

889200 10906 8EHQ-0992-12841  
8EHQ-92-12841

"Contains NO CBI"

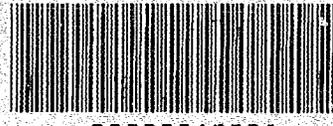


September 28, 1992

Document Processing Center (TS-790)  
Office of Pollution Prevention and Toxics  
U. S. Environmental Protection Agency  
401 M Street, SW  
Washington, DC 20460  
Attn: Section 8(e) Coordinator (CAP Agreement)



8EHQ-92-12841  
INIT 09/30/92



88920010906

Dear Sir or Madam:

Subject: Report submitted in accordance with guidelines established by the U. S. Environmental Protection Agency Registration and Agreement for the TSCA 8(e) Compliance Audit Program

Report submitted by: Eastman Kodak Company  
343 State Street  
Rochester, NY 14650  
(716) 724-4000  
CAP Agreement Identification Number (8ECAP-0039)

The report pertains to 2-ethylhexanoic acid [CAS # 149-57-5] and is being submitted because of effects observed in a developmental toxicity study in rats. The title of the study being submitted is "Developmental Toxicity Evaluation of 2-Ethylhexanoic Acid Administered by Gavage to Fischer Rats". The study is being identified as a study originally submitted under another mandatory reporting requirement of TSCA (Unit II.B.3 of CAP Agreement). That report was submitted under TSCA Section 4 Docket OPTS-42065.

Groups of twenty-five timed-pregnant Fischer 344 rats were exposed by gavage on gestational days 6 through 15 at doses of 100, 250 or 500 mg/kg/day. There were no treatment-related maternal deaths and no dams aborted. Maternal toxicity, observed only at the 500 mg/kg/day dose level, included hypoactivity, ataxia, audible respiration, ocular discharge, periocular encrustation, and increased absolute and relative liver weights. No embryotoxicity or teratogenicity was observed at any dose level. One visceral variation, dilated lateral ventricles on the brain with no tissue compression, was increased at the high-dose level. An increase in the number of fetal skeletal variations (most involving delayed fetal ossification) was observed at both the 250 and 500 mg/kg/day dose levels.

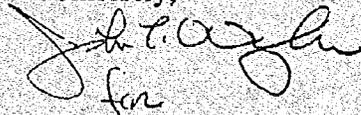


Document Processing Center (TS-790) -2

Questions regarding this submission should be addressed to:

Mr. William Hart  
Eastman Kodak Company  
Corporate Health and Environment Laboratories  
Rochester, NY 14652-3615  
(716) 722-5991

Sincerely,



*R. Hays Bell*  
for

R. Hays Bell, Ph.D.  
Vice President  
Corporate Health, Safety and Environment  
(716) 722-5036

RHB:JAF  
Enclosure

**BUSHY RUN RESEARCH CENTER**

R. D. 4, Mellon Road, Export, Pennsylvania 15632

Telephone (412) 733-5200

PROJECT REPORT 51-529

**TITLE:** Developmental Toxicity Evaluation of 2-Ethylhexanoic Acid Administered by Gavage to Fischer 344 Rats

**AUTHOR:** Rochelle W. Tyl

**SPONSOR:** 2-Ethylhexanoic Acid Program  
Chemical Manufacturers Association  
2501 M Street, NW  
Washington, DC 20037

**SPONSOR REPRESENTATIVE:** H. J. Sauer, Manager  
2-Ethylhexanoic Acid Program

**DATE:** June 10, 1988

TABLE OF CONTENTS

|  | <u>Page</u> |
|--|-------------|
| Abstract . . . . .   | 1           |
| Objectives . . . . .   | 2           |
| Materials and Methods . . . . .  | 2           |
| Results . . . . .  | 6           |
| Discussion . . . . .   | 8           |
| Conclusions . . . . .  | 8           |
| References . . . . .   | 10          |
| Good Laboratory Practices Compliance Statement . . . . .   | 38          |
| Quality Assurance Unit Study Inspection Summary . . . . .  | 39          |
| Analytical Chemistry Report . . . . .  | Appendix 1  |
| Individual In-Life Maternal Data. . . . .  | Appendix 2  |
| Necropsy and Laparotomy Data. . . . .  | Appendix 3  |
| Incidence of Malformations and Variations by Individual Fetuses<br>and Litters (Including Individual Fetal Body Weights) . . . . . | Appendix 4  |
| Protocols and Amendments. . . . .  | Appendix 5  |
| Dose Range-Finding Study of 2-Ethylhexanoic Acid<br>in Fischer 344 Rats . . . . .  | Appendix 6  |
| Dose Range-Finding Study of 2-Ethylhexanoic Acid<br>in Fischer 344 Rats II. . . . .  | Appendix 7  |

LIST OF TABLES

| <u>Table No.</u> | <u>Title</u>   | <u>Page</u> |
|------------------|--|-------------|
| 1                | Analyses of Dosing Formulations. . . . .                           | 12          |
| 2                | Distribution and Fate. . . . .                                     | 13          |
| 3                | Mean Gestational Body Weights and Body Weight<br>Changes . . . . . | 14          |
| 4                | Incidence of Clinical Observations by Gestation Day. .             | 16          |
| 5                | Mean Food Consumed During Gestation. . . . .                       | 17          |
| 6                | Gross Observations - Incidence Summary . . . . .                   | 19          |
| 7                | Maternal Organ Weights at Sacrifice. . . . .                       | 20          |
| 8                | Summary of Mean Fetal Data at the Time of<br>Laparotomy. . . . .   | 21          |
| 9                | Malformations Observed in Fetuses and Litters. . . . .             | 23          |
| 10               | Variations Observed in Fetuses and Litters . . . . .               | 27          |



## BUSHY RUN RESEARCH CENTER

R. D. 4, Mellon Road, Export, Pennsylvania 15632

Telephone (412) 733-5200

CONFIDENTIAL

Project Report 51-529  
40 Pages  
June 10, 1988

### Developmental Toxicity Evaluation of 2-Ethylhexanoic Acid Administered by Gavage to Fischer Rats

Sponsor: Chemical Manufacturers Association

\* \* \* \* \*

#### ABSTRACT

Timed-pregnant Fischer 344 rats were exposed to 2-ethylhexanoic acid by gavage on gestational days (gd) 6 through 15 at doses of 0.0, 100.0, 250.0 or 500.0 mg/kg/day in certified corn oil, 25 plug-positive females per group. The dose volume employed was 2.0 ml/kg based on the weight of each female on gd 6. Clinical observations were taken daily and maternal body weights were taken on gd 0, 6, 12, 15, 18 and 21. Food consumption was measured for the intervals gd 0-3, 3-6, 6-9, 9-12, 12-15, 15-18 and 18-21. At scheduled sacrifice on gd 21, the dams were evaluated for body weight, liver weight, gravid uterine weight and status of implantation sites (i.e. resorptions, dead fetuses, live fetuses). Maternal livers were retained in fixative for possible subsequent microscopic examination. Live fetuses were dissected from the uterus, counted, weighed, sexed and examined for external abnormalities. Approximately one-half of the live fetuses in each litter were examined for visceral malformations and variations. These fetuses were then decapitated and the heads fixed in Bouin's solution; serial free hand sections of the heads were examined for soft tissue craniofacial malformations and variations. The remaining (intact) fetuses in each litter were eviscerated, fixed in alcohol, stained with alizarin red S and examined for skeletal malformations and variations.

There were no treatment-related maternal deaths. No dams aborted. One female, at 250.0 mg/kg/day, delivered early, and was removed from study. A total of 21-24 litters were examined in each dose group. There were no statistically significant differences among groups for gestational maternal body weights or weight gain, or for food consumption. Treatment-related clinical signs, observed only at 500.0 mg/kg/day, included hypoactivity, ataxia and audible respiration; clinical signs with significantly increased incidence at 500.0 mg/kg/day included ocular discharge and perocular encrustation. At the gd 21 sacrifice there were no effects of treatment on maternal body weight or gestational weight gain (absolute or corrected), or on gravid uterine

weight. Liver weights (absolute and relative) were significantly increased at 500.0 mg/kg/day. Gestational parameters, including number of ovarian corpora lutea, total, viable and nonviable implantations per litter, and sex ratio were unaffected by treatment. Fetal body weights per litter (all fetuses, males or females) were significantly reduced at 500.0 mg/kg/day.

There was no significant increase in the incidence of malformations (individual, pooled external, visceral, skeletal or total) in any treatment group relative to controls. There were no treatment-related differences among groups for individual external variations or for pooled external, visceral, skeletal or total variations. One visceral variation, dilated lateral ventricles on the brain with no tissue compression, exhibited an increased incidence at 500.0 mg/kg/day. Twenty-six fetal skeletal variations (out of 94 observed) exhibited significantly different incidences at 500.0 mg/kg/day relative to those in controls; 19 of these were significant increases in incidence and seven (7) were significant reductions in incidence (almost all of the reductions were in incidence of poorly ossified skeletal districts since the incidences of these same districts, unossified, were increased). In addition, there were skeletal variations with increased incidences at 250.0 mg/kg/day, indicative of minimal fetotoxicity.

Administration of 2-ethylhexanoic acid by gavage to Fischer 344 rats during organogenesis resulted in evidence of maternal toxicity at 500.0 mg/kg/day and consistent evidence of fetotoxicity at 500.0 mg/kg/day. Slight fetotoxicity (reduced ossification in skeletal districts unaccompanied by any other indications of fetotoxicity) was observed at 250.0 mg/kg/day. No embryotoxicity or teratogenicity was observed at any dosage employed, including that which produced maternal toxicity. The "no observable effect level" (NOEL) for maternal toxicity was 250.0 mg/kg/day, and the NOEL for developmental toxicity was 100.0 mg/kg/day.

#### OBJECTIVES

The present study was designed to evaluate the potential of 2-ethylhexanoic acid to produce maternal and developmental toxicity (including teratogenicity) when administered by gavage (oral intubation) during organogenesis in Fischer 344 rats.

#### MATERIALS AND METHODS

##### Test Chemical, Dosage Formulations and Analyses

The test chemical, 2-ethylhexanoic acid (butylethylacetic acid; CAS No. 149-57-5) was received from Union Carbide Corporation, Texas City, TX, Lot No. TK 9303 (Order Number D-4859) on May 21, 1987 and was assigned the Bushy Run Research Center (BRRC) Sample No. 50-269 A-E. The material was a clear, nonviscous liquid. The accompanying analytical sheet indicated a purity of 99.4%.

Standard solutions were prepared as follows. A standard stock solution (1.0 mg/ml) was prepared by weighing 50 mg of test chemical and diluting to volume with propanol. Standards ranging from 50 to 150 ng/μl were prepared by diluting the stock solution with propanol. For each analysis session, a

standard curve was generated by injecting 1.0  $\mu$ l aliquots of each standard solution into the gas chromatograph for analysis. The instrument used was a Hewlett-Packard 5880 Gas Chromatograph with a flame ionization detector. The column was a DB-1 fused Silica Capillary Column, 30 m, 1.0  $\mu$ m film thickness. The carrier gas was ultra high purity helium and the column flow rate was ~2.0 ml/min. Dosing formulations were prepared by weighing the amount of test chemical into a volumetric flask and diluting to volume with certified corn oil (Mazola®, Best Foods, Inc., CPC International, CAS No. 8001-30-7). The resulting solutions were mixed by inversion. A 1.0 ml aliquot of each dosing solution was appropriately diluted with propanol, and a 1.0  $\mu$ l sample of each diluted solution was injected into the gas chromatograph for analysis. The volume administered was 2.0 ml/kg based on the body weight of each study female on gestational day (gd) 6. Control group animals received the vehicle (certified corn oil) at 2.0 ml/kg based on the gd 6 body weight.

The dosing solutions as prepared were homogeneous and stable for at least 21 days. Therefore, these dosing formulations were prepared once and analyzed prior to the onset of the dosing period. The doses were 0.0, 100.0, 250.0 and 500.0 mg/kg/day (0.0, 50.0, 125.0 and 250.0 mg/ml, respectively). (See Appendix 1 for details of the analytical procedures and results.)

#### Animals and Animal Husbandry

Virgin male (203) and female (208) Fischer 344 inbred albino rats [CDF® (F344)/Crl/Br] (males' date of birth September 21, 1987, 70 days old upon arrival; approximately 175-200 g and females' date of birth September 28, 1987, 63 days old upon arrival; approximately 130-150 g) were received from Charles River Breeding Laboratories, Inc., Kingston, NY, on November 30, 1987. All animals were quarantined for two weeks in animal room 103, during which time representative animals were subjected to fecal sampling, histologic examination of selected organs and to serum viral antibody examination. Quality control results indicated that the animals were suitable for use. Rats were housed in stainless steel wire-mesh cages (22.5 cm x 15.5 cm x 18 cm high for females during acclimation and on study, 22.5 X 31.0 x 18.0 cm high for males during acclimation and during mating) with food (Prolab Certified Ground Rodent Chow®, RMH-3200, Batch No. 7261 W1 and 7321 W2, Agway, Inc., St. Marys, OH) and water (Municipal Authority of Westmoreland County, Greensburg, PA) available ad libitum. Females and males were housed one-two per cage per sex during quarantine. All animals were assigned a unique number and received a stainless steel "Monel" ear tag (Gey Band and Tag Co., Morristown, PA).

Deotized Animal Cage Board® (Shepherd Specialty Papers, Inc., Kalamazoo, MI) was placed beneath the cages and changed frequently. Animals were kept on a 12-hour photoperiod and room temperatures and humidity were recorded continuously (Cole-Parmer Hygrothermograph® Seven-Day Continuous Recorder, Model #8368-00, Cole-Parmer Instrument Company, Chicago, IL). Temperature was maintained at 69-72°F, and relative humidity was maintained at 45-65% throughout the study.

Rats were mated 1:1 (one male:one female) in stainless steel wire-mesh cages (22.5 cm x 31 cm x 18 cm high) and the paperboard beneath the cages was checked twice daily for dropped copulation plugs (Hafez, 1970). Each male was used only once in this study. Successfully mated (plug-positive) females weighing 147-174 g were housed singly in animal room 103 for the duration of

the study. The day a copulation plug was found was designated gestational day (gd) 0 (Hafez, 1970). Twenty-five (25) plug-positive females were assigned to each experimental group by a randomization procedure stratified by body weight such that all groups were equivalent in both mean body weight and body weight range on gd 0. The mating period for these animals was December 13 through December 17, 1987 (gd 0 was December 14 through December 17, 1987).

#### Treatment

Timed-pregnant Fischer 344 dams were dosed daily with 2-ethylhexanoic acid in vehicle or vehicle alone (certified corn oil) on gd 6 through 15. All treatments were administered by gavage using a 16 gauge straight stainless steel dosing tube 3.0 inches long (Perfektum®, Popper and Sons, Inc., New Hyde Park, NY) attached to a 1.0 cc syringe (Becton-Dickinson). A dose volume of 2.0 ml/kg body weight was employed based on the gd 6 body weight of each animal on study. The doses employed were 0.0, 100.0, 250.0 or 500.0 mg/kg/day based on results from dose range-finding studies also performed on timed-pregnant Fischer 344 rats (Appendices 6 and 7).

All females on study were weighed on gd 0, 6 (prior to onset of dosing), 12, 15 (during the dosing period), 18 and 21. Food consumption was measured for the intervals gd 0-3, 3-6, 6-9, 9-12, 12-15, 15-18 and gd 18-21. All females were examined daily for clinical signs of toxicity. The treatment period for all study females was gd 6 through 15, December 20, 1987 through January 1, 1988.

#### Thoracotomy and Maternal and Fetal Examinations

All surviving study females were sacrificed on gd 21 by carbon dioxide asphyxiation. The sacrifice period was January 4 through January 7, 1988. The maternal body cavities were opened by midline thoracotomy. The gravid uterus, ovaries (including corpora lutea), cervix, vagina and abdominal and thoracic cavities were examined grossly. Ovarian corpora lutea of pregnancy were counted. Maternal liver and uterine weights were determined. Maternal livers were fixed in buffered neutral 10% formalin for possible subsequent histopathologic examination. The uterus was externally examined for signs of hemorrhage, removed from the abdominal cavity and dissected longitudinally to expose the contents. All live and dead fetuses and resorption sites were noted and recorded. Uteri from females that appeared nongravid were placed in a 10% ammonium sulfide solution for detection of early resorptions (Salewski, 1964).

All live fetuses were weighed and sexed. All fetuses were examined for external malformations including cleft palate, and variations. One-half of the fetuses (even numbered fetuses from litters with an even number of live fetuses, odd numbered fetuses from litters with an odd number of live fetuses) in each litter were examined for thoracic and abdominal visceral abnormalities by modification of methods described by Staples (1974). These fetuses were decapitated and their heads were fixed in Bouin's solution for examination of craniofacial structures by sectioning methods modified from Wilson (1965; 1973) and van Julsingha and Bennett (1977). The remaining (intact) fetuses in each litter were eviscerated, fixed in ethanol, and then processed for skeletal staining with alizarin red S (Crary, 1962; Peltzer and Schardein, 1966), and examined for skeletal malformations and variations. The decapitated fetuses were also processed for staining but were not examined.

### Statistical Analyses

The unit of comparison was the pregnant female or the litter (Weil, 1970). Results of the quantitative continuous variables (e.g., maternal body weights, organ weights, etc.) were intercompared for the three 2-ethylhexanoic acid-exposed groups and the vehicle control group by use of Levene's test for equal variances (Levene, 1960), analysis of variance (ANOVA), and t-tests with Bonferroni probabilities for pairwise comparisons. When Levene's test indicated homogeneous variances and the ANOVA was significant, the pooled t-test was used. When Levene's test indicated heterogeneous variances, all groups were compared by an ANOVA for unequal variances (Brown and Forsythe, 1974) followed, when necessary, by the separate variance t-test.

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

### Personnel

The evaluation of 2-ethylhexanoic acid for developmental toxicity in Fischer 344 rats was conducted at Bushy Run Research Center (BRRC), Export, PA under contract to the Chemical Manufacturers Association, Washington, DC, Mr. H. J. Sauer, Sponsor Representative. The BRRC personnel indicated below contributed to the completion of this study.

Dr. R. W. Tyl served as Study Director. Developmental toxicology personnel included T. R. Brownfield, B. L. Butler, M. A. Copeman, D. L. Fait (Study Leader for the second range-finding study), L. C. Fisher, L. J. Fosnight (Study Leader for the definitive study), M. F. Kubena (Study Leader for the first range-finding study), T. A. Rebeck and D. J. Tarasi. Analytical personnel included Dr. J. P. Van Miller and M. A. Vrbancic. Quality Assurance personnel included L. J. Calisti, J. R. Bernard and J. H. Coleman. Animal care was performed by R. R. Altman.

The final report was prepared by Dr. R. W. Tyl with assistance from L. C. Fisher on data compilation and statistical analyses. The individual scientist reports were prepared and signed by the author(s).

The protocol and two (2) amendments detailing the design and conduct of the study are presented in Appendix 5.

### Storage of Records

All original data sheets for the present study are stored in the BRRC Archives along with all biological samples collected during the course of the study which remain the responsibility of BRRC. Work sheets and computer printouts which were generated in the statistical analysis of data are stored in the BRRC Archives. Copies of this report will be filed with the BRRC Archives as well as with The Chemical Manufacturers Association, Washington, DC.

### Compliance

All records, data and reports will be maintained in storage for ten (10) years or for as long as the quality of the preparation affords evaluation, whichever is less. This study was performed according to Environmental Protection Agency (EPA) Good Laboratory Practices (EPA, 1983), and EPA TSCA Testing Guidelines (1985; 1987), and the EPA Final Test Rule for 2-Ethylhexanoic Acid (EPA, 1986).

### RESULTS

Analysis of dosing formulations indicated that all formulations were within 98.4-105.6% of target (Table 1) prior to dosing period. The dosing solutions were homogeneous and stable for at least 21 days (see Appendix 1 for details).

The distribution and fate of all plug-positive rats on study are presented in Table 2. No females aborted. One female, at 250.0 mg/kg/day, delivered early (on gd 20), was euthanized, and removed from study. Her data were eliminated from the results. Pregnancy rate was approximately equivalent for all dose groups except for a slight, nonsignificant reduction at 500.0 mg/kg/day. All litters had one or more live fetuses at scheduled sacrifice. A total of 21 to 24 litters were examined in each group.

Periodic maternal body weights and weight gain (Table 3) exhibited no significant differences across groups. Clinical observations of the dams were recorded daily (Table 4). Clinical signs which were observed only at 500.0 mg/kg/day included hypoactivity, ataxia and audible respiration. There was also a significantly increased incidence of ocular discharge and periorbital encrustation at 500.0 mg/kg/day. Signs at lower doses did not appear to be treatment related. Food consumption during gestation expressed as grams/dam/day was unaffected by treatment (Table 5). Individual maternal in-life data are presented in Appendix 2.

There were no treatment-related necropsy findings of the dams at sacrifice (Table 6). At sacrifice on gd 21, there were no treatment-related differences in maternal terminal body weight, corrected terminal body weight (body weight at sacrifice minus gravid uterine weight), corrected body weight change (gestational weight gain minus gravid uterine weight) or in gravid uterine weight. Liver weight (absolute and relative to corrected body weight) was significantly increased at 500.0 mg/kg/day (Table 7). Individual maternal necropsy data are presented in Appendix 3.

Gestational parameters are presented in Table 8. There was no effect of treatment on the number of ovarian corpora lutea, total, viable or nonviable (early and late resorptions and dead fetuses) implantations per litter or on sex ratio (percent males). Percent preimplantation and postimplantation loss were equivalent across groups. (Individual maternal laparotomy data are presented in Appendix 3.) Fetal body weights (all fetuses, male or female) per litter were significantly reduced at 500.0 mg/kg/day. However, these findings may be confounded by the slightly larger mean litter size (9.3 viable implants per litter versus 8.9 viable implants per litter in the control group) which

is typically associated with reduced individual fetal weights per litter. Individual fetal body weights are presented in Appendix 4A (with external findings).

The results of fetal evaluations are summarized in Table 9 for malformations and Table 10 for variations. (Malformations and variations by individual fetuses and litters are presented in Appendix 4.)

There were no significant differences in the incidence of individual malformations, malformations by category (external, visceral including craniofacial or skeletal) or of total malformations among all groups (Table 9).

There were no significant differences among groups in the incidence of individual fetal external variations. One visceral variation, dilated lateral ventricles of the brain with no tissue compression, exhibited a significantly increased incidence at 500.0 mg/kg/day relative to that in controls. A total of 94 different types of fetal skeletal variations were observed. Of these, 26 findings exhibited incidences at 500.0 mg/kg/day which differed significantly from the vehicle control group. Those which exhibited significantly different incidences at 500.0 mg/kg/day included: statistically significant increases in the incidence of unossified cervical centra numbers 5 and 6, of unossified anterior arch of the atlas, bilobed thoracic centra numbers 1, 2, 3, 4, 12 and 13, of extra fourteenth thoracic centrum and arches, and of poorly ossified thoracic centrum number 1. Also, there were significant increases in the incidence of a reduced number of ossified caudal segments (five or less), of some (1-4) and majority (5-7) of the proximal phalanges of the forelimb, unossified, of all proximal phalanges of the hindlimb unossified, some (1-5) metatarsals of the hindlimb unossified, of poorly ossified sternbrae numbers 2 and 6, and of bilobed sternbra number 5. There were also statistically significant reductions in the incidence of the following skeletal variations at 500.0 mg/kg/day: poorly ossified cervical centra No. 1, 2, 3 and/or four, of poorly ossified cervical centrum 5, poorly ossified anterior arch of the atlas, some (1-4) and majority (5-7) of the proximal phalanges of the hindlimb poorly ossified, and some and majority of the proximal phalanges of the hindlimb unossified. The significant reductions in incidence of indications of reduced ossification for most of the above skeletal variations were due to the significant increases in the incidences of no observable ossification (designated unossified) in these same limb elements.

Four (4) of the skeletal findings also exhibited statistically significantly different incidences at 250.0 mg/kg/day relative to those in controls. These were significant increases in the incidence of unossified anterior arch of the atlas (also observed at 500.0 mg/kg/day), of some (1-4) proximal phalanges of the forelimb unossified (also observed at 500.0 mg/kg/day), and of all proximal phalanges of the hindlimb unossified (also observed at 500.0 mg/kg/day), and therefore a significant reduction in the incidence of some (1-4) proximal phalanges of the hindlimb unossified (also observed at 500.0 mg/kg/day). There were no treatment-related increases in the incidence of variations by category (external, visceral including craniofacial, or skeletal) or of total variations (Table 10).

### DISCUSSION

2-Ethylhexanoic acid, administered by gavage during organogenesis in Fischer 344 rats, produced indications of maternal toxicity, including clinical signs of toxicity and increased absolute and relative liver weight at 500.0 mg/kg/day. The finding of increased liver weight (absolute and relative) at sacrifice does not appear to be due to changes in body weight since terminal body weights were equivalent across all groups. This finding may be due to hepatic toxicity and/or to induction of metabolizing enzymes which can result in increased hepatic mass (Gonney, 1967). Fetotoxicity was observed at 500.0 mg/kg/day, including reduced fetal body weights and consistent indications of reduced ossification in those skeletal districts identified by Aliverti *et al.* (1979) as indicative of toxicity in the gd 21 rat fetus in teratologic investigations. At 250.0 mg/kg/day, there were indications of reduced ossification in fetal skeletal fore- and hindlimbs and in the first cervical arch (the atlas) in the absence of any other indications of fetotoxicity.

Dilation of lateral ventricles of the brain with tissue compression (a visceral malformation) was observed in two fetuses (in two litters) at 0.0 mg/kg/day, in one fetus each at 100.0 and 250.0 mg/kg/day and in six fetuses (in six litters) at 500.0 mg/kg/day with no pairwise comparisons statistically significant (Table 9). Dilation of lateral ventricles of the brain with no tissue compression (a visceral variation) was observed in three fetuses (in three litters) at 0.0 mg/kg/day, in seven fetuses (in five litters) at 100.0 mg/kg/day, in ten fetuses (in eight litters) at 250.0 mg/kg/day and in 21 fetuses (in 15 litters) at 500.0 mg/kg/day, with the incidence at 500.0 mg/kg/day statistically significantly increased over that in the control group (Table 10). Dilation of lateral ventricles without tissue compression is a common finding in term fetuses, associated with reduced fetal body weight and indications of reduced ossification in the fetal skeleton and is consistent with delayed development, interpreted as fetotoxicity. There is usually no association of this variation with the malformation involving dilation of lateral ventricles with tissue compression. This latter malformation may imply postnatal alterations in cerebral structure and/or functioning and did not exhibit a significantly increased incidence in this study.

### CONCLUSIONS

Administration of 2-ethylhexanoic acid by gavage to timed-pregnant Fischer 344 rats during organogenesis at 0.0, 100.0, 250.0 or 500.0 mg/kg/day resulted in maternal toxicity at 500.0 mg/kg/day (clinical signs of toxicity and increased absolute and relative liver weight), and fetotoxicity (reduced fetal body weights and consistent indications of reduced skeletal ossification) at 500.0 mg/kg/day. There was slight fetotoxicity (reduced skeletal ossification) at 250.0 mg/kg/day. There was no treatment-related increased incidence of malformations at any dosage employed. The "no observable effect level" (NOEL) for maternal toxicity was 250.0 mg/kg/day, and the NOEL for developmental toxicity was 100.0 mg/kg/day.



REFERENCES

- Aliverti, V., Bonanomi, L., Giavini, E. Leone, V. G. and Mariani, L. The extent of fetal ossification as an index of delayed development in teratogenic studies of the rat. *Teratology* 20:237-242 (1979).
- Brown, M. B. and Forsythe, A. B. The small sample behavior of some statistics which test the equality of several means. *Technometrics* 16:129-132 (1974).
- Conney, A. H. Pharmacological implications of microsomal enzyme induction. *Pharmacol. Reviews* 19:327-336 (1967).
- Crary, D. D. Modified benzyl alcohol clearing of alizarin-stained specimens without loss of flexibility. *Stain Technology* 37:124-125 (1962).
- Environmental Protection Agency (EPA) Part IV. Environmental Protection Agency Toxic Substances Control; Good Laboratory Practice Standards; Final Rule. *Federal Register* 48(230):53922-53944 (1983).
- Environmental Protection Agency (EPA) 40 CFR. Toxic Substances Control Act Test Guidelines; Final Rule. Part 798.4900 Developmental Toxicity Study. *Federal Register* 50(188):39433-39434 (September 27, 1985).
- Environmental Protection Agency (EPA). 40 CFR Parts 795 and 799. 2-Ethylhexanoic Acid; Final Test Rule. *Federal Register* 51(215):40318-40330 (November 6, 1986).
- Environmental Protection Agency (EPA) 40 CFR. Revision of TSCA Test Guidelines; Final Rule. Part 798.4900 amended Developmental Toxicity Study. *Federal Register* 52(97):19077-19078 (May 21, 1987).
- Hafez, E. S. E. (editor). Reproduction and Breeding Techniques for Laboratory Animals. Lea and Febiger, Philadelphia (1970).
- Levene, H. Robust tests for equality of variance. In: Contributions to Probability and Statistics (I. Olkin et al., Editor). Stanford University Press, Stanford, CA, pp. 278-292 (1960).
- Peltzer, M.A. and Schardein, J. L. A convenient method for processing fetuses for skeletal staining. *Stain Technology* 41:300-302 (1966).
- Salewski, E. Färbemethode Zum Makroskopischen Nachweis Von Implantations-Stellen am Uterus Der Ratte. Naunyn-Schmiedebergs, *Arch. Exp. Pathol. Pharmacol.* 247:367 (1964).
- Sokal, R. R. and Rohlf, F. J. Biometry, W. H. Freeman and Co., San Francisco, pp. 369-371, 299-340, 370-372, 589-595 (1969).
- Staples, R. E. Detection of visceral alterations in mammalian fetuses. *Teratology*, 9:A-37 (1974).

REFERENCES  
(Continued)

- Van Julsingha, E. B. and Bennett, C. G. A dissecting procedure for the detection of anomalies in the rabbit foetal head. In: Methods in Prenatal Toxicology (D. Neubert, H. J. Merker, and T. E. Kwasigroch, Editors). PSG Publishing Company, Inc., Littleton, Massachusetts, pp. 126-144 (1977).
- Weil, C. S. Selection of the valid number of sampling units and a consideration of their combination in toxicological studies involving reproduction, teratogenesis or carcinogenesis. Fd. Cosmet. Toxicol. 8:177-182 (1970).
- Wilson, J. G. Embryological considerations in teratology. In: Teratology Principles and Techniques (J. G. Wilson and J. Warkany, Editors). The University of Chicago Press, pp. 251-277 (1965).
- Wilson, J. G. Environment and Birth Defects. Academic Press, NY (1973).

PATH/esk/1339P-1  
06-08-88

Table 1  
Analyses of Dosing Formulations

| <u>Target Concentrations</u> |                             | <u>Analytical Concentrations<sup>b</sup></u> |                        |
|------------------------------|-----------------------------|--|------------------------|
| <u>in mg/kg/day</u>          | <u>in mg/ml<sup>a</sup></u> | <u>Concentration<br/>in mg/ml</u>            | <u>% of<br/>Target</u> |
| 500.0                        | 250.0                       | 246.0  | 98.4                   |
| 250.0                        | 125.0                       | 132.0  | 105.6                  |
| 100.0                        | 50.0                        | 50.4   | 100.8                  |
| 0.0                          | 0.0                         | <MDL <sup>c</sup>                            | -                      |

<sup>a</sup> Dosing volume was 2.0 ml/kg and the vehicle was certified corn oil.

<sup>b</sup> Dosing solutions were formulated and analyzed prior to use; the dosing solutions were homogeneous and stable for at least 21 days.

<sup>c</sup> Less than the minimum detection limit of 0.01 mg/ml.

PATH/esk/1339P-1  
06-08-88

TABLE B  
DEVELOPMENTAL TOXICITY EVALUATION OF 2-ETHYLHEXANOIC ACID  
ADMINISTERED BY GAVAGE TO FISCHER 344 RATS  
SUMMARY OF MEAN FETAL DATA AT TIME OF LAPAROTOMY

| GROUP (MG/KG/DAY):                        | 0.0   | 100.0 | 250.0 | 500.0 |
|---|-------|-------|-------|-------|
| CORPORA LUTEA                             |       |       |       |       |
| MEAN                                      | 11.8  | 11.9  | 12.5  | 12.1  |
| S.D.                                      | 1.78  | 2.15  | 2.37  | 1.35  |
| N   | 23    | 24    | 22    | 21    |
| TOTAL IMPLANTS                            |       |       |       |       |
| MEAN                                      | 8.9   | 7.7   | 8.7   | 9.7   |
| S.D.                                      | 3.13  | 3.95  | 3.31  | 2.73  |
| N   | 23    | 24    | 22    | 21    |
| PERCENT PREIMPLANTATION LOSS <sup>a</sup> |       |       |       |       |
| MEAN                                      | 26.0  | 36.0  | 29.4  | 20.7  |
| S.D.                                      | 22.57 | 30.51 | 28.11 | 18.26 |
| N   | 23    | 24    | 22    | 21    |
| VIABLE IMPLANTS                           |       |       |       |       |
| MEAN                                      | 8.4   | 7.5   | 8.4   | 9.3   |
| S.D.                                      | 2.92  | 3.80  | 3.29  | 2.92  |
| N   | 23    | 24    | 22    | 21    |
| NON-VIABLE IMPLANTS                       |       |       |       |       |
| MEAN                                      | 0.5   | 0.2   | 0.3   | 0.4   |
| S.D.                                      | 0.73  | 0.53  | 0.57  | 0.74  |
| N   | 23    | 24    | 22    | 21    |
| EARLY RESORPTIONS                         |       |       |       |       |
| MEAN                                      | 0.5   | 0.2   | 0.3   | 0.4   |
| S.D.                                      | 0.73  | 0.38  | 0.55  | 0.74  |
| N   | 23    | 24    | 22    | 21    |
| LATE RESORPTIONS                          |       |       |       |       |
| MEAN                                      | 0.0   | 0.0   | 0.0   | 0.0   |
| S.D.                                      | 0.00  | 0.00  | 0.21  | 0.00  |
| N   | 23    | 24    | 22    | 21    |
| DEAD FETUSES                              |       |       |       |       |
| MEAN                                      | 0.0   | 0.1   | 0.0   | 0.0   |
| S.D.                                      | 0.21  | 0.28  | 0.00  | 0.00  |
| N   | 23    | 24    | 22    | 21    |
| PERCENT LIVE FETUSES                      |       |       |       |       |
| MEAN                                      | 94.8  | 97.4  | 96.4  | 95.4  |
| S.D.                                      | 7.50  | 5.39  | 6.50  | 9.42  |
| N   | 23    | 24    | 22    | 21    |

TABLE 6 (Continued)  
DEVELOPMENTAL TOXICITY EVALUATION OF 2-ETHYLHEXANOIC ACID  
ADMINISTERED BY GAVAGE TO FISCHER 344 RATS  
SUMMARY OF MEAN FETAL DATA AT TIME OF LAPAROTOMY

| GROUP (MG/KG/DAY):                    | 0.0             | 100.0           | 250.0           | 500.0   |
|---------------------------------------|-----------------|-----------------|-----------------|---------|
| SEX RATIO (% MALE FETUSES)            |                 |                 |                 |         |
| MEAN                                  | 49.2            | 53.3            | 43.4            | 55.2    |
| S.D.                                  | 17.86           | 21.71           | 16.92           | 19.01   |
| N                                     | 23              | 24              | 22              | 21      |
| FETAL BODY WEIGHTS PER LITTER (GRAMS) |                 |                 |                 |         |
| ALL FETUSES                           |                 |                 |                 |         |
| MEAN                                  | 4.41            | 4.50            | 4.36            | 4.06*** |
| S.D.                                  | 0.24            | 0.38            | 0.28            | 0.18    |
| N                                     | 23              | 24              | 22              | 21      |
| MALE FETUSES                          |                 |                 |                 |         |
| MEAN                                  | 4.54            | 4.62            | 4.49            | 4.18*** |
| S.D.                                  | 0.18            | 0.40            | 0.23            | 0.16    |
| N                                     | 22 <sup>b</sup> | 23 <sup>b</sup> | 21 <sup>b</sup> | 21      |
| FEMALE FETUSES                        |                 |                 |                 |         |
| MEAN                                  | 4.25            | 4.24            | 4.24            | 3.91*** |
| S.D.                                  | 0.25            | 0.28            | 0.31            | 0.17    |
| N                                     | 23              | 22 <sup>c</sup> | 22              | 21      |

\*\*\* p < 0.001 compared to control.  
 a Percent preimplantation loss = [(corpora lutea - total implants)/corpora lutea] X 100.  
 b The N is reduced because one litter contained only female fetuses.  
 c The N is reduced because of litters containing only male fetuses.

TABLE 9  
DEVELOPMENTAL TOXICITY EVALUATION OF 2-ETHYLHEXANOIC ACID  
ADMINISTERED BY GAVAGE TO FISCHER 344 RATS  
MALFORMATIONS OBSERVED IN FETUSES AND LITTERS<sup>a</sup>

| DOSE GROUP (MG/KG/DAY):                 | F E T U S E S |     |     |     | L I T T E R S |     |     |     |
|---|---------------|-----|-----|-----|---------------|-----|-----|-----|
|   | 0             | 100 | 250 | 500 | 0             | 100 | 250 | 500 |
| NUMBER EXAMINED EXTERNALLY <sup>b</sup> | 193           | 179 | 184 | 195 | 23            | 24  | 22  | 21  |
| CLEFT PALATE                            | 1             | 0   | 0   | 0   | 1             | 0   | 0   | 0   |
|   | 0.5           | 0.0 | 0.0 | 0.0 | 4.3           | 0.0 | 0.0 | 0.0 |

<sup>a</sup>None significantly different from control ( 0.0 MG/KG/DAY )  
<sup>b</sup>See footnotes on last page of table.

TABLE 9 (Continued)  
DEVELOPMENTAL TOXICITY EVALUATION OF 2-ETHYLHEXANOIC ACID  
ADMINISTERED BY GAVAGE TO FISCHER 344 RATS  
MALFORMATIONS OBSERVED IN FETUSES AND LITTERS<sup>a</sup>

|  | F E T U S E S |     |     |     | L I T T E R S |     |     |      |
|--|---------------|-----|-----|-----|---------------|-----|-----|------|
|  | 0             | 100 | 250 | 500 | 0             | 100 | 250 | 500  |
| NUMBER EXAMINED VISCERALLY <sup>c</sup>      | 100           | 95  | 97  | 104 | 23            | 24  | 22  | 21   |
| CLEFT PALATE                                 | 1             | 0   | 0   | 0   | 1             | 0   | 0   | 0    |
|  | 1.0           | 0.0 | 0.0 | 0.0 | 4.3           | 0.0 | 0.0 | 0.0  |
| LATERAL VENTRICLE DILATED - TISSUE DEPRESSED | 2             | 1   | 1   | 6   | 2             | 1   | 1   | 6    |
|  | 2.0           | 1.1 | 1.0 | 5.8 | 8.7           | 4.2 | 4.5 | 28.6 |
| HYDROURETER - UNILATERAL                     | 0             | 0   | 1   | 0   | 0             | 0   | 1   | 0    |
|  | 0.0           | 0.0 | 1.0 | 0.0 | 0.0           | 0.0 | 4.5 | 0.0  |
| EPIDIDYMIS ABSENT - BILATERAL                | 0             | 1   | 0   | 0   | 0             | 1   | 0   | 0    |
|  | 0.0           | 1.1 | 0.0 | 0.0 | 0.0           | 4.2 | 0.0 | 0.0  |
| EPIDIDYMIS ABSENT - UNILATERAL               | 0             | 1   | 0   | 0   | 0             | 1   | 0   | 0    |
|  | 0.0           | 1.1 | 0.0 | 0.0 | 0.0           | 4.2 | 0.0 | 0.0  |

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

TABLE 9 (Continued)  
DEVELOPMENTAL TOXICITY EVALUATION OF 2-ETHYLHEXANOIC ACID  
ADMINISTERED BY GAVAGE TO FISCHER 344 RATS  
MALFORMATIONS OBSERVED IN FETUSES AND LITTERS<sup>a</sup>

| NUMBER EXAMINED SKELETALLY <sup>d</sup> | DOSE GROUP (MG/KG/DAY): |     |     |     |  | F E T U S E S |    |    |    |  | L I T T E R S |     |     |     |  |    |    |    |    |
|---|-------------------------|-----|-----|-----|--|---------------|----|----|----|--|---------------|-----|-----|-----|--|----|----|----|----|
|   | 0                       | 100 | 250 | 500 |  | 93            | 84 | 87 | 91 |  | 0             | 100 | 250 | 500 |  | 22 | 22 | 21 | 21 |
| LUMBAR ARCH #3 MISSING                  | 0.0                     | 1.2 | 0.0 | 0.0 |  | 0             | 1  | 0  | 0  |  | 0.0           | 4.5 | 0.0 | 0.0 |  | 0  | 1  | 0  | 0  |
| 13TH RIB - FORKED                       | 0.0                     | 1.2 | 0.0 | 0.0 |  | 0             | 1  | 0  | 0  |  | 0.0           | 4.5 | 0.0 | 0.0 |  | 0  | 1  | 0  | 0  |
| PROXIMAL PHALANGES - HINDLIMB - MISSING | 0.0                     | 1.2 | 2.3 | 0.0 |  | 0             | 1  | 2  | 0  |  | 0.0           | 4.5 | 9.5 | 0.0 |  | 0  | 1  | 2  | 0  |
| DISTAL PHALANGES - HINDLIMB - MISSING   | 0.0                     | 1.2 | 2.3 | 0.0 |  | 0             | 1  | 2  | 0  |  | 0.0           | 4.5 | 9.5 | 0.0 |  | 0  | 1  | 2  | 0  |

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

TABLE 9 (Continued)  
 DEVELOPMENTAL TOXICITY EVALUATION OF 2-ETHYLHEXANOIC ACID  
 ADMINISTERED BY GAVAGE TO FISCHER 344 RATS  
 MALFORMATIONS OBSERVED IN FETUSES AND LITTERS<sup>a</sup>

|  | F E T U S E S |     |     |     | L I T T E R S |      |      |      |
|--|---------------|-----|-----|-----|---------------|------|------|------|
|  | 0             | 100 | 250 | 500 | 0             | 100  | 250  | 500  |
| DOSE GROUP (MG/KG/DAY):                | 0             | 100 | 250 | 500 | 0             | 100  | 250  | 500  |
| TOTAL MALFORMATIONS                    | 1             | 0   | 0   | 0   | 1             | 0    | 0    | 0    |
| NUMBER WITH EXTERNAL MALFORMATIONS     | 0.5           | 0.0 | 0.0 | 0.0 | 4.3           | 0.0  | 0.0  | 0.0  |
| PERCENT WITH EXTERNAL MALFORMATIONS    | 2.0           | 3.2 | 2.1 | 5.8 | 8.7           | 8.3  | 9.1  | 28.6 |
| NUMBER WITH SOFT TISSUE MALFORMATIONS  | 0             | 2   | 2   | 0   | 0             | 2    | 2    | 0    |
| PERCENT WITH SOFT TISSUE MALFORMATIONS | 0.0           | 2.4 | 2.3 | 0.0 | 0.0           | 9.1  | 9.5  | 0.0  |
| TOTAL NUMBER WITH MALFORMATIONS        | 2             | 5   | 4   | 6   | 2             | 4    | 4    | 6    |
| TOTAL PERCENT WITH MALFORMATIONS       | 1.0           | 2.8 | 2.2 | 3.1 | 8.7           | 16.7 | 18.2 | 28.6 |

None significantly different from control ( .0 MG/KG/DAY )

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

<sup>b</sup> All fetuses were examined externally.

<sup>c</sup> Approximately 50% of each litter were examined visceraally (Staples, 1974), and for soft tissue craniofacial defects (Wilson, 1965; van Juislingha and Bennett, 1977).

<sup>d</sup> Approximately 50% of each litter were examined for skeletal defects after staining with Alizarin Red S.

TABLE 10  
DEVELOPMENTAL TOXICITY EVALUATION OF 2-ETHYLHEXANOIC ACID  
ADMINISTERED BY GAVAGE TO FISCHER 344 RATS  
VARIATIONS OBSERVED IN FETUSES AND LITTERS<sup>a</sup>

|   | DOSE GROUP (MG/KG/DAY): |     |     |     | F E T U S E S |      |      |      | L I T T E R S |      |      |      |
|---|-------------------------|-----|-----|-----|---------------|------|------|------|---------------|------|------|------|
|   | 0                       | 100 | 250 | 500 | 0             | 100  | 250  | 500  | 0             | 100  | 250  | 500  |
| NUMBER EXAMINED EXTERNALLY <sup>b</sup> | 193                     | 179 | 184 | 195 | 23            | 24   | 22   | 21   | 23            | 24   | 22   | 21   |
| ECCHYMOSIS - TRUNK                      | 23                      | 20  | 23  | 34  | 11.9          | 11.2 | 12.5 | 17.4 | 17            | 13   | 15   | 16   |
| ECCHYMOSIS - HEAD                       | 1                       | 1   | 4   | 0   | 0.5           | 0.6  | 2.2  | 0.0  | 4.3           | 4.2  | 18.2 | 0.0  |
| ECCHYMOSIS - EXTREMITIES                | 0                       | 1   | 0   | 0   | 0.0           | 0.6  | 0.0  | 0.0  | 0.0           | 4.2  | 0.0  | 0.0  |
|   |                         |     |     |     |               |      |      |      | 73.9          | 54.2 | 68.2 | 76.2 |

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

TABLE 10 (Continued)  
DEVELOPMENTAL TOXICITY EVALUATION OF 2-ETHYLHEXANOIC ACID  
ADMINISTERED BY GAVAGE TO FISCHER 344 RATS  
VARIATIONS OBSERVED IN FETUSES AND LITTERS

| DOSE GROUP (MG/KG/DAY):                   | F E T U S E S |      |      |      | L I T T E R S |      |      |      |      |
|---|---------------|------|------|------|---------------|------|------|------|------|
|   | 0             | 100  | 250  | 500  | 0             | 100  | 250  | 500  | 500  |
| NUMBER EXAMINED VISCERALLY <sup>c</sup>   | 100           | 95   | 97   | 104  | 23            | 24   | 22   | 21   | 21   |
| NASAL PASSAGES CONSTRICTED - BILATERAL    | 0             | 0    | 0    | 1    | 0             | 0    | 0    | 1    | 1    |
|   | 0.0           | 0.0  | 0.0  | 1.0  | 0.0           | 0.0  | 0.0  | 4.8  | 4.8  |
| LATERAL VENTRICLE DILATED - NO DEPRESSION | 3             | 7    | 10   | 21   | 3             | 5    | 8    | 15** | 15** |
|   | 3.0           | 7.4  | 10.3 | 20.2 | 13.0          | 20.8 | 36.4 | 71.4 | 71.4 |
| THIRD VENTRICLE DILATED - NO DEPRESSION   | 0             | 0    | 0    | 1    | 0             | 0    | 0    | 1    | 1    |
|   | 0.0           | 0.0  | 0.0  | 1.0  | 0.0           | 0.0  | 0.0  | 4.8  | 4.8  |
| FETAL ATELECTASIS                         | 21            | 20   | 17   | 39   | 16            | 11   | 11   | 19   | 19   |
|   | 21.0          | 21.1 | 17.5 | 37.5 | 69.6          | 45.8 | 50.0 | 90.5 | 90.5 |
| PARTIAL FETAL ATELECTASIS                 | 28            | 28   | 34   | 39   | 14            | 16   | 18   | 18   | 18   |
|   | 28.0          | 29.5 | 35.1 | 37.5 | 60.9          | 66.7 | 81.8 | 85.7 | 85.7 |
| LIVER - NODULE                            | 0             | 1    | 2    | 0    | 0             | 1    | 2    | 0    | 0    |
|   | 0.0           | 1.1  | 2.1  | 0.0  | 0.0           | 4.2  | 9.1  | 0.0  | 0.0  |
| STOMACH - NODULE                          | 0             | 0    | 1    | 0    | 0             | 0    | 1    | 0    | 0    |
|   | 0.0           | 0.0  | 1.0  | 0.0  | 0.0           | 0.0  | 4.5  | 0.0  | 0.0  |
| STOMACH EMPTY                             | 2             | 0    | 0    | 0    | 2             | 0    | 0    | 0    | 0    |
|   | 2.0           | 0.0  | 0.0  | 0.0  | 8.7           | 0.0  | 0.0  | 0.0  | 0.0  |
| DILATED RENAL PELVIS - UNILATERAL         | 0             | 0    | 3    | 3    | 0             | 0    | 2    | 3    | 3    |
|   | 0.0           | 0.0  | 3.1  | 2.9  | 0.0           | 0.0  | 9.1  | 14.3 | 14.3 |
| DILATED RENAL PELVIS - BILATERAL          | 2             | 1    | 1    | 0    | 2             | 1    | 1    | 0    | 0    |
|   | 2.0           | 1.1  | 1.0  | 0.0  | 8.7           | 4.2  | 4.5  | 0.0  | 0.0  |
| DILATED URETER - UNILATERAL               | 2             | 0    | 0    | 2    | 1             | 0    | 0    | 2    | 2    |
|   | 2.0           | 0.0  | 0.0  | 1.9  | 4.3           | 0.0  | 0.0  | 9.5  | 9.5  |
| DILATED URETERS - BILATERAL               | 0             | 1    | 0    | 1    | 0             | 1    | 0    | 1    | 1    |
|   | 0.0           | 1.1  | 0.0  | 1.0  | 0.0           | 4.2  | 0.0  | 4.8  | 4.8  |

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

TABLE 10 (Continued)  
 DEVELOPMENTAL TOXICITY EVALUATION OF 2-ETHYLHEXANOIC ACID  
 ADMINISTERED BY GAVAGE TO FISCHER 344 RATS  
 VARIATIONS OBSERVED IN FETUSES AND LITTERS

| DOSE GROUP (MG/KG/DAY):                              | F E T U S E S |       |       |       | L I T T E R S |       |       |       |
|--|---------------|-------|-------|-------|---------------|-------|-------|-------|
|  | 0             | 100   | 250   | 500   | 0             | 100   | 250   | 500   |
| NUMBER EXAMINED SKELETALLY                           | 93            | 84    | 87    | 91    | 22            | 22    | 21    | 21    |
| CERVICAL CENTRA #1, #2, #3 AND/OR #4 POORLY OSSIFIED | 51            | 48    | 44    | 9     | 22            | 20    | 18    | 7**   |
|  | 54.8          | 57.1  | 50.6  | 9.9   | 100.0         | 90.9  | 85.7  | 33.3  |
| CERVICAL CENTRA #1, #2, #3 AND/OR #4 UNOSSIFIED      | 93            | 84    | 87    | 91    | 22            | 22    | 21    | 21    |
|  | 100.0         | 100.0 | 100.0 | 100.0 | 100.0         | 100.0 | 100.0 | 100.0 |
| CERVICAL CENTRA #1, #2, #3 AND/OR #4 BILOBED         | 1             | 2     | 0     | 0     | 1             | 2     | 0     | 0     |
|  | 1.1           | 2.4   | 0.0   | 0.0   | 4.5           | 9.1   | 0.0   | 0.0   |
| CERVICAL CENTRUM #5 POORLY OSSIFIED                  | 52            | 49    | 61    | 28    | 22            | 22    | 20    | 15*   |
|  | 55.9          | 58.3  | 70.1  | 30.8  | 100.0         | 100.0 | 95.2  | 71.4  |
| CERVICAL CENTRUM #5 UNOSSIFIED                       | 10            | 6     | 12    | 61    | 8             | 6     | 10    | 21**  |
|  | 10.8          | 7.1   | 13.8  | 67.0  | 36.4          | 27.3  | 47.6  | 100.0 |
| CERVICAL CENTRUM #6 POORLY OSSIFIED                  | 53            | 48    | 58    | 60    | 22            | 22    | 20    | 21    |
|  | 57.0          | 57.1  | 66.7  | 65.9  | 100.0         | 100.0 | 95.2  | 100.0 |
| CERVICAL CENTRUM #6 UNOSSIFIED                       | 4             | 2     | 4     | 25    | 4             | 2     | 3     | 15**  |
|  | 4.3           | 2.4   | 4.6   | 27.5  | 18.2          | 9.1   | 14.3  | 71.4  |
| CERVICAL CENTRUM #6 BILOBED                          | 0             | 0     | 0     | 1     | 0             | 0     | 0     | 1     |
|  | 0.0           | 0.0   | 0.0   | 1.1   | 0.0           | 0.0   | 0.0   | 4.8   |
| CERVICAL CENTRUM #7 POORLY OSSIFIED                  | 33            | 31    | 33    | 60    | 18            | 18    | 17    | 20    |
|  | 35.5          | 36.9  | 37.9  | 65.9  | 81.8          | 81.8  | 81.0  | 95.2  |
| CERVICAL CENTRUM #7 UNOSSIFIED                       | 0             | 0     | 1     | 1     | 0             | 0     | 1     | 1     |
|  | 0.0           | 0.0   | 1.1   | 1.1   | 0.0           | 0.0   | 4.8   | 4.8   |
| CERVICAL CENTRUM #7 BILOBED                          | 7             | 6     | 5     | 8     | 5             | 5     | 5     | 8     |
|  | 7.5           | 7.1   | 5.7   | 8.8   | 22.7          | 22.7  | 23.8  | 38.1  |
| ANTERIOR ARCH OF THE ATLAS POORLY OSSIFIED           | 69            | 62    | 62    | 31    | 22            | 21    | 21    | 16*   |
|  | 74.2          | 73.8  | 71.3  | 34.1  | 100.0         | 95.5  | 100.0 | 76.2  |

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

TABLE 10 (Continued)  
DEVELOPMENTAL TOXICITY EVALUATION OF 2-ETHYLHEXANOIC ACID  
ADMINISTERED BY GAVAGE TO FISCHER 344 RATS  
VARIATIONS OBSERVED IN FETUSES AND LITTERS<sup>a</sup>

| NUMBER EXAMINED                              | F E T U S E S           |      |      |      | L I T T E R S |      |      |      |      |
|--|-------------------------|------|------|------|---------------|------|------|------|------|
|  | DOSE GROUP (MG/KG/DAY): | 0    | 100  | 250  | 500           | 0    | 100  | 250  | 500  |
| ANTERIOR ARCH OF THE ATLAS UNOSSIFIED        |                         | 93   | 84   | 87   | 91            | 22   | 22   | 21   | 21   |
| ANTERIOR ARCH OF THE ATLAS BILOBED           |                         | 3    | 7    | 12   | 50            | 2    | 7    | 10*  | 19** |
|  |                         | 3.2  | 8.3  | 13.8 | 54.9          | 9.1  | 31.8 | 47.6 | 90.5 |
| ANTERIOR ARCH OF THE ATLAS SPLIT             |                         | 1    | 0    | 1    | 0             | 1    | 0    | 1    | 0    |
|  |                         | 1.1  | 0.0  | 1.1  | 0.0           | 4.5  | 0.0  | 4.8  | 0.0  |
| CERVICAL CENTRA - SPLIT                      |                         | 1    | 1    | 5    | 6             | 1    | 1    | 5    | 3    |
|  |                         | 1.1  | 1.2  | 5.7  | 6.6           | 4.5  | 4.5  | 23.8 | 14.3 |
| BONE ISLAND - 7TH CERVICAL ARCH - UNILATERAL |                         | 3    | 3    | 1    | 1             | 3    | 2    | 1    | 1    |
|  |                         | 3.2  | 3.6  | 1.1  | 1.1           | 13.6 | 9.1  | 4.8  | 4.8  |
| THORACIC CENTRUM #1 BILOBED                  |                         | 0    | 0    | 0    | 1             | 0    | 0    | 0    | 1    |
|  |                         | 0.0  | 0.0  | 0.0  | 1.1           | 0.0  | 0.0  | 0.0  | 4.8  |
| THORACIC CENTRUM #2 BILOBED                  |                         | 10   | 13   | 9    | 25            | 8    | 9    | 7    | 16*  |
|  |                         | 10.8 | 15.5 | 10.3 | 27.5          | 36.4 | 40.9 | 33.3 | 76.2 |
| THORACIC CENTRUM #3 BILOBED                  |                         | 2    | 2    | 2    | 11            | 2    | 2    | 2    | 10*  |
|  |                         | 2.2  | 2.4  | 2.3  | 12.1          | 9.1  | 9.1  | 9.5  | 47.6 |
| THORACIC CENTRUM #4 BILOBED                  |                         | 0    | 3    | 0    | 5             | 0    | 3    | 0    | 5*   |
|  |                         | 0.0  | 3.6  | 0.0  | 5.5           | 0.0  | 13.6 | 0.0  | 23.8 |
| THORACIC CENTRUM #5 BILOBED                  |                         | 0    | 1    | 2    | 8             | 0    | 1    | 2    | 6*   |
|  |                         | 0.0  | 1.2  | 2.3  | 8.8           | 0.0  | 4.5  | 9.5  | 28.6 |
| THORACIC CENTRUM #6 BILOBED                  |                         | 0    | 1    | 2    | 4             | 0    | 1    | 2    | 4    |
|  |                         | 0.0  | 1.2  | 2.3  | 4.4           | 0.0  | 4.5  | 9.5  | 19.0 |
| THORACIC CENTRUM #8 BILOBED                  |                         | 0    | 1    | 2    | 0             | 0    | 1    | 2    | 0    |
|  |                         | 0.0  | 1.2  | 2.3  | 0.0           | 0.0  | 4.5  | 9.5  | 0.0  |
| THORACIC CENTRUM #8 BILOBED                  |                         | 0    | 0    | 0    | 2             | 0    | 0    | 0    | 2    |
|  |                         | 0.0  | 0.0  | 0.0  | 2.2           | 0.0  | 0.0  | 0.0  | 9.5  |

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

TABLE 10 (Continued)  
DEVELOPMENTAL TOXICITY EVALUATION OF 2-ETHYLHEXANOIC ACID  
ADMINISTERED BY GAVAGE TO FISCHER 344 RATS  
VARIATIONS OBSERVED IN FETUSES AND LITTERS<sup>a</sup>

| NUMBER EXAMINED SKELETALLY <sup>d</sup> | F E T U S E S |      |      |      | L I T T E R S |      |      |      |
|---|---------------|------|------|------|---------------|------|------|------|
|   | 0             | 100  | 250  | 500  | 0             | 100  | 250  | 500  |
| DOSE GROUP (MG/KG/DAY):                 | 93            | 84   | 87   | 91   | 22            | 22   | 21   | 21   |
| THORACIC CENTRUM #9 BILOBED             | 4             | 2    | 7    | 7    | 4             | 2    | 6    | 7    |
|   | 4.3           | 2.4  | 8.0  | 7.7  | 18.2          | 9.1  | 28.6 | 33.3 |
| THORACIC CENTRUM #10 BILOBED            | 17            | 17   | 12   | 21   | 13            | 14   | 10   | 13   |
|   | 18.3          | 20.2 | 13.8 | 23.1 | 59.1          | 63.6 | 47.6 | 61.9 |
| THORACIC CENTRUM #11 BILOBED            | 22            | 16   | 25   | 23   | 15            | 15   | 15   | 14   |
|   | 23.7          | 19.0 | 28.7 | 25.3 | 68.2          | 68.2 | 71.4 | 66.7 |
| THORACIC CENTRUM #12 BILOBED            | 9             | 18   | 21   | 26   | 9             | 14   | 14   | 16*  |
|   | 9.7           | 21.4 | 24.1 | 28.6 | 40.9          | 63.6 | 66.7 | 76.2 |
| THORACIC CENTRUM #13 BILOBED            | 3             | 3    | 4    | 17   | 3             | 2    | 3    | 15** |
|   | 3.2           | 3.6  | 4.6  | 18.7 | 13.6          | 9.1  | 14.3 | 71.4 |
| EXTRA #14 THORACIC CENTRUM AND ARCHES   | 0             | 0    | 0    | 16   | 0             | 0    | 0    | 10** |
|   | 0.0           | 0.0  | 0.0  | 17.6 | 0.0           | 0.0  | 0.0  | 47.6 |
| THORACIC CENTRUM #1 POORLY OSSIFIED     | 5             | 8    | 9    | 24   | 4             | 6    | 7    | 12*  |
|   | 5.4           | 9.5  | 10.3 | 26.4 | 18.2          | 27.3 | 33.3 | 57.1 |
| THORACIC CENTRUM #2 POORLY OSSIFIED     | 0             | 1    | 3    | 4    | 0             | 1    | 3    | 4    |
|   | 0.0           | 1.2  | 3.4  | 4.4  | 0.0           | 4.5  | 14.3 | 19.0 |
| THORACIC CENTRUM #3 POORLY OSSIFIED     | 0             | 1    | 1    | 0    | 0             | 1    | 1    | 0    |
|   | 0.0           | 1.2  | 1.1  | 0.0  | 0.0           | 4.5  | 4.8  | 0.0  |
| THORACIC CENTRUM #4 POORLY OSSIFIED     | 0             | 0    | 0    | 1    | 0             | 0    | 0    | 1    |
|   | 0.0           | 0.0  | 0.0  | 1.1  | 0.0           | 0.0  | 0.0  | 4.8  |
| THORACIC CENTRUM #8 POORLY OSSIFIED     | 0             | 0    | 0    | 1    | 0             | 0    | 0    | 1    |
|   | 0.0           | 0.0  | 0.0  | 1.1  | 0.0           | 0.0  | 0.0  | 4.8  |
| THORACIC CENTRUM #10 POORLY OSSIFIED    | 0             | 0    | 0    | 2    | 0             | 0    | 0    | 1    |
|   | 0.0           | 0.0  | 0.0  | 2.2  | 0.0           | 0.0  | 0.0  | 4.8  |

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

TABLE 10 (Continued)  
DEVELOPMENTAL TOXICITY EVALUATION OF 2-ETHYLHEXANOIC ACID  
ADMINISTERED BY GAVAGE TO FISCHER 344 RATS  
VARIATIONS OBSERVED IN FETUSES AND LITTERS<sup>a</sup>

| NUMBER EXAMINED SKELETALLY           | DOSE GROUP (MG/KG/DAY): |     |     |     |     | F E T U S E S |     |     |     |     | L I T T E R S |     |     |     |     |     |     |     |
|--------------------------------------|-------------------------|-----|-----|-----|-----|---------------|-----|-----|-----|-----|---------------|-----|-----|-----|-----|-----|-----|-----|
|                                      | 0                       | 100 | 250 | 500 | 500 | 93            | 84  | 87  | 91  | 91  | 0             | 100 | 22  | 22  | 21  | 21  | 21  | 500 |
| THORACIC CENTRUM #11 POORLY OSSIFIED | 0                       | 1   | 0   | 0   | 0   | 0             | 1   | 0   | 0   | 0   | 0             | 0   | 0   | 1   | 0   | 0   | 0   | 0   |
| THORACIC CENTRUM #12 POORLY OSSIFIED | 0.0                     | 1.2 | 0.0 | 0.0 | 0.0 | 0.0           | 0.0 | 0.0 | 1.1 | 0.0 | 0.0           | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 4.8 | 0.0 |
| THORACIC CENTRUM #13 POORLY OSSIFIED | 0.0                     | 1.2 | 0.0 | 2.2 | 0.0 | 0.0           | 1.2 | 0.0 | 2.2 | 0.0 | 0.0           | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 4.5 | 0.0 |
| THORACIC CENTRUM #11 SPLIT           | 1.1                     | 1.2 | 1.1 | 1.1 | 1.1 | 1.1           | 1.2 | 1.1 | 1.1 | 1.1 | 1.1           | 1.1 | 4.5 | 4.5 | 4.8 | 4.8 | 4.8 | 1.1 |
| THORACIC CENTRUM #5 SPLIT            | 0                       | 0   | 1   | 1   | 1   | 0             | 0   | 1   | 1   | 1   | 0             | 0   | 0   | 0   | 1   | 1   | 1   | 1   |
| THORACIC CENTRUM #8 SPLIT            | 1.1                     | 0.0 | 0.0 | 0.0 | 0.0 | 1.1           | 0.0 | 0.0 | 0.0 | 0.0 | 1.1           | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 4.8 | 0.0 |
| THORACIC CENTRUM #4 SPLIT            | 0                       | 0   | 0   | 1   | 1   | 0             | 0   | 0   | 1   | 1   | 0             | 0   | 0   | 0   | 0   | 0   | 4.8 | 0.0 |
| LUMBAR CENTRUM #1 POORLY OSSIFIED    | 0                       | 0   | 0   | 1   | 1   | 0             | 0   | 0   | 1   | 1   | 0             | 0   | 0   | 0   | 0   | 0   | 4.8 | 0.0 |
| LUMBAR CENTRUM #3 POORLY OSSIFIED    | 0                       | 1   | 0   | 0   | 0   | 0             | 1.2 | 0.0 | 0.0 | 0.0 | 0             | 0   | 0   | 1   | 0   | 0   | 0.0 | 0.0 |
| LUMBAR CENTRUM #4 POORLY OSSIFIED    | 0                       | 0   | 0   | 1   | 1   | 0             | 0   | 0   | 1   | 1   | 0             | 0   | 0   | 0   | 0   | 0   | 4.8 | 0.0 |
| LUMBAR CENTRUM #1 BILOBED            | 0                       | 0   | 0   | 4   | 4   | 0             | 0   | 0   | 4   | 4   | 0             | 0   | 0   | 0   | 0   | 0   | 9.5 | 0.0 |
| LUMBAR CENTRUM #2 BILOBED            | 0                       | 0   | 0   | 1   | 1   | 0             | 0   | 0   | 1   | 1   | 0             | 0   | 0   | 0   | 0   | 0   | 4.8 | 0.0 |

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

TABLE 10 (Continued)  
DEVELOPMENTAL TOXICITY EVALUATION OF 2-ETHYLHEXANOIC ACID  
ADMINISTERED BY GAVAGE TO FISCHER 344 RATS  
VARIATIONS OBSERVED IN FETUSES AND LITTERS<sup>a</sup>

| NUMBER EXAMINED SKELETALLY <sup>d</sup>                 | F E T U S E S |     |     |     | L I T T E R S |     |     |      |
|---|---------------|-----|-----|-----|---------------|-----|-----|------|
|   | 0             | 100 | 250 | 500 | 0             | 100 | 250 | 500  |
| DOSE GROUP (MG/KG/DAY):                                 | 93            | 84  | 87  | 91  | 22            | 22  | 21  | 21   |
| LUMBAR CENTRUM #3 BILOBED                               | 0             | 0   | 0   | 1   | 0             | 0   | 0   | 1    |
|   | 0.0           | 0.0 | 0.0 | 1.1 | 0.0           | 0.0 | 0.0 | 4.8  |
| REDUCED NUMBER OF VERTEBRAL SEGMENTS (5 OR LESS)        | 0             | 0   | 1   | 5   | 5             | 0   | 1   | 5*   |
|   | 0.0           | 0.0 | 1.1 | 5.5 | 0.0           | 0.0 | 4.8 | 23.8 |
| BONE ISLAND - ON THORACIC ARCH #14 - UNILATERAL         | 0             | 0   | 0   | 5   | 0             | 0   | 0   | 4    |
|   | 0.0           | 0.0 | 0.0 | 5.5 | 0.0           | 0.0 | 0.0 | 19.0 |
| BONE ISLAND - ON THORACIC ARCH #14 - BILATERAL          | 0             | 0   | 0   | 6   | 0             | 0   | 0   | 4    |
|   | 0.0           | 0.0 | 0.0 | 6.6 | 0.0           | 0.0 | 0.0 | 19.0 |
| BONE ISLAND - FIRST LUMBAR ARCH - UNILATERAL            | 1             | 0   | 2   | 9   | 1             | 0   | 2   | 4    |
|   | 1.1           | 0.0 | 2.3 | 9.9 | 4.5           | 0.0 | 9.5 | 19.0 |
| BONE ISLAND - FIRST LUMBAR ARCH - BILATERAL             | 0             | 0   | 0   | 4   | 0             | 0   | 0   | 2    |
|   | 0.0           | 0.0 | 0.0 | 4.4 | 0.0           | 0.0 | 0.0 | 9.5  |
| EXTRA RIB #14 - ON THORACIC ARCH #14 - UNILATERAL       | 0             | 0   | 0   | 1   | 0             | 0   | 0   | 1    |
|   | 0.0           | 0.0 | 0.0 | 1.1 | 0.0           | 0.0 | 0.0 | 4.8  |
| RUDIMENTARY RIB #14 - ON THORACIC ARCH #14 - UNILATERAL | 0             | 0   | 0   | 2   | 0             | 0   | 0   | 2    |
|   | 0.0           | 0.0 | 0.0 | 2.2 | 0.0           | 0.0 | 0.0 | 9.5  |
| RUDIMENTARY RIB #14 - ON THORACIC ARCH #14 - BILATERAL  | 0             | 0   | 0   | 1   | 0             | 0   | 0   | 1    |
|   | 0.0           | 0.0 | 0.0 | 1.1 | 0.0           | 0.0 | 0.0 | 4.8  |
| EXTRA RIB #14 - FIRST LUMBAR ARCH - UNILATERAL          | 0             | 0   | 0   | 1   | 0             | 0   | 0   | 1    |
|   | 0.0           | 0.0 | 0.0 | 1.1 | 0.0           | 0.0 | 0.0 | 4.8  |
| RUDIMENTARY RIB #14 - FIRST LUMBAR ARCH - UNILATERAL    | 0             | 0   | 0   | 1   | 0             | 0   | 0   | 1    |
|   | 0.0           | 0.0 | 0.0 | 1.1 | 0.0           | 0.0 | 0.0 | 4.8  |
| HYOID - POORLY OSSIFIED                                 | 0             | 0   | 2   | 0   | 0             | 0   | 2   | 0    |
|   | 0.0           | 0.0 | 2.3 | 0.0 | 0.0           | 0.0 | 9.5 | 0.0  |

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

TABLE 10 (Continued)  
 DEVELOPMENTAL TOXICITY EVALUATION OF 2-ETHYLHEXANOIC ACID  
 ADMINISTERED BY GAVAGE TO FISCHER 344 RATS  
 VARIATIONS OBSERVED IN FETUSES AND LITTERS<sup>a</sup>

| DOSE GROUP (MG/KG/DAY):                                | F E T U S E S |      |      |      |     | L I T T E R S |      |      |      |     |
|--|---------------|------|------|------|-----|---------------|------|------|------|-----|
|  | 93            | 84   | 87   | 91   | 500 | 0             | 100  | 250  | 500  | 500 |
| NUMBER EXAMINED SKELETALLY <sup>b</sup>                |               |      |      |      |     | 22            | 22   | 21   | 21   |     |
| SUPRAOCCIPITAL - POORLY OSSIFIED                       | 1             | 0    | 3    | 7    |     | 1             | 0    | 2    | 5    |     |
|  | 1.1           | 0.0  | 3.4  | 7.7  |     | 4.5           | 0.0  | 9.5  | 23.8 |     |
| MANDIBLE - POORLY OSSIFIED                             | 0             | 0    | 3    | 0    |     | 0             | 0    | 2    | 0    |     |
|  | 0.0           | 0.0  | 3.4  | 0.0  |     | 0.0           | 0.0  | 9.5  | 0.0  |     |
| INTERPARIETAL - POORLY OSSIFIED                        | 0             | 0    | 0    | 1    |     | 0             | 0    | 0    | 1    |     |
|  | 0.0           | 0.0  | 0.0  | 1.1  |     | 0.0           | 0.0  | 0.0  | 4.8  |     |
| HYOID SPLIT  | 0             | 0    | 0    | 1    |     | 0             | 0    | 0    | 1    |     |
|  | 0.0           | 0.0  | 0.0  | 1.1  |     | 0.0           | 0.0  | 0.0  | 4.8  |     |
| SOME PROXIMAL PHALANGES (FORELIMB) POORLY OSSIFIED     | 9             | 14   | 19   | 17   |     | 6             | 12   | 11   | 11   |     |
|  | 9.7           | 16.7 | 21.8 | 18.7 |     | 27.3          | 54.5 | 52.4 | 52.4 |     |
| SOME PROXIMAL PHALANGES (FORELIMB) UNOSSIFIED          | 7             | 12   | 37   | 74   |     | 6             | 7    | 15** | 20** |     |
|  | 7.5           | 14.3 | 42.5 | 81.3 |     | 27.3          | 31.8 | 71.4 | 95.2 |     |
| MAJORITY PROXIMAL PHALANGES (FORELIMB) UNOSSIFIED      | 0             | 0    | 0    | 16   |     | 0             | 0    | 0    | 9**  |     |
|  | 0.0           | 0.0  | 0.0  | 17.6 |     | 0.0           | 0.0  | 0.0  | 42.9 |     |
| ALL PROXIMAL PHALANGES (FORELIMB) UNOSSIFIED           | 0             | 0    | 0    | 1    |     | 0             | 0    | 0    | 1    |     |
|  | 0.0           | 0.0  | 0.0  | 1.1  |     | 0.0           | 0.0  | 0.0  | 4.8  |     |
| SOME PROXIMAL PHALANGES (HINDLIMB) POORLY OSSIFIED     | 44            | 26   | 24   | 0    |     | 20            | 14   | 16   | 0**  |     |
|  | 47.3          | 31.0 | 27.6 | 0.0  |     | 90.9          | 63.6 | 76.2 | 0.0  |     |
| MAJORITY PROXIMAL PHALANGES (HINDLIMB) POORLY OSSIFIED | 0             | 7    | 5    | 0    |     | 6             | 7    | 5    | 0*   |     |
|  | 10.9          | 8.3  | 5.7  | 0.0  |     | 27.3          | 31.8 | 23.8 | 0.0  |     |
| SOME PROXIMAL PHALANGES (HINDLIMB) UNOSSIFIED          | 54            | 35   | 26   | 0    |     | 21            | 16   | 14*  | 0**  |     |
|  | 58.1          | 41.7 | 29.9 | 0.0  |     | 95.5          | 72.7 | 66.7 | 0.0  |     |
| MAJORITY PROXIMAL PHALANGES (HINDLIMB) UNOSSIFIED      | 21            | 18   | 11   | 0    |     | 12            | 10   | 10   | 0**  |     |
|  | 22.6          | 21.4 | 12.6 | 0.0  |     | 54.5          | 45.5 | 47.6 | 0.0  |     |

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

TABLE 10 (Continued)  
DEVELOPMENTAL TOXICITY EVALUATION OF 2-ETHYLHEXANOIC ACID  
ADMINISTERED BY GAVAGE TO FISCHER 344 RATS  
VARIATIONS OBSERVED IN FETUSES AND LITTERS<sup>a</sup>

|  | F E T U S E S |      |      |       | L I T T E R S |      |      |       |
|--|---------------|------|------|-------|---------------|------|------|-------|
|  | 0             | 100  | 250  | 500   | 0             | 100  | 250  | 500   |
| DOSE GROUP (MG/KG/DAY):                      | 0             | 100  | 250  | 500   | 0             | 100  | 250  | 500   |
| NUMBER EXAMINED SKELETALLY <sup>b</sup>      | 93            | 84   | 87   | 91    | 22            | 22   | 21   | 21    |
| ALL PROXIMAL PHALANGES (HINDLIMB) UNOSSIFIED | 13            | 26   | 49   | 91    | 8             | 11   | 18** | 21**  |
|  | 14.0          | 31.0 | 56.3 | 100.0 | 36.4          | 50.0 | 85.7 | 100.0 |
| SOME METATARSALS (HINDLIMB) POORLY OSSIFIED  | 0             | 0    | 1    | 4     | 0             | 0    | 1    | 3     |
|  | 0.0           | 0.0  | 1.1  | 4.4   | 0.0           | 0.0  | 4.8  | 14.3  |
| SOME METATARSALS (HINDLIMB) UNOSSIFIED       | 0             | 1    | 2    | 69    | 0             | 1    | 1    | 18**  |
|  | 0.0           | 1.2  | 2.3  | 75.8  | 0.0           | 4.5  | 4.8  | 85.7  |
| STERNEBRA #1 POORLY OSSIFIED                 | 0             | 0    | 0    | 2     | 0             | 0    | 0    | 2     |
|  | 0.0           | 0.0  | 0.0  | 2.2   | 0.0           | 0.0  | 0.0  | 9.5   |
| STERNEBRA #2 POORLY OSSIFIED                 | 1             | 4    | 2    | 15    | 1             | 4    | 2    | 11**  |
|  | 1.1           | 4.8  | 2.3  | 16.5  | 4.5           | 18.2 | 9.5  | 52.4  |
| STERNEBRA #3 POORLY OSSIFIED                 | 9             | 4    | 5    | 18    | 7             | 4    | 4    | 13    |
|  | 9.7           | 4.8  | 5.7  | 19.8  | 31.8          | 18.2 | 19.0 | 61.9  |
| STERNEBRA #4 POORLY OSSIFIED                 | 28            | 23   | 30   | 49    | 15            | 16   | 17   | 18    |
|  | 30.1          | 27.4 | 34.5 | 53.8  | 68.2          | 72.7 | 81.0 | 85.7  |
| STERNEBRA #5 POORLY OSSIFIED                 | 52            | 51   | 54   | 46    | 21            | 21   | 20   | 19    |
|  | 55.9          | 60.7 | 62.1 | 50.5  | 95.5          | 95.5 | 95.2 | 90.5  |
| STERNEBRA #6 POORLY OSSIFIED                 | 1             | 2    | 4    | 38    | 1             | 2    | 3    | 15**  |
|  | 1.1           | 2.4  | 4.6  | 41.8  | 4.5           | 9.1  | 14.3 | 71.4  |
| STERNEBRA #3 BILOBED                         | 0             | 2    | 0    | 3     | 0             | 2    | 0    | 3     |
|  | 0.0           | 2.4  | 0.0  | 3.3   | 0.0           | 9.1  | 0.0  | 14.3  |
| STERNEBRA #4 BILOBED                         | 2             | 6    | 4    | 8     | 2             | 5    | 4    | 7     |
|  | 2.2           | 7.1  | 4.6  | 8.8   | 9.1           | 22.7 | 19.0 | 33.3  |
| STERNEBRA #5 BILOBED                         | 21            | 15   | 21   | 32    | 13            | 10   | 14   | 19*   |
|  | 22.6          | 17.9 | 24.1 | 35.2  | 59.1          | 45.5 | 66.7 | 90.5  |

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

TABLE 10 (Continued)  
DEVELOPMENTAL TOXICITY EVALUATION OF 2-ETHYLHEXANOIC ACID  
ADMINISTERED BY GAVAGE TO FISCHER 344 RATS  
VARIATIONS OBSERVED IN FETUSES AND LITTERS<sup>a</sup>

| NUMBER EXAMINED SKELETALLY <sup>d</sup> | F E T U S E S           |     |     |      |  | L I T T E R S |      |      |      |  |
|---|-------------------------|-----|-----|------|--|---------------|------|------|------|--|
|   | DOSE GROUP (MG/KG/DAY): |     |     |      |  |               |      |      |      |  |
|   | 0                       | 100 | 250 | 500  |  | 0             | 100  | 250  | 500  |  |
| STERNEBRA #5 SPLIT                      | 93                      | 84  | 87  | 91   |  | 22            | 22   | 21   | 21   |  |
|   | 7.5                     | 7   | 4   | 10   |  | 7             | 6    | 4    | 8    |  |
|   |                         | 8.3 | 4.6 | 11.0 |  | 31.8          | 27.3 | 19.0 | 38.1 |  |
| STERNEBRA #4 SPLIT                      | 1                       | 1   | 0   | 3    |  | 1             | 1    | 0    | 3    |  |
|   | 1.1                     | 1.2 | 0.0 | 3.3  |  | 4.5           | 4.5  | 0.0  | 14.3 |  |
| STERNEBRA #5 UNOSSIFIED                 | 6                       | 5   | 3   | 1    |  | 5             | 3    | 3    | 1    |  |
|   | 6.5                     | 6.0 | 3.4 | 1.1  |  | 22.7          | 13.6 | 14.3 | 4.8  |  |
| STERNEBRA #3 SPLIT                      | 0                       | 0   | 0   | 1    |  | 0             | 0    | 0    | 1    |  |
|   | 0.0                     | 0.0 | 0.0 | 1.1  |  | 0.0           | 0.0  | 0.0  | 4.8  |  |
| THORACIC CENTRUM #12 SPLIT              | 1                       | 0   | 0   | 1    |  | 1             | 0    | 0    | 1    |  |
|   | 1.1                     | 0.0 | 0.0 | 1.1  |  | 4.5           | 0.0  | 0.0  | 4.8  |  |
| THORACIC CENTRUM #3 SPLIT               | 0                       | 0   | 1   | 1    |  | 0             | 0    | 1    | 1    |  |
|   | 0.0                     | 0.0 | 1.1 | 1.1  |  | 0.0           | 0.0  | 4.8  | 4.8  |  |
| THORACIC CENTRUM #7 SPLIT               | 1                       | 0   | 0   | 0    |  | 1             | 0    | 0    | 0    |  |
|   | 1.1                     | 0.0 | 0.0 | 0.0  |  | 4.5           | 0.0  | 0.0  | 0.0  |  |
| THORACIC CENTRUM #9 SPLIT               | 0                       | 0   | 0   | 2    |  | 0             | 0    | 0    | 2    |  |
|   | 0.0                     | 0.0 | 0.0 | 2.2  |  | 0.0           | 0.0  | 0.0  | 9.5  |  |
| EXTRA 14TH THORACIC CENTRUM BILOBED     | 0                       | 0   | 0   | 2    |  | 0             | 0    | 0    | 1    |  |
|   | 0.0                     | 0.0 | 0.0 | 2.2  |  | 0.0           | 0.0  | 0.0  | 4.8  |  |
| THORACIC CENTRUM #1 UNOSSIFIED          | 0                       | 0   | 0   | 1    |  | 0             | 0    | 0    | 1    |  |
|   | 0.0                     | 0.0 | 0.0 | 1.1  |  | 0.0           | 0.0  | 0.0  | 4.8  |  |

<sup>a</sup>None significantly different from control ( 0.0 MG/KG/DAY )  
<sup>b</sup>See footnotes on last page of table.

TABLE 10 (Continued)  
DEVELOPMENTAL TOXICITY EVALUATION OF 2-ETHYLHEXANOIC ACID  
ADMINISTERED BY GAVAGE TO FISCHER 344 RATS  
VARIATIONS OBSERVED IN FETUSES AND LITTERS<sup>a</sup>

| DOSE GROUP (MG/KG/DAY):             | F E T U S E S |       |       |       | L I T T E R S |       |       |       |
|-------------------------------------|---------------|-------|-------|-------|---------------|-------|-------|-------|
|                                     | 0             | 100   | 250   | 500   | 0             | 100   | 250   | 500   |
| TOTAL VARIATIONS                    |               |       |       |       |               |       |       |       |
| NUMBER WITH EXTERNAL VARIATIONS     | 24            | 21    | 27    | 34    | 17            | 14    | 16    | 16    |
| PERCENT WITH EXTERNAL VARIATIONS    | 12.4          | 11.7  | 14.7  | 17.4  | 73.9          | 58.3  | 72.7  | 76.2  |
| NUMBER WITH SOFT TISSUE VARIATIONS  | 52            | 53    | 57    | 80    | 20            | 20    | 20    | 21    |
| PERCENT WITH SOFT TISSUE VARIATIONS | 52.0          | 55.8  | 58.8  | 76.9  | 87.0          | 83.3  | 90.9  | 100.0 |
| NUMBER WITH SKELETAL VARIATIONS     | 93            | 84    | 87    | 91    | 22            | 22    | 21    | 21    |
| PERCENT WITH SKELETAL VARIATIONS    | 100.0         | 100.0 | 100.0 | 100.0 | 100.0         | 100.0 | 100.0 | 100.0 |
| TOTAL NUMBER WITH VARIATIONS        | 150           | 141   | 152   | 176   | 23            | 22    | 22    | 21    |
| TOTAL PERCENT WITH VARIATIONS       | 77.7          | 78.8  | 82.6  | 90.3  | 100.0         | 91.7  | 100.0 | 100.0 |

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

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

b All fetuses were examined externally.

c Approximately 50% of each litter were examined visceraally (Staples, 1974), and for soft tissue craniofacial defects (Wilson, 1965; van Julsingha and Bennett, 1977).

d Approximately 50% of each litter were examined for skeletal defects after staining with Alizarin Red S.