 N Sodium Hydroxide (NaOH - 0.2519 N) Volumetric Solution; "Baker Analyzed"
Indicator:	Phenyl Violet Indicator (50/50 - Mixture of Solution A and B)
Solution A:	0.25% Thymol Blue 0.25g. Thymol Blue - Acid Salt 2.18 mL 0.25 N Sodium Hydroxide in 100 mL bottled water
Solution B:	0.05% Phenolphthalein indicator 0.05g. Phenolphthalein indicator powder in 100 mL of methanol.

PROCEDURE FOR TITRATING

Cracked ice (approximatly 50 g.) is weighed into a vessel and 1.5 mL of the phenyl violet indicator are added by pipette. The ice and indicator are mixed to make a slurry which should be a dark blue green color. NaOH solution (0.2519N) is added if color of the slurry is not achieved. This slurry is used for duplicate titrations on the same sample. The slurry (15 g.) is weighed into a 150 mL beaker and the sample introduced by pipette (a color change occurs if the test substance is present). The slurry is mixed before and during titration. The sample is titrated with the NaOH solution (0.2519N) until the dark blue green color of the indicator returns. This is the equivalence end-point of the free acid.

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX B:1 (CONT.)

ANALYSIS OF GLYCOLIC ACID IN DOSING FORMULATIONS

HA-95-029p3

CALIBRATION & QUANTITATION

A stock solution of glycolic acid was prepared in water using the 70% glycolic acid test substance. Aliquots of this solution were used to make calibration points which bracketed the sample concentrations. These aliquots were titrated with a standardized volumetric sodium hydroxide solution (0.2519N - Baker Chemical) using the phenyl violet indicator/ice slurry to detect the equivalence end-point of the free acid. The milliliters of the NaOH solution for replicate titrations were used to construct a calibration curve by least-squares regression. Measured concentrations for each glycolic acid solution were determined by applying the milliliters of NaOH solution to reach the equivalence end-point of the free acid to the calibration curve.

RESULTS

STABILITY

Analytical results from glycolic acid formulations prepared December 29, 1994, and January 12, 1995, and submitted for stability are shown in Table I.

Measured concentrations of glycolic acid in dosing formulations were from 98.0 to 111% of nominal for 7-day room temperature samples (December 29, 1994); from 94.0 to 98.0% of nominal for 7-day refrigerated samples (January 12, 1995); and from 93.6 to 98.1% of nominal for 11-day refrigerated samples samples (January 12, 1995). These data indicate that the test substance was stable for all storage conditions. The reported values are the mean values of duplicate titrations.

CONCENTRATION VERIFICATION

Analytical results from glycolic acid formulations prepared January 5, 1995, and submitted to verify concentration are shown in Table II.

Duplicate samples at each dose level were analyzed. Measured concentrations were from 106% to 113% of nominal. The reported values are the mean of duplicate titrations of duplicate samples (n = 4).

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX B.1 (CONT.)

ANALYSIS OF GLYCOLIC ACID IN DOSING FORMULATIONS

HA-95-029p4

SIGNATURE PAGE

Analysis and report by: Janet C. Maslanka 5/30/95
Janet C. Maslanka (Date)
Chemistry Associate

Reviewed by: Charlotte H. Lattin 5/30/95
Charlotte H. Lattin (Date)
Chemist

Date issued: 5/30/95

Total Report Pages: 6

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX B.1 (CONT.)

ANALYSIS OF GLYCOLIC ACID IN DOSING FORMULATIONS

HA-95-029p5

TABLE I

STABILITY OF GLYCOLIC ACID IN DOSING FORMULATIONS

SAMPLE TYPE	mg/mL GLYCOLIC ACID NOMINAL	MEASURED	AVERAGE MEASURED	PERCENT NOMINAL
7-DAY ROOM TEMPERATURE[A]	0	ND[B]		
	0	ND		
	12.5	13.8		
		13.9	13.9	111
	25.0	25.2		
		25.1	25.2	101
	50.0	48.8		
		49.2	49.0	98.0
	100	101		
		100	101	101
7-DAY REFRIGERATED[C]	0	ND		
	0	ND		
	12.5	11.7		
		11.8	11.8	94.4
	25.0	23.5		
		23.5	23.5	94.0
	50.0	47.1		
		47.2	47.2	94.4
	100	97.9		
		98.0	98.0	98.0
11-DAY REFRIGERATED[C]	0	ND		
	0	ND		
	12.5	11.7		
		11.7	11.7	93.6
	25.0	23.4		
		22.7	23.1	92.4
	50.0	48.2		
		48.2	48.2	96.4
	100	98.2		
		97.9	98.1	98.1

(A) Samples prepared December 29, 1994.
(B) ND denotes not detected.
(C) Samples prepared January 12, 1995.

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX B.1 (CONT.)

ANALYSIS OF GLYCOLIC ACID IN DOSING FORMULATIONS

HA-95-029p6

TABLE II

CONCENTRATION OF GLYCOLIC ACID IN DOSING FORMULATIONS
PREPARED JANUARY 5, 1995

SAMPLE TYPE	mg/mL GLYCOLIC ACID NOMINAL	MEASURED	AVERAGE MEASURED[A]	PERCENT NOMINAL
FRESH	0-A	ND[B]		
		ND		
	0-B	ND		
		ND		
FRESH	12.5-A	13.2		
		13.2		
	12.5-B	13.3		
		13.5	13.3	106
FRESH	25.0-A	26.6		
		26.7		
	25.0-B	27.0		
		27.0	26.8	107
FRESH	50-A	55.4		
		54.8		
	50-B	55.4		
		54.9	55.1	110
FRESH	100-A	115		
		113		
	100-B	112		
		113	113	113

(A) Duplicate samples (A, B) from each dosing formulation were submitted and analyzed in duplicate. The mean of all analyses is reported.
(B) ND denotes not detected.

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX B.1 (CONT.)

ANALYSIS OF GLYCOLIC ACID IN DOSING FORMULATIONS

SUMMARY OF GLYCOLIC ACID FORMULATION ANALYSIS

	CONCENTRATION OF GLYCOLIC ACID (mg/mL)			
Nominal	12.5	25.0	50.0	100
Stability Samples				
7 Day Room Temperature 12/29/94	13.9 (111)[a]	25.2 (101)	49.0(98.0)	101 (101)
7 Day Refrigerated 1/12/95	11.8 (94.4)	23.5 (94.0)	47.2 (94.4)	98.0 (98.0)
11 Day Refrigerated 1/12/95	11.7 (93.6)	23.1 (92.4)	48.2 (96.4)	98.1 (98.1)
Concentration Samples[b]				
1/5/95	13.3 (106)	26.8 (107)	55.1(110)	113 (113)

[a] Numbers in parentheses are percent of nominal for each concentration.
[b] Duplicate samples from each dosing formulation were submitted and analyzed in duplicate.

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX B.2

DuPont Specialty Chemicals
901 W. DuPont Avenue
Belle, West Virginia 25015

DuPont Specialty Chemicals

May 10, 1995

Susan Munley
Stine-Haskell Research Center
Haskell, Building 1, Room 917a
Elkton Road
Newark, DE 19711

Dear Mrs. Munley:

I used Dupont method No. H7000.005.02.BE to analyze the 10 samples you sent to me on January 1995 for total acidity.

The principle of the method summarized in:

A sample of Hydroxyacetic acid is saponified with a excess of standard sodium hydroxide. It is then titrated with standardized hydrochloric acid using an autotitrator. The sample is titrated to its equivalence point recording electrode potential vs. titrant volume. The total acid content of the sample is expressed as percent hydroxyacetic acid.

The 10 samples you sent was in two groups, A and B, the theoretical Hydroxyacetic acid concentration in both group was 0mg/ml, 12.5mg/ml, 25mg/ml 50mg/ml and 100mg/ml, using 70% acid.

Conversion of the above concentration to gram % of the 100% acid, the theoretical acid concentration should be 0%, 0.88%, 1.75%, 3.5% and 7%.

The analytical results and % from targeted concentrations are:

Group	0mg/ml	12.5mg/ml	25mg/ml	50mg/ml	100mg/ml
A	N/D*	0.76%	1.57%	3.31%	6.96%
Targ.%	100%	86.4%	89.7%	94.6%	99.4%
B	N/D*	0.76%	1.57%	3.33%	6.97%
Targ.%	100%	88.6%	89.7%	95.1%	99.6%

N/D* = Not Detectable.

If you need more information, please call me at DUCOM 8-357-1013.

Respectfully yours,

Mohamed Younis

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX C

INDIVIDUAL BODY WEIGHT CHANGES (grams)

GROUP I: 0 mg/kg

ANIMAL NUMBER	DAYS OF GESTATION									
	1-7	7-9	9-11	11-13	13-15	15-17	17-19	19-21	21-22	7-22
559459	24.3	4.7	0.5	7.4	9.2	10.1	19.5	40.4	18.0	109.8
559462	24.2	4.1	12.6	3.2	5.9	14.0	34.1	28.6	25.9	128.4
559465▪	23.3	-2.0	0.5	6.6	-11.6	-4.4	4.1	-5.1	2.0	-9.9
559468	33.9	0.7	11.5	1.4	2.1	22.1	14.7	27.9	15.4	95.8
559477	29.3	3.1	2.3	11.2	5.5	6.3	19.9	15.5	20.7	84.5
559486	28.5	0.3	12.8	7.3	6.4	22.2	32.0	29.8	18.3	129.1
559492	32.7	7.9	15.8	3.4	15.1	18.0	27.4	34.4	24.8	146.8
559495	40.5	7.3	1.9	11.4	4.9	22.4	31.7	28.8	15.1	123.5
MEAN	30.5	4.0	8.2	6.5	7.0	16.4	25.6	29.3	19.7	116.8
S.D.	5.77	2.94	6.36	3.96	4.14	6.48	7.55	7.56	4.28	21.46
S.E.	2.18	1.11	2.41	1.50	1.56	2.45	2.85	2.86	1.62	8.11
N	7	7	7	7	7	7	7	7	7	7

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX C (CONT.)

INDIVIDUAL BODY WEIGHT CHANGES (grams)

GROUP II: 125 mg/kg

ANIMAL NUMBER	DAYS OF GESTATION 1-7	7-9	9-11	11-13	13-15	15-17	17-19	19-21	21-22	7-22
559463	27.4	2.5	12.5	6.8	4.7	18.1	25.4	27.4	14.7	112.1
559475	25.2	7.8	-1.1	11.0	14.4	11.7	32.1	34.6	28.3	138.8
559490	38.1	7.2	9.9	11.4	10.7	14.3	25.7	29.2	14.8	123.2
559493[a]	28.3	4.1	6.8	-0.2	-2.8	3.7	-7.9	-0.5	-4.0	-0.8
559494	28.3	10.1	2.5	6.7	8.1	10.9	24.2	29.8	16.1	108.4
559497	27.5	0.1	8.5	10.4	4.1	16.3	27.6	25.1	19.3	111.4
559498[a]	-12.6	7.8	-8.1	-5.0	5.1	-4.3	7.8	-4.5	-0.4	-1.6
559500	24.8	-7.0	9.3	0.6	5.8	23.9	25.6	33.9	28.6	120.7
MEAN	28.6	3.5	6.9	7.8	8.0	15.9	26.8	30.0	20.3	119.1
S.D.	4.88	6.30	5.14	4.10	3.98	4.78	2.83	3.68	6.53	11.23
S.E.	1.99	2.57	2.10	1.67	1.62	1.95	1.16	1.50	2.67	4.58
N	6	6	6	6	6	6	6	6	6	6

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX C (CONT.)

INDIVIDUAL BODY WEIGHT CHANGES (grams)

GROUP III: 250 mg/kg

ANIMAL NUMBER	DAYS OF GESTATION 1-7	7-9	9-11	11-13	13-15	15-17	17-19	19-21	21-22	7-22
559454	32.6	1.0	10.5	10.3	6.6	19.5	25.8	33.5	17.0	124.2
559458	36.9	12.3	-2.3	17.1	9.4	14.7	25.2	39.7	21.2	137.3
559464	38.0	2.1	12.2	17.1	1.1	11.1	19.6	25.4	22.5	111.1
559474	21.6	-1.2	13.0	13.1	11.4	16.7	18.0	26.3	24.0	121.3
559476	32.1	11.3	5.3	7.6	12.2	6.5	26.4	21.0	13.9	104.2
559480	25.0	0.6	3.7	7.6	9.1	15.4	17.6	27.9	12.8	94.7
559482	10.0	0.3	9.8	9.4	-4.4	21.6	21.4	34.1	14.0	106.2
559503	20.7	3.6	3.0	15.7	1.9	2.6	33.9	22.7	16.1	99.5
MEAN	27.1	3.8	6.9	12.2	5.9	13.5	23.5	28.8	17.7	112.3
S.D.	9.55	5.16	5.34	4.05	5.83	6.44	5.47	6.39	4.31	14.27
S.E.	3.38	1.83	1.89	1.43	2.06	2.28	1.93	2.26	1.52	5.05
N	8	8	8	8	8	8	8	8	8	8

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX C (CONT.)

INDIVIDUAL BODY WEIGHT CHANGES (grams)

GROUP IV: 500 mg/kg

ANIMAL NUMBER	DAYS OF GESTATION 1-7	7-9	9-11	11-13	13-15	15-17	17-19	19-21	21-22	7-22
559460[a]	20.3	-25.8	17.2	-6.4	4.5	-22.5	6.4	12.0	9.9	-4.7
559466	26.1	-6.1	12.7	1.9	15.1	20.7	21.5	32.6	15.3	113.7
559484	39.7	-0.6	10.5	15.2	4.1	17.8	12.6	45.2	19.6	124.4
559487	20.5	4.9	10.4	-5.5	11.9	18.9	18.4	22.5	12.1	93.6
559488	25.7	-1.8	-7.1	-1.6	16.9	24.2	19.7	35.0	5.0	90.3
559489[a]	32.8	-5.6	-2.5	-6.9	4.4	-17.2	2.7	-6.4	8.1	-23.4
559501	28.5	0.0	7.6	10.7	5.8	14.0	27.4	29.1	10.3	104.9
559502[a]	4.0	5.2	7.9	0.4	1.7	3.8	0.7	2.2	-10.6	11.3
MEAN	28.1	-0.7	6.8	4.1	10.8	19.1	19.9	32.9	12.5	105.4
S.D.	7.11	3.94	7.99	8.61	5.63	3.75	5.35	8.34	5.47	14.12
S.E.	3.18	1.76	3.57	3.85	2.52	1.68	2.39	3.73	2.44	6.31
N	5	5	5	5	5	5	5	5	5	5

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX C (CONT.)

INDIVIDUAL BODY WEIGHT CHANGES (grams)

GROUP V: 1000 mg/kg

ANIMAL NUMBER	DAYS OF GESTATION 1-7	7-9	9-11	11-13	13-15	15-17	17-19	19-21	21-22	7-22
559456	30.1	-3.1	-18.8	0.2	12.9	11.8	13.2	34.2	9.4	59.8
559467	40.7	-1.3	11.8	9.4	1.9	6.7	15.3	12.0	11.4	67.2
559478	24.4	3.5	10.4	-33.5	12.7	21.8	14.9	25.8	18.0	73.6
559481[b]	27.5	-47.5	-27.0	...	...	...	...	...	...	...
559483	26.9	5.8	-5.7	9.6	5.9	15.3	23.8	20.5	17.7	92.9
559485[c]	17.2	-18.7	...	...	...	...	...	...	...	...
559491	11.0	-0.7	8.6	-31.6	21.0	10.2	19.7	26.9	18.6	72.7
559496	32.9	-25.9	18.6	4.2	5.5	2.4	23.4	18.8	18.6	65.6
MEAN	27.7	-3.6	4.2	-7.0	10.0	11.4	18.4	23.0	15.6	72.0
S.D.	9.92	11.40	13.78	20.15	6.92	6.75	4.58	7.66	4.10	11.43
S.E.	4.05	4.65	5.63	8.22	2.82	2.76	1.87	3.13	1.68	4.66
N	6	6	6	6	6	6	6	6	6	6

[a] Not pregnant, data excluded from the calculations.
[b] Sacrificed in extremis, data excluded from the calculations.
[c] Accidentally killed, data excluded from the calculations.

... = No data

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX D

INDIVIDUAL BODY WEIGHTS (grams)

GROUP I: 0 mg/kg

ANIMAL NUMBER	DAYS OF GESTATION 1	7	9	11	13	15	17	19	22
559459	297.5	321.8	326.5	327.0	334.4	343.6	353.7	373.2	431.6
559462	289.5	313.7	317.8	330.4	333.6	339.5	353.5	387.6	442.1
559465[a]	316.6	339.9	337.9	338.4	345.0	333.4	329.0	333.1	330.0
559468	237.3	271.2	271.9	283.4	284.8	286.9	309.0	323.7	367.0
559477	229.1	258.4	261.5	263.8	275.0	280.5	286.8	306.7	342.9
559486	313.9	342.4	342.7	355.5	362.8	369.2	391.4	423.4	471.5
559492	306.6	339.3	347.2	363.0	366.4	381.5	399.5	426.9	486.1
559495	330.0	370.5	377.8	379.7	391.1	396.0	418.4	450.1	494.0
MEAN	286.3	316.8	320.8	329.0	335.4	342.5	358.9	384.5	433.6
S.D.	38.50	39.94	41.58	42.36	42.87	44.80	48.29	54.01	58.56
S.E.	14.55	15.09	15.72	16.01	16.20	16.93	18.25	20.41	22.14
N	7	7	7	7	7	7	7	7	7

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX D (CONT.)

INDIVIDUAL BODY WEIGHTS (grams)

GROUP II: 125 mg/kg

ANIMAL NUMBER	DAYS OF GESTATION 1	7	9	11	13	15	17	19	22
559463	290.4	317.8	320.3	332.8	339.6	344.3	362.4	387.8	429.9
559475	301.6	326.8	334.6	333.5	344.5	358.9	370.6	402.7	465.6
559490	245.6	283.7	290.9	300.8	312.2	322.9	337.2	362.9	406.9
559493[a]	318.7	347.0	351.1	357.9	357.7	354.9	358.6	350.7	346.2
559494	265.0	293.3	303.4	305.9	312.6	320.7	331.6	355.8	401.7
559497	288.2	315.7	315.8	324.3	334.7	338.8	355.1	382.7	427.1
559498[a]	304.8	292.2	300.0	291.9	286.9	292.0	287.7	295.5	290.6
559500	306.7	331.5	324.5	333.8	334.4	340.2	364.1	389.7	452.2
MEAN	282.9	311.5	314.9	321.9	329.7	337.6	353.5	380.3	430.6
S.D.	23.29	18.95	15.61	14.85	13.88	14.20	15.70	17.64	24.90
S.E.	9.51	7.74	6.37	6.06	5.67	5.80	6.41	7.20	10.17
N	6	6	6	6	6	6	6	6	6

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX D (CONT.)

INDIVIDUAL BODY WEIGHTS (grams)

GROUP III: 250 mg/kg

ANIMAL NUMBER	DAYS OF GESTATION 1	7	9	11	13	15	17	19	22
559454	236.6	269.2	270.2	280.7	291.0	297.6	317.1	342.9	393.4
559458	296.4	333.3	345.6	343.3	360.4	369.8	384.5	409.7	470.6
559464	274.0	312.0	314.1	326.3	343.4	344.5	355.6	375.2	423.1
559474	317.7	339.3	338.1	351.1	364.2	375.6	392.3	410.3	460.6
559476	262.7	294.8	306.1	311.4	319.0	331.2	337.7	364.1	399.0
559480	311.5	336.5	337.1	340.8	348.4	357.5	372.9	390.5	431.2
559482	356.6	366.6	366.9	376.7	386.1	381.7	403.3	424.7	472.8
559503	266.6	287.3	290.9	293.9	309.6	311.5	314.1	348.0	386.8
MEAN	290.3	317.4	321.1	328.0	340.3	346.2	359.7	383.2	429.7
S.D.	38.00	32.26	31.67	31.58	31.57	30.71	34.12	30.48	35.12
S.E.	13.43	11.41	11.20	11.17	11.16	10.86	12.06	10.78	12.42
N	8	8	8	8	8	8	8	8	8

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX D (CONT.)

INDIVIDUAL BODY WEIGHTS (grams)

GROUP IV: 500 mg/kg

ANIMAL NUMBER	DAYS OF GESTATION 1	7	9	11	13	15	17	19	22
559460[a]	297.5	317.8	292.0	309.2	302.8	307.3	284.8	291.2	313.1
559466	318.2	344.3	338.2	350.9	352.8	367.9	388.6	410.1	458.0
559484	293.6	333.3	332.7	343.2	358.4	362.5	380.3	392.9	457.7
559487	264.3	284.8	289.7	300.1	294.6	306.5	325.4	343.8	378.4
559488	302.1	327.8	326.0	318.9	317.3	334.2	358.4	378.1	418.1
559489[a]	350.5	383.3	377.7	375.2	368.3	372.7	355.5	358.2	359.9
559501	270.2	298.7	298.7	306.3	317.0	322.8	336.8	364.2	403.6
559502[a]	291.9	295.9	301.1	309.0	309.4	311.1	314.9	315.6	307.2
MEAN	289.7	317.8	317.1	323.9	328.0	338.8	357.9	377.8	423.2
S.D.	22.40	24.98	21.55	22.38	26.88	26.12	27.14	25.56	34.71
S.E.	10.02	11.17	9.64	10.01	12.02	11.68	12.14	11.43	15.52
N	5	5	5	5	5	5	5	5	5

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX D (CONT.)

INDIVIDUAL BODY WEIGHTS (grams)

GROUP V: 1000 mg/kg

ANIMAL NUMBER	DAYS OF GESTATION 1	7	9	11	13	15	17	19	22
559456	285.2	315.3	312.2	293.4	293.6	306.5	318.3	331.5	375.1
559467	238.7	279.4	278.1	289.9	299.3	301.2	307.9	323.2	346.6
559478	258.9	283.3	286.8	297.2	263.7	276.4	298.2	313.1	356.9
559481[b]	261.0	288.5	241.0	214.0	...	...	...	...	...
559483	314.5	341.4	347.2	341.5	351.1	357.0	372.3	396.1	434.3
559485[c]	356.2	373.4	354.7	...	...	...	...	...	...
559491	292.9	303.9	303.2	311.8	280.2	301.2	311.4	331.1	376.6
559496	304.2	337.1	311.2	329.8	334.0	339.5	341.9	365.3	402.7
MEAN	282.4	310.1	306.5	310.6	303.7	313.6	325.0	343.4	382.0*
S.D.	28.59	26.21	24.15	21.11	32.98	29.31	27.44	31.23	32.01
S.E.	11.67	10.70	9.86	8.62	13.46	11.97	11.20	12.75	13.07
N	6	6	6	6	6	6	6	6	6

[a] Not pregnant, data excluded from the calculations.
[b] Sacrificed in extremis, data excluded from the calculations.
[c] Accidentally killed, data excluded from the calculations.
* Significant trend (linear contrast of means from ANOVA); $p \leq 0.05$.

... = No data

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX E

MATERNAL ADJUSTED BODY WEIGHTS AND WEIGHT CHANGES

GROUP I: 0 mg/kg

ANIMAL NUMBER	DAYS 22 [a]	1-22[a]	7-22[a]
559459	336.1	38.6	14.3
559462	343.6	54.1	29.9
559465[b]	...	...	...
559468	290.2	52.9	19.0
559477	269.3	40.2	10.9
559486	371.3	57.4	28.9
559492	383.6	77.0	44.3
559495	399.7	69.7	29.2
MEAN	342.0	55.7	25.2
S.D.	48.18	14.12	11.39
S.E.	18.21	5.34	4.30
N	7	7	7

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX E (CONT.)

MATERNAL ADJUSTED BODY WEIGHTS AND WEIGHT CHANGES

GROUP II: 125 mg/kg

ANIMAL NUMBER	DAYS 22 [a]	1-22[a]	7-22[a]
559463	351.1	60.7	33.3
559475	358.8	57.2	32.0
559490	311.7	66.1	28.0
559493[b]	...	...	...
559494	317.8	52.8	24.5
559497	339.4	51.2	23.7
559498[b]	...	...	...
559500	353.2	46.5	21.7
MEAN	338.7	55.8	27.2
S.D.	19.69	7.05	4.70
S.E.	8.04	2.88	1.92
N	6	6	6

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX E (CONT.)

MATERNAL ADJUSTED BODY WEIGHTS AND WEIGHT CHANGES

GROUP III: 250 mg/kg

ANIMAL NUMBER	DAYS 22 [a]	1-22[a]	7-22[a]
559454	296.6	60.0	27.4
559458	372.6	76.2	39.3
559464	343.0	69.0	31.0
559474	365.5	47.8	26.2
559476	315.7	53.0	20.9
559480	345.6	34.1	9.1
559482	370.9	14.3	4.3
559503	297.1	30.5	9.8
MEAN	338.4	48.1	21.0
S.D.	31.63	20.84	12.24
S.E.	11.18	7.37	4.33
N	8	8	8

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX E (CONT.)

MATERNAL ADJUSTED BODY WEIGHTS AND WEIGHT CHANGES[a]

GROUP IV: 500 mg/kg

ANIMAL NUMBER	DAYS 22 [a]	1-22[a]	7-22[a]
559460[b]	...	...	...
559466	360.5	42.4	16.3
559484	362.3	68.7	29.0
559487	309.7	45.4	24.9
559488	340.3	38.2	12.5
559489[b]	...	...	...
559501	308.4	38.2	9.7
559502[b]	...	...	...
MEAN	336.2	46.6	18.5
S.D.	26.32	12.73	8.21
S.E.	11.77	5.69	3.67
N	5	5	5

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX E (CONT.)

MATERNAL ADJUSTED BODY WEIGHTS AND WEIGHT CHANGES

GROUP V: 1000 mg/kg

ANIMAL NUMBER	DAYS 22 [a]	1-22[a]	7-22[a]
559456	328.0	42.8	12.7
559467	307.3	68.6	27.9
559478	289.5	30.6	6.2
559481[c]	...	...	...
559483	345.7	31.2	4.3
559485[d]	...	...	...
559491	299.7	6.8	-4.2
559496	332.2	28.0	-4.9
MEAN	317.1	34.7	7.0
S.D.	21.57	20.33	12.20
S.E.	8.81	8.30	4.98
N	6	6	6

[a] Maternal body weight minus the products of conception. Body weight changes are calculated using the adjusted weight.
[b] Not pregnant
[c] Sacrificed in extremis
[d] Accidentally killed

... = No Data

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX F

INDIVIDUAL FOOD CONSUMPTION (grams)

GROUP I: 0 mg/kg

ANIMAL NUMBER	DAYS OF GESTATION 1-7	7-9	9-11	11-13	13-15	15-17	17-19	19-21	21-22	7-22
559459	21.3	19.6	19.3	19.2	22.9	20.1	21.1	24.3	19.0	20.8
559462	20.0	18.6	20.8	18.9	21.4	21.6	24.5	23.9	27.7	21.8
559465[a]	20.4	19.6	16.5	19.8	15.8	12.5	15.3	12.1	12.4	15.7
559468	19.6	17.1	22.1	17.3	20.8	22.6	20.1	25.2	20.0	20.7
559477	19.8	20.1	17.4	21.9	21.3	17.5	19.8	18.9	18.5	19.5
559486	21.8	21.8	21.2	22.9	20.0	23.4	25.9	24.8	22.3	22.8
559492	20.8	21.1	24.7	19.9	23.5	23.2	24.6	23.4	25.0	23.0
559495	23.2	24.8	17.4	23.9	21.3	24.0	27.4	24.8	24.0	23.4
MEAN	20.9	20.4	20.4	20.6	21.6	21.8	23.3	23.6	22.4	21.7
S.D.	1.29	2.47	2.63	2.38	1.21	2.29	3.00	2.17	3.41	1.44
S.E.	0.49	0.93	0.99	0.90	0.46	0.86	1.13	0.82	1.29	0.54
N	7	7	7	7	7	7	7	7	7	7

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX F (CONT.)

INDIVIDUAL FOOD CONSUMPTION (grams)

GROUP II: 125 mg/kg

ANIMAL NUMBER	DAYS OF GESTATION 1-7	7-9	9-11	11-13	13-15	15-17	17-19	19-21	21-22	7-22
559463	21.6	20.7	22.9	20.6	22.6	23.5	24.6	26.2	23.7	23.1
559475	20.6	21.5	21.0	18.8	23.9	19.7	23.1	24.0	26.6	22.0
559490	22.8	23.7	23.1	23.5	24.2	22.8	24.7	24.0	23.8	23.7
559493[a]	20.0	22.3	21.9	...	20.8	20.2	19.1	17.0	14.9	...
559494	21.3	22.2	21.5	21.3	21.1	21.9	22.6	25.2	22.6	22.3
559497	22.0	23.4	21.8	21.2	21.0	20.9	23.1	22.6	22.2	22.0
559498[a]	15.3	16.7	15.4	12.2	15.5	14.6	15.2	16.3	14.9	15.1
559500	21.8	15.5	19.6	...	21.1	24.1	23.8	22.3	27.6	...
MEAN	21.7	21.2	21.7	21.1	22.3	22.2	23.6	24.1	24.4	22.6
S.D.	0.73	3.00	1.29	1.68	1.47	1.65	0.86	1.49	2.19	0.75
S.E.	0.30	1.22	0.53	0.75	0.60	0.68	0.35	0.61	0.89	0.34
N	6	6	6	5	6	6	6	6	6	5

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX F (CONT.)

INDIVIDUAL FOOD CONSUMPTION (grams)

GROUP III: 250 mg/kg

ANIMAL NUMBER	DAYS OF GESTATION 1-7	7-9	9-11	11-13	13-15	15-17	17-19	19-21	21-22	7-22
559454	19.7	18.6	19.1	20.8	19.5	22.2	21.4	24.3	25.3	21.1
559458	23.6	24.6	21.5	22.9	24.8	24.2	22.3	27.1	25.3	24.0
559464	21.6	22.5	22.5	25.1	23.3	25.5	25.0	27.1	26.1	24.5
559474	19.7	17.8	21.4	24.8	24.1	23.9	20.8	22.4	25.3	22.4
559476	21.6	25.1	22.3	22.4	22.1	21.0	23.6	18.9	20.2	22.1
559480	21.9	22.0	21.1	...	21.5	20.9	25.6	17.5	23.6	...
559482	18.3	18.9	19.7	21.0	20.8	20.8	24.2	25.6	24.2	21.7
559503	18.3	18.1	18.1	18.8	17.0	18.3	22.4	20.8	18.6	19.0
MEAN	20.6	21.0	20.7	22.3	21.6	22.1	23.2	23.0	23.6	22.1
S.D.	1.89	2.97	1.58	2.26	2.56	2.33	1.72	3.67	2.72	1.84
S.E.	0.67	1.05	0.56	0.85	0.90	0.82	0.61	1.30	0.96	0.69
N	8	8	8	7	8	8	8	8	8	7

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX F (CONT.)

INDIVIDUAL FOOD CONSUMPTION (grams)

GROUP IV: 500 mg/kg

ANIMAL NUMBER	DAYS OF GESTATION 1-7	7-9	9-11	11-13	13-15	15-17	17-19	19-21	21-22	7-22
559460[a]	20.5	13.0	16.8	16.4	16.6	7.4	11.9	18.3	20.8	14.8
559466	21.4	15.8	19.4	16.9	23.9	26.2	23.7	26.6	21.5	21.8
559484	25.0	21.3	22.1	25.5	21.2	20.9	27.9	25.6	26.6	23.7
559487	19.8	19.4	19.2	14.4	17.9	19.3	22.5	20.1	20.1	19.0
559488	17.7	18.2	15.6	10.3	18.8	23.0	22.1	24.1	17.9	18.8
559489[a]	23.9	20.4	21.1	16.1	17.7	12.2	17.2	14.5	16.3	17.0
559501	20.8	20.6	22.2	21.5	20.8	22.3	24.5	21.3	17.4	21.6
559502[a]	18.7	21.8	20.1	21.8	17.2	23.9	18.5	23.4	14.0	20.5
MEAN	20.9	19.1	19.7	17.7	20.5	22.3	24.1	23.5	20.7	21.0
S.D.	2.67	2.17	2.70	5.95	2.33	2.58	2.31	2.77	3.69	2.07
S.E.	1.19	0.97	1.21	2.66	1.04	1.15	1.03	1.24	1.65	0.93
N	5	5	5	5	5	5	5	5	5	5

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX F (CONT.)

INDIVIDUAL FOOD CONSUMPTION (grams)

GROUP V: 1000 mg/kg

ANIMAL NUMBER	DAYS OF GESTATION 1-7	7-9	9-11	11-13	13-15	15-17	17-19	19-21	21-22	7-22
559456	21.4	18.6	9.4	4.8	19.1	22.0	21.5	22.9	22.6	17.3
559467	21.6	20.9	20.8	21.6	19.6	21.2	23.9	22.8	23.5	21.7
559478	18.9	21.3	18.9	2.4	8.4	19.9	21.4	20.4	22.3	16.5
559481[b]	20.5	0.0	0.0	...	...	...	...	...	...	...
559483	23.1	23.9	17.5	16.9	19.3	19.0	21.7	16.5	15.2	19.0
559485[c]	27.0	15.7	...	...	...	...	...	...	...	...
559491	19.0	18.6	16.5	7.0	11.7	18.8	20.1	22.6	22.9	16.9
559496	23.0	9.2	15.6	18.2	17.4	13.1	21.4	20.1	21.6	16.8
MEAN	21.2	18.7	16.4	11.8	15.9	19.0	21.7	20.9	21.4	18.0
S.D.	1.85	5.08	3.91	8.04	4.73	3.15	1.23	2.48	3.08	2.00
S.E.	0.76	2.07	1.60	3.28	1.93	1.28	0.50	1.01	1.26	0.82
N	6	6	6	6	6	6	6	6	6	6

[a] Not pregnant, data excluded from the calculations.
[b] Sacrificed in extremis, data excluded from the calculations.
[c] Accidentally killed, data excluded from the calculations.

... = No data

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX G

INDIVIDUAL CLINICAL OBSERVATIONS

GROUP I: 0 mg/kg

ANIMAL NUMBER	OBSERVATION	DAYS OF GESTATION ON WHICH SIGN WAS OBSERVED 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22
559459		
	SACRIFICED BY DESIGN 01/20/95	a: ,22
559462		
	ALOPECIA PAW BOTH FRONT	a: 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22
	ALOPECIA LEG BOTH FRONT	b: , , , , , ,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,
		a: , , , , ,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22
	SACRIFICED BY DESIGN 01/20/95	b: , , , , , ,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,
		a: ,22
559465		
	SACRIFICED BY DESIGN 01/18/95	a: ,22
559468		
	SACRIFICED BY DESIGN 01/20/95	a: ,22
559477		
	SACRIFICED BY DESIGN 01/18/95	a: ,22
559486		
	SACRIFICED BY DESIGN 01/18/95	a: ,22
559492		
	SACRIFICED BY DESIGN 01/20/95	a: ,22
559495		
	STAIN PERINASAL (SLIGHT)	a: , ,3,4, , , , , , , , , , , , , , , , , , ,
	SACRIFICED BY DESIGN 01/18/95	a: ,22

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX G (CONT.)

INDIVIDUAL CLINICAL OBSERVATIONS

GROUP II: 125 mg/kg

ANIMAL NUMBER	OBSERVATION		DAYS OF GESTATION ON WHICH SIGN WAS OBSERVED 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22
559463			
	SACRIFICED BY DESIGN 01/20/95	a:	, ,22
559475			
	SACRIFICED BY DESIGN 01/20/95	a:	, ,22
559490			
	ALOPECIA LEFT FRONT LEG	a:	, , , , , , ,8,9,10,11,12,13,14,15, , , , , , ,
		b:	, , , , , , ,8,9,10,11,12,13,14,15, , , , , , ,
	TEETH CLIPPED 1/8/94	a:	, , , , , , , , , ,12, , , , , , , , , , ,
	ALOPECIA LEG LEFT FRONT	a:	, , , , , , , , , , , , , , , , ,18,19,20,21,22
		b:	, , , , , , , , , , , , , , , , ,18,19,20,21,
	SACRIFICED BY DESIGN 01/18/95	a:	, ,22
559493			
	SACRIFICED BY DESIGN 01/19/95	a:	, ,22
559494			
	SACRIFICED BY DESIGN 01/20/95	a:	, ,22
559497			
	SACRIFICED BY DESIGN 01/18/95	a:	, ,22
559498			
	SACRIFICED BY DESIGN 01/20/95	a:	, ,22
559500			
	SACRIFICED BY DESIGN 01/19/95	a:	, ,22

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX G (CONT.)

INDIVIDUAL CLINICAL OBSERVATIONS

GROUP III: 250 mg/kg

ANIMAL NUMBER	OBSERVATION	DAYS OF GESTATION ON WHICH SIGN WAS OBSERVED 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22
559454		
	TEETH BROKEN OR CHIPPED	a: 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22
		b: , , , , , ,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,
	ALOPECIA CHEST	a: 1,2,3, , , ,7,8,9,10,11,12,13,14,15,16,17,18,19,20, ,
		b: , , , , , ,7,8,9,10,11,12,13,14,15,16,17,18,19,20, ,
	ALOPECIA LEG BOTH FRONT	a: 1,2,3, , , , , , , , , , , , , , , , , , , ,
	TEETH CLIPPED 01/01/95	a: , ,3, , , , , , , , , , , , , , , , , , , ,
	ALOPECIA INGUINAL	a: , , , , , ,7,8, , , , , , , , , , , , , ,
		b: , , , , , ,7, , , , , , , , , , , , , , ,
	ALOPECIA LEFT FRONT LEG	a: , , , , , ,7,8,9,10,11,12,13,14, , , , , , , ,
		b: , , , , , ,7,8,9,10,11,12,13,14, , , , , , , ,
	ALOPECIA SHOULDER BOTH	a: , , , , , , , , , , , , , ,15,16,17,18,19,20,21,22
		b: , , , , , , , , , , , , , ,15,16,17,18,19,20,21,
	ALOPECIA UNDERBODY	a: ,21,22
		b: ,21,
	SACRIFICED BY DESIGN 01/20/95	a: ,22
559458		
	SACRIFICED BY DESIGN 01/20/95	a: ,22
559464		
	SACRIFICED BY DESIGN 01/20/95	a: ,22
559474		
	SACRIFICED BY DESIGN 01/18/95	a: ,22
559476		
	SACRIFICED BY DESIGN 01/18/95	a: ,22
559480		
	SACRIFICED BY DESIGN 01/19/95	a: ,22
559482		
	SACRIFICED BY DESIGN 01/23/95	a: ,22
559503		
	SACRIFICED BY DESIGN 1/24/95	a: ,22

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX G (CONT.)

INDIVIDUAL CLINICAL OBSERVATIONS

GROUP IV: 500 mg/kg

ANIMAL NUMBER	OBSERVATION		DAYS OF GESTATION ON WHICH SIGN WAS OBSERVED 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22
559460			
	LUNG NOISE	a:	,20,21,22
		b:	,20,21,
	SACRIFICED BY DESIGN 01/18/95	a:	,22
559466			
	SACRIFICED BY DESIGN 01/20/95	a:	,22
559484			
	ALOPECIA PAW BOTH FRONT	a:	1,2,3,4,5,6,7,8,9,10,11,12,13, , ,16,17,18,19,20,21,22
		b:	,7,8,9,10,11,12,13, , ,16,17,18,19,20,21,
		c:	,17,18, , , ,
		d:	,17, , , , ,
	ALOPECIA RIGHT FRONT PAW	a:	,15, , , , , , ,
		b:	,15, , , , , , ,
	SACRIFICED BY DESIGN 01/19/95	a:	,22
559487			
	SACRIFICED BY DESIGN 01/18/95	a:	,22
559488			
	ALOPECIA LEFT FRONT PAW	a:	,7, , , , , , , , , , , , , , , , , ,
		b:	,7, , , , , , , , , , , , , , , , , ,
	WET CHIN	a:	, , , , , , , , , , , , , , , , , , , ,
		b:	,14,15, , , , , , ,
	LUNG NOISE	a:	,15, , , , , , ,
	SACRIFICED BY DESIGN 01/19/95	a:	,22
559489			
	WET CHIN	a:	, , , , , , , , , , , , , , , , , , , ,
		b:	,14, , , , , , , ,
	SACRIFICED BY DESIGN 01/19/95	a:	,22
559501			
	WET CHIN	a:	, , , , , , , , , , , , , , , , , , , ,
		b:	,14, , , , , , , ,
	SACRIFICED BY DESIGN 01/19/95	a:	,22

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX G (CONT.)

INDIVIDUAL CLINICAL OBSERVATIONS

GROUP IV: 500 mg/kg (Cont.)

ANIMAL NUMBER	OBSERVATION	DAYS OF GESTATION ON WHICH SIGN WAS OBSERVED 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22
559502		
	WET CHIN	a: , , , , , , , , , , , , , ,15, , , , , , , ,
		b: , , , , , , , , , , , , , ,15, , , , , , , ,
	SACRIFICED BY DESIGN 01/20/95	a: ,22

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX G (CONT.)

INDIVIDUAL CLINICAL OBSERVATIONS

GROUP V: 1000 mg/kg

ANIMAL NUMBER	OBSERVATION		DAYS OF GESTATION ON WHICH SIGN WAS OBSERVED 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22
559456			
	ABNORMAL GAIT OR MOBILITY	a:	
		b:	,8,
	SALIVATION	a:	
		b:	,11,
	LUNG NOISE	a:	,12,13,14,15,16,
		b:	,12,13,14,
		c:	,11, ,15,
	WET PERINASAL	a:	
		b:	
		c:	,11,
	WET PERIORAL	a:	
		b:	
		c:	,11,
	WET CHIN	a:	
		b:	,15,16,
		c:	,16,
	SACRIFICED BY DESIGN 01/19/95	a:	,22
559467			
	WET CHIN	a:	
		b:	,20,
	LUNG NOISE	a:	,21,22
		b:	,21,
		c:	,20,
	SACRIFICED BY DESIGN 01/18/95	a:	,22
559478			
	LUNG NOISE	a:	,12,13,
		b:	,12,13,
		c:	,12,
	SALIVATION	a:	
		b:	,12,
	WET PERINASAL	a:	
		b:	
		c:	,12,
	WET CHIN	a:	
		b:	,14,15, ,18,
		c:	,12,

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX G (CONT.)

INDIVIDUAL CLINICAL OBSERVATIONS

GROUP V: 1000 mg/kg (Cont.)

ANIMAL NUMBER	OBSERVATION		DAYS OF GESTATION ON WHICH SIGN WAS OBSERVED 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22
559478			
	STAIN PERINASAL BROWN	a:	,14,
	SACRIFICED BY DESIGN 01/18/95	a:	,22
559481			
	LUNG NOISE	a:	,9,10,11,12,
		b:	,8,9,10,11,
	WET PERINASAL	a:	
		b:	,8,
	WET PERINEUM	a:	,10,11,12,
		b:	,10,11,
	STAIN PERIORAL RED	a:	,11,12,
		b:	,10,11,
	LETHARGY	a:	,11,
		b:	,10,11,
	ABNORMAL GAIT OR MOBILITY	a:	,11,
		b:	,10,11,
	STAIN PERINEUM YELLOW	a:	,11,
		b:	,10,11,
	WET INGUINAL	a:	
		b:	,11,
	STAIN INGUINAL YELLOW	a:	
		b:	,11,
	STAIN MOUTH BROWN	a:	
		b:	,11,
	MORIBUND	a:	,12,
	SACRIFICED IN EXTREMIS 1/10/95	a:	,12,
559483			
	SALIVATION	a:	
		b:	,12, ,20,
	WET CHIN	a:	
		b:	,12,13,14,15, ,17, ,19, ,21,
	SACRIFICED BY DESIGN 01/18/95	a:	,22
559485			
	STAIN PERINEUM YELLOW	a:	,9,10,
		b:	,9,

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX G (CONT.)

INDIVIDUAL CLINICAL OBSERVATIONS

GROUP V: 1000 mg/kg (Cont.)

ANIMAL NUMBER	OBSERVATION		DAYS OF GESTATION ON WHICH SIGN WAS OBSERVED 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22
559485			
	LUNG NOISE	a:	, , , , , , , ,9,10, , , , , , , , , , , ,
		b:	, , , , , , , ,9, , , , , , , , , , , ,
	STAIN MOUTH BROWN	a:	, , , , , , , , ,10, , , , , , , , , , ,
		b:	, , , , , , , ,9, , , , , , , , , , , ,
	PALLOR	a:	, , , , , , , , ,10, , , , , , , , , , ,
		b:	, , , , , , , ,9, , , , , , , , , , , ,
	ACCIDENTLY KILLED 01/06/95	a:	, , , , , , , , ,10, , , , , , , , , , ,
559491			
	ALOPECIA PAW BOTH FRONT	a:	1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22
		b:	, , , , , ,7,8,9,10,11,12,13,14,15,16,17,18,19, , ,
		c:	, , , , , , , , , , , , , , , , , ,18,19,20,21,
	ALOPECIA LEG BOTH FRONT	a:	, , , , , , ,8,9,10,11,12,13, , , , , , , , ,
		b:	, , , , , , ,8,9,10,11,12,13, , , , , , , , ,
	ALOPECIA ABDOMINAL	a:	, , , , , , , ,9,10,11,12,13, , , , , , , , ,
		b:	, , , , , , ,8,9,10,11,12,13, , , , , , , , ,
	LUNG NOISE	a:	, , , , , , , , , , , , ,14,15,16,17,18,19,20,21,22
		b:	, , , , , , , , , , , , ,14,15,16,17,18,19, , ,
		c:	, , , , , , , , , , , ,13, , , , ,18,19,20,21,
	ALOPECIA UNDERBODY	a:	, , , , , , , , , , , , , ,15,16,17,18,19,20,21,22
		b:	, , , , , , , , , , , , , ,15,16,17,18,19, , ,
		c:	, , , , , , , , , , , , , , , , ,18,19,20,21,
	WET CHIN	a:	, ,
		b:	, , , , , , , , , , , , , , , , ,18, ,20,21,
	SACRIFICED BY DESIGN 01/18/95	a:	, ,22
559496			
	LUNG NOISE	a:	, , , , , , , , ,10,11, , , , ,16,17, , , ,21,22
		b:	, , , , , , , ,9,10, , , , , , , , , , ,21,
		c:	, , , , , , , , , , , ,13, ,15,16, , , ,20, ,
	SALIVATION	a:	, ,
		b:	, , , , , , , , , , ,12, , , , , , , , , ,
	WET CHIN	a:	, ,
		b:	, , , , , , , , , , , ,13, ,15,16,17, ,19,20, ,
		c:	, , , , , , , , , , , , , , , ,17, , , , ,
	SACRIFICED BY DESIGN 01/18/95	a:	, ,22

[a] The first observation recorded each day (in the morning) is indicated by "a" after the observation, the second, third, and fourth by "b", "c", and "d", respectively. At least twice daily observations were made on Days 7-21 of gestation.

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX H

GROSS POSTMORTEM FINDINGS

GROUP I: 0 mg/kg

ANIMAL NUMBER	DAMCODE	STRUCTURE	FINDING(S)
559459	(36)	...	NAD
559462	(30)	...	NAD
559465[a]	(12)	...	NAD
559468	(32)	Stomach	Empty
559477	(15)	...	NAD
559486	(8)	...	NAD
559492	(29)	...	NAD
559495	(14)	...	NAD

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX H (CONT.)

GROSS POSTMORTEM FINDINGS

GROUP II: 125 mg/kg

ANIMAL NUMBER	DAMCODE	STRUCTURE	FINDING(S)
559463	(28)	...	NAD
559475	(33)	...	NAD
559490	(13)	...	NAD
559493[a]	(21)	...	NAD
559494	(25)	...	NAD
559497	(1)	...	NAD
559498[a]	(31)	...	NAD
559500	(24)	...	NAD

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX H (CONT.)

GROSS POSTMORTEM FINDINGS

GROUP III: 250 mg/kg

ANIMAL NUMBER	DAMCODE	STRUCTURE	FINDING(S)
559454	(26)	...	NAD
559458	(27)	...	NAD
559464	(34)	...	NAD
559474	(4)	...	NAD
559476	(6)	...	NAD
559480	(17)	...	NAD
559482	(39)	...	NAD
559503	(40)	...	NAD

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX H (CONT.)

GROSS POSTMORTEM FINDINGS

GROUP IV: 500 mg/kg

ANIMAL NUMBER	DAMCODE	STRUCTURE	FINDING(S)
559460[a]	(5)	...	NAD
559466	(37)	...	NAD
559484	(18)	...	NAD
559487	(16)	...	NAD
559488	(22)	...	NAD
559489[a]	(20)	...	NAD
559501	(19)	...	NAD
559502[a]	(35)	...	NAD

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX H (CONT.)

GROSS POSTMORTEM FINDINGS

GROUP V: 1000 mg/kg

ANIMAL NUMBER	DAMCODE	STRUCTURE	FINDING(S)
559456	(23)	Stomach	Empty
559467	(7)	...	NAD
559478	(11)	...	NAD
559481[b]	(38)	...	SE 1/10/95, G14
		...	7 Implants, rt.; 11 lt.
		Stomach	Small ulcerations with mucosal lining
		Small intestine	Distended with air and empty
		Large intestine	Distended with air and empty
		Kidney	Mottled
		Spleen	Small
559483	(2)	...	NAD
559485[c]	(3)	Esophagus	Punctured
		Stomach	Distended with air, slighty ulcerated lining
		Lungs	Filled with blood
559491	(9)	...	NAD
559496	(10)	...	NAD

[a] Not pregnant
[b] Sacrificed in extremis
[c] Accidentally killed (gavage trauma)

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX I

INDIVIDUAL REPRODUCTIVE DATA

GROUP I: 0 mg/kg

ANIMAL NUMBER	CORPORA LUTEA	NIDA-TIONS	RESORPTIONS TOTAL	RESORPTIONS EARLY	RESORPTIONS LATE	DEAD FETUSES	LIVE FETUSES TOTAL	LIVE FETUSES FEMALE	LIVE FETUSES MALE	MEAN FETAL WEIGHT (G)
559459	16	16	0	0	0	0	16	9	7	4.46
559462	18	16	0	0	0	0	16	6	10	4.86
559465[a]	...	...	...	...	...	...	...	...	...	...
559468	15	12	0	0	0	0	12	6	6	4.99
559477	14	14	2	2	0	0	12	8	4	4.71
559486	15	15	0	0	0	0	15	9	6	5.23
559492	17	17	0	0	0	0	17	8	9	4.65
559495	15	15	1	1	0	0	14	8	6	5.12
MEAN	15.7	15.0	0.4	0.4	0.0	0.0	14.6	7.7	6.9	4.86
S.D.	1.38	1.63	0.79	0.79	0.00	0.00	1.99	1.25	2.04	0.27
S.E.	0.52	0.62	0.30	0.30	0.00	0.00	0.75	0.47	0.77	0.10
N	7	7	7	7	7	7	7	7	7	7

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX I (CONT.)

INDIVIDUAL REPRODUCTIVE DATA

GROUP II: 125 mg/kg

ANIMAL NUMBER	CORPORA LUTEA	NIDA-TIONS	RESORPTIONS TOTAL	RESORPTIONS EARLY	RESORPTIONS LATE	DEAD FETUSES	LIVE FETUSES TOTAL	LIVE FETUSES FEMALE	LIVE FETUSES MALE	MEAN FETAL WEIGHT (G)
559463	16	14	2	2	0	0	12	9	3	4.43
559475	18	17	0	0	0	0	17	7	10	4.87
559490	17	16	1	1	0	0	15	11	4	4.90
559493[a]	...	...	...	...	...	...	...	...	...	...
559494	15	14	0	0	0	0	14	7	7	4.37
559497	15	15	1	1	0	0	14	7	7	5.01
559498[a]	...	...	...	...	...	...	...	...	...	...
559500	17	15	0	0	0	0	15	8	7	5.23
MEAN	16.3	15.2	0.7	0.7	0.0	0.0	14.5	8.2	6.3	4.80
S.D.	1.21	1.17	0.82	0.82	0.00	0.00	1.64	1.60	2.50	0.34
S.E.	0.49	0.48	0.33	0.33	0.00	0.00	0.67	0.65	1.02	0.14
N	6	6	6	6	6	6	6	6	6	6

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX I (CONT.)

INDIVIDUAL REPRODUCTIVE DATA

GROUP III: 250 mg/kg

ANIMAL NUMBER	CORPORA LUTEA	NIDA-TIONS	RESORPTIONS TOTAL	RESORPTIONS EARLY	RESORPTIONS LATE	DEAD FETUSES	LIVE FETUSES TOTAL	LIVE FETUSES FEMALE	LIVE FETUSES MALE	MEAN FETAL WEIGHT (G)
559454	16	15	0	0	0	0	15	7	8	5.03
559458	16	16	0	0	0	0	16	8	8	4.58
559464	17	16	1	0	1	0	14	7	7	4.30
559474	14	14	0	0	0	0	14	7	7	5.28
559476	15	13	0	0	0	0	13	6	7	5.00
559480	16	16	1	1	0	0	15	9	6	4.40
559482	21	19	0	0	0	0	19	10	9	4.07
559503	18	18	1	1	0	0	16	10	6	4.29
MEAN	16.6	15.9	0.4	0.3	0.1	0.0	15.3	8.0	7.3	4.62
S.D.	2.13	1.96	0.52	0.46	0.35	0.00	1.83	1.51	1.04	0.43
S.E.	0.75	0.69	0.18	0.16	0.13	0.00	0.65	0.53	0.37	0.15
N	8	8	8	8	8	8	8	8	8	8

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX I (CONT.)

INDIVIDUAL REPRODUCTIVE DATA

GROUP IV: 500 mg/kg

ANIMAL NUMBER	CORPORA LUTEA	NIDA-TIONS	RESORPTIONS TOTAL	RESORPTIONS EARLY	RESORPTIONS LATE	DEAD FETUSES	LIVE FETUSES TOTAL	LIVE FETUSES FEMALE	LIVE FETUSES MALE	MEAN FETAL WEIGHT (G)
559460[a]	...	...	...	...	...	...	...	...	...	...
559466	16	16	0	0	0	0	16	10	6	4.61
559484	16	15	0	0	0	0	15	8	7	4.84
559487	12	12	2	2	0	0	10	5	5	5.22
559488	14	14	2	1	1	0	12	6	6	3.75
559489[a]	...	...	...	...	...	...	...	...	...	...
559501	17	16	0	0	0	0	16	11	5	3.66
559502[a]	...	...	...	...	...	...	...	...	...	...
MEAN	15.0	14.6	0.8	0.6	0.2	0.0	13.8	8.0	5.8	4.42
S.D.	2.00	1.67	1.10	0.89	0.45	0.00	2.68	2.55	0.84	0.69
S.E.	0.89	0.75	0.49	0.40	0.20	0.00	1.20	1.14	0.37	0.31
N	5	5	5	5	5	5	5	5	5	5

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX I (CONT.)

INDIVIDUAL REPRODUCTIVE DATA

GROUP V: 1000 mg/kg

ANIMAL NUMBER	CORPORA LUTEA	NIDA-TIONS	RESORPTIONS TOTAL	RESORPTIONS EARLY	RESORPTIONS LATE	DEAD FETUSES	LIVE FETUSES TOTAL	LIVE FETUSES FEMALE	LIVE FETUSES MALE	MEAN FETAL WEIGHT (G)
559456	14	13	2	2	0	0	11	4	7	3.54
559467	18	7	1	1	0	0	6	5	1	4.73
559478	13	13	1	1	0	0	12	5	7	4.19
559481[b]	...	...	...	...	...	...	...	...	...	...
559483	19	19	1	1	0	0	18	11	7	3.54
559485[c]	...	...	...	...	...	...	...	...	...	...
559491	20	17	3	3	0	0	14	7	7	4.04
559496	14	14	1	1	0	0	13	4	9	3.88
MEAN	16.3	13.8	1.5	1.5	0.0	0.0	12.3	6.0	6.3	3.99
S.D.	3.01	4.12	0.84	0.84	0.00	0.00	3.93	2.68	2.73	0.45
S.E.	1.23	1.68	0.34	0.34	0.00	0.00	1.61	1.10	1.12	0.18
N	6	6	6	6	6	6	6	6	6	6

[a] Not pregnant, data excluded from the calculations.
[b] Sacrificed in extremis, data excluded from the calculations.
[c] Accidentally killed, data excluded from the calculations.

... = No data

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX J

SIRE RECORD

GROUP I: 0 mg/kg

FEMALE NUMBER	BREEDING LOT	MALE NUMBER
559459	C	557739
559462	C	557742
559465	A	557745
559468	C	557748
559477	A	557758
559486	A	557767
559492	C	557773
559495	A	557776

GROUP II: 125 mg/kg

FEMALE NUMBER	BREEDING LOT	MALE NUMBER
559463	C	557743
559475	C	557756
559490	A	557771
559493	B	557774
559494	C	557775
559497	A	557778
559498	C	557779
559500	B	557781

GROUP III: 250 mg/kg

FEMALE NUMBER	BREEDING LOT	MALE NUMBER
559454	C	557734
559458	C	557738
559464	C	557744
559474	A	557755
559476	A	557757
559480	B	557761
559482	D	557752
559503	E	557754

GROUP IV: 500 mg/kg

FEMALE NUMBER	BREEDING LOT	MALE NUMBER
559460	A	557740
559466	C	557746
559484	B	557765
559487	A	557768
559488	B	557769
559489	B	557770
559501	B	557782
559502	C	557703

GROUP V: 1000 mg/kg

FEMALE NUMBER	BREEDING LOT	MALE NUMBER
559456	B	557736
559467	A	557747
559478	A	557759
559481	C	557762
559483	A	557764
559485	A	557766
559491	A	557772
559496	A	557777

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX K

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP I: 0 mg/kg

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559459				
1	3.88	Sternebra	Retarded Ossification (6)	VR
2	4.61	Rib	Rudimentary (th2 rt)	DV
		Rib	Thickened (th3 rt)	N
3	4.65	Vertebra	Retarded Ossification (th6,12 centra)	VR
4	4.71	Vertebra	Retarded Ossification (th5,12 centra)	VR
5	3.98	Vertebra	Retarded Ossification (th10, lu1 centra)	VR
6	4.85	...	NAD	...
7	4.63	Rib	Rudimentary (th 1 rt)	DV
		Sternebra	Misaligned (3-5)	DV
8	5.21	Vertebra	Retarded Ossification (th5,11 centra)	VR
9	4.16	Kidney	Papilla - Size 3 (bil)	N
		Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th1,13 centra)	VR
10	4.14	Tongue	Protruding	N
11	3.82	Tongue	Protruding	N
		Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th1,11 centra)	VR
12	4.37	...	NAD	...
13	4.33	Vertebra	Retarded Ossification (th11 centrum)	VR
14	4.99	Vertebra	Retarded Ossification (th12 centrum)	VR
15	4.45	Kidney	Papilla - Size 3 (bil)	N
16	4.57	Sternebra	Misaligned (4,5)	DV
		Rib	Absent (th1 rt)	M
		Rib	Thickened (th2 rt)	N
559462				
1	4.46	Vertebra	Retarded Ossification (centrum th12)	VR
2	4.86	Vertebra	Retarded Ossification (centrum th7)	VR
3	5.45	...	NAD	...

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP I: 0 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559462 (Cont.)				
4	5.15	Vertebra	Retarded Ossification (centrum th10)	VR
5	5.17	Vertebra	Retarded Ossification (centrum th10)	VR
6	4.78	Skull	Retarded Ossification (interparietal)	VR
7	3.75	Vertebra	Retarded Ossification (centra th5,11)	VR
8	4.92	Vertebra	Retarded Ossification (centra th10,11,13)	VR
9	4.62	...	NAD	...
10	5.19	Vertebra	Retarded Ossification (centra th5,10)	VR
11	4.40	Sternebra	Retarded Ossification (1)	VR
12	5.01	Skull	Retarded Ossification (interparietal)	VR
13	4.77	Sternebra	Retarded Ossification (1,6)	VR
		Vertebra	Retarded Ossification (centra th10,11)	VR
14	4.84	Skull	Retarded Ossification (interparietal)	VR
15	4.87	Sternebra	Retarded Ossification (1)	VR
16	5.47	Skull	Retarded Ossification (interparietal)	VR
		Vertebra	Retarded Ossification (centra th8,11)	VR
559468				
1	5.43	Kidney	Papilla - Size 3 (bil)	N
		Vertebra	Retarded Ossification (centra th6,8-10)	VR
2	4.24	Skull	Retarded Ossification (1,12)	VR
		Sternebra	Retarded Ossification (1,6)	VR
3	5.29	Vertebra	Retarded Ossification (centra th2,5,7,10-13)	VR
4	4.95	Vertebra	Retarded Ossification (centra th2,11-13, lu1)	VR

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP I: 0 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559468 (Cont.)				
5	4.95	Vertebra	Retarded Ossification (centra th2,4,5,12)	VR
6	5.23	Skull	Retarded Ossification (interparietal)	VR
		Vertebra	Retarded Ossification (centra th10-13)	VR
7	4.64	Vertebra	Retarded Ossification (centra th11,12)	VR
8	5.04	Vertebra	Absent (centrum th6)	M
		Vertebra	Retarded Ossification (centra th4,9,11-13)	VR
9	5.05	Kidney	Small Papilla - Size 2 (lt)	VR
		Vertebra	Retarded Ossification (centra th6,10-13)	VR
10	5.03	Skull	Retarded Ossification (interparietal)	VR
		Vertebra	Retarded Ossification (centra th6,10,12; lul)	VR
11	5.23	Vertebra	Retarded Ossification (centra th5,7,9,11-13)	VR
12	4.82	Vertebra	Retarded Ossification (centra th10,12,13)	VR
559477				
1	3.98	Rib	Rudimentary Cervical (6 bil)	DV
2	5.20	...	NAD	...
3	5.42	Rib	Rudimentary Cervical (6 lt)	DV
		Vertebra	Retarded Ossification (centra th1,10)	VR
4	5.17	...	NAD	...
5	4.22	Rib	Rudimentary Cervical (6 lt)	DV
6	4.96	...	NAD	...
7	4.60	...	NAD	...
8	4.95	Vertebra	Retarded Ossification (th10 centrum)	VR
9	4.02	Rib	Rudimentary Cervical (6 lt)	DV
10	4.15	Rib	Rudimentary Cervical (6 rt)	DV
11	4.33	...	NAD	...
12	5.46	...	NAD	...

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP I: 0 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559486				
1	5.25	...	NAD	...
2	5.10	...	NAD	...
3	5.34	Vertebra	Retarded Ossification (th12 centrum)	VR
4	5.08	...	NAD	...
5	5.29	...	NAD	...
6	5.57	Vertebra	Retarded Ossification (th11 centrum)	VR
7	5.12	Sternebra	Retarded Ossification (6)	VR
8	4.72	...	NAD	...
9	5.28	Subcutis	Hemorrhage (back *)	N
		Vertebra	Retarded Ossification (th12 centrum)	VR
10	4.84	...	NAD	...
11	5.59	...	NAD	...
12	4.76	...	NAD	...
13	5.31	...	NAD	...
14	5.29	...	NAD	...
15	5.84	Kidney	Papilla - Size 3 (lt)	N
559492				
1	3.61	Pulmonary Arteries	Common Trunk	N
		Rib	Absent (3 on rt)	M
		Vertebra	Fused (arches th4-5, rt)	M
		Vertebra	Hemi (th1 arch, rt)	M
		Sternebra	Retarded Ossification (1-6)	VR
		Vertebra	Retarded Ossification (centra th2,3,5-7,9-12)	VR
2	3.25	Subcutis	Hemorrhage (chin, 3mm*)	N
		Skull	Retarded Ossification (1,12)	VR
		Sternebra	Retarded Ossification (1,6)	VR
		Vertebra	Retarded Ossification (centra th4,5,7,9-12)	VR
3	4.43	Vertebra	Retarded Ossification (centra th5,9,11,12)	VR
4	4.90	Skull	Retarded Ossification (1)	VR

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP I: 0 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559492 (Cont.)				
		Vertebra	Retarded Ossification (centrum th12)	VR
5	4.80	Vertebra	Retarded Ossification (centra th4,9,11,12)	VR
6	4.67	Skull	Retarded Ossification (interparietal)	VR
		Sternebra	Retarded Ossification (1)	VR
		Vertebra	Retarded Ossification (centra th11,12)	VR
7	4.69	Vertebra	Retarded Ossification (centra th5,12)	VR
8	4.75	Vertebra	Retarded Ossification (centra th11,12)	VR
9	4.48	Pulmonary Arteries	Common Trunk	N
		Rib	Absent (th5, rt)	M
		Vertebra	Hemi (th4 centrum)	M
		Sternebra	Retarded Ossification (1)	VR
		Vertebra	Retarded Ossification (centra th9,11,12)	VR
10	4.79	Vertebra	Retarded Ossification (centra th12,13)	VR
11	5.26	Kidney	Papilla - Size 3 (lt)	N
		Vertebra	Retarded Ossification (centra th10,12)	VR
12	4.56	...	NAD	...
13	5.34	...	NAD	...
14	4.73	Vertebra	Retarded Ossification (centra th5,6,11,13)	VR
15	5.11	Vertebra	Retarded Ossification (centrum th11)	VR
16	4.97	...	NAD	...
17	4.69	Kidney	Papilla - Size 3 (lt)	N
		Vertebra	Hemi (th7 centrum)	M
		Vertebra	Retarded Ossification (centra th4,10-12)	VR

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP I: 0 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559495				
1	5.29	...	NAD	...
2	5.23	...	NAD	...
3	4.71	...	NAD	...
4	4.82	Vertebra	Retarded Ossification (th11,13 centra)	VR
5	5.25	Vertebra	Retarded Ossification (th10,11 centra)	VR
6	4.79	...	NAD	...
7	5.11	Vertebra	Retarded Ossification (th12 centrum)	VR
8	5.39	...	NAD	...
9	5.55	Kidney	Papilla - Size 3 (bil)	N
10	4.58	...	NAD	...
11	5.40	...	NAD	...
12	5.37	...	NAD	...
13	4.88	...	NAD	...
14	5.27	...	NAD	...

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP II: 125 mg/kg

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559463				
1	3.90	...	NAD	...
2	5.20	...	NAD	...
3	3.79	Heart &/or Greater Vessels	Patent Ductus Arteriosis	VR
		Sternebra	Retarded Ossification (1,3,4,6)	VR
		Vertebra	Retarded Ossification (centra th11,12)	VR
4	4.37	Skull	Retarded Ossification (interparietal)	VR
5	4.12	Sternebra	Retarded Ossification (1,3,4,6)	VR
6	4.99	...	NAD	...
7	4.72	Vertebra	Retarded Ossification (centrum th12)	VR
8	4.59	Skull	Retarded Ossification (interparietal)	VR
9	4.40	Sternebra	Retarded Ossification (6)	VR
10	4.84	...	NAD	...
11	4.31	...	NAD	...
12	3.94	Skull	Retarded Ossification (interparietal)	VR
559475				
1	4.76	Kidney	Small Papilla - Size 2 (bil)	VR
		Vertebra	Retarded Ossification (centrum th12)	VR
2	5.37	Skull	Retarded Ossification (interparietal)	VR
3	5.10	Kidney	Papilla - Size 3 (bil)	N
		Vertebra	Retarded Ossification (centrum th11)	VR
4	4.68	...	NAD	...
5	4.85	Kidney	Small Papilla - Size 2 (bil)	VR
		Vertebra	Retarded Ossification (centrum th10)	VR
6	5.12	...	NAD	...

PILOT DEVELOPMENTAL TOXICITY STUDY OF
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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP II: 125 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559475 (Cont.)				
7	4.81	Kidney	Papilla - Size 3 (bil)	N
8	4.75	Vertebra	Retarded Ossification (centrum th13)	VR
9	4.86	Vertebra	Retarded Ossification (centrum th11)	VR
10	5.17	Skull	Retarded Ossification (parietal, rt)	VR
11	4.80	Kidney	Small Papilla - Size 2 (lt)	VR
		Vertebra	Retarded Ossification (centrum th12)	VR
12	4.43	...	NAD	...
13	4.86	Kidney	Small Papilla - Size 2 (lt)	VR
		Vertebra	Retarded Ossification (centra th10,11,13)	VR
14	4.45	...	NAD	...
15	4.46	...	NAD	...
16	5.23	Vertebra	Retarded Ossification (centra th10,11)	VR
17	5.17	Kidney	Papilla - Size 3 (lt)	N
		Vertebra	Retarded Ossification (centrum th12)	VR
559490				
1	5.05	...	NAD	...
2	4.77	...	NAD	...
3	5.30	Sternebra	Misaligned (4)	DV
		Sternebra	Retarded Ossification (4)	VR
4	5.58	...	NAD	...
5	5.05	...	NAD	...
6	4.92	...	NAD	...
7	3.46	Rib	Rudimentary Cervical (6rt)	DV
8	4.28	...	NAD	...
9	3.36	Sternebra	Retarded Ossification (4,6)	VR
10	5.44	...	NAD	...
11	5.20	Kidney	Papilla - Size 3 (rt)	N
		Vertebra	Retarded Ossification (th10 centrum)	VR
12	5.03	...	NAD	...

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP II: 125 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559490 (Cont.)				
13	5.22	...	NAD	...
14	5.32	...	NAD	...
15	5.56	Kidney	Papilla - Size 3 (bil)	N
559494				
1	4.72	...	NAD	...
2	3.74	Tongue	Protruding	N
		Skull	Retarded Ossification (2 bil)	VR
		Sternebra	Retarded Ossification (6)	VR
3	4.10	...	NAD	...
4	3.22	Tongue	Protruding	N
		Sternebra	Retarded Ossification (6)	VR
5	4.86	...	NAD	...
6	4.97	...	NAD	...
7	3.90	...	NAD	...
8	4.41	Vertebra	Retarded Ossification (th10 centrum)	VR
9	4.58	...	NAD	...
10	3.68	Tongue	Protruding	N
		Sternebra	Retarded Ossification (6)	VR
11	5.06	...	NAD	...
12	5.03	...	NAD	...
13	4.30	...	NAD	...
14	4.66	...	NAD	...
559497				
1	4.91	...	NAD	...
2	5.07	...	NAD	...
3	5.09	Pulmonary Arteries	Common Trunk	N
4	4.84	...	NAD	...
5	4.63	...	NAD	...
6	5.57	...	NAD	...
7	4.99	...	NAD	...
8	4.94	...	NAD	...
9	5.08	...	NAD	...
10	4.69	...	NAD	...
11	5.11	...	NAD	...

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP II: 125 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559497 (Cont.)				
12	4.85	...	NAD	...
13	5.25	...	NAD	...
14	5.18	...	NAD	...
559500				
1	5.12	Kidney	Papilla - Size 3 (bil)	N
2	5.58	...	NAD	...
3	5.37	Kidney	Small Papilla - Size 2 (lt)	VR
4	5.17	Subcutis	Hemorrhage (neck ~4x2mm*)	N
5	5.44	...	NAD	...
6	5.34	...	NAD	...
7	5.00	Kidney	Papilla - Size 3 (lt)	N
8	5.39	...	NAD	...
9	4.66	...	NAD	...
10	5.35	...	NAD	...
11	5.50	...	NAD	...
12	5.24	...	NAD	...
13	4.83	...	NAD	...
14	5.14	...	NAD	...
15	5.32	Kidney	Papilla - Size 3 (bil)	N

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP III: 250 mg/kg

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559454				
1	4.74	Pulmonary Arteries	Common Trunk	N
		Kidney	Papilla - Size 3 (bil)	N
2	4.98	...	NAD	...
3	4.74	Kidney	Small Papilla - Size 2 (lt; size 3 rt)	VR
4	4.87	...	NAD	...
5	5.44	Heart &/or Greater Vessels	Patent Ductus Arteriosis	VR
		Sternebra	Retarded Ossification (6)	VR
6	4.95	...	NAD	...
7	5.00	Vertebra	Retarded Ossification (th11 centrum)	VR
8	5.11	Vertebra	Retarded Ossification (th11 centrum)	VR
9	4.76	Rib	Rudimentary Cervical (7 bil)	DV
10	5.25	...	NAD	...
11	4.84	...	NAD	...
12	5.04	...	NAD	...
13	5.35	Kidney	Papilla - Size 3 (lt)	N
		Rib	Rudimentary Cervical (7 bil)	DV
		Vertebra	Retarded Ossification (th11 centrum)	VR
14	4.92	...	NAD	...
15	5.48	...	NAD	...
559458				
1	4.23	Kidney	Papilla - Size 3 (lt)	N
		Vertebra	Retarded Ossification (th10,11,13 centra)	VR
2	4.55	Rib	Rudimentary Cervical (6 lt)	DV
		Vertebra	Retarded Ossification (th13 centrum)	VR
3	4.36	...	NAD	...
4	4.49	Vertebra	Retarded Ossification (th11,12 centra)	VR
5	4.49	Kidney	Papilla - Size 3 (bil)	N
6	4.65	...	NAD	...

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP III: 250 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559458 (Cont.)				
7	4.84	...	NAD	...
8	4.87	Vertebra	Retarded Ossification (th12,13 centra)	VR
9	4.16	Vertebra	Retarded Ossification (th12 centrum)	VR
10	4.61	Vertebra	Retarded Ossification (th12 centrum)	VR
11	4.70	...	NAD	...
12	4.74	Vertebra	Retarded Ossification (th10,11,12 centra)	VR
13	4.70	Vertebra	Retarded Ossification (th11 centrum)	VR
14	3.99	...	NAD	...
15	4.66	...	NAD	...
16	5.22	...	NAD	...
559464				
1	3.79	Kidney	Papilla - Size 3 (rt)	N
2	5.10	...	NAD	...
3	4.40	...	NAD	...
4	3.80	Tongue	Protruding	N
		Rib	Rudimentary Cervical (7 rt)	DV
		Sternebra	Retarded Ossification (6)	VR
5	4.40	...	NAD	...
6	4.67	...	NAD	...
7	4.64	...	NAD	...
8	4.71	Sternebra	Retarded Ossification (6)	VR
9	4.79	Rib	Rudimentary Cervical (7 rt)	DV
10	4.29	Sternebra	Retarded Ossification (6)	VR
11	3.54	Sternebra	Retarded Ossification (1,6)	VR
12	3.51	Rib	Rudimentary Cervical (7 rt)	DV
		Sternebra	Retarded Ossification (1,6)	VR
13	4.52	...	NAD	...
14	4.08	Sternebra	Retarded Ossification (6)	VR
559474				
1	5.27	Kidney	Papilla - Size 3 (bil)	N

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP III: 250 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559474 (Cont.)				
		Vertebra	Retarded Ossification (th11 centrum)	VR
2	5.09	...	NAD	...
3	5.32	...	NAD	...
4	5.11	...	NAD	...
5	5.36	Sternebra	Misaligned (4)	DV
6	5.42	...	NAD	...
7	5.26	Kidney	Papilla - Size 3 (bil)	N
		Vertebra	Retarded Ossification (th8,11,12 centra)	VR
8	5.52	...	NAD	...
9	5.61	Kidney	Papilla - Size 3 (bil)	N
10	4.57	Sternebra	Retarded Ossification (6)	VR
11	5.37	Vertebra	Retarded Ossification (th11-13 centra)	VR
12	5.18	Sternebra	Retarded Ossification (6)	VR
13	5.42	Kidney	Papilla - Size 3 (rt)	N
		Vertebra	Retarded Ossification (th11,12 centra)	VR
14	5.37	...	NAD	...
559476				
1	5.11	...	NAD	...
2	4.97	...	NAD	...
3	4.97	...	NAD	...
4	5.42	...	NAD	...
5	4.04	Vertebra	Retarded Ossification (th12 centrum)	VR
6	4.63	...	NAD	...
7	5.11	...	NAD	...
8	5.05	...	NAD	...
9	4.62	...	NAD	...
10	5.39	...	NAD	...
11	5.42	...	NAD	...
12	5.30	Vertebra	Retarded Ossification (th10 centrum)	VR
13	4.98	...	NAD	...

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP III: 250 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559480				
1	3.96	Vertebra	Retarded Ossification (th10 centrum)	VR
2	4.41	Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th10,11,13 centra)	VR
3	4.47	...	NAD	...
4	4.30	Vertebra	Retarded Ossification (th10 centrum)	VR
5	4.63	...	NAD	...
6	4.34	...	NAD	...
7	4.68	Vertebra	Retarded Ossification (th10 centrum)	VR
8	4.51	Vertebra	Retarded Ossification (th11,13 centra)	VR
9	4.48	Heart &/or Greater Vessels	Patent Ductus Arteriosis	VR
10	4.43	...	NAD	...
11	4.44	Vertebra	Retarded Ossification (th11 centrum)	VR
12	4.66	...	NAD	...
13	4.08	Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th10,12,13 centra)	VR
14	4.36	Sternebra	Retarded Ossification (6)	VR
15	4.23	Vertebra	Retarded Ossification (th10 centrum)	VR
559482				
1	3.85	Tongue	Protruding	N
2	3.94	Rib	Rudimentary Cervical (7 rt)	DV
3	4.04	Kidney	Small Papilla - Size 2 (bil)	VR
		Rib	Rudimentary Cervical (7 rt)	DV
		Sternebra	Retarded Ossification (6)	VR
4	3.79	Sternebra	Retarded Ossification (6)	VR
5	4.02	...	NAD	...
6	3.97	Sternebra	Retarded Ossification (6)	VR
7	3.85	...	NAD	...
8	4.38	...	NAD	...

PILOT DEVELOPMENTAL TOXICITY STUDY OF
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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP III: 250 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559482 (Cont.)				
9	4.33	Kidney	Papilla - Size 3 (rt)	N
10	4.50	...	NAD	...
11	3.57	Tongue	Protruding	N
		Sternebra	Retarded Ossification (6)	VR
12	4.25	Skull	Retarded Ossification (1,12,13; 7 rt)	VR
		Sternebra	Retarded Ossification (6)	VR
13	3.77	Sternebra	Retarded Ossification (6)	VR
14	3.83	Sternebra	Retarded Ossification (6)	VR
15	4.39	...	NAD	...
16	4.51	...	NAD	...
17	4.38	...	NAD	...
18	4.05	Tongue	Protruding	N
19	3.91	Vertebra	Retarded Ossification (th12 centrum)	VR
559503				
1	4.07	Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th11,12 centra)	VR
2	4.20	Sternebra	Retarded Ossification (6)	VR
3	4.31	Kidney	Papilla - Size 3 (bil)	N
		Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th1,11 centra)	VR
4	4.65	Vertebra	Retarded Ossification (th11 centrum)	VR
5	4.24	Sternebra	Retarded Ossification (6)	VR
6	4.14	Sternebra	Retarded Ossification (6)	VR
7	4.24	Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th12 centrum)	VR
8	3.90	Skull	Retarded Ossification (13)	VR
		Sternebra	Retarded Ossification (6)	VR
9	4.09	Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th11,13 centra)	VR

PILOT DEVELOPMENTAL TOXICITY STUDY OF
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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP III: 250 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559503 (Cont.)				
10	3.52	Sternebra	Retarded Ossification (6)	VR
11	4.02	Sternebra	Retarded Ossification (6)	VR
12	4.44	Sternebra	Retarded Ossification (6)	VR
13	4.74	Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th7,11 centra)	VR
14	4.51	Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th12 centrum)	VR
15	4.75	Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th12,13 centra)	VR
16	4.76	...	NAD	...

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP IV: 500 mg/kg

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559466				
1	4.62	...	NAD	...
2	4.52	Sternebra	Retarded Ossification (1)	VR
		Vertebra	Retarded Ossification (centra th10,13)	VR
3	4.67	Sternebra	Retarded Ossification (1)	VR
		Vertebra	Retarded Ossification (centra th10-12, lu5)	VR
4	4.43	Skull	Retarded Ossification (interparietal)	VR
		Sternebra	Retarded Ossification (1)	VR
5	4.76	Sternebra	Retarded Ossification (1)	VR
		Vertebra	Retarded Ossification (centra th11-13, lu4)	VR
6	5.20	Sternebra	Retarded Ossification (1)	VR
7	4.99	Sternebra	Retarded Ossification (1)	VR
		Vertebra	Retarded Ossification (centra th10-12,14)	VR
8	4.63	Sternebra	Retarded Ossification (1)	VR
9	4.67	Kidney	Papilla - Size 3 (lt)	N
10	4.19	Sternebra	Retarded Ossification (1,6)	VR
		Vertebra	Retarded Ossification (centra th13)	VR
11	4.89	Sternebra	Retarded Ossification (1)	VR
12	4.54	Sternebra	Retarded Ossification (1)	VR
13	4.48	Sternebra	Retarded Ossification (1)	VR
		Vertebra	Retarded Ossification (centra th11-13)	VR
14	4.62	Sternebra	Retarded Ossification (1)	VR
		Vertebra	Retarded Ossification (centra th14, lu1)	VR
15	3.94	Sternebra	Retarded Ossification (1)	VR
		Vertebra	Retarded Ossification (centra lu1)	VR
16	4.58	Sternebra	Retarded Ossification (1)	VR
		Vertebra	Retarded Ossification (centra th10-12)	VR

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP IV: 500 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559484				
1	4.74	Vertebra	Retarded Ossification (th11-13 centra)	VR
2	5.00	Vertebra	Retarded Ossification (th10,12 centra)	VR
3	5.04	Vertebra	Retarded Ossification (th1,4,11,12 centra)	VR
4	5.10	Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th11 centrum)	VR
5	4.49	Sternebra	Retarded Ossification (6)	VR
6	5.22	Vertebra	Retarded Ossification (th11,12 centra)	VR
7	4.37	Vertebra	Retarded Ossification (th1,5,12 centra)	VR
8	5.27	Vertebra	Retarded Ossification (th10 centrum)	VR
9	4.80	Vertebra	Retarded Ossification (th12 centrum)	VR
10	4.50	Vertebra	Retarded Ossification (th13 centrum)	VR
11	5.32	Vertebra	Retarded Ossification (th1,11,12 centra)	VR
12	4.70	...	NAD	...
13	4.86	...	NAD	...
14	4.95	...	NAD	...
15	4.26	Vertebra	Retarded Ossification (th13 centrum)	VR
559487				
1	5.96	Brain	Hydrocephaly (both lateral ventricles)	M
		Vertebra	Retarded Ossification (th11,13 centra)	VR
2	5.15	...	NAD	...
3	4.43	Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th11 centrum)	VR

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP IV: 500 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559487 (Cont.)				
4	4.92	Vertebra	Retarded Ossification (th10,12 centra)	VR
5	5.18	Vertebra	Retarded Ossification (th13 centrum)	VR
6	5.17	...	NAD	...
7	4.89	...	NAD	...
8	5.16	Sternebra	Retarded Ossification (6)	VR
9	5.76	Vertebra	Retarded Ossification (th11 centrum)	VR
10	5.62	Vertebra	Retarded Ossification (th12 centrum)	VR
559488				
1	4.05	Kidney	Small Papilla - Size 2 (lt)	VR
		Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th1,8-13; lu1 centra)	VR
2	4.04	Skull	Retarded Ossification (2 bil)	VR
		Sternebra	Retarded Ossification (1,4,6)	VR
		Vertebra	Retarded Ossification (th1,10-14; lu1-4 centra)	VR
3	3.03	Sternebra	Retarded Ossification (1,3,4,6)	VR
		Vertebra	Retarded Ossification (th11,12; lu2 centra)	VR
4	3.85	Skull	Retarded Ossification (2 bil)	VR
		Vertebra	Retarded Ossification (th9-13 centra)	VR
5	3.64	Vertebra	Retarded Ossification (th10-13 centra)	VR
6	3.85	Sternebra	Retarded Ossification (1,6)	VR
		Vertebra	Retarded Ossification (th9,11-14;lu1,3 centra)	VR
7	4.02	Vertebra	Retarded Ossification (th11 centrum)	VR
8	3.94	Skull	Retarded Ossification (13)	VR
		Sternebra	Retarded Ossification (6)	VR

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP IV: 500 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559488 (Cont.)				
		Vertebra	Retarded Ossification (th10-13 centra)	VR
9	2.86	Vertebra	Retarded Ossification (th1-4,6,10,11;lu1,6centra)	VR
10	4.02	Sternebra	Misaligned (3,4)	DV
		Sternebra	Retarded Ossification (1,3,4,6)	VR
		Vertebra	Retarded Ossification (th13; lu1 centra)	VR
11	3.61	Sternebra	Retarded Ossification (1,6)	VR
		Vertebra	Retarded Ossification (th11-13; lu1 centra)	VR
12	4.06	Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th12,13; lu1 centra)	VR
559501				
1	3.79	Tongue	Protruding	N
2	3.51	...	NAD	...
3	3.50	Kidney	Papilla - Size 3 (lt)	N
4	3.86	Tongue	Protruding	N
		Vertebra	Retarded Ossification (lu1 centrum)	VR
5	3.90	...	NAD	...
6	3.32	Sternebra	Retarded Ossification (6)	VR
7	3.95	Kidney	Papilla - Size 3 (lt)	N
		Sternebra	Retarded Ossification (1,6)	VR
		Vertebra	Retarded Ossification (th10 centrum)	VR
8	3.43	Subcutis	Hemorrhage (lt rear paw *)	N
		Sternebra	Retarded Ossification (1,6)	VR
9	3.69	Sternebra	Retarded Ossification (1,6)	VR
10	3.69	Vertebra	Retarded Ossification (th11 centrum)	VR
11	3.56	Vertebra	Retarded Ossification (th10,11,13 centra)	VR

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP IV: 500 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559501 (Cont.)				
12	3.78	Vertebra	Retarded Ossification (th11,13 centra)	VR
13	3.93	Vertebra	Retarded Ossification (th11-13 centra)	VR
14	3.42	...	NAD	...
15	3.94	...	NAD	...
16	3.32	...	NAD	...

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP-V: 1000 mg/kg

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559456				
1	3.61	Sternebra	Misaligned (3,4)	DV
		Rib	Fused (th11-12 distal, rt)	M
		Vertebra	Fused (centra lu4-5)	M
		Vertebra	Hemi (ce7, th12 arches, rt)	M
		Sternebra	Retarded Ossification (1-6)	VR
		Vertebra	Retarded Ossification (centra th1-4,9-12,lu1-3)	VR
2	3.35	Rib	Rudimentary Cervical (7, rt)	DV
		Sternebra	Misaligned (3,4)	DV
		Vertebra	Fused (th13-14 arches, rt)	M
		Vertebra	Hemi (th1 arch, rt)	M
		Skull	Retarded Ossification (1,12)	VR
		Sternebra	Retarded Ossification (3,4,6)	VR
		Vertebra	Retarded Ossification (centra th11-13,lu2)	VR
3	2.65	Subcutis	Hemorrhage (lt rear leg *)	N
		Rib	Fused (th5-6, proximal)	M
		Vertebra	Hemi (th6)	M
		Sternebra	Retarded Ossification (1-6)	VR
		Vertebra	Retarded Ossification (centra th1-13)	VR
4	3.09	Sternebra	Misaligned (4)	DV
		Rib	Fused (th11-12, proximal, rt)	M
		Vertebra	Fused (ce6-7,th11-12,lu2-3,3-4)	M
		Vertebra	Hemi (th1, rt)	M
		Skull	Retarded Ossification (2,3 bil; 1,12)	VR
		Sternebra	Retarded Ossification (4,6)	VR
		Vertebra	Retarded Ossification (arch ce3-7,centra th9-13)	VR
5	3.57	Rib	Fused (th12-13, proximal, rt)	M
		Vertebra	Hemi (ce7)	M
		Sternebra	Retarded Ossification (3,4,6)	VR
		Vertebra	Retarded Ossification (centra th4,10-13,lu1-4,6)	VR
6	3.88	Sternebra	Misaligned (1,2,3,4)	DV

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP V: 1000 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559456 (Cont.)				
		Rib	Fused (th13-14, proximal, lt)	M
		Vertebra	Fused (lu3-4)	M
		Vertebra	Hemi (ce7,lu1)	M
		Skull	Retarded Ossification (2,3 bil;1,12)	VR
		Sternebra	Retarded Ossification (1,3,4,6)	VR
		Vertebra	Retarded Ossification (centra th9-14)	VR
7	3.85	Rib	Fused (th10-11,lt;th12-13, proximal, rt)	M
		Vertebra	Fused (th12-13)	M
		Vertebra	Hemi (th1)	M
		Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (centra th11-13,lu1-4)	VR
8	3.97	Sternebra	Misaligned (2-5)	DV
		Rib	Fused (th11-12, proximal, rt)	M
		Vertebra	Hemi (lu1)	M
		Skull	Retarded Ossification (2,3 bil;1,12)	VR
		Sternebra	Retarded Ossification (1,3,4,6)	VR
		Vertebra	Retarded Ossification (centra th10-13;lu2,3)	VR
9	3.51	Rib	Absent (th11, lt)	M
		Rib	Fused (th8-9-10,rt; 12-13,lt; proximal)	M
		Vertebra	Fused (th9-10)	M
		Vertebra	Hemi (th10 centrum)	M
		Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (centra th11-13,lu2)	VR
10	3.90	Rib	Fused (th12-13,distal,lt;11-13, proximal,rt)	M
		Vertebra	Fused (lu5-6)	M
		Vertebra	Hemi (ce7,lu3,4)	M

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP V: 1000 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559456 (Cont.)				
		Skull	Retarded Ossification (2,3 bil;1,12)	VR
		Sternebra	Retarded Ossification (1,3,4,6)	VR
		Vertebra	Retarded Ossification (centra th9,11-13,lu1,2)	VR
11	3.58	Subcutis	Hemorrhage (chin *)	N
		Rib	Fused (th12-13, proximal, lt)	M
		Vertebra	Hemi (th13, lu3)	M
		Sternebra	Retarded Ossification (1,3,4,6)	VR
		Vertebra	Retarded Ossification (centra th9-12,lu1,2,4)	VR
559467				
1	4.76	Sternebra	Retarded Ossification (1)	VR
		Vertebra	Retarded Ossification (centrum th10)	VR
2	5.05	Skull	Retarded Ossification (interparietal)	VR
		Vertebra	Retarded Ossification (centra th4,7,10-13,lu2,3)	VR
3	4.66	Abdomen	Gastroschisis	M
		Intestine	Gastroschisis	M
		Sternebra	Misaligned (3,4)	DV
		Vertebra	Retarded Ossification (centra th9-12)	VR
4	4.89	Skull	Retarded Ossification (interparietal)	VR
		Vertebra	Retarded Ossification (centra th4,10-12,lu1,2)	VR
5	4.44	Brain	Hydrocephaly (both lateral ventricles)	M
		Vertebra	Retarded Ossification (centra th10-12,lu1,2)	VR
6	4.60	Skull	Retarded Ossification (interparietal)	VR

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP V: 1000 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559467 (Cont.)				
		Vertebra	Retarded Ossification (centra th10,lu2)	VR
559478				
1	4.02	Rib	Fused (3-4 rt)	M
		Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th1-5,8,10-13;lu1-6centra)	VR
2	4.37	Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th1-5,7,10,11 centra)	VR
3	4.26	Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th1,11 centra)	VR
4	4.23	Tongue	Protruding	N
		Rib	Fused (5-6-7-8 rt)	M
		Vertebra	Hemi (th4,6,8 centra)	M
		Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th1-3,10-13;lu7 centra)	VR
5	3.84	Sternebra	Misaligned (3,4)	DV
		Rib	Fused (2-3 rt)	M
		Vertebra	Fused (2-3 rt)	M
		Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th1-4,9-13; lu1-7 centra)	VR
6	4.37	Sternebra	Retarded Ossification (1,6)	VR
		Vertebra	Retarded Ossification (th1-13;lu6 centra)	VR
7	4.01	Tongue	Protruding	N
		Vertebra	Retarded Ossification (th1-4,8,13; lu4,7 centra)	VR
8	4.54	Rib	Fused (4-5 rt)	M
		Vertebra	Absent (th3 rt)	M
		Vertebra	Hemi (th 3 centrum)	M
		Sternebra	Retarded Ossification (1,4,6)	VR

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP V: 1000 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559478 (Cont.)				
		Vertebra	Retarded Ossification (th1-6,10-12;lu1,6 centra)	VR
9	3.44	Head	Domed	N
		Tongue	Protruding	N
		Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th1-3;lu1,4,5 centra)	VR
10	4.34	Vertebra	Retarded Ossification (th1-3,10-13;lu3 centra)	VR
11	4.38	Vertebra	Retarded Ossification (th1-4,10 centra)	VR
12	4.44	Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th11 centrum)	VR
559483				
1	3.36	Sternebra	Retarded Ossification (1,3,4,6)	VR
		Vertebra	Retarded Ossification (th1,2,3,7,10-13,lulcentra)	VR
2	3.71	Sternebra	Misaligned (3,4)	DV
		Sternebra	Retarded Ossification (1-6)	VR
		Vertebra	Retarded Ossification (th1-4,11,12;lu1,5 centra)	VR
3	3.95	Sternebra	Retarded Ossification (1,6)	VR
		Vertebra	Retarded Ossification (th9,12 centra)	VR
4	2.99	Tongue	Protruding	N
		Sternebra	Retarded Ossification (1-6)	VR
		Vertebra	Retarded Ossification (th9-12 centra;ce2-7 arch)	VR
5	3.96	Sternebra	Retarded Ossification (1,3,4,6)	VR
6	3.61	Sternebra	Retarded Ossification (1,6)	VR
		Vertebra	Retarded Ossification (th1,13 centra)	VR
7	3.81	Sternebra	Retarded Ossification (1,6)	VR
8	4.09	Tongue	Protruding	N

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP V: 1000 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559483 (Cont.)				
		Sternebra	Retarded Ossification (1,6)	VR
		Vertebra	Retarded Ossification (th1,3,11-12;lu1-4 centra)	VR
9	3.15	Tongue	Protruding	N
		Vertebra	Retarded Ossification (th1,10-13;lu2 centra)	VR
10	2.77	Subcutis	Hemorrhage (head *)	N
		Tongue	Protruding	N
		Skull	Retarded Ossification (1,12)	VR
		Sternebra	Retarded Ossification (1,3,4,6)	VR
		Vertebra	Retarded Ossification (th1,9-13,lu1 centra)	VR
11	3.68	Heart &/or Greater Vessels	Septal Defect (high ventricular septum)	M
		Heart &/or Greater Vessels	Patent Ductus Arteriosis	VR
		Sternebra	Retarded Ossification (1,6)	VR
		Vertebra	Retarded Ossification (th1,11,13;lu1 centra)	VR
12	3.65	Tongue	Protruding	N
		Skull	Retarded Ossification (12)	VR
		Sternebra	Retarded Ossification (1,6)	VR
		Vertebra	Retarded Ossification (th1,12; lu1 centra)	VR
13	3.62	Heart &/or Greater Vessels	Patent Ductus Arteriosis	VR
		Sternebra	Retarded Ossification (1,6)	VR
		Vertebra	Retarded Ossification (th1,2,10,12 centra)	VR
14	3.32	Tongue	Protruding	N
		Skull	Retarded Ossification (1,12; 2 bil)	VR
		Sternebra	Retarded Ossification (1,3,4,6)	VR
		Vertebra	Retarded Ossification (th6,11centra; ce2-6 arch)	VR

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP V: 1000 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559483 (Cont.)				
15	3.44	Vertebra	Retarded Ossification (th11-12;lu1,2,4 centra)	VR
16	3.06	Sternebra	Misaligned (4,5)	DV
		Sternebra	Retarded Ossification (1,3,4,6)	VR
		Vertebra	Retarded Ossification (th10-13; lu1 centra)	VR
17	3.72	Vertebra	Retarded Ossification (lu1,2,6 centra)	VR
18	3.88	Tongue	Protruding	N
		Sternebra	Retarded Ossification (1,3,4,6)	VR
		Vertebra	Retarded Ossification (th10-13 centra)	VR
559491				
1	4.24	Sternebra	Fused (1-2)	DV
		Vertebra	Retarded Ossification (centra th5,11,12,lu1,2)	VR
2	4.11	Vertebra	Hemi (lu6, centrum)	M
		Skull	Retarded Ossification (1,12,13)	VR
		Sternebra	Retarded Ossification (1,6)	VR
		Vertebra	Retarded Ossification (centra th3,9-14,lu1-4)	VR
3	4.26	Tongue	Protruding	N
		Heart &/or Greater Vessels	Patent Ductus Arteriosis	VR
		Brain	Hemorrhage (olfactory bulb)	N
		Sternebra	Retarded Ossification (1,6)	VR
		Vertebra	Retarded Ossification (centra th8,10-12,14,lu1,6)	VR
4	4.39	Skull	Retarded Ossification (1,12)	VR
		Vertebra	Retarded Ossification (centra th5,10,12,13,lu1-6)	VR
5	3.90	Head	Domed	N
		Tongue	Protruding	N

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP V: 1000 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559491 (Cont.)				
		Heart &/or Greater Vessels	Patent Ductus Arteriosis	VR
		Sternebra	Retarded Ossification (1,3,4,6)	VR
		Vertebra	Retarded Ossification (centra th10-13,lu1-6)	VR
6	4.80	Sternebra	Misaligned (3,4,5)	DV
		Skull	Retarded Ossification (1,12)	VR
		Sternebra	Retarded Ossification (1,3,4,6)	VR
		Vertebra	Retarded Ossification (centra th8,11-13,lu1,3)	VR
7	3.47	Head	Domed	N
		Subcutis	Hemorrhage (lt rear leg *)	N
		Sternebra	Retarded Ossification (1,6)	VR
		Vertebra	Retarded Ossification (centra th6,9-14,lu1-3)	VR
8	3.45	Head	Domed	N
		Tongue	Protruding	N
		Skull	Retarded Ossification (2,3 bil; 1,12,13)	VR
		Sternebra	Retarded Ossification (1-6)	VR
		Vertebra	Retarded Ossification (centra th11,12,lu2,3,5,6)	VR
9	3.86	Sternebra	Fused (1-2)	DV
		Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (centra th10-13,lu1,3,4)	VR
10	4.31	Skull	Retarded Ossification (1,12)	VR
		Sternebra	Retarded Ossification (1)	VR
		Vertebra	Retarded Ossification (centra th11-13,lu4)	VR
11	3.75	Rib	Absent (th2 rt)	M
		Vertebra	Hemi (th2 centrum)	M
		Sternebra	Retarded Ossification (1-6)	VR
		Vertebra	Retarded Ossification (centra th11-13,lu6,7)	VR

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP V: 1000 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559491 (Cont.)				
12	4.11	Head	Domed	N
		Skull	Retarded Ossification (1,12)	VR
		Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (centra th7,9-12,lu3)	VR
13	3.89	Heart &/or Greater Vessels	Patent Ductus Arteriosis	VR
		Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (centra th4,6,10-13,lu1-7)	VR
14	3.99	Tongue	Protruding	N
		Skull	Retarded Ossification (1,12)	VR
		Vertebra	Retarded Ossification (centra th10,12,14,lu2-4)	VR
559496				
1	4.03	Kidney	Papilla - Size 3 (lt)	N
		Vertebra	Hemi (th 6,12 centra)	M
		Sternebra	Retarded Ossification (3,6)	VR
		Vertebra	Retarded Ossification (th1,2,10,11,13;lu1,2)	VR
2	3.97	Sternebra	Misaligned (1-6)	DV
		Skull	Retarded Ossification (1,12)	VR
		Sternebra	Retarded Ossification (1-6)	VR
		Vertebra	Retarded Ossification (th1-3,11,13;lu1-3 centra)	VR
3	4.53	Sternebra	Misaligned (3,4)	DV
		Sternebra	Retarded Ossification (1,6)	VR
		Vertebra	Retarded Ossification (th1,5,10,11 centra)	VR
4	3.77	Tongue	Protruding	N
		Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th1-3,11-13;lu1-2 centra)	VR
5	2.03	Tongue	Protruding	N
		Sternebra	Retarded Ossification (1-6)	VR

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP V: 1000 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559496 (Cont.)				
		Vertebra	Retarded Ossification (ce2-7 bil arches, th1-4,6, 11-13 centra, lu1-6 centra)	VR
6	4.11	Tongue	Protruding	N
		Skull	Retarded Ossification (1,12,13)	VR
		Sternebra	Retarded Ossification (1-6)	VR
		Vertebra	Retarded Ossification (ce2-7 lt arches, th1-4,11 centra, lu2,3,5 centra)	VR
7	4.18	Tongue	Protruding	N
		Brain	Hydrocephaly (both lateral ventricles)	M
		Sternebra	Retarded Ossification (1-6)	VR
		Vertebra	Retarded Ossification (ce5-6 arch bil, th1-3,13 centra, lu1-2 centra)	VR
8	2.98	Abdomen	Gastroschisis	M
		Head	Domed	N
		Tongue	Protruding	N
		Sternebra	Retarded Ossification (1-6)	VR
		Vertebra	Retarded Ossification (ce2-7 bil arches, th1-4,11 centra, lu1-2 centra)	VR
9	4.12	Rib	Fused (11 to 12 rt 13 ribs lt)	M
		Vertebra	Hemi (5 centrum)	M
		Vertebra	Retarded Ossification (th1-2,9,11-13 centra, lu2 centra, ce2-7 bil arches)	VR
10	3.84	Tongue	Protruding	N
		Vertebra	Fused (ce6-7 ce7-th1 rt)	M
		Vertebra	Malformation (only 5 ce vrt on lt)	M
		Skull	Retarded Ossification (1,12,14)	VR
		Sternebra	Retarded Ossification (1-6)	VR
		Vertebra	Retarded Ossification (th1-5,9-11 centra)	VR

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APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

GROUP V: 1000 mg/kg (Cont.)

DAM #/ FETUS #	FETUS WT.	STRUCTURE	FINDING(S)	CLASSIF-ICATION
559496 (Cont.)				
11	4.55	Head	Domed	N
		Tongue	Protruding	N
		Brain	Hydrocephaly (both lateral ventricles)	M
		Rib	Fused (1-2,9-10)	M
		Vertebra	Retarded Ossification (ce2-5 lt arches, th1-4,9, 11-13 centra, lu1-3,6 centra)	VR
12	4.34	Sternebra	Misaligned (4)	DV
		Skull	Retarded Ossification (1,12)	VR
		Sternebra	Retarded Ossification (6)	VR
		Vertebra	Retarded Ossification (th1-5,11-13 centra)	VR
13	4.01	Head	Domed	N
		Tongue	Protruding	N
		Brain	Hydrocephaly (both lateral ventricles)	M
		Rib	Fused (3-4-5,6-7 rt,3-4,6-7 lt)	M
		Vertebra	Fused (th 6-7 lt arch)	M
		Vertebra	Hemi (th5 centrum)	M
		Sternebra	Retarded Ossification (1-6)	VR
		Vertebra	Retarded Ossification (th1-4,6,11-13 centra)	VR

PILOT DEVELOPMENTAL TOXICITY STUDY OF
70% GLYCOLIC ACID TECHNICAL SOLUTION IN RATS

APPENDIX K (CONT.)

INDIVIDUAL FETAL WEIGHTS (grams) AND ALTERATIONS

NOTES:

Numbers are used to:

- refer to skeletal position for ribs or vertebra
- identify specific sternebra
- indicate renal papillary size
- specify skull bones according to the following key:

1. interparietal	8. squamosal
2. parietal	9. tymanic annulus
3. frontal	10. basioccipital
4. nasal	11. exoccipital
5. premaxilla	12. supraoccipital
6. maxilla	13. hyoid
7. zygoma	

Asterisks (*) are used to indicate when an observed subcutaneous hemorrhage was not present in utero.

ABBREVIATIONS:

bil	= Bilateral
ce	= Cervical
lt	= Left
lu	= Lumbar
NAD	= No Abnormalities Detected
rt	= Right
th	= Thoracic
...	= No Data

Alterations are classed as:

M = Malformations
DV = Developmental Variations
VR = Variation due to Retarded development
N = Notes

APPENDIX L

CLINICAL PATHOLOGY REPORT NO. 9-95

PILOT DEVELOPMENTAL TOXICITY STUDY OF GLYCOLIC ACID IN RATS

PILOT DEVELOPMENTAL TOXICITY STUDY OF GLYCOLIC ACID IN RATS

SUMMARY

This report describes the clinical pathology findings from a pilot developmental toxicity study in rats with glycolic acid. Five groups of eight female Crl:CD®BR rats were given 0 (control), 125, 250, 500 or 1000 mg/kg of glycolic acid by gavage. Dosing occurred once per day on days 7 - 21 of gestation. Clinical pathologic evaluations were done on blood collected from the tail vein of all surviving rats during the third week after mating. Blood was collected approximately 22 hours after the previous dose of glycolic acid was administered.

Evaluation of clinical chemistry was done to determine whether glycolic acid may have altered the acid-base status of the mated rats. There were no statistically significant or toxicologically important effects on the clinical chemistry parameters measured. Therefore, under the conditions of this study there was no evidence that glycolic acid changed the acid-base status of the rats. For the clinical pathology parameters measured the no-observed-adverse-effect level (NOAEL) in female rats was 1000 mg/kg.

Prepared by: Cheryl L. Samson

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Pathology Associate

Report by: Glenn S. Elliott

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Date Issued: 6/1/95

PROCEDURE

Five groups of eight female Crl:CD®BR rats were given 0 (control), 125, 250, 500 or 1000 mg/kg of glycolic acid by gavage. Dosing occurred once per day on days 7 - 21 of gestation. Clinical pathologic evaluations were done on blood collected from the tail vein of all surviving rats during the third week after mating. Blood was collected approximately 22 hours after the previous dose of glycolic acid was administered.

The following serum chemical parameters were measured: serum osmolality (OSMOL) and serum concentrations of glucose (GLUCO), urea nitrogen (BUN), calcium (CALC), phosphate (PHOS) sodium (Na), potassium (K), chloride (Cl), and bicarbonate (HCO_3). Clinical chemistry parameters were measured on a Boehringer Mannheim/Hitachi 717 clinical chemistry analyzer using Boehringer Mannheim reagents. Serum osmolality was determined on a Precision Systems Multi-Osmette™ model 2430 osmometer. The anion gap was calculated as follows: Anion Gap = $(Na + K) - (Cl + HCO_3)$.

STATISTICAL ANALYSES

A one-way analysis of variance (ANOVA) and Bartlett's test were calculated for each sampling time. Dunnett's test was used to compare means from the control group and each of the groups dosed with glycolic acid. When the results of the Bartlett's test were significant ($p \leq 0.005$), the Kruskal-Wallis test was employed and the Mann-Whitney U test was used to compare means from the control group and each of the groups dosed with glycolic acid. Significance was judged at the 5% probability level.

RESULTS AND DISCUSSION

Evaluation of clinical chemistry was done to determine whether glycolic acid may have altered the acid-base status of the mated rats. There were no statistically significant or toxicologically important effects on the clinical chemistry parameters measured. Therefore, under the conditions of this study there was no evidence that glycolic acid changed the acid-base status of the rats.

The anticipated acid-base alteration due to glycolic acid administration was metabolic acidosis. Lack of evidence for metabolic acidosis in this study may have been related to the time of sample collection, relative to the time of dosing with glycolic acid. Blood samples were collected approximately 22 hours after rats were dosed with glycolic acid. The compensatory response for metabolic acidosis is increased ventilation which begins within a few minutes after development of acidosis.[1] It is possible that the rats in this study had compensated for metabolic acidosis which may have occurred in the first few hours after glycolic acid administration.

REFERENCE

1. Carlson, GP, "Fluid, Electrolyte, and Acid-Base Balance", In Clinical Biochemistry of Domestic Animals, Kaneko, JJ, ed., 4th ed., Academic Press, Inc., pp. 551-552, 1989.

PILOT DEVELOPMENTAL TOXICITY STUDY OF GLYCOLIC ACID IN RATS

TABLE 1

SUMMARY OF CLINICAL CHEMICAL FINDINGS FOR FEMALE RATS

TESTS	CONCENTRATION (mg/kg)	
GLUCO mg/dl	0	123.(26.)[a]
	125	131.(31.)
	250	110.(34.)
	500	135.(26.)
	1,000	114.(13.)
BUN mg/dl	0	17.(2.)
	125	17.(3.)
	250	17.(7.)
	500	19.(3.)
	1,000	16.(3.)
PHOS mg/dl	0	5.9(0.8)
	125	6.3(1.0)
	250	5.4(1.8)
	500	6.6(1.1)
	1,000	6.3(0.5)
CALC mg/dl	0	10.7(0.2)
	125	10.6(0.4)
	250	9.4(2.9)
	500	10.6(0.3)
	1,000	10.5(0.4)
Na mmol/L	0	143.(4.)
	125	141.(2.)
	250	139.(3.)
	500	142.(3.)
	1,000	139.(2.)
K mmol/L	0	5.2(0.3)
	125	5.2(0.6)
	250	4.9(0.4)
	500	5.3(0.6)
	1,000	5.0(0.4)

PILOT DEVELOPMENTAL TOXICITY STUDY OF GLYCOLIC ACID IN RATS

TABLE 1 (continued)

SUMMARY OF CLINICAL CHEMICAL FINDINGS FOR FEMALE RATS

TESTS	CONCENTRATION (mg/kg)	
Cl mmol/L	0	104.(3.)
	125	104.(2.)
	250	102.(4.)
	500	104.(4.)
	1,000	100.(2.)
HCO3 mEq/L	0	28.1(1.7)
	125	26.8(2.0)
	250	25.4(6.6)
	500	26.6(3.4)
	1,000	28.6(1.8)
Anion Gap[b]	0	15.7(1.7)
	125	15.5(1.6)
	250	16.0(5.8)
	500	16.9(3.9)
	1,000	15.1(1.8)
OSMOL mOs	0	295.(6.)
	125	296.(7.)
	250	294.(6.)
	500	301.(7.)
	1,000	291.(5.)

[a] Group means and standard deviations(SD)
[b] Anion Gap = (Na + K) - (Cl + HCO3)

PILOT DEVELOPMENTAL TOXICITY STUDY OF GLYCOLIC ACID IN RATS

APPENDIX

INDIVIDUAL CLINICAL CHEMICAL FINDINGS FOR FEMALE RATS

GROUP: I
SAMPLE DATE: 01/16/95

CONCENTRATION: 0 mg/kg

ANIMAL#:	GLUCO mg/dl	BUN mg/dl	PHOS mg/dl	CALC mg/dl	Na mmol/L	K mmol/L	Cl mmol/L
559459	107.	18.	7.3	10.7	144.	5.8	103.
559462	134.	16.	6.3	10.7	141.	4.9	103.
559465	183.	19.	5.2	10.8	146.	4.8	107.
559468	124.	19.	5.8	10.8	140.	5.0	103.
559477	107.	18.	4.7	10.3	138.	5.4	101.
559486	104.	15.	5.7	10.4	139.	5.0	101.
559492	114.	14.	6.4	11.1	141.	5.1	102.
559495	110.	16.	5.7	10.7	151.	5.5	111.
AVG.	123.	17.	5.9	10.7	143.	5.2	104.
S. D.	26.	2.	0.8	0.2	4.	0.3	3.
S. E.	9.	1.	0.3	0.1	2.	0.1	1.

GROUP: II
SAMPLE DATE: 01/16/95

CONCENTRATION: 125 mg/kg

ANIMAL#:	GLUCO mg/dl	BUN mg/dl	PHOS mg/dl	CALC mg/dl	Na mmol/L	K mmol/L	Cl mmol/L
559463	109.	16.	8.2	10.7	141.	5.9	102.
559475	152.	16.	6.4	10.3	141.	4.4	105.
559490	95.	17.	6.3	10.4	139.	5.3	101.
559493	191.	22.	6.1	10.7	144.	5.9	107.
559494	133.	19.	6.5	10.2	140.	4.8	104.
559497	104.	15.	5.6	10.8	139.	5.5	102.
559498	145.	18.	4.7	11.4	145.	5.3	106.
559500	117.	14.	6.4	10.3	140.	4.7	105.
AVG.	131.	17.	6.3	10.6	141.	5.2	104.
S. D.	31.	3.	1.0	0.4	2.	0.6	2.
S. E.	11.	1.	0.3	0.1	1.	0.2	1.

PILOT DEVELOPMENTAL TOXICITY STUDY OF GLYCOLIC ACID IN RATS

APPENDIX (continued)

INDIVIDUAL CLINICAL CHEMICAL FINDINGS FOR FEMALE RATS

GROUP: III CONCENTRATION: 250 mg/kg
SAMPLE DATE: 01/16/95

ANIMAL#:	GLUCO mg/dl	BUN mg/dl	PHOS mg/dl	CALC mg/dl	Na mmol/L	K mmol/L	Cl mmol/L
559454	34.	4.	1.2	2.2	132.	4.8	97.
559458	113.	19.	6.5	11.0	141.	4.9	102.
559464	132.	30.	5.8	10.7	138.	4.5	100.
559474	100.	16.	6.3	10.3	139.	5.0	100.
559476	110.	17.	5.3	10.1	140.	4.9	104.
559480	125.	17.	5.3	10.3	136.	5.3	101.
559482	144.	18.	6.3	10.4	143.	4.4	108.
559503	125.	15.	6.7	10.6	141.	5.7	106.
AVG.	110.	17.	5.4	9.4	139.	4.9	102.
S. D.	34.	7.	1.8	2.9	3.	0.4	4.
S. E.	12.	2.	0.6	1.0	1.	0.1	1.

GROUP: IV CONCENTRATION: 500 mg/kg
SAMPLE DATE: 01/16/95

ANIMAL#:	GLUCO mg/dl	BUN mg/dl	PHOS mg/dl	CALC mg/dl	Na mmol/L	K mmol/L	Cl mmol/L
559460	153.	19.	7.5	10.9	144.	5.4	104.
559466	122.	21.	7.0	11.1	140.	5.0	100.
559484	143.	23.	7.6	10.6	140.	5.4	102.
559487	113.	15.	6.2	10.1	139.	4.9	102.
559488	101.	17.	6.7	10.7	141.	5.3	103.
559489	173.	18.	7.7	10.6	145.	6.6	106.
559501	116.	17.	5.6	10.4	139.	4.4	101.
559502	162.	20.	4.6	10.6	146.	5.5	111.
AVG.	135.	19.	6.6	10.6	142.	5.3	104.
S. D.	26.	3.	1.1	0.3	3.	0.6	4.
S. E.	9.	1.	0.4	0.1	1.	0.2	1.

PILOT DEVELOPMENTAL TOXICITY STUDY OF GLYCOLIC ACID IN RATS

APPENDIX (continued)

INDIVIDUAL CLINICAL CHEMICAL FINDINGS FOR FEMALE RATS

GROUP: V
SAMPLE DATE: 01/16/95

CONCENTRATION: 1,000 mg/kg

ANIMAL#:	GLUCO mg/dl	BUN mg/dl	PHOS mg/dl	CALC mg/dl	Na mmol/L	K mmol/L	Cl mmol/L
559456	137.	19.	6.7	10.7	139.	5.0	101.
559467	103.	19.	6.8	10.7	142.	5.4	102.
559478	107.	12.	6.2	10.1	136.	4.7	97.
559483	124.	16.	5.4	10.1	139.	4.5	102.
559491	111.	15.	6.0	11.1	137.	5.0	99.
559496	104.	14.	6.7	10.4	138.	5.4	98.
AVG.	114.	16.	6.3	10.5	139.	5.0	100.
S. D.	13.	3.	0.5	0.4	2.	0.4	2.
S. E.	5.	1.	0.2	0.2	1.	0.1	1.

PILOT DEVELOPMENTAL TOXICITY STUDY OF GLYCOLIC ACID IN RATS

APPENDIX (continued)

INDIVIDUAL CLINICAL CHEMICAL FINDINGS FOR FEMALE RATS

GROUP: I
SAMPLE DATE: 01/16/95

CONCENTRATION: 0 mg/kg

ANIMAL#:	HCO3 mEq/L	Anion Gap[a]	OSMOL mOs
559459	29.7	17.1	299.
559462	27.2	15.7	290.
559465	26.7	17.1	307.
559468	26.2	15.8	292.
559477	29.9	12.5	289.
559486	28.7	14.3	290.
559492	26.3	17.8	295.
559495	30.0	15.5	297.
AVG.	28.1	15.7	295.
S. D.	1.7	1.7	6.
S. E.	0.6	0.6	2.

GROUP: II
SAMPLE DATE: 01/16/95

CONCENTRATION: 125 mg/kg

ANIMAL#:	HCO3 mEq/L	Anion Gap[a]	OSMOL mOs
559463	29.9	15.0	299.
559475	25.8	14.6	292.
559490	29.8	13.5	295.
559493	26.3	16.6	308.
559494	25.7	15.1	293.
559497	24.3	18.2	291.
559498	27.3	17.0	304.
559500	25.5	14.2	285.
AVG.	26.8	15.5	296.
S. D.	2.0	1.6	7.
S. E.	0.7	0.6	3.

PILOT DEVELOPMENTAL TOXICITY STUDY OF GLYCOLIC ACID IN RATS

APPENDIX (continued)

INDIVIDUAL CLINICAL CHEMICAL FINDINGS FOR FEMALE RATS

GROUP: III
SAMPLE DATE: 01/16/95

CONCENTRATION: 250 mg/kg

ANIMAL#:	HCO3 mEq/L	Anion Gap[a]	OSMOL mOs
559454	9.8	30.0	283.
559458	30.4	13.5	296.
559464	27.7	14.8	290.
559474	30.3	13.7	298.
559476	27.1	13.8	292.
559480	27.2	13.1	301.
559482	27.1	12.3	291.
559503	23.9	16.8	299.
AVG.	25.4	16.0	294.
S. D.	6.6	5.8	6.
S. E.	2.3	2.1	2.

GROUP: IV
SAMPLE DATE: 01/16/95

CONCENTRATION: 500 mg/kg

ANIMAL#:	HCO3 mEq/L	Anion Gap[a]	OSMOL mOs
559460	26.5	18.9	304.
559466	23.6	21.4	295.
559484	20.4	23.0	305.
559487	28.3	13.6	293.
559488	31.5	11.8	297.
559489	29.0	16.6	312.
559501	26.8	15.6	292.
559502	26.6	13.9	307.
AVG.	26.6	16.9	301.
S. D.	3.4	3.9	7.
S. E.	1.2	1.4	3.

PILOT DEVELOPMENTAL TOXICITY STUDY OF GLYCOLIC ACID IN RATS

APPENDIX (continued)

INDIVIDUAL CLINICAL CHEMICAL FINDINGS FOR FEMALE RATS

GROUP: V
SAMPLE DATE: 01/16/95

CONCENTRATION: 1,000 mg/kg

ANIMAL#:	HCO3 mEq/L	Anion Gap[a]	OSMOL mOs
559456	26.1	16.9	295.
559467	28.8	16.6	297.
559478	31.4	12.3	285.
559483	27.8	13.7	288.
559491	27.9	15.1	288.
559496	29.7	15.7	290.
AVG.	28.6	15.1	291.
S. D.	1.8	1.8	5.
S. E.	0.7	0.7	2.

[a] Anion Gap = (Na +K) - (Cl + HCO3)

GLYCOLIC ACID - 70% SOLUTION

4450CR Revised 8-JUN-1995 Printed 12-JUN-1995

CHEMICAL PRODUCT/COMPANY IDENTIFICATION

Material Identification

Corporate MSDS Number : DU002202
CAS Number : 79-14-1
Formula : HO-CH2-COOH
CAS Name : ACETIC ACID, HYDROXY
Grade : TECHNICAL

Tradenames and Synonyms

HYDROXYACETIC ACID
HYDROXYETHANOIC ACID
HAA

Company Identification

MANUFACTURER/DISTRIBUTOR
DuPont
1007 Market Street
Wilmington, DE 19898

PHONE NUMBERS
Product Information : 1-800-441-9442
Transport Emergency : CHEMTREC: 1-800-424-9300
Medical Emergency : 1-800-441-3637

COMPOSITION/INFORMATION ON INGREDIENTS

Components

Material	CAS Number	%
GLYCOLIC ACID	79-14-1	62.8-65.7
METHOXYACETIC ACID	625-45-6	0.5-2.0
DIGLYCOLIC ACID	110-99-6	0.4-1.2
WATER	7732-18-5	30.0

Components (Remarks)

NOTE FOR GLYCOLIC ACID COMPONENT:

The total acid specification for 70% Solution is 70 - 72%, and the typical free acid is 62.8 - 65.7%. At high concentrations, free glycolic acid exists in equilibrium with low molecular weight, polyester oligomers. Upon dilution, neutralization, etc., these components revert to free glycolic acid.

HAZARDS IDENTIFICATION

Potential Health Effects

This compound may cause burns and ulceration of the eyes, and is a severe skin irritant. Prolonged exposure may cause skin burns and ulceration. Inhalation may cause nose, throat, and lung irritation. Ingestion may cause burns and/or perforation of the gastrointestinal tract.

Gross overexposure may result in death.

HUMAN HEALTH EFFECTS:

Eye contact may cause eye corrosion with corneal or conjunctival ulceration. Skin contact may cause skin irritation with discomfort or rash. Higher or prolonged skin contact may cause burns or ulceration. Inhalation may cause irritation of the respiratory passages with cough and difficulty in breathing. Ingestion may cause irritation of the gastrointestinal tract with abdominal pain, nausea, vomiting, diarrhea, and abnormal kidney function. Reports suggest that overexposure to methoxyacetic acid (MAA) may cause cause abnormal blood forming system function with anemia, or altered immune system function with possible increased susceptibility to disease. MAA may be absorbed through the skin. Gross overexposure to the product by ingestion may be fatal.

Based on effects seen in animal testing with 2-methoxyethanol (2-ME), of which MAA is a known metabolite, and the similarity of effects between 2-ME and MAA, the following precautions should be considered for MAA. DuPont considers 2-ME to be a potential developmental hazard. Animal testing indicates that overexposure to 2-ME may result in an increased incidence of developmental abnormalities. DuPont also considers 2-ME a potential reproductive hazard affecting male and female reproductive processes. However, exposure to 2-ME at or below the DuPont recommended exposure limit of 1 ppm (8-hour TWA, with avoidance of skin contact) should not represent a risk of injury to a man, woman, or unborn child. Therefore, MAA exposure should be similarly controlled. At the MAA concentrations present in the product, no increased risk of adverse human health effects is expected.

Individuals with preexisting diseases of the skin, kidneys, or reproductive system may have increased susceptibility to the toxicity of excessive exposures.

Carcinogenicity Information

None of the components present in this material at concentrations equal to or greater than 0.1% are listed by IARC, NTP, OSHA or ACGIH as a carcinogen.

FIRST AID MEASURES

First Aid

EYE CONTACT
Immediately flush eyes with plenty of water for at least 15 minutes. Call a physician.

SKIN CONTACT
Immediately flush skin with plenty of water for at least 15 minutes while removing contaminated clothing and shoes. Call a physician. Wash clothing before reuse.

INHALATION
Remove to fresh air immediately. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Call a physician.

INGESTION
Do not induce vomiting. Give large quantities of water. Call a physician. Never give anything by mouth to an unconscious person.

FIRE FIGHTING MEASURES

Flammable Properties

Flammable limits in Air, % by Volume

Will not burn.

Fire and Explosion Hazards:

Contact with active metals may produce flammable hydrogen gas.

Will not burn.

Fire and Explosion Hazards:

Contact with metals may produce flammable hydrogen gas.

Extinguishing Media

As appropriate for combustibles in area.

Fire Fighting Instructions

None.

ACCIDENTAL RELEASE MEASURES

Safeguards (Personnel)

NOTE: Review FIRE FIGHTING MEASURES and HANDLING (PERSONNEL) sections before proceeding with clean-up. Use appropriate PERSONAL PROTECTIVE EQUIPMENT during clean-up.

\# Accidental Release Measures

Neutralize spills with lime or soda ash. Flush spill area with plenty of water.

If GLYCOLIC ACID - 70% TECHNICAL SOLUTION is spilled and not recovered, or is recovered as a waste for treatment or disposal, the CERCLA Reportable Quantity is 100 lbs. (Release of an unlisted Hazardous Waste Characteristic of Corrosivity).

HANDLING AND STORAGE

Handling (Personnel)

Avoid breathing mist. Do not get in eyes, on skin, or on clothing. Wash thoroughly after handling.

Storage

Keep in a well-ventilated area. Protect bulk storage area from sparks and flame. Keep packages tightly closed. Store above 10 deg C (50 deg F) melting point.

EXPOSURE CONTROLS/PERSONAL PROTECTION

Engineering Controls

Good general ventilation should be provided to keep mist concentrations below the recommended exposure limit.

Personal Protective Equipment

Chemical splash goggles and rubber gloves. Wear a butyl rubber acid suit and NIOSH/MSHA permissible respiratory protection if there is a reasonable possibility for exposure.

Exposure Guidelines

Exposure Limits
GLYCOLIC ACID - 70% SOLUTION

PEL	(OSHA)	: None Established
TLV	(ACGIH)	: None Established
AEL *	(DuPont)	: 10 mg/m3, 8 & 12 Hr. TWA

* AEL is DuPont's Acceptable Exposure Limit. Where governmentally imposed occupational exposure limits which are lower than the AEL are in effect, such limits shall take precedence.

PHYSICAL AND CHEMICAL PROPERTIES

Physical Data

Boiling Point	: 112 C (234 F) @ 760 mm Hg
Vapor Pressure	: Vapor is water
Vapor Density	: Vapor is water
Melting Point	: 10 C (50 F) (Precipitates)
Solubility in Water	: Miscible
pH	: 0.1 @ 25 deg C (77 deg F)
Odor	: Mild (like burnt sugar)
Form	: Clear liquid
Color	: Light amber
Density	: 1.25 g/cc at 26 deg C (79 deg F)

STABILITY AND REACTIVITY

Chemical Stability

Stable.

Decomposition

Decomposition will not occur.

Polymerization

Polymerization will not occur.

Other Hazards

Incompatibility : Reacts with active metals (like sodium), oxidizing agents (such as strong nitric acid), cyanides, sulfides to produce hydrogen, oxides of nitrogen, hydrogen cyanide or hydrogen sulfide gases, respectively.

TOXICOLOGICAL INFORMATION

Animal Data

Glycolic Acid

Inhalation 4-hour LC50: 7.7 mg/L in rats
Oral LD50 : 4,240 mg/kg in rats

The compound is a skin and eye corrosive, but is not a skin sensitizer in animals.

Toxic effects described in animals from a single exposure by inhalation include body weight losses, ocular and nasal discharges, and other nonspecific effects. Repeated inhalation exposures produced liver, spleen, and thymus changes, and gastrointestinal tract alterations. By ingestion, the administration of single high oral doses produced severe gastrointestinal tract irritation, liver damage, increased kidney weights, and the formation of calcium oxalate crystals in the kidneys. Repeated ingestion dosing in cats produced weight loss, depression, vomiting, coma, convulsions, kidney failure due to calcium oxalate deposition, and death. Dogs given similar and higher doses exhibited no toxic effects. Long-term dosing in male and female rats resulted in high mortality in the male rats (60-70%) and kidney toxicity due to calcium oxalate deposition. The female rats exhibited no toxic effects.

At a high dietary level, a reduced number of offspring were observed in rats, but this effect occurred only at a maternally toxic dose. In a pilot developmental toxicity study, fetal abnormalities were indicated in rats orally dosed during gestation with glycolic acid at levels that also produced maternal toxicity. The compound does not produce genetic damage in bacterial cell cultures.

Methoxyacetic Acid

Inhalation 7-hour ALC: >3,200 ppm in rats
Oral LD50 : Approximately 1,000 mg/kg in rats

The compound is a skin and eye corrosive in tests with laboratory animals. Toxic effects described in animals from short, high inhalation exposures include respiratory irritation. By ingestion, the effects of single, high exposures include reduced body and testicular weights, testicular and epididymal changes, lowered spermatocyte counts, and increased hormonal blood levels. Repeated ingestion exposures produced lowered spleen and liver weights, and hematological changes due to bone marrow effects. Pathological changes of the adrenals, reduced thymus weights, and altered immune function have also been reported.

(TOXICOLOGICAL INFORMATION - Continued)

Tests in some animals indicate that MAA may have developmental and reproductive toxicity.

Diglycolic Acid

The compound is a skin irritant. Near lethal doses produced body weight loss, diarrhea, gastrointestinal tract irritation, and kidney damage.

ECOLOGICAL INFORMATION

Ecotoxicological Information

Aquatic Toxicity - Slight

24-48 hour LC50, bluegill sunfish: 93 mg/L
96 hour LC50, fathead minnows: 164 mg/L

These data indicate that glycolic acid has slight aquatic toxicity.

Biodegradability - Readily biodegradable

After 7 days, 89.6% is biodegraded (closed bottle test).

DISPOSAL CONSIDERATIONS

Waste Disposal

Comply with Federal, State, and local regulations. If approved, may be neutralized with lime or soda ash and flushed to wastewater treatment system. This material may may be a RCRA hazardous waste due to its corrosive characteristic (pH).

TRANSPORTATION INFORMATION

Shipping Information

DOT/IMO

Proper Shipping Name	: CORROSIVE LIQUIDS, ACIDIC, ORGANIC, N.O.S. (GLYCOLIC ACID)
Hazard Class	: 8
UN No.	: 3265
DOT/IMO Label	: CORROSIVE
Packing Group	: II

(TRANSPORTATION INFORMATION - Continued)

Shipping Containers

Tank Car
Tank Truck
Drums
Sample Bottles

REGULATORY INFORMATION

U.S. Federal Regulations

TSCA Inventory Status : Reported/Included.

TITLE III HAZARD CLASSIFICATIONS SECTIONS 311, 312

Acute : Yes
Chronic : No
Fire : No
Reactivity : No
Pressure : No

LISTS:

SARA Extremely Hazardous Substance	-No
CERCLA Hazardous Substance	-Yes*
SARA Toxic Chemical	-No

* SEE DISPOSAL SECTION.

CANADIAN WHMIS CLASSIFICATION:
E

OTHER INFORMATION

NFPA, NPCA-HMIS

NPCA-HMIS Rating

Health	: 3
Flammability	: 0
Reactivity	: 0

Personal Protection rating to be supplied by user depending on use conditions.

Additional Information

DuPont prohibits the use of 70% Technical Solution grade glycolic acid in personal care applications due to the higher level of impurities.

For further information, see DuPont Glycolic Acid "Properties, Uses, Storage, and Handling" Bulletin.

The data in this Material Safety Data Sheet relates only to the specific material designated herein and does not relate to use in combination with any other material or in any process.

Responsibility for MSDS : DuPont Chemicals
Address : Engineering & Product Safety
P. O. Box 80709, Chestnut Run
Wilmington, DE 19880-0709
Telephone : 302-999-4946

# Indicates updated section.

End of MSDS