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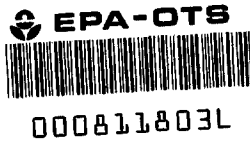
FINAL REPORT

PROTOCOL 418-011

ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE
IN RATS

SPONSOR'S STUDY NUMBER: T-6316.7

FINAL REPORT DATE: 17 DECEMBER 1998



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TITLE: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY
OF N-EtFOSE IN RATS

ARGUS RESEARCH LABORATORIES, INC.
PROTOCOL NUMBER: 418-011
SPONSOR'S STUDY NUMBER: T-6316.7

I. SUMMARY AND CONCLUSION

A. Methods^a

Twenty-five CrI:CD®BR VAF/Plus® (Sprague-Dawley) presumed pregnant female rats were assigned to each of five dosage groups (Groups I through V). Nineteen additional female rats were assigned to one of five dosage groups for the satellite study (three, five, three, three and five rats assigned to Groups I through V, respectively). The test article, N-EtFOSE, or vehicle, 2% Tween® 80 in Reverse Osmosis Membrane Processed Deionized Water (R.O. Deionized Water), was administered via gavage once daily to female rats on days 6 through 17 of presumed gestation (DGs 6 through 17). Dosages of 0 (Vehicle), 1, 5, 10 and 20 mg/kg/day were administered at a dosage volume of 5 mL/kg, adjusted daily on the basis of individual body weights.

The female rats were observed for viability at least twice each day of the study. The rats were also examined for clinical observations of effects of the test article, abortions, premature deliveries and deaths before and approximately one hour after dosage (DGs 6 through 17), and once daily during the postdosage period.

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- a. Detailed descriptions of all procedures used in the conduct of this study are provided in the appropriate sections of this report and in APPENDIX C (PROTOCOL AND AMENDMENT).

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Body weights were recorded on DGs 0 and 4 and daily during the dosage and postdosage periods. Feed consumption values were recorded on DGs 0, 4, 6, 8, 10, 12, 14, 16, 18 and 20.

All rats in the main study were sacrificed by carbon dioxide asphyxiation on DG 20 and a gross necropsy of the thoracic, abdominal and pelvic viscera was performed. The number of corpora lutea in each ovary was recorded. The uterus of each rat was examined for pregnancy, number and distribution of implantations, live and dead fetuses and early and late resorptions. Each fetus was identified, weighed and examined for sex and gross external alterations. Approximately one-half of the fetuses in each litter were examined for soft tissue alterations and the remaining fetuses in each litter were examined for skeletal alterations.

Rats in the satellite study were sacrificed on DG 18. Blood samples were collected and centrifuged. The liver was excised, weighed and sectioned. Fetuses were examined grossly to the extent possible as described for rats assigned to the main study. Fetuses and placentae were pooled per litter. After completion of sample collection, serum, liver section, fetal and placental samples were shipped to the Sponsor for analysis.

B. Results

No deaths, abortions or premature deliveries occurred during the study. All rats survived until scheduled sacrifice on gestation day 20 (DG 20).

All clinical and necropsy observations were considered unrelated to the test article.

Maternal body weight gains were significantly reduced in groups administered 5 mg/kg/day and higher dosages of the test article. The effect was minimal and transient in the 5 mg/kg/day dosage group, occurring only on DGs 8 to 10. In the 10 mg/kg/day dosage group, significant reductions in maternal body weight gains occurred on DGs 6 to 8 and 10 to 12, followed by a significant increase in weight gain on DGs 14 to 16. The 20 mg/kg/day dosage group had significant weight loss followed by significant reductions in maternal body weight gain on DGs 8 to 14 and 16 to 18. These effects of the test article resulted in a tendency for reduced weight gain in the 10 mg/kg/day dosage group and significant reductions in the 20 mg/kg/day dosage group for the entire treatment period (DGs 6 to 10), the entire interval after initiation of treatment (DGs 6 to 20) and the entire gestation period (DGs 0 to 20). Maternal body weights were

significantly reduced in the 10 and 20 mg/kg/day dosage groups on DGs 11 through 13 and 8 through 20, respectively.

Body weights and body weight gains were unaffected by the 1 mg/kg/day dosage of the test article.

The absolute feed consumption value was significantly reduced in the 10 mg/kg/day dosage group on DGs 6 to 8 and absolute and relative feed consumption values were significantly reduced in the 20 mg/kg/day dosage group for the entire dosage period and at all intervals within this period. The absolute feed consumption value continued to be significantly reduced and the relative feed consumption value tended to be reduced in the 20 mg/kg/day dosage group during the postdosage interval. These effects of the 20 mg/kg/day dosage of the test article resulted in significantly reduced absolute and relative feed consumption values on DGs 6 to 20 and DGs 0 to 20.

Absolute and relative feed consumption values were unaffected by dosages of the test article as high as 5 mg/kg/day.

Fetal body weights (total, male and/or female) were significantly reduced in the 10 and 20 mg/kg/day dosage groups, as compared to the control group values. Dosages of N-EtFOSE as high as 20 mg/kg/day did not affect any other Caesarean-sectioning or litter parameters. The litter averages for corpora lutea, implantations, litter sizes, live fetuses, early resorptions, percent resorbed conceptuses and percent male fetuses, as well as the numbers of dams with any resorptions or with viable fetuses were comparable in the five dosage groups and did not significantly differ. No dams had litters with all conceptuses resorbed, and there were no dead fetuses or late resorptions. All placentae appeared normal. All of these values were within the ranges observed historically at the Testing Facility.

Reversible delays in fetal ossification associated with the significantly reduced fetal body weights in the 10 and 20 mg/kg/day dosage groups, were evident as significant reductions in the litter averages for ossified caudal vertebrae in the 10 and 20 mg/kg/day dosage groups and a significant increase in the fetal incidence of wavy ribs in the 20 mg/kg/day dosage group.

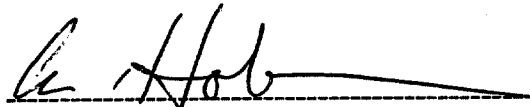
All other fetal gross external, soft tissue and skeletal alterations (malformations and variations) were considered unrelated to the test article because: 1) the incidences were not dosage-dependent; and/or 2) the incidences were within ranges observed historically at the Testing Facility.

C. Conclusion

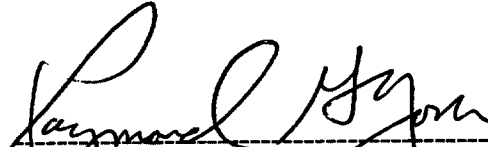
On the basis of these data, the maternal no-observable-effect-level (NOEL) of N-EtFOSE is 5 mg/kg/day (the 10 and 20 mg/kg/day dosages caused biologically important and statistically significant reductions in body weight gains or weight losses, and the 20 mg/kg/day dosage also persistently reduced the absolute and relative feed consumption values). The developmental NOEL is also 5 mg/kg/day (the 10 and 20 mg/kg/day dosages significantly reduced fetal body weights and caused minimal, but statistically significant reversible delays in ossification of the caudal vertebrae; the 20 mg/kg/day dosage also significantly increased the incidence of wavy ribs, an additional reversible delay in ossification associated with the reduced fetal body weights).

 17 Dec 88

Mildred S. Christian, Ph.D., Fellow, ATS Date
Executive Director of Research

 17 Dec 88

Alan M. Hoberman, Ph.D., DABT. Date
Director of Research

 17-Dec-88

Raymond G. York, Ph.D., DABT Date
Associate Director of Research
and Study Director

II. DESCRIPTION OF TEST PROCEDURES**A. Conduct of Study:****A.1. Sponsor:**

3M Corporate Toxicology, 3M Center, Building 220-2E-02, St. Paul,
Minnesota 55144-1000

A.2. Testing Facility:

Argus Research Laboratories, Inc., 905 Sheehy Drive, Building A, Horsham,
Pennsylvania 19044-1297

A.3. Study Number:

418-011

A.4. Sponsor's Study Number:

T-6316.7

A.5. Purpose of the Study:

The purpose of this study was to detect adverse effects of N-EtFOSE on Crl:CD®BR VAF/Plus® presumed pregnant female rats and development of the embryo and fetus consequent to exposure of the dam from implantation to closure of the hard palate. This study evaluated ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.

A.6. Study Design:

The requirements of the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline⁽¹⁾ were used as the basis of study design.

A.7. Regulatory Compliance:

The study was conducted in compliance with Good Laboratory Practice (GLP) regulations of the U.S. Food and Drug Administration (FDA)⁽²⁾, the Japanese Ministry of Health and Welfare (MHW)⁽³⁾ and the European Economic Community (EEC)⁽⁴⁾. There were no significant deviations from the GLP regulations that affected the quality or integrity of the study. Quality Assurance Unit findings derived from the inspections during the conduct of this study are documented

and have been provided to the Study Director and the Testing Facility Management.

A.8. Ownership of the Study:

The Sponsor owns the study. All raw data, analyses, reports and preserved tissues are the property of the Sponsor.

A.9. Study Monitor:

Marvin T. Case, D.V.M., Ph.D.

A.10. Alternate Study Monitor:

Andrew M. Seacat, Ph.D.

A.11. Study Director:

Raymond G. York, Ph.D., DABT (Associate Director of Research)

A.12. Technical Performance:

John F. Barnett, B.S. (Director of Laboratory Operations)
Kristen Iandola Sherer, B.S. (Research Associate/Fetal Evaluation)
Sharon Adamski (Laboratory Technician)

A.13. Report Preparation:

Raymond G. York, Ph.D., DABT
Jo Ann Frazee, M.S. (Study Coordinator)
Susan K. Bradshaw, B.S. (Data Management Specialist)
Karen G. Parker, A.A. (Administrative Assistant)

A.14. Report Review:

Alan M. Hoberman, Ph.D, DABT (Director of Research)
Mildred S. Christian, Ph.D., Fellow, ATS (Executive Director of Research)

A.15. Date Protocol Signed:

29 July 1998

A.16. Dates of Technical Performance:

Rat Arrival Date	11 AUG 98
Cohabitation Period	18 AUG 98 PM - 23 AUG 98 AM
Day 0 of Presumed Gestation (DG 0)	19 AUG 98 - 23 AUG 98
Dosage Period (DGs 6 through 17)	25 AUG 98 - 09 SEP 98
Toxicokinetic Sample Collection and Caesarean-Sectioning Period (DG 18) - Satellite Study	10 SEP 98
Caesarean-Sectioning Period - Main Study (DG 20)	08 SEP 98 - 12 SEP 98

A.17. Records Maintained:

The original report, raw data and reserve samples of the test article and vehicle are retained in the archives of Argus Research Laboratories, Inc. Any preserved tissues are retained in the archives of the Testing Facility for one year after the mailing of the draft final report, after which time the Sponsor will decide their final disposition. Prepared formulations were discarded at the Testing Facility. Unused bulk test article will remain at the Testing Facility until its disposition is decided by the Sponsor.

B. Test Article Information:**B.1. Description:**

N-EtFOSE - a waxy solid

B.2. Lot/Batch Number:

FM-3929 [30035, 30037, 30039 (Expiration date: May 2000)]

B.3. Date Received and Storage Conditions:

The test article was received on 20 May 1998, and stored at room temperature. Prepared formulations were stored refrigerated.

B.4. Special Handling Instructions:

Standard safety precautions (use of protective clothing, gloves, dust-mist respirator, safety goggles or safety glasses and a face-shield) were taken when handling the bulk test article and prepared formulations.

B.5. Analysis of Purity:

Information regarding the identity, composition, strength, and purity of the test article is on file with the Sponsor.

C. Vehicle Information:**C.1. Description:**

2% Tween® 80 in Reverse Osmosis Membrane Processed Deionized Water (R.O. Deionized Water).

C.2. Lot Number:

M03H05

C.3. Date Received and Storage Conditions:

The vehicle was received on 8 July 1998 from J.T. Baker, Phillipsburg, New Jersey, and stored at room temperature. R.O. Deionized Water is available from a continuous source at the Testing Facility and is maintained at room temperature.

C.4. Special Handling Instructions:

Standard safety precautions (use of protective clothing, gloves, dust-mist respirator, safety goggles or safety glasses and a face-shield) were taken when handling the vehicle.

C.5. Analysis of Purity:

Neither the Sponsor nor the Study Director was aware of any potential contaminants likely to be present in the vehicle that would interfere with the results of this study.

D. Test Article Preparation:

Suspensions of N-EtFOSE were prepared daily at concentrations of 0, 0.2, 1, 2 and 4 mg/mL. The test article was considered 100% pure for the purpose of dosage calculations.

D.1. Sample Information:

Sample Type	Components	Size	Date Retained	Storage Conditions	Shipped To	Date Shipped
Concentration (all levels)	N/A	2 mL ^a	25 AUG 98 ^b 09 SEP 98 ^c	Frozen	Sponsor	26 AUG 98 10 SEP 98
Bulk Test Article Reserve	N/A	1 g	25 AUG 98	Room Temperature	Testing Facility Archives	01 OCT 98
Vehicle Reserve	Tween ® 80	5 mL	25 AUG 98	Room Temperature	Testing Facility Archives	01 OCT 98
	R.O. Deionized Water	5 mL	25 AUG 98	Room Temperature	Testing Facility Archives	01 OCT 98

- a. Duplicate samples were taken from the first and last preparation on the day prepared. One sample of each set was shipped to the Sponsor for analysis. The remaining samples were retained at the Testing Facility as backup samples.
- b. First day of preparation.
- c. Last day of preparation.

Homogeneity and stability of prepared formulations are on file with the Sponsor.

D.2. Analytical Results:

Concentration samples (2 mL) were taken on the first and last days of preparation for analyses by 3M Environmental Technology and Safety Services. The results of these analyses were not available at the time of this report.

E. Test System:**E.1. Species:**

Rat

E.2. Strain:

CrI:CD®BR VAF/Plus® (Sprague-Dawley)

E.3. Supplier (Source):

Charles River Laboratories, Inc., Raleigh, North Carolina

E.4. Sex:

Female (Note: Male rats were used only for the purposes of breeding and are not considered part of the Test System.)

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E.5. Rationale for Test System:

The CrI:CD®BR VAF/Plus® (Sprague-Dawley) rat was selected as the Test System because: 1) it is one mammalian species accepted and widely used throughout industry for nonclinical studies of developmental toxicity (embryo-fetal toxicity/teratogenicity); 2) this strain has been demonstrated to be sensitive to developmental toxins; 3) historical data and experience exist at the Testing Facility⁽⁵⁻⁷⁾; and 4) the test article is biologically active in this species and strain.

E.6. Test System Data:

Number of Rats	190
Approximate Date of Birth	08 AUG 98
Approximate Age at Arrival	64 days
Weight (g) on the Day after Arrival	195 - 234
Weight (g) at Study Assignment	210 - 251

E.7. Breeder Male Rat Data:

	<u>Shipment 1</u>	<u>Shipment 2</u>
Number of Rats	110	120
Approximate Date of Birth	13 JAN 98	26 JAN 98
Approximate Age at Arrival	87 days	75 days
Weight (g) on the Day after Arrival	300 - 356	300 - 356
Weight (g) at Study Assignment	498 - 784	

E.8. Method of Randomization:

Upon arrival, rats were assigned to individual housing on the basis of computer-generated random units. Female rats were assigned to one of five dosage groups (Groups I through V), 25 rats per dosage group, using a computer-generated (weight-ordered) randomization procedure based on body weights recorded on DG 0. Nineteen additional female rats were assigned to one of five dosage groups for the satellite study (three, five, three, three and five rats assigned to Groups I through V, respectively) using a computer-generated randomization based on body weights recorded on DG 0.

E.9. System of Identification:

Each rat was individually identified with a Monel® self-piercing ear tag (Gey Band and Tag Co., Inc., No. MSPT 20101) inscribed with the rat's designated unique permanent number. Cage tags were marked with the study number and permanent rat number.

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F. Husbandry:**F.1. Research Facility Registration:**

USDA Registration No. 23-R-099 under the Animal Welfare Act, 7 U.S.C. 2131 *et seq.*

F.2. Study Rooms:

The study rooms were maintained under conditions of positive airflow relative to a hallway and independently supplied with a minimum of ten changes per hour of 100% fresh air that had been passed through 99.97% HEPA filters (Airo Clean® room). Room temperature and humidity were monitored constantly throughout the study. Room temperature was targeted at 64°F to 79°F (18°C to 26°C); relative humidity was targeted at 30% to 70%. See APPENDIX E (TEMPERATURE AND RELATIVE HUMIDITY REPORT).

F.3. Housing:

Rats were individually housed except during the cohabitation period. During cohabitation, each pair of male and female rats was housed in the male rat's cage. All cage sizes and housing conditions were in compliance with the *Guide for the Care and Use of Laboratory Animals*⁽⁸⁾.

F.4. Lighting:

An automatically-controlled fluorescent light cycle was maintained at 12-hours light: 12-hours dark, with each dark period beginning at 1900 hours EST.

F.5. Sanitization:

Cage pan liners were changed approximately three times each week. Cages were changed approximately every other week.

F.6. Feed:

Rats were given *ad libitum* access to Certified Rodent Diet® #5002 (PMI Nutrition International, St. Louis, Missouri) in individual feeders.

F.7. Feed Analysis:

Analyses were routinely performed by the feed supplier. No contaminants at levels exceeding the maximum concentration for certified feed or deviations from

expected nutritional requirements were detected by these analyses. Copies of the results of the feed analyses are available in the raw data.

Neither the Study Director nor the Sponsor was aware of any agent present in the feed that was known to interfere with the results of this study.

F.8. Water:

Local water that had been processed by passage through a reverse osmosis membrane (R.O. water) was available to the rats *ad libitum* from individual water bottles attached to the cages and/or from an automatic watering system. Chlorine was added to the processed water as a bacteriostat.

F.9. Water Analysis:

The processed water is analyzed twice annually for possible chemical contamination (Lancaster Laboratories, Lancaster, Pennsylvania) and monthly for possible bacterial contamination (Analytical Laboratories, Inc., Chalfont, Pennsylvania). Copies of the results of the water analyses are available in the raw data.

Neither the Study Director nor the Sponsor was aware of any agent present in the water that was known to interfere with the results of this study.

G. Methods:

G.1. Dosage Administration:

Dosage Group	Number of Rats	Dosage (mg/kg/day)	Concentration (mg/mL)	Dosage Volume (mL/kg)	Assigned Numbers	
					Main Study	Satellite Study ^a
I	25 + 3 ^a	0 (Vehicle)	0	5	12801 - 12825	12573 - 12575
II	25 + 5 ^a	1	0.2	5	12826 - 12850	12576 - 12580
III	25 + 3 ^a	5	1	5	12851 - 12875	12581 - 12583
IV	25 + 3 ^a	10	2	5	12876 - 12900	12584 - 12586
V	25 + 5 ^a	20	4	5	12901 - 12925	12587 - 12591

The test article was considered 100% pure for the purpose of dosage calculations.

a. Rats assigned to the satellite group for blood collection.

The test article was considered 100% pure for the purpose of dosage calculations.

003605

G.2. Rationale for Dosage Selection:

Dosages were selected on the basis of a dosage-range study (Argus Research Laboratories, Inc., Protocol 418-011P) that tested 0, 1, 5, 10, 25 and 35 mg/kg/day. In that study, body weight gain was decreased at 10 mg/kg/day and higher dosages, and feed consumption values were reduced at all dosages tested.

G.3. Route of Administration:

Oral (gavage)

G.4. Rationale for Route of Administration:

The oral (gavage) route was selected for use because: 1) in comparison with the dietary route, the exact dosage can be accurately administered; and 2) it is a proposed route of human exposure.

G.5. Frequency of Administration:

Appropriate dosages of the test article were administered orally (via gavage) once daily to female rats on DGs 6 through 17. Dosages of 0 (Vehicle), 1, 5, 10 and 20 mg/kg/day of the test article were administered at a dosage volume of 5 mL/kg, adjusted daily on the basis of the individual body weights recorded before dosage. The rats were dosed at approximately the same time each day.

G.6. Length of Study:

Approximately 4 weeks

G.7. Method of Study Performance:

After acclimation, 190 healthy virgin female rats were placed into cohabitation with 190 breeder male rats (one male rat per female rat in the male rat's cage). Female rats with spermatozoa observed in a smear of the vaginal contents and/or a copulatory plug *in situ* were considered to be at DG 0 and returned to individual housing.

The female rats were observed for viability at least twice each day of the study and for general appearance weekly during acclimation and on DG 0. The rats were also examined for clinical observations of effects of the test article,

abortions, premature deliveries and deaths before and approximately one hour after dosage (DGs 6 through 17^a), and once daily during the postdosage period.

Body weights were recorded weekly during acclimation, on DGs 0 and 4 and daily during the dosage and postdosage periods (DGs 6 through 20). Feed consumption values were recorded on DGs 0, 4, 6, 8, 10, 12, 14, 16, 18 and 20.

G.8. Gross Necropsy^b:

Rats Assigned to the Main Study:

All rats were sacrificed by carbon dioxide asphyxiation on DG 20, Caesarean-sectioned and a gross necropsy of the thoracic, abdominal and pelvic viscera was performed. Uteri of apparently nonpregnant rats were stained with 10% ammonium sulfide to confirm the absence of implantation sites⁽⁹⁾. Tissues with gross lesions were preserved in neutral buffered 10% formalin for possible future evaluation; all other maternal tissues were discarded.

The number of corpora lutea in each ovary was recorded. The uterus of each rat was excised and examined for pregnancy, number and distribution of implantations, live and dead fetuses and early and late resorptions. An early resorption was defined as one in which organogenesis was not grossly evident. A late resorption was defined as one in which the occurrence of organogenesis was grossly evident. A live fetus was defined as a term fetus that responded to stimuli. Nonresponding term fetuses are considered to be dead (there were no dead fetuses). Dead fetuses and late resorptions are differentiated by the degree of autolysis present; marked to extreme autolysis indicated that the fetus was a late resorption.

Each fetus was removed from the uterus, placed in an individual container and identified with a tag noting the study number, litter number, uterine distribution and fixative. Each fetus was subsequently weighed and examined for sex and gross external alterations. Live fetuses were sacrificed by an intraperitoneal

-
- a. See APPENDIX D (DEVIATIONS FROM THE PROTOCOL AND STANDARD OPERATING PROCEDURES OF THE TESTING FACILITY), item 1.
 - b. A table of random units was used to select one control group rat from which all tissues examined at necropsy were retained, in order to provide control tissues for any possible histopathological evaluations of gross lesions.

injection of Beuthanasia®-D Special (Schering-Plough Animal Health). Photographs of gross external fetal alterations are available in the raw data.

Approximately one-half of the fetuses in each litter were examined for soft tissue alterations using an adaptation of Wilson's sectioning technique⁽¹⁰⁾. The fetuses were initially fixed in Bouin's solution; sections were stored in alcohol. The remaining fetuses in each litter were eviscerated, cleared, stained with alizarin red S⁽¹¹⁾, fixed in alcohol and examined for skeletal alterations. Skeletal preparations were retained in glycerin with thymol added as a preservative.

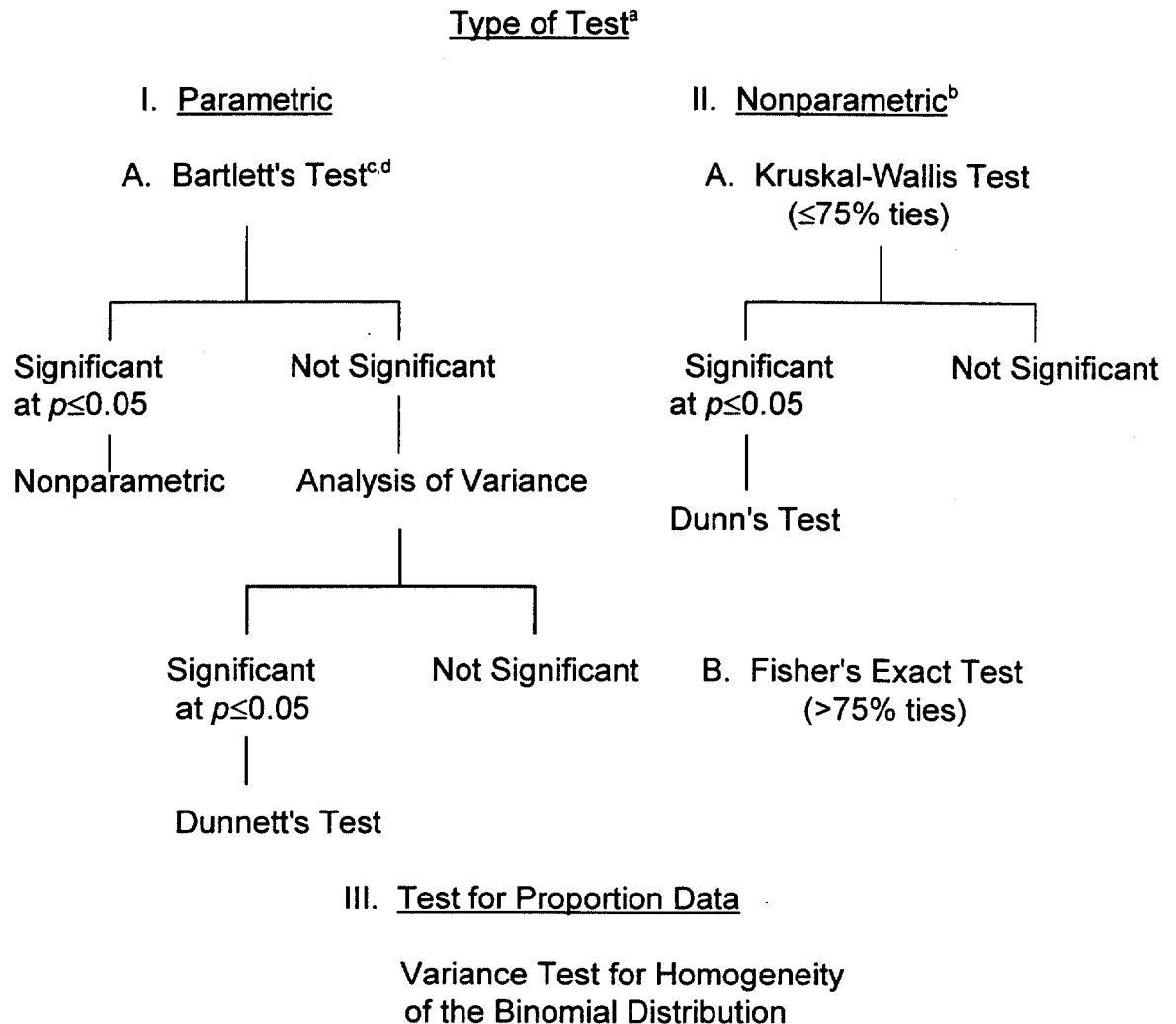
Rats Assigned to the Satellite Study:

On DG 18, rats assigned to the toxicokinetic evaluation were sacrificed and the following samples collected. Blood samples (approximately 4 mL per rat) were collected from the inferior vena cava into serum separator tubes and centrifuged. The resulting serum (approximately 2 mL) was immediately frozen on dry ice and maintained frozen (-70°C) until shipment to the Sponsor for analysis. The liver was excised, weighed, and a sample section (lateral lobe) was frozen and retained at -70°C until shipment to the Sponsor for analysis.

Rats were Caesarean-sectioned and fetuses were examined grossly to the extent possible as described above for rats assigned to the main study. Fetuses and placentae were pooled per litter and retained frozen (-70°C) until shipment to the Sponsor for analysis. After completion of sample collection, serum, liver section (lateral lobe), fetal and placental samples were shipped (frozen on dry ice) to the Sponsor for analysis.

G.9. Statistical Analyses:

The following schematic represents the statistical analyses of data:



-
- a. Statistically significant probabilities are reported as either $p \leq 0.05$ or $p \leq 0.01$.
 b. Proportion data are not included in this category.
 c. Used only to analyze data with homogeneity of variance.
 d. Test for homogeneity of variance.

Clinical observation and other proportion data were analyzed using the Variance Test for Homogeneity of the Binomial Distribution⁽¹²⁾.

Continuous data (e.g., maternal body weights, body weight changes, feed consumption values and litter averages for percent male fetuses, percent resorbed conceptuses, fetal body weights, fetal anomaly data and fetal ossification site data) were analyzed using Bartlett's Test of Homogeneity of Variances⁽¹³⁾ and the Analysis of Variance⁽¹⁴⁾, when appropriate [i.e., Bartlett's Test was not significant ($p > 0.05$)]. If the Analysis of Variance was significant ($p \leq 0.05$), Dunnett's Test⁽¹⁵⁾ was used to identify the statistical significance of the individual groups. If the Analysis of Variance was not appropriate [i.e., Bartlett's Test was significant ($p \leq 0.05$)], the Kruskal-Wallis Test⁽¹⁶⁾ was used, when less than or equal to 75% ties were present. In cases where the Kruskal-Wallis Test was statistically significant ($p \leq 0.05$), Dunn's Method of Multiple Comparisons⁽¹⁷⁾ was used to identify the statistical significance of the individual groups. If there were greater than 75% ties, Fisher's Exact Test⁽¹⁸⁾ was used to analyze the data.

Count data obtained at Cesarean-sectioning of the dams were evaluated using the procedures described above for the Kruskal-Wallis Test⁽¹⁶⁾.

Dam 12868 (5 mg/kg/day dosage group) had a litter consisting of five live fetuses and two early resorptions and dam 12889 (10 mg/kg/day dosage group) had a litter consisting of three live fetuses. Because such occurrences can abnormally skew the distribution of data⁽¹⁹⁾, statistical analyses were made with and without the values for these rats and litters. Maternal body weights, feed consumption values and Cesarean-section data for these dams and litters were excluded from summarization and statistical analyses; all values are presented on the individual tables.

III. RESULTS

A. Mortality, Clinical and Necropsy Observations (Summaries - Tables 1 and 2; Individual Data - Tables 14 and 15)

A.1. Mortality

No deaths, abortions or premature deliveries occurred during the study. All rats survived until scheduled sacrifice on gestation day 20 (DG 20).

A.2. Clinical Observations

All clinical observations were considered unrelated to the test article because: 1) the incidences were not dosage-dependent; 2) the observations occurred in only one rat; and/or 3) the observations are common events in the laboratory environment. Clinical observations included localized alopecia on the underside, limbs and/or neck, ungroomed coat, cold to touch and fused second and third digits on the right forepaw.

A.3. Necropsy Observations

The only necropsy finding was a tan area (0.6 cm x 0.8 cm) on the median lobe of the liver in one 20 mg/kg/day dosage group dam (12913). This observation was considered unrelated to the test article because it occurred in only one rat.

B. Maternal Body Weights and Body Weight Changes (Figure 1; Summaries - Tables 3 and 4; Individual Data - Table 16)

Maternal body weight gains were significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) in groups administered 5 mg/kg/day and higher dosages of the test article. The effect was minimal and transient in the 5 mg/kg/day dosage group, occurring only on DGs 8 to 10. In the 10 mg/kg/day dosage group, significant reductions ($p \leq 0.05$) in maternal body weight gains occurred on DGs 6 to 8 and 10 to 12, followed by a significant increase ($p \leq 0.05$) in weight gain on DGs 14 to 16. The 20 mg/kg/day dosage group had significant weight loss ($p \leq 0.01$) on DGs 6 to 8 followed by significant reductions ($p \leq 0.05$ or $p \leq 0.01$) in maternal body weight gain on DGs 8 to 14 and 16 to 18. These effects of the test article resulted in a tendency for reduced weight gain in the 10 mg/kg/day dosage group and significant reductions ($p \leq 0.01$) in the 20 mg/kg/day dosage group for the entire treatment period (calculated as DGs 6 to 18), the entire interval after initiation of treatment (DGs 6 to 20) and the entire gestation period (DGs 0 to 20). Maternal

body weights were significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) in the 10 and 20 mg/kg/day dosage groups on DGs 11 through 14 and 8 through 20, respectively.

Body weights and body weight gains were unaffected by the 1 mg/kg/day dosage of the test article.

C. Maternal Absolute (g/day) and Relative (g/kg/day) Feed Consumption Values (Summaries - Tables 5 and 6; Individual Data - Table 17)

The absolute (g/kg/day) feed consumption value was significantly reduced ($p \leq 0.05$) in the 10 mg/kg/day dosage group on DGs 6 to 8 and absolute (g/day) and relative (g/kg/day) feed consumption values were significantly reduced ($p \leq 0.01$) in the 20 mg/kg/day dosage group for the entire dosage period (calculated as DGs 6 to 18) and at all intervals within this period. The absolute feed consumption value continued to be significantly reduced ($p \leq 0.01$) and the relative feed consumption value tended to be reduced in the 20 mg/kg/day dosage group during the postdosage interval (DGs 18 to 20). These effects of the 20 mg/kg/day dosage of the test article resulted in significantly reduced ($p \leq 0.01$) absolute and relative feed consumption values on DGs 6 to 20 (the entire interval after the first dosage was administered) and DGs 0 to 20 (the entire gestation period).

Absolute and relative feed consumption values were unaffected by dosages of the test article as high as 5 mg/kg/day. The significant reduction ($p \leq 0.05$) in the relative feed consumption value in the 1 mg/kg/day dosage group on DGs 6 to 8 was considered unrelated to the test article because the value was not dosage-dependent.

D. Caesarean-Sectioning and Litter Observations (Summaries - Tables 7 and 8; Individual Data - Tables 18 through 20)

Pregnancy occurred in 24 (96%), 23 (92%), 24 (96%), 25 (100%) and 24 (96%) of the rats in the 0 (Vehicle), 1, 5, 10 and 20 mg/kg/day dosage groups, respectively. One 5 mg/kg/day dosage group litter consisted of five live fetuses and two early resorptions, and one 10 mg/kg/day dosage group litter consisted of three live fetuses. Because such occurrences can abnormally skew the distribution of the data⁽¹⁹⁾, values for these dams and litters were excluded from data summarization and statistical analyses. As a result, Caesarean-sectioning observations were based on 24, 23, 23, 24 and 24 pregnant dams.

Fetal body weights (total, male and/or female) were significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) in the 10 and 20 mg/kg/day dosage groups, as compared to the control group values. The reduced fetal body weights in the 10 and 20mg/kg/day dosage groups were a reflection of body weight reduction of the dams at these higher dosage levels. Dosages of N-EtFOSE as high as 20 mg/kg/day did not affect any other Cesarean-sectioning or litter parameters. The litter averages for corpora lutea, implantations, litter sizes, live fetuses, early resorptions, percent resorbed conceptuses and percent male fetuses, as well as the numbers of dams with any resorptions or with viable fetuses were comparable in the five dosage groups and did not significantly differ. No dams had litters with all conceptuses resorbed, and there were no dead fetuses or late resorptions. All placentae appeared normal. All of these values were within the ranges observed historically at the Testing Facility^a.

E. Fetal Alterations (Summaries - Tables 9 through 13; Individual Data - Table 21)

Fetal alterations were defined as: 1) malformations (irreversible changes that occur at low incidences in this species and strain); and 2) variations (common findings in this species/strain, and reversible delays or accelerations in development). Litter averages were calculated for specific fetal ossification sites as part of the evaluation of the degree of fetal ossification.

Fetal evaluations were based on 342, 349, 347, 354 and 326 DG 20 Cesarean-delivered live fetuses in 24, 23, 24, 25 and 24 litters in the 0 (Vehicle), 1, 5, 10 and 20 mg/kg/day dosage groups, respectively. Each fetus was examined for gross external alterations. Of these respective fetuses 166, 167, 169, 170 and 158 were examined for soft tissue alterations and 176, 182, 178, 184 and 168 were examined for skeletal alterations and fetal ossification site averages.

E.1. Summary of Fetal Alterations (Summary - Table 9; Individual Data - Table 21)

In the five respective dosage groups, litters with fetuses with alterations present numbered 6 (25.0%), 8 (34.8%), 4 (16.7%), 7 (28.0%) and 8 (33.3%). The numbers of fetuses with any alteration observed were 15 (4.4%), 10 (2.9%), 6 (1.7%), 8 (2.2%) and 12 (3.7%), and the percentages of fetuses with any alteration were 4.4%, 2.8%, 1.6%, 2.1% and 4.0%, in these same respective dosage groups.

a. See APPENDIX G (HISTORICAL CONTROL DATA).

Reversible delays in fetal ossification^(20,21) associated with the significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) fetal body weights in the 10 and 20 mg/kg/day dosage groups, were evident as significant reductions ($p \leq 0.05$) in the litter averages for ossified caudal vertebrae in the 10 and 20 mg/kg/day dosage groups and a significant increase ($p \leq 0.05$) in the fetal incidence of wavy ribs in the 20 mg/kg/day dosage group.

All other fetal gross external, soft tissue and skeletal alterations (malformations and variations) were considered unrelated to the test article because: 1) the incidences were not dosage-dependent; and/or 2) the incidences were within ranges observed historically at the Testing Facility.

E.2. Fetal Gross External Alterations (Summary - Table 10; Individual Data - Table 21)

E.2.a. Malformations

One 10 mg/kg/day dosage group fetus (12885-15) had a short trunk and absent tail. Subsequent skeletal examination of this fetus revealed that only four cervical vertebrae were present and that there were no thoracic, lumbar, sacral or caudal vertebrae, or ribs. This fetus also had a variation in pelvic ossification (the pubes were not ossified).

E.2.b. Variations

No gross external variations occurred in the fetuses in this study.

E.3. Fetal Soft Tissue Alterations (Summary - Table 11; Individual Data - Table 21)

E.3.a. Malformations

No fetal malformations were identified at visceral examination.

E.3.b. Variations

E.3.b.1. Vessels

Three control group fetuses (12801-10; 12810-10; 12821-6), one 1 mg/kg/day dosage group fetus (12834-14) and two 5 mg/kg/day dosage group littermates

(12860-5, -9) had the umbilical artery descending to the left of the bladder. These fetuses had no external findings and no other soft tissue alterations. Two 1 mg/kg/day dosage group fetuses (12826-12; 12837-9) had an absent innominate artery. No additional alterations occurred in these fetuses.

E.3.b.2. Lungs

One control group fetus (12822-4) had an absent apical lung lobe, and one 1 mg/kg/day dosage group fetus (12850-16) had an absent diaphragmatic lung lobe. No additional alterations occurred in these fetuses.

E.3.b.3. Kidneys

Two control group fetuses (12802-11; 12803-2) and one 10 mg/kg/day dosage group fetus (12877-14) had slight or moderate dilation of the pelvis of one or both kidneys, a reversible developmental delay⁽²²⁾. No additional alterations occurred in these fetuses.

E.4. Fetal Skeletal Alterations (Summaries - Tables 12 and 13; Individual Data - Table 21)

E.4.a. Malformations

Externally malformed 10 mg/kg/day dosage group fetus 12885-15 had only four cervical vertebrae and no thoracic, lumbar, sacral or caudal vertebrae or ribs, as well as a variation in pelvic ossification (not ossified pubes), as previously described.

E.4.b. Variations

E.4.b.1. Skull

A large nasal-frontal suture occurred in one 10 mg/kg/day dosage group fetus (12893-13). No additional alterations occurred in this fetus.

E.4.b.2. Ribs

A cervical rib at the 7th cervical vertebra, a common variation in this strain of rat⁽²³⁾, occurred in 0, 3, 1, 3 and 4 fetuses from 0, 2, 1, 3 and 4 litters in the 0 (Vehicle), 1, 5, 10 and 20 mg/kg/day dosage groups, respectively. These fetuses had no other external or skeletal alterations.

Wavy ribs, a reversible delay in ossification⁽²¹⁾, occurred in one 1 mg/kg/day dosage group fetus (12848-1) and seven ($p \leq 0.05$) 20 mg/kg/day group fetuses (12904-1; 12909-5, -7, -10, -12; 12919-3, -9). One 20 mg/kg/day dosage group fetus (12909-7) also had incompletely ossified ribs. The significant increase in the fetal incidence of wavy ribs in the 20 mg/kg/day dosage group was considered a treatment-related developmental delay, associated with the significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) fetal body weights in this dosage group.

E.4.b.3. Sternum

Delayed sternal ossification (incompletely ossified or not ossified 1st sternebra) occurred in 7, 2**, 1**, 1** and 1** fetuses from 3, 2, 1, 1 and 1 litters in the 0 (Vehicle), 1, 5, 10 and 20 mg/kg/day dosage groups, respectively. Of these fetuses, one control group fetus (12802-1) had incompletely ossified pubes in addition to an unossified 1st sternal centrum.

E.4.b.4. Pelvis

The ischia and/or pubes were incompletely or not ossified in 3, 0, 2, 2 and 0 fetuses from 1, 0, 1, 2 and 0 litters in the 0 (Vehicle), 1, 5, 10 and 20 mg/kg/day dosage groups, respectively. One fetus in the control group (12802-1) and one 10 mg/kg/day dosage group fetus (12885-15) had additional skeletal alterations, as previously described.

E.4.b.5. Fetal Ossification Site Averages

The litter averages for ossified caudal vertebrae per fetus were significantly reduced ($p \leq 0.05$) in the 10 and 20 mg/kg/day dosage groups. These delays in caudal vertebral ossification were considered effects of the test article associated with the significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) fetal body weights in these dosage groups.

Analyses of the average numbers of fetal ossification sites per fetus did not reveal any other statistically significant differences among the five dosage groups. Ossification of the hyoid, vertebrae (cervical, thoracic, lumbar and sacral), ribs, sternum (manubrium, sternal centers and xiphoid), forelimbs (carpals, metacarpals and phalanges) and hindlimbs (tarsals, metatarsals and phalanges) occurred at similar incidences in litters in all dosage groups. All values were within the ranges observed historically at the Testing Facility.

** Significantly different from the vehicle control group ($p \leq 0.01$).

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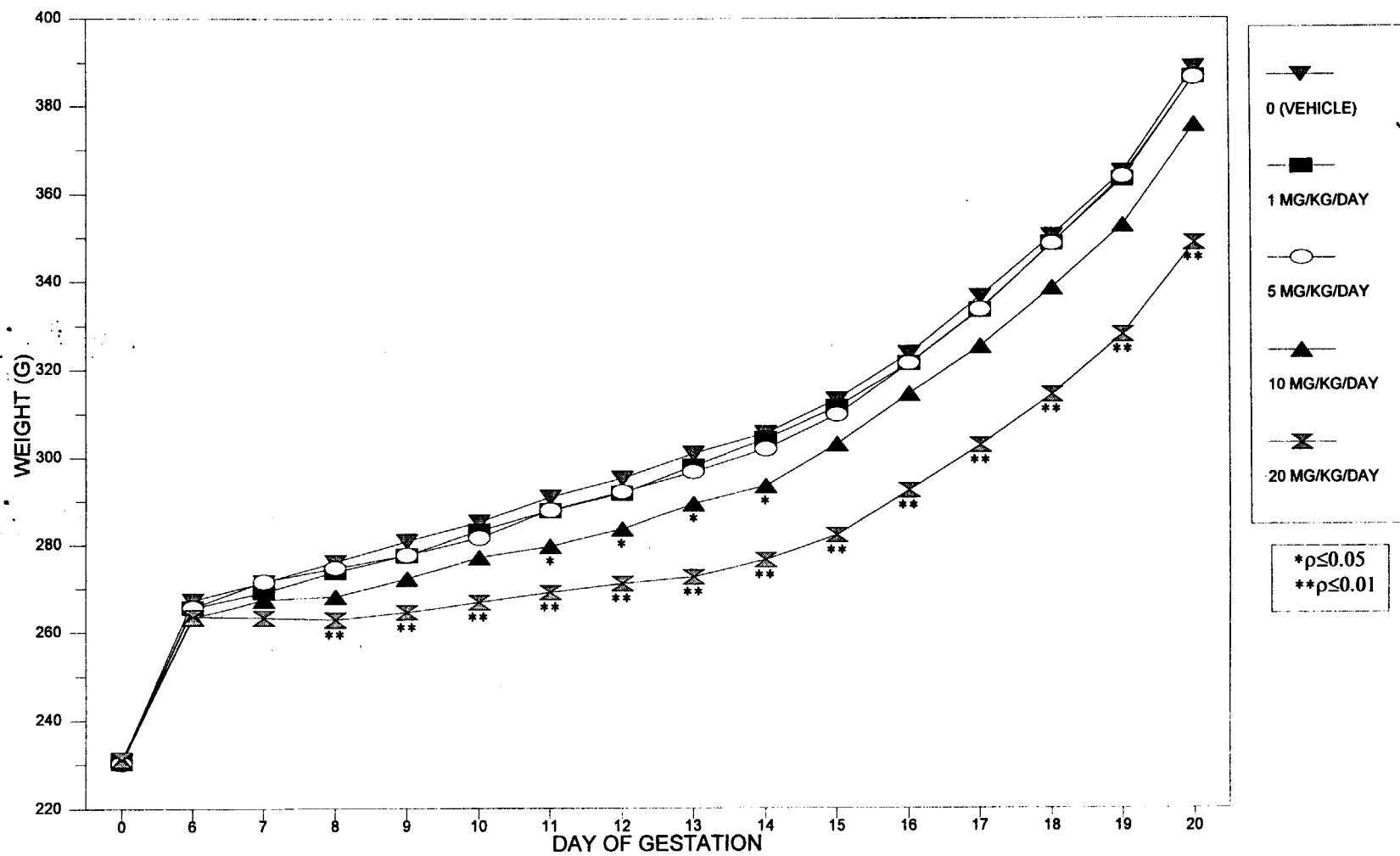
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APPENDIX A
REPORT FIGURE

003620

MATERNAL BODY WEIGHTS

Figure 1



APPENDIX B
REPORT TABLES

003622

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 1 (PAGE 1): CLINICAL OBSERVATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY) ^a	I 0 (VEHICLE)	II 1	III 5	IV 10	V 20
MAXIMUM POSSIBLE INCIDENCE	375/ 25	375/ 25	375/ 25	375/ 25	375/ 25
MORTALITY	0	0	0	0	0
LOCALIZED ALOPECIA: TOTAL	12/ 1	29/ 3	9/ 3	15/ 2	33/ 5
UNDERSIDE	0/ 0	28/ 3	7/ 2	11/ 1	18/ 3
LIMBS	12/ 1	2/ 1	0/ 0	7/ 2	15/ 2
NECK	0/ 0	0/ 0	2/ 1	0/ 0	0/ 0
UNGROOMED COAT	0/ 0	0/ 0	0/ 0	0/ 0	3/ 1
COLD TO TOUCH	0/ 0	0/ 0	0/ 0	0/ 0	3/ 1
RIGHT FOREPAW: SECOND AND THIRD DIGITS FUSED	0/ 0	0/ 0	4/ 1	0/ 0	0/ 0

STATISTICAL ANALYSES OF CLINICAL OBSERVATION DATA WERE RESTRICTED TO THE NUMBER OF RATS WITH OBSERVATIONS.

MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP ON DAYS 6 THROUGH 20 OF PRESUMED GESTATION.

N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RATS WITH OBSERVATION.

a. Dosage occurred on days 6 through 17 of presumed gestation.

003623

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 2 (PAGE 1): NECROPSY OBSERVATIONS - SUMMARY

DOSAGE GROUP		I	II	III	IV	V
DOSAGE (MG/KG/DAY) a		0 (VEHICLE)	1	5	10	20
RATS EXAMINED	N	25	25	25	25	25
MORTALITY	N	0	0	0	0	0
APPEARED NORMAL	N	25	25	25	25	24
LIVER:						
MEDIAN LOBE, TAN AREA	N	0	0	0	0	1

a. Dosage occurred on days 6 through 17 of presumed gestation.

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 3 (PAGE 1): MATERNAL BODY WEIGHTS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY) a		I 0 (VEHICLE)	II 1	III 5	IV 10	V 20
RATS TESTED	N	25	25	25	25	25
PREGNANT	N	24	23	24	25	24
INCLUDED IN ANALYSES	N	24	23	23b	24c	24
MATERNAL BODY WEIGHT (G)						
DAY 0	MEAN+S.D.	230.8 ± 9.9	231.0 ± 9.6	230.1 ± 10.5	230.5 ± 10.0	231.0 ± 9.5
DAY 6	MEAN+S.D.	267.1 ± 12.1	265.4 ± 14.0	265.4 ± 15.4	263.2 ± 12.5	263.4 ± 8.1
DAY 7	MEAN+S.D.	271.3 ± 12.7	269.0 ± 14.2	271.5 ± 15.0	267.3 ± 12.2	263.2 ± 9.6
DAY 8	MEAN+S.D.	276.1 ± 12.6	273.8 ± 14.4	274.6 ± 16.1 [22]d	268.1 ± 14.7	262.7 ± 9.3**
DAY 9	MEAN+S.D.	280.8 ± 13.1	277.5 ± 13.8	277.6 ± 17.0	272.2 ± 14.1	264.4 ± 10.8**
DAY 10	MEAN+S.D.	285.2 ± 13.6	283.2 ± 15.4	281.6 ± 18.2	277.1 ± 13.6	266.7 ± 9.8**
DAY 11	MEAN+S.D.	290.8 ± 14.8	287.8 ± 15.8	287.9 ± 17.3	279.6 ± 13.4*	269.0 ± 10.8**
DAY 12	MEAN+S.D.	295.1 ± 15.3	291.6 ± 16.0	291.9 ± 17.7	283.5 ± 14.4*	271.0 ± 12.8**
DAY 13	MEAN+S.D.	300.7 ± 16.2	297.8 ± 17.1	296.5 ± 20.2	289.2 ± 17.1*	272.4 ± 13.1**
DAY 14	MEAN+S.D.	305.4 ± 17.1	304.0 ± 17.7	301.8 ± 21.0	293.3 ± 18.0*	276.4 ± 14.3**
DAY 15	MEAN+S.D.	313.0 ± 17.6	311.4 ± 17.8	309.5 ± 22.1	302.9 ± 16.5	282.1 ± 17.1**

DAY = DAY OF GESTATION

[] = NUMBER OF VALUES AVERAGED

a. Dosage occurred on days 6 through 17 of gestation.

b. Excludes values for dam 12868, which had a litter consisting of 7 conceptuses.

c. Excludes values for dam 12889, which had a litter consisting of 3 conceptuses.

d. Excludes a value that was not recorded.

* Significantly different from the vehicle control group value ($p \leq 0.05$).

** Significantly different from the vehicle control group value ($p \leq 0.01$).

003625

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 3 (PAGE 2): MATERNAL BODY WEIGHTS - SUMMARY

DOSAGE GROUP		I	II	III	IV	V
DOSAGE (MG/KG/DAY) a		0 (VEHICLE)	1	5	10	20
RATS TESTED	N	25	25	25	25	25
PREGNANT	N	24	23	24	25	24
INCLUDED IN ANALYSES	N	24	23	23b	24c	24
MATERNAL BODY WEIGHT (G)						
DAY 16	MEAN+S.D.	323.5 ± 19.3	321.3 ± 18.5	321.3 ± 22.7	314.4 ± 18.4	292.4 ± 18.5**
DAY 17	MEAN+S.D.	336.5 ± 19.6	333.3 ± 17.8	333.6 ± 23.4	325.2 ± 19.1	302.7 ± 17.7**
DAY 18	MEAN+S.D.	350.3 ± 19.9	348.6 ± 19.3	348.5 ± 24.7	338.4 ± 20.9	314.2 ± 15.9**
DAY 19	MEAN+S.D.	364.8 ± 19.5	363.3 ± 20.6	363.9 ± 27.5	352.8 ± 20.3	327.8 ± 17.3**
DAY 20	MEAN+S.D.	388.7 ± 21.6	386.7 ± 23.2	386.6 ± 29.4	375.7 ± 23.0	348.7 ± 19.6**

DAY = DAY OF GESTATION

a. Dosage occurred on days 6 through 17 of gestation.

b. Excludes values for dam 12868, which had a litter consisting of 7 conceptuses.

c. Excludes values for dam 12889, which had a litter consisting of 3 conceptuses.

** Significantly different from the vehicle control group value ($p \leq 0.01$).

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 4 (PAGE 1): MATERNAL BODY WEIGHT CHANGES - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY) a		I 0 (VEHICLE)	II 1	III 5	IV 10	V 20
RATS TESTED	N	25	25	25	25	25
PREGNANT	N	24	23	24	25	24
INCLUDED IN ANALYSES	N	24	23	23b	24c	24
MATERNAL BODY WEIGHT CHANGE (G)						
DAYS 0 - 6	MEAN±S.D.	+36.3 ± 8.7	+34.4 ± 12.0	+35.3 ± 10.9	+32.6 ± 8.2	+32.5 ± 8.0
DAYS 6 - 8	MEAN±S.D.	+9.0 ± 4.3	+8.4 ± 3.0	+9.9 ± 6.8 [22]d	+4.9 ± 5.4*	-0.8 ± 8.0**
DAYS 8 - 10	MEAN±S.D.	+9.1 ± 4.0	+9.4 ± 3.4	+6.0 ± 4.6* [22]d	+9.0 ± 5.3	+4.0 ± 4.4**
DAYS 10 - 12	MEAN±S.D.	+9.9 ± 4.2	+8.4 ± 5.0	+10.3 ± 5.6	+6.4 ± 4.5*	+4.3 ± 9.0*
DAYS 12 - 14	MEAN±S.D.	+10.3 ± 4.4	+12.3 ± 4.8	+9.9 ± 5.3	+9.8 ± 5.6	+5.3 ± 8.6*
DAYS 14 - 16	MEAN±S.D.	+18.1 ± 6.6	+17.3 ± 4.7	+19.5 ± 4.5	+21.1 ± 3.9*	+16.1 ± 6.9
DAYS 16 - 18	MEAN±S.D.	+26.8 ± 3.8	+27.3 ± 5.7	+27.3 ± 5.2	+24.0 ± 6.2	+21.7 ± 7.5**
DAYS 6 - 18	MEAN±S.D.	+83.2 ± 11.4	+83.3 ± 11.2	+83.1 ± 11.9	+75.2 ± 12.0	+50.7 ± 15.8**
DAYS 18 - 20	MEAN±S.D.	+38.3 ± 6.3	+38.1 ± 7.3	+38.0 ± 7.9	+37.2 ± 6.0	+34.5 ± 6.7
DAYS 6 - 20	MEAN±S.D.	+121.5 ± 13.2	+121.3 ± 15.9	+121.1 ± 16.0	+112.5 ± 15.1	+85.2 ± 19.2**
DAYS 0 - 20	MEAN±S.D.	+157.9 ± 17.9	+155.7 ± 20.3	+156.5 ± 24.3	+145.1 ± 18.9	+117.7 ± 22.6**

DAYS = DAYS OF GESTATION

[] = NUMBER OF VALUES AVERAGED

a. Dosage occurred on days 6 through 17 of gestation.

b. Excludes values for dam 12868, which had a litter consisting of 7 conceptuses.

c. Excludes values for dam 12889, which had a litter consisting of 3 conceptuses.

d. Excludes values that were not recorded.

* Significantly different from the vehicle control group value ($p \leq 0.05$).

** Significantly different from the vehicle control group value ($p \leq 0.01$).

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TABLE 5 (PAGE 1): MATERNAL ABSOLUTE FEED CONSUMPTION VALUES (G/DAY) - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY) a		I 0 (VEHICLE)	II 1	III 5	IV 10	V 20
RATS TESTED	N	25	25	25	25	25
PREGNANT	N	24	23	24	25	24
INCLUDED IN ANALYSES	N	24	23	23b	24c	24
MATERNAL FEED CONSUMPTION (G/DAY)						
DAYS 0 - 6	MEAN±S.D.	21.5 ± 3.0 [23]d	21.1 ± 3.3	21.6 ± 3.0	21.1 ± 3.3	21.2 ± 2.1
DAYS 6 - 8	MEAN±S.D.	24.6 ± 3.1	23.0 ± 2.0	24.1 ± 3.6	22.4 ± 2.8*	19.4 ± 3.0**
DAYS 8 - 10	MEAN±S.D.	23.9 ± 2.3	22.9 ± 1.9	22.6 ± 3.0	22.6 ± 2.4	19.2 ± 3.2**
DAYS 10 - 12	MEAN±S.D.	24.6 ± 3.2	23.5 ± 2.4	24.0 ± 2.5	23.6 ± 2.3 [23]d	19.8 ± 4.4**
DAYS 12 - 14	MEAN±S.D.	25.7 ± 2.8	24.5 ± 2.8	24.7 ± 3.4	23.9 ± 3.0	20.5 ± 4.2**
DAYS 14 - 16	MEAN±S.D.	26.0 ± 3.4	25.2 ± 3.0	25.7 ± 3.6	26.1 ± 2.8	21.3 ± 4.3**
DAYS 16 - 18	MEAN±S.D.	27.6 ± 2.3	26.6 ± 2.8	27.2 ± 3.3	26.2 ± 2.7	22.5 ± 2.5**
DAYS 6 - 18	MEAN±S.D.	25.4 ± 2.3	24.3 ± 1.9	24.7 ± 2.7	24.2 ± 1.9	20.4 ± 2.6**
DAYS 18 - 20	MEAN±S.D.	26.4 ± 2.4	25.2 ± 2.8	25.9 ± 3.1	24.9 ± 2.7	22.5 ± 2.4**
DAYS 6 - 20	MEAN±S.D.	25.5 ± 2.2	24.4 ± 1.9	24.9 ± 2.7	24.2 ± 1.9	20.7 ± 2.4**
DAYS 0 - 20	MEAN±S.D.	24.6 ± 2.4	23.4 ± 2.1	23.9 ± 2.7	23.3 ± 2.1	20.9 ± 2.0**

DAYS = DAYS OF GESTATION

[] = NUMBER OF VALUES AVERAGED

a. Dosage occurred on days 6 through 17 of gestation.

b. Excludes values for dam 12868, which had a litter consisting of 7 conceptuses.

c. Excludes values for dam 12889, which had a litter consisting of 3 conceptuses.

d. Excludes values that were incorrectly recorded, as well as those associated with spillage.

* Significantly different from the vehicle control group value ($p \leq 0.05$).

** Significantly different from the vehicle control group value ($p \leq 0.01$).

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TABLE 6 (PAGE 1): MATERNAL RELATIVE FEED CONSUMPTION VALUES (G/KG/DAY) - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY) a		I 0 (VEHICLE)	II 1	III 5	IV 10	V 20
RATS TESTED	N	25	25	25	25	25
PREGNANT	N	24	23	24	25	24
INCLUDED IN ANALYSES	N	24	23	23b	24c	24
MATERNAL FEED CONSUMPTION (G/KG/DAY)						
DAYS 0 - 6	MEAN+S.D.	85.5 ± 10.1 [23]d	84.4 ± 11.4	86.4 ± 9.8	85.1 ± 12.1	85.3 ± 7.6
DAYS 6 - 8	MEAN+S.D.	90.3 ± 8.4	85.3 ± 5.5*	89.0 ± 10.2	83.9 ± 8.5	73.7 ± 10.7**
DAYS 8 - 10	MEAN+S.D.	85.1 ± 6.4	82.3 ± 5.0	81.3 ± 8.5	82.9 ± 7.3	72.4 ± 10.2**
DAYS 10 - 12	MEAN+S.D.	84.4 ± 8.7	81.8 ± 6.5	83.5 ± 6.9	84.3 ± 6.2 [23]d	73.2 ± 15.0**
DAYS 12 - 14	MEAN+S.D.	85.4 ± 6.3	82.3 ± 6.9	83.1 ± 8.6	82.5 ± 8.0	74.6 ± 14.0**
DAYS 14 - 16	MEAN+S.D.	82.7 ± 8.6	80.6 ± 7.2	82.7 ± 8.9	86.0 ± 8.6	74.6 ± 12.9**
DAYS 16 - 18	MEAN+S.D.	82.0 ± 6.0	79.6 ± 8.2	81.5 ± 8.3	80.5 ± 7.7	74.3 ± 6.5**
DAYS 6 - 18	MEAN+S.D.	84.6 ± 4.5	81.7 ± 4.2	83.0 ± 5.8	83.1 ± 4.1	73.6 ± 7.5**
DAYS 18 - 20	MEAN+S.D.	71.6 ± 5.6	68.8 ± 6.2	70.6 ± 6.3	70.0 ± 6.1	68.2 ± 5.3
DAYS 6 - 20	MEAN+S.D.	82.2 ± 4.2	79.3 ± 4.2	80.8 ± 5.6	80.7 ± 4.2	72.6 ± 6.5**
DAYS 0 - 20	MEAN+S.D.	80.2 ± 4.3	77.8 ± 4.4	79.4 ± 5.8	79.0 ± 4.9	74.3 ± 4.8**

DAYS = DAYS OF GESTATION

[] = NUMBER OF VALUES AVERAGED

a. Dosage occurred on days 6 through 17 of gestation.

b. Excludes values for dam 12868, which had a litter consisting of 7 conceptuses.

c. Excludes values for dam 12889, which had a litter consisting of 3 conceptuses.

d. Excludes values were incorrectly recorded, as well as those associated with spillage.

* Significantly different from the vehicle control group value ($p \leq 0.05$).

** Significantly different from the vehicle control group value ($p \leq 0.01$).

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TABLE 7 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY) a		I 0 (VEHICLE)	II 1	III 5	IV 10	V 20
RATS TESTED	N	25	25	25	25	25
PREGNANT	N(%)	24 (96.0)	23 (92.0)	24 (96.0)	25 (100.0)	24 (96.0)
RATS PREGNANT AND CAESAREAN-SECTIONED ON DAY 20 OF GESTATION	N	24	23	24	25	24
INCLUDED IN ANALYSES	N	24	23	23b	24c	24
CORPORA LUTEA	MEAN+S.D.	17.1 ± 1.8	17.2 ± 1.9	17.2 ± 2.1	16.8 ± 2.0	16.5 ± 1.8
IMPLANTATIONS	MEAN+S.D.	15.1 ± 1.8	15.6 ± 2.0	15.6 ± 1.4	15.1 ± 1.3	14.5 ± 1.7
LITTER SIZES	MEAN+S.D.	14.2 ± 1.8	15.2 ± 2.1	14.9 ± 1.9	14.6 ± 1.6	13.6 ± 1.9
LIVE FETUSES	N	342	349	342	351	327
	MEAN+S.D.	14.2 ± 1.8	15.2 ± 2.1	14.9 ± 1.9	14.6 ± 1.6	13.6 ± 1.9
DEAD FETUSES	N	0	0	0	0	0
RESORPTIONS	MEAN+S.D.	0.9 ± 1.2	0.4 ± 0.6	0.8 ± 1.2	0.5 ± 0.8	0.9 ± 1.0
EARLY RESORPTIONS	N	21	10	18	12	21
	MEAN+S.D.	0.9 ± 1.2	0.4 ± 0.6	0.8 ± 1.2	0.5 ± 0.8	0.9 ± 1.0
LATE RESORPTIONS	N	0	0	0	0	0
DAMS WITH ANY RESORPTIONS	N(%)	12 (50.0)	9 (39.1)	11 (47.8)	9 (37.5)	14 (58.3)
DAMS WITH ALL CONCEPTUSES RESORBED	N(%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
DAMS WITH VIABLE FETUSES	N(%)	24 (100.0)	23 (100.0)	23 (100.0)	24 (100.0)	24 (100.0)
PLACENTAE APPEARED NORMAL	N(%)	24 (100.0)	23 (100.0)	23 (100.0)	24 (100.0)	24 (100.0)

a. Dosage occurred on days 6 through 17 of gestation.

b. Excludes values for dam 12868, which had a litter consisting of 7 conceptuses.

c. Excludes values for dam 12889, which had a litter consisting of 3 conceptuses.

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TABLE 8 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY) a		I 0 (VEHICLE)	II 1	III 5	IV 10	V 20
LITTERS WITH ONE OR MORE LIVE FETUSES	N	24	23	24	25	24
INCLUDED IN ANALYSES	N	24	23	23b	24c	24
IMPLANTATIONS	MEAN+S.D.	15.1 ± 1.8	15.6 ± 2.0	15.6 ± 1.4	15.1 ± 1.3	14.5 ± 1.7
LIVE FETUSES	N	342	349	342	351	327
	MEAN+S.D.	14.2 ± 1.8	15.2 ± 2.1	14.9 ± 1.9	14.6 ± 1.6	13.6 ± 1.9
LIVE MALE FETUSES	N	166	171	165	180	172
% LIVE MALE FETUSES/LITTER	MEAN+S.D.	48.8 ± 13.1	48.8 ± 12.2	48.6 ± 11.8	51.7 ± 10.6	52.4 ± 13.0
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN+S.D.	3.50 ± 0.50	3.36 ± 0.22	3.39 ± 0.20	3.32 ± 0.20*	3.16 ± 0.17**
MALE FETUSES	MEAN+S.D.	3.61 ± 0.50	3.48 ± 0.23	3.50 ± 0.22	3.38 ± 0.20**	3.26 ± 0.19**
FEMALE FETUSES	MEAN+S.D.	3.38 ± 0.52	3.25 ± 0.24	3.30 ± 0.19	3.25 ± 0.23	3.05 ± 0.16**
% RESORBED CONCEPTUSES/LITTER	MEAN+S.D.	5.5 ± 7.2	2.8 ± 3.7	5.1 ± 7.7	3.4 ± 5.0	6.0 ± 6.8

a. Dosage occurred on days 6 through 17 of gestation.

b. Excludes values for dam 12868, which had a litter consisting of 7 conceptuses.

c. Excludes values for dam 12889, which had a litter consisting of 3 conceptuses.

* Significantly different from the vehicle control group value ($p \leq 0.05$).

** Significantly different from the vehicle control group value ($p \leq 0.01$).

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TABLE 9 (PAGE 1): FETAL ALTERATIONS - SUMMARY

DOSAGE GROUP		I	II	III	IV	V
DOSAGE (MG/KG/DAY)a		0 (VEHICLE)	1	5	10	20
LITTERS EVALUATED	N	24	23	24	25	24
FETUSES EVALUATED	N	342	349	347	354	326
LIVE	N	342	349	347	354	326
LITTERS WITH FETUSES WITH ANY ALTERATION OBSERVED	N(%)	6 (25.0)	8 (34.8)	4 (16.7)	7 (28.0)	8 (33.3)
FETUSES WITH ANY ALTERATION OBSERVED	N(%)	15 (4.4)	10 (2.9)	6 (1.7)	8 (2.2)	12 (3.7)
% FETUSES WITH ANY ALTERATION/LITTER	MEAN±S.D.	4.4 ± 10.3	2.8 ± 4.4	1.6 ± 3.9	2.1 ± 3.9	4.0 ± 7.6

a. Dosage occurred on days 6 through 17 of gestation.

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TABLE 10 (PAGE 1): FETAL GROSS EXTERNAL ALTERATIONS - SUMMARY

DOSAGE GROUP		I	II	III	IV	V
DOSAGE (MG/KG/DAY) a		0 (VEHICLE)	1	5	10	20
LITTERS EVALUATED	N	24	23	24	25	24
FETUSES EVALUATED	N	342	349	347	354	326
LIVE	N	342	349	347	354	326
BODY: TRUNK SHORT						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.3)	0(0.0)
TAIL: ABSENT						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.3)	0(0.0)

a. Dosage occurred on days 6 through 17 of gestation.

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TABLE 11 (PAGE 1): FETAL SOFT TISSUE ALTERATIONS - SUMMARY

DOSAGE GROUP		I	II	III	IV	V
DOSAGE (MG/KG/DAY) a		0 (VEHICLE)	1	5	10	20
LITTERS EVALUATED	N	24	23	24	25	24
FETUSES EVALUATED	N	166	167	169	170	158
LIVE	N	166	167	169	170	158
VESSELS: UMBILICAL ARTERY DESCENDS TO THE LEFT OF URINARY BLADDER						
LITTER INCIDENCE	N(%)	3(12.5)	1(4.3)	1(4.2)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	3(1.8)	1(0.6)	2(1.2)	0(0.0)	0(0.0)
VESSELS: INNOMINATE, ABSENT						
LITTER INCIDENCE	N(%)	0(0.0)	2(8.7)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	2(1.2)	0(0.0)	0(0.0)	0(0.0)
LUNGS: DIAPHRAGMATIC LOBE, ABSENT						
LITTER INCIDENCE	N(%)	0(0.0)	1(4.3)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)
LUNGS: APICAL LOBE, ABSENT						
LITTER INCIDENCE	N(%)	1(4.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
KIDNEYS: PELVIS, SLIGHT DILATION						
LITTER INCIDENCE	N(%)	2(8.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	2(1.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
KIDNEYS: PELVIS, MODERATE DILATION						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)

a. Dosage occurred on days 6 through 17 of gestation.

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TABLE 12 (PAGE 1): FETAL SKELETAL ALTERATIONS - SUMMARY
(See footnotes on the last page of this table.)

DOSAGE GROUP		I	II	III	IV	V
DOSAGE (MG/KG/DAY) a		0 (VEHICLE)	1	5	10	20
LITTERS EVALUATED	N	24	23	24	25	24
FETUSES EVALUATED	N	176	182	178	184	168
LIVE	N	176	182	178	184	168
SKULL: NASAL - FRONTAL, SUTURE LARGE						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.5)	0(0.0)
CERVICAL VERTEBRAE: CERVICAL RIB PRESENT AT 7TH CERVICAL VERTEBRA						
LITTER INCIDENCE	N(%)	0(0.0)	2(8.7)	1(4.2)	3(12.0)	4(16.7)
FETAL INCIDENCE	N(%)	0(0.0)	3(1.6)	1(0.6)	3(1.6)	4(2.4)
CERVICAL VERTEBRAE: 4 PRESENT						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.5)b	0(0.0)
THORACIC VERTEBRAE: 0 PRESENT						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.5)b	0(0.0)
THORACIC VERTEBRAE: ARCH, NOT OSSIFIED						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.5)b	0(0.0)
THORACIC VERTEBRAE: CENTRUM, NOT OSSIFIED						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.5)b	0(0.0)
LUMBAR VERTEBRAE: 0 PRESENT						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.5)b	0(0.0)
LUMBAR VERTEBRAE: ARCH, NOT OSSIFIED						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.5)b	0(0.0)
LUMBAR VERTEBRAE: CENTRUM, NOT OSSIFIED						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.5)b	0(0.0)

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TABLE 12 (PAGE 2): FETAL SKELETAL ALTERATIONS - SUMMARY
(See footnotes on the last page of this table.)

DOSAGE GROUP		I	II	III	IV	V
DOSAGE (MG/KG/DAY) a		0 (VEHICLE)	1	5	10	20
LITTERS EVALUATED	N	24	23	24	25	24
FETUSES EVALUATED	N	176	182	178	184	168
LIVE	N	176	182	178	184	168
SACRAL VERTEBRAE: 0 PRESENT						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.5)b	0(0.0)
SACRAL VERTEBRAE: ARCH, NOT OSSIFIED						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.5)b	0(0.0)
SACRAL VERTEBRAE: CENTRUM, NOT OSSIFIED						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.5)b	0(0.0)
CAUDAL VERTEBRAE: 0 PRESENT						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.5)b	0(0.0)
RIBS: WAVY						
LITTER INCIDENCE	N(%)	0(0.0)	1(4.3)	0(0.0)	0(0.0)	3(12.5)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.5)	0(0.0)	0(0.0)	7(4.2)**c
RIBS: 0 PRESENT						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.5)b	0(0.0)
RIBS: NOT OSSIFIED						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.5)b	0(0.0)
RIBS: INCOMPLETELY OSSIFIED (HYPOPLASTIC)						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(4.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)c

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 12 (PAGE 3): FETAL SKELETAL ALTERATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY) ^a		I 0 (VEHICLE)	II 1	III 5	IV 10	V 20
LITTERS EVALUATED	N	24	23	24	25	24
FETUSES EVALUATED	N	176	182	178	184	168
LIVE	N	176	182	178	184	168
STERNAL CENTRA: SUMMARIZATION (Includes incompletely ossified and not ossified sternal centra)						
LITTER INCIDENCE	N(%)	3 (12.5)	2 (8.7)	1 (4.2)	1 (4.0)	1 (4.2)
FETAL INCIDENCE	N(%)	7 (4.0)	2 (1.1)**	1 (0.6)**	1 (0.5)**	1 (0.6)**
STERNAL CENTRA: 1ST, INCOMPLETELY OSSIFIED						
LITTER INCIDENCE	N(%)	2 (8.3)	1 (4.3)	1 (4.2)	1 (4.0)	0 (0.0)
FETAL INCIDENCE	N(%)	4 (2.3)	1 (0.5)	1 (0.6)	1 (0.5)	0 (0.0)
STERNAL CENTRA: 1ST, NOT OSSIFIED						
LITTER INCIDENCE	N(%)	1 (4.2)	1 (4.3)	0 (0.0)	0 (0.0)	1 (4.2)
FETAL INCIDENCE	N(%)	3 (1.7) ^d	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.6)
PELVIS: SUMMARIZATION (Includes incompletely ossified pubes and ischia, and not ossified pubes)						
LITTER INCIDENCE	N(%)	1 (4.2)	0 (0.0)	1 (4.2)	2 (8.0)	0 (0.0)
FETAL INCIDENCE	N(%)	3 (1.7)	0 (0.0)	2 (1.1)	2 (1.1)	0 (0.0)
PELVIS: PUBIS, INCOMPLETELY OSSIFIED						
LITTER INCIDENCE	N(%)	1 (4.2)	0 (0.0)	0 (0.0)	1 (4.0)	0 (0.0)
FETAL INCIDENCE	N(%)	3 (1.7) ^d	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
PELVIS: PUBIS, NOT OSSIFIED						
LITTER INCIDENCE	N(%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.0)	0 (0.0)
FETAL INCIDENCE	N(%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5) ^b	0 (0.0)
PELVIS: ISCHIUM, INCOMPLETELY OSSIFIED						
LITTER INCIDENCE	N(%)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
FETAL INCIDENCE	N(%)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)

a. Dosage occurred on days 6 through 17 of gestation.

b. Fetus 12885-15 had other skeletal alterations.

c. Fetus 12909-7 had other skeletal alterations.

d. Fetus 12802-1 had other skeletal alterations.

** Significantly different from the control group value ($p \leq 0.01$).

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ElFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 13 (PAGE 1): FETAL OSSIFICATION SITES - CAESAREAN-DELIVERED LIVE FETUSES (DAY 20 OF GESTATION) - SUMMARY

DOSAGE GROUP		I	II	III	IV	V
DOSAGE (MG/KG/DAY) a		0 (VEHICLE)	1	5	10	20
LITTERS EXAMINED	N	24	23	23	24	24
FETUSES EXAMINED	N	176	182	178	184	168
LIVE	N	176	182	178	184	168
OSSIFICATION SITES PER FETUS PER LITTER						
HYOID	MEAN±S.D.	0.97 ± 0.08	0.98 ± 0.06	0.98 ± 0.06	0.97 ± 0.06	1.00 ± 0.02
VERTEBRAE						
CERVICAL	MEAN±S.D.	7.00 ± 0.00	7.00 ± 0.00	7.00 ± 0.00	7.00 ± 0.00	7.00 ± 0.00
THORACIC	MEAN±S.D.	13.08 ± 0.14	13.05 ± 0.09	13.07 ± 0.17	13.10 ± 0.19	13.13 ± 0.16
LUMBAR	MEAN±S.D.	5.91 ± 0.14	5.95 ± 0.09	5.92 ± 0.17	5.89 ± 0.20	5.84 ± 0.16
SACRAL	MEAN±S.D.	3.00 ± 0.00	3.00 ± 0.00	3.00 ± 0.00	3.00 ± 0.00	3.00 ± 0.00
CAUDAL	MEAN±S.D.	4.96 ± 1.08	4.89 ± 0.41	4.74 ± 0.37	4.70 ± 0.23*	4.59 ± 0.43*
RIBS (PAIRS)	MEAN±S.D.	13.06 ± 0.10	13.03 ± 0.06	13.04 ± 0.10	13.09 ± 0.17	13.12 ± 0.14
STERNUM						
MANUBRIUM	MEAN±S.D.	0.99 ± 0.04	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.02	1.00 ± 0.00
STERNAL CENTERS	MEAN±S.D.	3.70 ± 0.55	3.56 ± 0.33	3.80 ± 0.24	3.68 ± 0.25	3.74 ± 0.32
XIPHOID	MEAN±S.D.	0.98 ± 0.08	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.02	1.00 ± 0.00
FORELIMB b						
CARPALS	MEAN±S.D.	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
METACARPALS	MEAN±S.D.	3.72 ± 0.27	3.73 ± 0.29	3.68 ± 0.31	3.72 ± 0.27	3.69 ± 0.28
DIGITS	MEAN±S.D.	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00
PHALANGES	MEAN±S.D.	5.20 ± 0.73	5.12 ± 0.30	5.04 ± 0.18	5.09 ± 0.28	5.01 ± 0.03
HINDLIMB b						
TARSALS	MEAN±S.D.	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
METATARSALS	MEAN±S.D.	3.99 ± 0.28	4.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.02	3.99 ± 0.04
DIGITS	MEAN±S.D.	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00
PHALANGES	MEAN±S.D.	4.82 ± 0.90	5.00 ± 0.00	5.00 ± 0.00	4.98 ± 0.12	4.96 ± 0.20

a. Dosage occurred on days 6 through 17 of gestation.

b. Calculated as average per limb.

* Significantly different from the vehicle control group value ($p \leq 0.05$).

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 14 (PAGE 1): CLINICAL OBSERVATIONS - INDIVIDUAL DATA

RAT #		DESCRIPTION
DOSAGE GROUP I		0 (VEHICLE) MG/KG/DAY
12801		NO ADVERSE FINDINGS
12802		NO ADVERSE FINDINGS
12803		NO ADVERSE FINDINGS
12804		NO ADVERSE FINDINGS
12805		NO ADVERSE FINDINGS
12806		NO ADVERSE FINDINGS
12807		NO ADVERSE FINDINGS
12808		NO ADVERSE FINDINGS
12809		NO ADVERSE FINDINGS
12810		NO ADVERSE FINDINGS
12811		NO ADVERSE FINDINGS
12812		NO ADVERSE FINDINGS
12813		NO ADVERSE FINDINGS
12814		NO ADVERSE FINDINGS
12815		NO ADVERSE FINDINGS
12816		NO ADVERSE FINDINGS
12817		NO ADVERSE FINDINGS
12818		NO ADVERSE FINDINGS
12819		NO ADVERSE FINDINGS
12820		NO ADVERSE FINDINGS
12821		NO ADVERSE FINDINGS
12822	DG(8- 19) DG(20)	LOCALIZED ALOPECIA: LIMBS ALOPECIA NO LONGER APPARENT
12823		NO ADVERSE FINDINGS
12824		NO ADVERSE FINDINGS
12825		NO ADVERSE FINDINGS

DG = DAY OF PRESUMED GESTATION

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 14 (PAGE 2): CLINICAL OBSERVATIONS - INDIVIDUAL DATA

RAT #		DESCRIPTION
DOSAGE GROUP II		1 MG/KG/DAY
12826		NO ADVERSE FINDINGS
12827		NO ADVERSE FINDINGS
12828		NO ADVERSE FINDINGS
12829		NO ADVERSE FINDINGS
12830		NO ADVERSE FINDINGS
12831	DG(9- 19)	LOCALIZED ALOPECIA: UNDERSIDE
	DG(19- 20)	LOCALIZED ALOPECIA: LIMBS a
12832		NO ADVERSE FINDINGS
12833		NO ADVERSE FINDINGS
12834	DG(14- 19)	LOCALIZED ALOPECIA: UNDERSIDE
	DG(20)	ALOPECIA NO LONGER APPARENT
12835		NO ADVERSE FINDINGS
12836		NO ADVERSE FINDINGS
12837		NO ADVERSE FINDINGS
12838		NO ADVERSE FINDINGS
12839		NO ADVERSE FINDINGS
12840		NO ADVERSE FINDINGS
12841		NO ADVERSE FINDINGS
12842		NO ADVERSE FINDINGS
12843		NO ADVERSE FINDINGS
12844		NO ADVERSE FINDINGS
12845		NO ADVERSE FINDINGS
12846		NO ADVERSE FINDINGS
12847		NO ADVERSE FINDINGS
12848		NO ADVERSE FINDINGS
12849	DG(10- 20)	LOCALIZED ALOPECIA: UNDERSIDE a
12850		NO ADVERSE FINDINGS

DG = DAY OF PRESUMED GESTATION

a. Observation confirmed at necropsy.

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 14 (PAGE 3): CLINICAL OBSERVATIONS - INDIVIDUAL DATA

RAT #		DESCRIPTION
DOSAGE GROUP III		5 MG/KG/DAY
12851		NO ADVERSE FINDINGS
12852		NO ADVERSE FINDINGS
12853		NO ADVERSE FINDINGS
12854		NO ADVERSE FINDINGS
12855		NO ADVERSE FINDINGS
12856		NO ADVERSE FINDINGS
12857		NO ADVERSE FINDINGS
12858	DG(18- 20)	LOCALIZED ALOPECIA: UNDERSIDE a
12859		NO ADVERSE FINDINGS
12860		NO ADVERSE FINDINGS
12861		NO ADVERSE FINDINGS
12862		NO ADVERSE FINDINGS
12863	DG(17- 20)	LOCALIZED ALOPECIA: UNDERSIDE a
12864		NO ADVERSE FINDINGS
12865		NO ADVERSE FINDINGS
12866	DG(19- 20)	LOCALIZED ALOPECIA: NECK a
12867		NO ADVERSE FINDINGS
12868	DG(17- 20)	RIGHT FOREPAW: SECOND AND THIRD DIGITS FUSED a
12869		NO ADVERSE FINDINGS
12870		NO ADVERSE FINDINGS
12871		NO ADVERSE FINDINGS
12872		NO ADVERSE FINDINGS
12873		NO ADVERSE FINDINGS
12874		NO ADVERSE FINDINGS
12875		NO ADVERSE FINDINGS

DG = DAY OF PRESUMED GESTATION

a. Observation confirmed at necropsy.

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 14 (PAGE 4): CLINICAL OBSERVATIONS - INDIVIDUAL DATA

RAT #		DESCRIPTION
DOSAGE GROUP IV		10 MG/KG/DAY
12876		NO ADVERSE FINDINGS
12877		NO ADVERSE FINDINGS
12878		NO ADVERSE FINDINGS
12879		NO ADVERSE FINDINGS
12880		NO ADVERSE FINDINGS
12881		NO ADVERSE FINDINGS
12882		NO ADVERSE FINDINGS
12883		NO ADVERSE FINDINGS
12884		NO ADVERSE FINDINGS
12885		NO ADVERSE FINDINGS
12886		NO ADVERSE FINDINGS
12887		NO ADVERSE FINDINGS
12888		NO ADVERSE FINDINGS
12889		NO ADVERSE FINDINGS
12890		NO ADVERSE FINDINGS
12891	DG(10- 20)	LOCALIZED ALOPECIA: UNDERSIDE a
	DG(18- 20)	LOCALIZED ALOPECIA: LIMBS a
12892		NO ADVERSE FINDINGS
12893		NO ADVERSE FINDINGS
12894	DG(17- 20)	LOCALIZED ALOPECIA: LIMBS a
12895		NO ADVERSE FINDINGS
12896		NO ADVERSE FINDINGS
12897		NO ADVERSE FINDINGS
12898		NO ADVERSE FINDINGS
12899		NO ADVERSE FINDINGS
12900		NO ADVERSE FINDINGS

DG = DAY OF PRESUMED GESTATION

a. Observation confirmed at necropsy.

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 14 (PAGE 5): CLINICAL OBSERVATIONS - INDIVIDUAL DATA

RAT #		DESCRIPTION
DOSAGE GROUP V		20 MG/KG/DAY
12901		NO ADVERSE FINDINGS
12902		NO ADVERSE FINDINGS
12903		NO ADVERSE FINDINGS
12904		NO ADVERSE FINDINGS
12905		NO ADVERSE FINDINGS
12906		NO ADVERSE FINDINGS
12907		NO ADVERSE FINDINGS
12908		NO ADVERSE FINDINGS
12909	DG(10- 20)	LOCALIZED ALOPECIA: LIMBS a
12910		NO ADVERSE FINDINGS
12911		NO ADVERSE FINDINGS
12912		NO ADVERSE FINDINGS
12913	DG(13- 20)	LOCALIZED ALOPECIA: UNDERSIDE a
12914		NO ADVERSE FINDINGS
12915		NO ADVERSE FINDINGS
12916		NO ADVERSE FINDINGS
12917		NO ADVERSE FINDINGS
12918	DG(16- 20)	LOCALIZED ALOPECIA: UNDERSIDE a
12919	DG(16- 20)	LOCALIZED ALOPECIA: UNDERSIDE
12920		NO ADVERSE FINDINGS
12921		NO ADVERSE FINDINGS
12922		NO ADVERSE FINDINGS
12923		NO ADVERSE FINDINGS
12924	DG(17- 20)	LOCALIZED ALOPECIA: LIMBS a
12925	DG(15- 17)	COLD TO TOUCH
	DG(15- 17)	UNGROOMED COAT

DG = DAY OF PRESUMED GESTATION

a. Observation confirmed at necropsy.

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 14 (PAGE 6): CLINICAL OBSERVATIONS - INDIVIDUAL DATA

RAT #	DESCRIPTION

SATELLITE DOSAGE GROUP I	0 (VEHICLE) MG/KG/DAY

12573	NO ADVERSE FINDINGS
12574	NO ADVERSE FINDINGS
12575	NO ADVERSE FINDINGS

SATELLITE DOSAGE GROUP II	1 MG/KG/DAY

12576	NO ADVERSE FINDINGS
12577	NO ADVERSE FINDINGS
12578	NO ADVERSE FINDINGS
12579	NO ADVERSE FINDINGS
12580	NO ADVERSE FINDINGS

SATELLITE DOSAGE GROUP III	5 MG/KG/DAY

12581	NO ADVERSE FINDINGS
12582	DG (17- 18) LOCALIZED ALOPECIA: UNDERSIDE a
12583	NO ADVERSE FINDINGS

SATELLITE DOSAGE GROUP IV	10 MG/KG/DAY

12584	NO ADVERSE FINDINGS
12585	NO ADVERSE FINDINGS
12586	NO ADVERSE FINDINGS

SATELLITE DOSAGE GROUP V	20 MG/KG/DAY

12587	NO ADVERSE FINDINGS
12588	NO ADVERSE FINDINGS
12589	NO ADVERSE FINDINGS
12590	NO ADVERSE FINDINGS
12591	NO ADVERSE FINDINGS

DG = DAY OF PRESUMED GESTATION

a. Observation confirmed at necropsy.

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 15 (PAGE 1): NECROPSY OBSERVATIONS - INDIVIDUAL DATA

DOSAGE GROUP DOSAGE (MG/KG/DAY)	RAT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS
I					
0 (VEHICLE)	12801	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12802	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12803	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12804	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12805	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12806	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12807	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12808	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12809	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12810	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12811	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12812	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12813	DG 20	NP	12	ALL TISSUES APPEARED NORMAL.
	12814	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12815	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12816	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12817	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12818	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12819	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12820	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12820	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12821	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12822	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12823	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12824	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12825	DG 20	P	12	ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF GESTATION

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 15 (PAGE 2): NECROPSY OBSERVATIONS - INDIVIDUAL DATA

DOSAGE GROUP DOSAGE (MG/KG/DAY)	RAT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS
II					
1	12826	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12827	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12828	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12829	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12830	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12831	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12832	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12833	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12834	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12835	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12836	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12837	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12838	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12839	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12840	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12841	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12842	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12843	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12844	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12845	DG 20	NP	12	ALL TISSUES APPEARED NORMAL.
	12846	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12847	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12848	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12849	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12850	DG 20	P	12	ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF GESTATION

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 15 (PAGE 3): NECROPSY OBSERVATIONS - INDIVIDUAL DATA

DOSAGE GROUP DOSAGE (MG/KG/DAY)	RAT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS
III					
5	12851	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12852	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12853	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12854	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12855	DG 20	NP	12	ALL TISSUES APPEARED NORMAL.
	12856	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12857	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12858	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12859	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12860	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12861	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12862	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12863	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12864	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12865	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12866	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12867	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12868	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12869	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12870	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12871	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12872	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12873	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12874	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12875	DG 20	P	12	ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT

DG = DAY OF GESTATION

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 15 (PAGE 4): NECROPSY OBSERVATIONS - INDIVIDUAL DATA

DOSAGE GROUP DOSAGE (MG/KG/DAY)	RAT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS
IV 10	12876	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12877	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12878	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12879	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12880	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12881	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12882	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12883	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12884	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12885	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12886	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12887	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12888	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12889	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12890	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12891	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12892	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12893	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12894	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12895	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12896	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12897	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12898	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12899	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12900	DG 20	P	12	ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF GESTATION

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 15 (PAGE 5): NECROPSY OBSERVATIONS - INDIVIDUAL DATA

DOSAGE GROUP DOSAGE (MG/KG/DAY)	RAT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS
V 20	12901	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12902	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12903	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12904	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12905	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12906	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12907	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12908	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12909	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12910	DG 20	NP	12	ALL TISSUES APPEARED NORMAL.
	12911	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12912	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12913	DG 20	P	12	LIVER: MEDIAN LOBE, TAN AREA (0.6 CM X 0.8 CM). ALL OTHER TISSUES APPEARED NORMAL.
	12914	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12915	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12916	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12917	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12918	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12919	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12920	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12921	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12922	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12923	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12924	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	12925	DG 20	P	12	ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF GESTATION

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 15 (PAGE 6): NECROPSY OBSERVATIONS - INDIVIDUAL DATA

SATELLITE DOSAGE GROUP DOSAGE (MG/KG/DAY)	RAT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS
I					
0 (VEHICLE)	12573	DG 18	P	12	ALL TISSUES APPEARED NORMAL.
	12574	DG 18	P	12	ALL TISSUES APPEARED NORMAL.
	12575	DG 18	P	12	ALL TISSUES APPEARED NORMAL.
II					
1	12576	DG 18	P	12	ALL TISSUES APPEARED NORMAL.
	12577	DG 18	P	12	ALL TISSUES APPEARED NORMAL.
	12578	DG 18	P	12	ALL TISSUES APPEARED NORMAL.
	12579	DG 18	P	12	ALL TISSUES APPEARED NORMAL.
	12580	DG 18	P	12	ALL TISSUES APPEARED NORMAL.
III					
5	12581	DG 18	P	12	ALL TISSUES APPEARED NORMAL.
	12582	DG 18	P	12	ALL TISSUES APPEARED NORMAL.
	12583	DG 18	P	12	ALL TISSUES APPEARED NORMAL.
IV					
10	12584	DG 18	P	12	ALL TISSUES APPEARED NORMAL.
	12585	DG 18	P	12	ALL TISSUES APPEARED NORMAL.
	12586	DG 18	P	12	ALL TISSUES APPEARED NORMAL.
V					
20	12587	DG 18	P	12	ALL TISSUES APPEARED NORMAL.
	12588	DG 18	P	12	ALL TISSUES APPEARED NORMAL.
	12589	DG 18	P	12	ALL TISSUES APPEARED NORMAL.
	12590	DG 18	P	12	ALL TISSUES APPEARED NORMAL.
	12591	DG 18	P	12	ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF GESTATION

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 16 (PAGE 1): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS	DAY	0 4 6 7 8 9 10 11 12 13 14 15 16												
		0 (VEHICLE) MG/KG/DAY												
RAT #	DOSAGE GROUP I													
12801 P	226.	261.	272.	277.	284.	286.	297.	304.	312.	316.	325.	329.	335.	
12802 P	212.	242.	250.	254.	262.	263.	270.	274.	280.	282.	288.	297.	303.	
12803 P	236.	267.	285.	292.	292.	301.	310.	317.	319.	327.	331.	345.	357.	
12804 P	221.	245.	255.	256.	261.	262.	269.	273.	269.	279.	281.	289.	300.	
12805 P	242.	256.	276.	278.	281.	286.	288.	294.	299.	310.	316.	315.	333.	
12806 P	229.	252.	256.	266.	270.	275.	283.	285.	288.	292.	299.	302.	314.	
12807 P	224.	263.	273.	284.	285.	290.	293.	300.	304.	309.	314.	314.	326.	
12808 P	244.	267.	277.	290.	293.	299.	299.	308.	317.	317.	321.	333.	345.	
12809 P	228.	262.	276.	280.	287.	288.	297.	301.	308.	308.	318.	332.	357.	
12810 P	247.	273.	283.	284.	291.	295.	292.	298.	307.	316.	320.	323.	328.	
12811 P	238.	253.	257.	265.	276.	281.	289.	289.	291.	295.	303.	308.	314.	
12812 P	232.	254.	266.	270.	273.	277.	278.	289.	291.	298.	294.	308.	313.	
12813 NP	228.	257.	267.	273.	279.	283.	285.	290.	287.	286.	288.	288.	289.	
12814 P	240.	274.	288.	284.	292.	293.	299.	303.	312.	316.	325.	330.	344.	
12815 P	226.	259.	271.	274.	279.	286.	287.	294.	298.	303.	310.	317.	327.	
12816 P	230.	a	275.	277.	279.	285.	292.	297.	301.	307.	304.	316.	323.	
12817 P	220.	a	249.	256.	259.	262.	266.	272.	281.	288.	289.	298.	306.	
12818 P	237.	a	277.	280.	283.	295.	296.	309.	309.	316.	323.	331.	338.	
12819 P	234.	a	256.	261.	266.	268.	268.	273.	279.	283.	287.	292.	300.	
12820 P	242.	a	265.	272.	274.	276.	281.	287.	288.	295.	299.	306.	317.	
12821 P	222.	a	260.	266.	271.	277.	283.	285.	287.	299.	302.	309.	318.	
12822 P	245.	a	280.	283.	291.	298.	299.	305.	309.	322.	322.	334.	352.	
12823 P	215.	a	249.	248.	249.	258.	259.	266.	268.	270.	276.	280.	296.	
12824 P	219.	a	253.	249.	256.	264.	262.	261.	270.	268.	270.	281.	289.	
12825 P	230.	246.	262.	265.	272.	273.	287.	294.	295.	301.	312.	322.	329.	

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAY = DAY OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Value was not recorded.

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 16 (PAGE 2): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY				
STATUS	DAY 17	18	19	20

RAT #	DOSAGE GROUP I		0 (VEHICLE) MG/KG/DAY	

12801 P	354.	367.	379.	400.
12802 P	309.	323.	340.	356.
12803 P	373.	387.	401.	429.
12804 P	312.	323.	337.	367.
12805 P	345.	366.	374.	393.
12806 P	326.	338.	350.	376.
12807 P	333.	353.	365.	385.
12808 P	354.	367.	378.	402.
12809 P	367.	383.	387.	421.
12810 P	342.	350.	366.	391.
12811 P	325.	343.	354.	382.
12812 P	322.	341.	351.	378.
12813 NP	292.	293.	295.	311.
12814 P	360.	366.	387.	420.
12815 P	343.	357.	373.	402.
12816 P	341.	353.	365.	388.
12817 P	323.	336.	350.	375.
12818 P	354.	370.	382.	399.
12819 P	313.	329.	347.	367.
12820 P	328.	340.	357.	382.
12821 P	334.	346.	363.	394.
12822 P	360.	374.	396.	419.
12823 P	308.	323.	334.	355.
12824 P	306.	315.	336.	347.
12825 P	344.	358.	384.	400.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAY = DAY OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

003652

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 16 (PAGE 3): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS		DAY 0	4	6	7	8	9	10	11	12	13	14	15	16
RAT #	DOSAGE GROUP II	1 MG/KG/DAY												
12826 P		224.	258.	273.	280.	284.	288.	293.	295.	309.	314.	322.	330.	340.
12827 P		236.	248.	261.	264.	264.	272.	274.	279.	286.	291.	291.	304.	303.
12828 P		212.	249.	269.	277.	276.	286.	284.	293.	302.	298.	312.	314.	331.
12829 P		212.	224.	234.	245.	243.	241.	244.	248.	257.	257.	259.	272.	278.
12830 P		228.	256.	260.	264.	275.	275.	277.	280.	287.	291.	292.	305.	315.
12831 P		238.	252.	268.	273.	274.	284.	286.	296.	292.	302.	311.	316.	323.
12832 P		227.	244.	254.	260.	264.	268.	277.	279.	284.	287.	295.	299.	312.
12833 P		239.	261.	274.	275.	281.	284.	292.	290.	289.	292.	298.	302.	306.
12834 P		225.	236.	249.	252.	253.	257.	265.	267.	274.	279.	284.	292.	305.
12835 P		230.	274.	293.	298.	302.	291.	310.	311.	316.	326.	333.	338.	347.
12836 P		220.	247.	259.	265.	264.	273.	275.	281.	282.	292.	296.	303.	306.
12837 P		240.	248.	255.	249.	268.	269.	275.	282.	282.	284.	296.	298.	315.
12838 P		228.	239.	253.	253.	261.	266.	267.	270.	274.	288.	290.	297.	306.
12839 P		243.	a	281.	286.	292.	292.	300.	308.	315.	321.	325.	332.	341.
12840 P		230.	a	263.	268.	270.	278.	283.	288.	292.	302.	309.	319.	329.
12841 P		222.	a	272.	273.	279.	285.	292.	295.	303.	312.	320.	330.	342.
12842 P		234.	a	278.	280.	289.	293.	302.	304.	303.	308.	314.	325.	339.
12843 P		222.	a	241.	246.	252.	256.	262.	266.	264.	270.	276.	278.	291.
12844 P		242.	a	281.	282.	287.	290.	294.	304.	303.	311.	314.	326.	340.
12845 NP		217.	a	233.	232.	228.	227.	232.	234.	234.	230.	239.	239.	238.
12846 NP		230.	a	257.	258.	263.	266.	269.	268.	269.	272.	277.	267.	266.
12847 P		236.	a	263.	261.	270.	275.	277.	284.	285.	289.	303.	306.	318.
12848 P		240.	256.	267.	268.	272.	274.	284.	288.	288.	298.	305.	314.	327.
12849 P		237.	260.	274.	282.	284.	290.	298.	301.	303.	317.	322.	333.	335.
12850 P		248.	272.	282.	287.	293.	296.	302.	310.	317.	320.	324.	330.	341.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAY = DAY OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Value was not recorded.

003653

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 16 (PAGE 4): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY				
STATUS	DAY 17	18	19	20

RAT #	DOSAGE GROUP II		1 MG/KG/DAY	

12826 P	352.	364.	371.	396.
12827 P	317.	323.	340.	362.
12828 P	350.	366.	383.	402.
12829 P	293.	306.	324.	331.
12830 P	323.	346.	360.	378.
12831 P	340.	356.	370.	394.
12832 P	322.	340.	343.	373.
12833 P	318.	335.	340.	357.
12834 P	323.	337.	354.	381.
12835 P	354.	362.	376.	391.
12836 P	313.	327.	342.	359.
12837 P	327.	341.	353.	383.
12838 P	319.	333.	344.	372.
12839 P	357.	377.	396.	418.
12840 P	343.	362.	378.	408.
12841 P	351.	364.	374.	402.
12842 P	346.	368.	382.	414.
12843 P	306.	313.	333.	352.
12844 P	342.	358.	372.	412.
12845 NP	235.	239.	240.	245.
12846 NP	265.	266.	261.	265.
12847 P	326.	346.	359.	387.
12848 P	340.	363.	384.	405.
12849 P	350.	365.	388.	407.
12850 P	354.	367.	391.	411.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAY = DAY OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

003654

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 16 (PAGE 5): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY		DAY	0	4	6	7	8	9	10	11	12	13	14	15	16
RAT #	STATUS	DOSAGE GROUP III 5 MG/KG/DAY													
12851	P	225.	268.	278.	288.	292.	295.	303.	310.	314.	325.	330.	340.	350.	
12852	P	223.	253.	265.	267.	276.	281.	278.	283.	285.	292.	298.	305.	315.	
12853	P	222.	259.	274.	273.	278.	280.	288.	290.	299.	302.	308.	318.	328.	
12854	P	232.	267.	267.	289.	290.	294.	302.	300.	299.	300.	312.	317.	329.	
12855	NP	244.	259.	269.	275.	282.	283.	285.	285.	286.	280.	271.	279.	280.	
12856	P	228.	249.	256.	259.	256.	266.	271.	279.	278.	279.	283.	288.	305.	
12857	P	246.	264.	276.	281.	282.	287.	291.	300.	306.	312.	320.	329.	344.	
12858	P	219.	236.	235.	244.	260.	260.	263.	273.	269.	268.	273.	273.	287.	
12859	P	233.	254.	281.	286.	292.	297.	296.	303.	301.	316.	320.	333.	344.	
12860	P	230.	262.	275.	282.	291.	281.	296.	300.	306.	312.	317.	328.	339.	
12861	P	227.	238.	236.	254.	255.	260.	267.	268.	268.	274.	273.	281.	290.	
12862	P	210.	238.	248.	251.	254.	258.	258.	265.	269.	276.	282.	286.	301.	
12863	P	221.	247.	260.	265.	270.	273.	275.	283.	290.	288.	290.	289.	307.	
12864	P	228.	a	272.	275.	279.	284.	283.	297.	300.	303.	316.	320.	331.	
12865	P	220.	a	246.	256.	255.	246.	250.	251.	273.	266.	271.	289.	299.	
12866	P	247.	a	289.	296.	301.	301.	307.	311.	321.	326.	333.	348.	359.	
12867	P	214.	a	245.	247.	246.	246.	249.	256.	258.	265.	266.	275.	284.	
12868	P b	240.	a	278.	279.	279.	281.	287.	291.	292.	289.	297.	309.	315.	
12869	P	236.	a	270.	268.	281.	281.	283.	292.	296.	302.	307.	312.	325.	
12870	P	238.	264.	278.	284.	285.	284.	290.	298.	299.	310.	311.	322.	335.	
12871	P	230.	249.	252.	261.	258.	261.	261.	272.	275.	274.	279.	290.	294.	
12872	P	252.	271.	281.	286.	a	302.	304.	310.	318.	327.	327.	326.	348.	
12873	P	233.	258.	274.	278.	284.	286.	290.	294.	298.	301.	314.	317.	324.	
12874	P	242.	269.	282.	287.	293.	297.	305.	304.	311.	318.	321.	334.	347.	
12875	P	236.	252.	265.	267.	263.	265.	266.	282.	281.	284.	290.	299.	304.	

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAY = DAY OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Value was not recorded.

b. Dam 12868 had a litter consisting of 7 conceptuses; values excluded from group averages and statistical analyses.

003655

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 16 (PAGE 6): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY				
STATUS	DAY 17	18	19	20
RAT #	DOSAGE GROUP III			
	5 MG/KG/DAY			
12851 P	364.	381.	397.	416.
12852 P	333.	353.	367.	393.
12853 P	346.	362.	378.	400.
12854 P	347.	368.	384.	399.
12855 NP	274.	268.	272.	282.
12856 P	320.	333.	348.	376.
12857 P	358.	374.	389.	420.
12858 P	296.	313.	320.	341.
12859 P	361.	374.	388.	421.
12860 P	350.	361.	380.	409.
12861 P	300.	309.	318.	341.
12862 P	315.	330.	338.	363.
12863 P	314.	331.	342.	357.
12864 P	338.	357.	368.	400.
12865 P	310.	324.	338.	358.
12866 P	368.	388.	403.	429.
12867 P	294.	308.	317.	344.
12868 P a	315.	330.	333.	349.
12869 P	337.	352.	368.	394.
12870 P	346.	355.	387.	405.
12871 P	307.	320.	331.	342.
12872 P	355.	372.	372.	400.
12873 P	339.	355.	383.	400.
12874 P	359.	373.	402.	422.
12875 P	315.	323.	352.	361.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAY = DAY OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Dam 12868 had a litter consisting of 7 conceptuses; values excluded from group averages and statistical analyses.

003656

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 16 (PAGE 7): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY		DAY 0	4	6	7	8	9	10	11	12	13	14	15	16
STATUS														
RAT #		DOSAGE GROUP IV				10 MG/KG/DAY								
12876	P	219.	266.	278.	286.	290.	297.	300.	296.	300.	312.	324.	324.	341.
12877	P	230.	262.	273.	274.	276.	282.	289.	290.	294.	298.	306.	313.	326.
12878	P	212.	242.	247.	253.	258.	264.	268.	270.	266.	275.	277.	291.	300.
12879	P	228.	244.	254.	258.	260.	262.	268.	270.	275.	274.	276.	290.	300.
12880	P	230.	248.	258.	258.	259.	267.	268.	272.	274.	279.	282.	291.	304.
12881	P	211.	235.	236.	242.	231.	239.	247.	250.	250.	246.	246.	263.	268.
12882	P	244.	254.	274.	277.	282.	288.	291.	294.	306.	313.	318.	327.	339.
12883	P	244.	a	276.	284.	286.	288.	295.	296.	298.	308.	311.	321.	335.
12884	P	224.	a	254.	270.	262.	273.	282.	280.	283.	298.	292.	304.	312.
12885	P	237.	a	270.	274.	274.	284.	286.	291.	290.	297.	300.	310.	327.
12886	P	235.	a	266.	273.	273.	277.	279.	284.	286.	288.	294.	301.	311.
12887	P	247.	a	279.	279.	289.	288.	291.	296.	301.	308.	314.	323.	337.
12888	P	239.	a	270.	272.	273.	278.	283.	284.	290.	297.	301.	310.	317.
12889	P b	228.	a	263.	272.	271.	272.	271.	271.	278.	281.	283.	286.	285.
12890	P	242.	a	274.	271.	273.	280.	282.	281.	293.	297.	297.	303.	317.
12891	P	236.	a	256.	262.	262.	265.	269.	272.	274.	280.	286.	295.	300.
12892	P	226.	a	256.	265.	263.	260.	263.	265.	275.	282.	289.	292.	304.
12893	P	232.	a	278.	276.	278.	286.	294.	295.	303.	313.	313.	330.	339.
12894	P	221.	a	253.	251.	242.	256.	259.	267.	271.	273.	270.	284.	296.
12895	P	221.	a	244.	252.	254.	257.	267.	266.	267.	269.	279.	283.	293.
12896	P	236.	a	271.	275.	273.	268.	279.	284.	288.	297.	301.	305.	323.
12897	P	233.	a	269.	278.	275.	275.	281.	282.	284.	291.	292.	302.	314.
12898	P	240.	265.	276.	279.	287.	284.	286.	297.	297.	301.	310.	322.	336.
12899	P	220.	244.	256.	261.	260.	266.	262.	270.	274.	277.	285.	296.	307.
12900	P	226.	237.	248.	246.	254.	250.	261.	259.	265.	268.	276.	290.	300.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAY = DAY OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Value was not recorded.

b. Dam 12889 had a litter consisting of 3 conceptuses; values excluded from group averages and statistical analyses.

003657

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 16 (PAGE 8): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY				
STATUS	DAY 17	18	19	20

RAT #	DOSAGE GROUP IV			
10 MG/KG/DAY				

12876 P	358.	360.	375.	390.
12877 P	329.	344.	354.	378.
12878 P	313.	329.	346.	374.
12879 P	309.	326.	342.	367.
12880 P	314.	333.	341.	372.
12881 P	280.	282.	298.	310.
12882 P	358.	378.	385.	420.
12883 P	348.	365.	373.	392.
12884 P	320.	334.	344.	371.
12885 P	330.	344.	358.	378.
12886 P	315.	332.	344.	379.
12887 P	349.	360.	373.	396.
12888 P	329.	337.	351.	369.
12889 P a	289.	301.	309.	321.
12890 P	328.	339.	354.	374.
12891 P	306.	318.	331.	349.
12892 P	319.	328.	347.	371.
12893 P	348.	369.	383.	412.
12894 P	309.	321.	341.	364.
12895 P	307.	313.	328.	343.
12896 P	331.	345.	355.	380.
12897 P	326.	335.	344.	374.
12898 P	350.	365.	390.	414.
12899 P	314.	327.	352.	364.
12900 P	314.	338.	359.	375.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAY = DAY OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Dam 12889 had a litter consisting of 3 conceptuses; values excluded from group averages and statistical analyses.

003658

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 16 (PAGE 9): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY															
STATUS	DAY	0	4	6	7	8	9	10	11	12	13	14	15	16	
RAT #	DOSAGE GROUP	V 20 MG/KG/DAY													
12901 P	219.	243.	254.	254.	264.	269.	266.	273.	277.	282.	286.	292.	306.		
12902 P	229.	244.	251.	252.	259.	256.	258.	264.	265.	271.	274.	275.	284.		
12903 P	211.	249.	260.	260.	263.	258.	267.	271.	276.	267.	282.	283.	295.		
12904 P	227.	255.	261.	263.	259.	265.	264.	266.	260.	264.	256.	270.	273.		
12905 P	222.	242.	259.	258.	261.	261.	269.	272.	269.	277.	279.	285.	294.		
12906 P	228.	242.	254.	253.	257.	259.	263.	266.	274.	269.	280.	282.	298.		
12907 P	230.	251.	271.	278.	276.	276.	272.	267.	283.	290.	286.	294.	302.		
12908 P	238.	254.	268.	268.	276.	275.	272.	283.	285.	284.	285.	288.	303.		
12909 P	239.	257.	268.	265.	267.	275.	271.	271.	274.	268.	278.	275.	289.		
12910 NP	212.	243.	253.	254.	259.	251.	256.	260.	247.	243.	246.	246.	240.		
12911 P	215.	241.	253.	251.	252.	253.	258.	259.	260.	263.	268.	275.	286.		
12912 P	224.	a	256.	258.	262.	259.	264.	266.	274.	287.	287.	287.	298.		
12913 P	243.	a	272.	274.	274.	278.	282.	280.	284.	286.	292.	300.	308.		
12914 P	225.	a	274.	279.	274.	284.	285.	290.	295.	300.	301.	315.	325.		
12915 P	237.	a	267.	279.	275.	278.	282.	289.	292.	287.	290.	300.	314.		
12916 P	248.	a	275.	260.	256.	264.	263.	245.	238.	250.	264.	271.	289.		
12917 P	236.	a	254.	252.	250.	251.	252.	252.	257.	263.	266.	269.	282.		
12918 P	245.	a	265.	266.	245.	248.	258.	263.	264.	266.	264.	266.	280.		
12919 P	228.	a	269.	257.	271.	279.	277.	272.	268.	276.	276.	293.	304.		
12920 P	222.	a	255.	250.	253.	254.	250.	256.	272.	266.	281.	284.	285.		
12921 P	230.	a	268.	271.	273.	273.	277.	280.	278.	278.	281.	293.	304.		
12922 P	233.	a	259.	258.	251.	251.	255.	259.	260.	260.	258.	263.	273.		
12923 P	240.	268.	278.	279.	269.	271.	277.	276.	281.	280.	292.	304.	311.		
12924 P	234.	250.	259.	262.	255.	257.	256.	266.	261.	258.	272.	276.	285.		
12925 P	240.	260.	273.	270.	262.	253.	263.	270.	258.	247.	235.	230.	231.		

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAY = DAY OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Value was not recorded.

003659

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 16 (PAGE 10): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY				
STATUS	DAY 17	18	19	20

RAT #	DOSAGE GROUP V			
20 MG/KG/DAY				

12901 P	313.	320.	333.	360.
12902 P	295.	310.	320.	337.
12903 P	309.	322.	329.	353.
12904 P	279.	292.	301.	309.
12905 P	294.	310.	323.	350.
12906 P	306.	320.	337.	352.
12907 P	301.	310.	328.	352.
12908 P	313.	323.	330.	352.
12909 P	303.	315.	323.	343.
12910 NP	239.	240.	245.	252.
12911 P	296.	303.	321.	345.
12912 P	309.	322.	338.	364.
12913 P	310.	317.	333.	354.
12914 P	336.	337.	355.	384.
12915 P	325.	338.	350.	379.
12916 P	304.	317.	330.	352.
12917 P	294.	305.	322.	343.
12918 P	294.	302.	325.	335.
12919 P	311.	322.	335.	347.
12920 P	298.	313.	322.	347.
12921 P	313.	325.	339.	358.
12922 P	283.	292.	298.	323.
12923 P	328.	346.	366.	385.
12924 P	303.	307.	325.	341.
12925 P	247.	272.	284.	303.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAY = DAY OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

003660

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 16 (PAGE 11): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY		DAY	0	4	6	7	8	9	10	11	12	13	14	15	16
STATUS															
RAT #	SATELLITE DOSAGE GROUP I														
		0 (VEHICLE) MG/KG/DAY													
12573	P	236.	254.	266.	271.	271.	279.	283.	293.	296.	301.	305.	310.	317.	
12574	P	233.	259.	273.	280.	280.	290.	295.	299.	304.	309.	318.	328.	333.	
12575	P	248.	269.	283.	288.	293.	296.	299.	305.	309.	314.	320.	328.	334.	
		DAY 17	18												
12573	P	332.	347.												
12574	P	348.	367.												
12575	P	350.	366.												

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAY = DAY OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

003661

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 16 (PAGE 12): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS	DAY 0	4	6	7	8	9	10	11	12	13	14	15	16
RAT #	SATELLITE DOSAGE GROUP II 1 MG/KG/DAY												
12576 P	227.	244.	253.	259.	260.	260.	267.	272.	280.	285.	290.	296.	310.
12577 P	245.	259.	280.	282.	284.	290.	296.	301.	306.	308.	318.	328.	337.
12578 P	221.	232.	258.	257.	260.	265.	271.	271.	278.	278.	286.	293.	305.
12579 P	232.	253.	269.	271.	282.	282.	288.	292.	294.	302.	309.	317.	325.
12580 P	248.	261.	273.	272.	277.	280.	291.	296.	302.	305.	312.	319.	333.
	DAY 17	18											
12576 P	312.	339.											
12577 P	358.	382.											
12578 P	314.	343.											
12579 P	343.	367.											
12580 P	353.	370.											

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAY = DAY OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

003662

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 16 (PAGE 13): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS	DAY 0	4	6	7	8	9	10	11	12	13	14	15	16
RAT #	SATELLITE DOSAGE GROUP III 5 MG/KG/DAY												
12581 P	228.	244.	257.	258.	258.	256.	258.	267.	272.	282.	287.	297.	301.
12582 P	243.	260.	271.	274.	279.	283.	290.	291.	295.	306.	305.	314.	325.
12583 P	251.	275.	296.	306.	309.	313.	319.	322.	328.	338.	344.	356.	373.
	DAY 17	18											
12581 P	316.	334.											
12582 P	338.	360.											
12583 P	389.	412.											

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAY = DAY OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

003663

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 16 (PAGE 14): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY		DAY	0	4	6	7	8	9	10	11	12	13	14	15	16
STATUS															
RAT #		SATELLITE DOSAGE GROUP IV							10 MG/KG/DAY						
12584 P		228.	252.	265.	269.	272.	270.	274.	275.	281.	290.	290.	297.	309.	
12585 P		242.	265.	276.	273.	277.	283.	287.	290.	296.	303.	308.	310.	322.	
12586 P		250.	262.	273.	275.	277.	282.	283.	290.	289.	294.	296.	306.	316.	
		DAY 17	18												
12584 P		318.	340.												
12585 P		334.	351.												
12586 P		323.	339.												

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAY = DAY OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

003664

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 16 (PAGE 15): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY															
STATUS	DAY	0	4	6	7	8	9	10	11	12	13	14	15	16	
RAT #	SATELLITE DOSAGE GROUP V														
20 MG/KG/DAY															
12587 P	228.	232.	249.	232.	243.	241.	243.	258.	260.	249.	255.	266.	285.		
12588 P	243.	262.	282.	286.	289.	288.	287.	291.	289.	294.	305.	318.	328.		
12589 P	221.	240.	252.	258.	262.	267.	256.	246.	254.	267.	268.	283.	284.		
12590 P	236.	256.	270.	266.	268.	268.	268.	274.	279.	280.	284.	292.	304.		
12591 P	249.	267.	288.	292.	293.	295.	300.	306.	302.	297.	295.	316.	327.		
DAY 17		18													
12587 P	294.	319.													
12588 P	346.	360.													
12589 P	299.	321.													
12590 P	314.	336.													
12591 P	345.	362.													

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAY = DAY OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

003665

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 17 (PAGE 1): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY									
STATUS	DAYS	0 - 4	4 - 6	6 - 8	8 - 10	10 - 12	12 - 14	14 - 16	16 - 18 18 - 20
RAT #	DOSAGE GROUP I	0 (VEHICLE) MG/KG/DAY							
12801 P	56.	48.	52.	50.	58.	60.	50.	60.	59.
12802 P	54.	40.	43.	44.	47.	49.	50.	49.	52.
12803 P	82.	51.	55.	53.	57.	59.	62.	63.	60.
12804 P	86.	44.	42.	41.	32.	44.	50.	58.	52.
12805 P	79.	47.	51.	49.	55.	52.	46.	55.	54.
12806 P	53.	41.	49.	48.	47.	51.	45.	54.	53.
12807 P	71.	51.	52.	50.	49.	51.	45.	50.	53.
12808 P	96.	45.	61.	49.	51.	47.	52.	63.	56.
12809 P	91.	47.	57.	49.	53.	61.	64.	50.	51.
12810 P	103.	45.	53.	47.	50.	56.	46.	58.	58.
12811 P	88.	35.	51.	44.	40.	44.	40.	52.	48.
12812 P	190. a	a	48.	48.	49.	47.	46.	48.	48.
12813 NP	89.	45.	49.	53.	41.	44.	51.	54.	43.
12814 P	102.	54.	48.	50.	50.	54.	58.	61.	59.
12815 P	94.	49.	50.	47.	49.	49.	53.	60.	56.
12816 P	97.	56.	56.	53.	57.	53.	58.	59.	53.
12817 P	74.	43.	45.	45.	46.	48.	53.	52.	45.
12818 P	104.	61.	58.	62.	62.	63.	65.	61.	60.
12819 P	85.	39.	43.	41.	44.	47.	46.	49.	45.
12820 P	81.	42.	44.	42.	48.	50.	54.	55.	57.
12821 P	84.	44.	49.	51.	48.	52.	54.	51.	53.
12822 P	85.	47.	53.	52.	54.	55.	62.	55.	51.
12823 P	71.	45.	41.	44.	42.	43.	47.	54.	48.
12824 P	81.	46.	35.	45.	47.	45.	48.	54.	50.
12825 P	80.	44.	44.	44.	44.	54.	53.	53.	44.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAYS = DAYS OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Value appeared incorrectly recorded and was excluded from group averages and statistical analyses.

003666

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 17 (PAGE 2): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS DAYS	PREGNANCY STATUS DAYS								
	0 - 4	4 - 6	6 - 8	8 - 10	10 - 12	12 - 14	14 - 16	16 - 18	18 - 20
RAT #	DOSAGE GROUP II 1 MG/KG/DAY								
12826 P	82.	49.	49.	47.	48.	56.	55.	57.	55.
12827 P	71.	41.	42.	43.	45.	47.	41.	50.	45.
12828 P	91.	47.	49.	45.	50.	47.	45.	58.	57.
12829 P	14.	41.	44.	33.	40.	43.	47.	51.	44.
12830 P	90.	38.	48.	45.	43.	45.	46.	55.	52.
12831 P	89.	48.	49.	50.	50.	54.	52.	60.	57.
12832 P	87.	43.	48.	46.	44.	48.	46.	46.	46.
12833 P	90.	45.	45.	47.	36.	43.	40.	50.	40.
12834 P	73.	44.	40.	43.	44.	45.	47.	60.	55.
12835 P	101.	57.	55.	47.	52.	62.	64.	60.	55.
12836 P	91.	47.	46.	50.	49.	52.	49.	50.	40.
12837 P	87.	30.	39.	47.	46.	40.	49.	58.	55.
12838 P	70.	40.	43.	43.	41.	50.	44.	50.	48.
12839 P	95.	47.	50.	48.	50.	51.	54.	55.	52.
12840 P	80.	49.	49.	50.	55.	56.	62.	62.	60.
12841 P	86.	47.	45.	48.	50.	55.	56.	42.	47.
12842 P	93.	50.	51.	51.	47.	52.	54.	58.	54.
12843 P	76.	36.	41.	43.	45.	42.	47.	48.	46.
12844 P	94.	52.	48.	47.	56.	49.	57.	54.	57.
12845 NP	69.	35.	77.	47.	42.	66.	a	40.	43.
12846 NP	64.	40.	45.	46.	45.	45.	32.	33.	30.
12847 P	77.	39.	40.	44.	45.	43.	51.	52.	49.
12848 P	82.	43.	44.	42.	44.	45.	50.	49.	44.
12849 P	82.	45.	49.	47.	51.	56.	52.	54.	52.
12850 P	86.	46.	44.	48.	52.	48.	52.	43.	51.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAYS = DAYS OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Spilled feed precluded the calculation of this value.

003667

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 17 (PAGE 3): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY									
STATUS	DAYS	0 - 4	4 - 6	6 - 8	8 - 10	10 - 12	12 - 14	14 - 16	16 - 18 18 - 20

RAT #	DOSAGE GROUP III				5 MG/KG/DAY				

12851 P	97.	48.	53.	52.	55.	55.	59.	61.	54.
12852 P	48.	45.	47.	44.	43.	49.	48.	53.	51.
12853 P	69.	49.	49.	48.	50.	54.	46.	57.	59.
12854 P	103.	39.	60.	51.	41.	48.	48.	69.	57.
12855 NP	81.	40.	47.	41.	38.	32.	37.	31.	34.
12856 P	88.	38.	39.	47.	41.	47.	50.	58.	52.
12857 P	103.	49.	50.	49.	50.	55.	56.	52.	57.
12858 P	78.	32.	42.	41.	43.	39.	40.	45.	45.
12859 P	101.	57.	63.	55.	52.	58.	58.	65.	61.
12860 P	103.	57.	58.	49.	56.	63.	67.	62.	59.
12861 P	78.	33.	47.	47.	45.	47.	43.	52.	53.
12862 P	82.	44.	47.	47.	47.	48.	46.	59.	51.
12863 P	80.	42.	46.	45.	48.	42.	40.	46.	44.
12864 P	96.	54.	53.	46.	58.	58.	61.	63.	60.
12865 P	56.	54.	41.	29.	39.	37.	53.	51.	46.
12866 P	95.	52.	57.	51.	52.	53.	60.	57.	52.
12867 P	76.	43.	36.	38.	45.	45.	49.	48.	44.
12868 P a	87.	50.	48.	48.	49.	46.	58.	54.	52.
12869 P	76.	43.	48.	46.	53.	46.	51.	50.	49.
12870 P	87.	44.	45.	42.	44.	52.	54.	53.	54.
12871 P	71.	35.	40.	37.	46.	38.	45.	43.	35.
12872 P	90.	44.	46.	45.	49.	50.	43.	48.	52.
12873 P	83.	52.	52.	42.	50.	59.	55.	56.	53.
12874 P	96.	46.	51.	52.	50.	50.	59.	54.	54.
12875 P	81.	46.	37.	36.	46.	44.	53.	51.	48.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAYS = DAYS OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Dam 12868 had a litter consisting of 7 conceptuses; values excluded from group averages and statistical analyses.

003668

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 17 (PAGE 4): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY										
STATUS	DAYS	0 - 4	4 - 6	6 - 8	8 - 10	10 - 12	12 - 14	14 - 16	16 - 18	18 - 20
RAT #	DOSAGE GROUP IV	10 MG/KG/DAY								
12876 P	101.	56.	54.	52.	50.	54.	56.	46.	50.	
12877 P	88.	47.	49.	50.	50.	50.	50.	47.	48.	
12878 P	20.	36.	42.	46.	41.	40.	48.	56.	54.	
12879 P	94.	45.	49.	43.	53.	41.	46.	56.	55.	
12880 P	90.	43.	43.	45.	44.	47.	48.	54.	48.	
12881 P	77.	26.	35.	38.	37.	31.	43.	43.	38.	
12882 P	86.	48.	51.	49.	54.	53.	45.	57.	54.	
12883 P	88.	52.	47.	47.	48.	50.	56.	52.	49.	
12884 P	84.	43.	49.	52.	46.	48.	53.	55.	54.	
12885 P	70.	43.	45.	47.	47.	47.	52.	50.	44.	
12886 P	100.	50.	50.	54.	53.	50.	55.	55.	59.	
12887 P	86.	47.	53.	50.	53.	54.	59.	56.	52.	
12888 P	85.	51.	46.	46.	50.	54.	56.	57.	49.	
12889 P a	74.	48.	45.	42.	41.	46.	43.	50.	48.	
12890 P	84.	48.	40.	45.	51.	49.	53.	55.	48.	
12891 P	94.	44.	46.	46.	48.	50.	48.	52.	45.	
12892 P	91.	40.	42.	39.	47.	55.	49.	56.	55.	
12893 P	87.	51.	45.	49.	b	54.	59.	62.	56.	
12894 P	74.	47.	32.	43.	44.	35.	55.	53.	51.	
12895 P	67.	35.	37.	45.	39.	44.	45.	43.	39.	
12896 P	77.	46.	37.	37.	49.	47.	50.	52.	48.	
12897 P	78.	43.	46.	44.	45.	44.	47.	40.	45.	
12898 P	92.	51.	48.	39.	46.	52.	60.	60.	57.	
12899 P	77.	47.	47.	43.	48.	47.	54.	49.	46.	
12900 P	77.	38.	41.	36.	41.	50.	66.	53.	51.	

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAYS = DAYS OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Dam 12889 had a litter consisting of 3 conceptuses; values excluded from group averages and statistical analyses.

b. Spilled feed precluded the calculation of this value.

003669

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 17 (PAGE 5): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY									
STATUS	DAYS	0 - 4	4 - 6	6 - 8	8 - 10	10 - 12	12 - 14	14 - 16	16 - 18 18 - 20
RAT #	DOSAGE GROUP	V 20 MG/KG/DAY							
12901 P	49.	45.	46.	42.	44.	50.	49.	45.	46.
12902 P	83.	43.	41.	37.	41.	44.	40.	50.	40.
12903 P	71.	48.	45.	43.	46.	42.	35.	46.	52.
12904 P	68.	44.	38.	41.	34.	31.	35.	37.	39.
12905 P	83.	45.	39.	43.	40.	46.	45.	48.	49.
12906 P	81.	42.	38.	37.	45.	47.	40.	48.	46.
12907 P	97.	52.	49.	40.	39.	49.	43.	40.	49.
12908 P	98.	49.	50.	47.	47.	49.	45.	41.	42.
12909 P	92.	46.	38.	47.	40.	33.	33.	47.	48.
12910 NP	84.	44.	38.	37.	36.	31.	32.	31.	41.
12911 P	84.	46.	39.	39.	39.	43.	48.	46.	40.
12912 P	81.	43.	41.	41.	47.	50.	49.	51.	51.
12913 P	87.	45.	39.	47.	40.	46.	49.	40.	46.
12914 P	90.	51.	42.	45.	55.	50.	53.	45.	49.
12915 P	101.	44.	45.	44.	51.	46.	53.	56.	54.
12916 P	80.	44.	29.	31.	9.	42.	53.	52.	47.
12917 P	76.	40.	37.	30.	33.	39.	39.	44.	45.
12918 P	68.	52.	26.	30.	39.	37.	34.	40.	46.
12919 P	79.	44.	39.	45.	31.	41.	52.	48.	43.
12920 P	74.	43.	34.	29.	45.	42.	38.	41.	40.
12921 P	85.	46.	43.	39.	39.	35.	48.	48.	44.
12922 P	76.	42.	33.	33.	37.	35.	37.	42.	41.
12923 P	89.	49.	35.	34.	39.	41.	48.	49.	50.
12924 P	75.	42.	34.	30.	37.	33.	41.	42.	37.
12925 P	90.	48.	31.	28.	32.	12.	16.	36.	38.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAYS = DAYS OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

003670

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 17 (PAGE 6): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY									
STATUS	DAYS	0 - 4	4 - 6	6 - 8	8 - 10	10 - 12	12 - 14	14 - 16	16 - 18
RAT #	SATELLITE DOSAGE GROUP I					0 (VEHICLE) MG/KG/DAY			
12573 P	87.	48.	44.	48.	50.	48.	42.	45.	
12574 P	89.	48.	49.	50.	52.	52.	44.	45.	
12575 P	97.	53.	56.	50.	57.	59.	64.	62.	
RAT #	SATELLITE DOSAGE GROUP II					1 MG/KG/DAY			
12576 P	85.	42.	47.	43.	48.	46.	53.	43.	
12577 P	92.	56.	53.	52.	52.	50.	55.	54.	
12578 P	71.	40.	42.	43.	44.	42.	50.	48.	
12579 P	86.	47.	53.	48.	46.	49.	53.	51.	
12580 P	78.	41.	39.	45.	48.	49.	57.	52.	
RAT #	SATELLITE DOSAGE GROUP III					5 MG/KG/DAY			
12581 P	82.	52.	42.	40.	53.	57.	52.	55.	
12582 P	85.	43.	41.	46.	45.	47.	51.	48.	
12583 P	92.	49.	54.	50.	49.	56.	60.	55.	
RAT #	SATELLITE DOSAGE GROUP IV					10 MG/KG/DAY			
12584 P	83.	48.	46.	45.	46.	48.	54.	46.	
12585 P	90.	42.	40.	49.	53.	55.	53.	48.	
12586 P	85.	43.	42.	43.	40.	41.	51.	32.	
RAT #	SATELLITE DOSAGE GROUP V					20 MG/KG/DAY			
12587 P	74.	37.	23.	34.	42.	32.	53.	46.	
12588 P	85.	50.	48.	41.	42.	50.	51.	44.	
12589 P	76.	42.	44.	33.	24.	44.	40.	39.	
12590 P	90.	46.	43.	40.	42.	44.	55.	47.	
12591 P	100.	57.	54.	44.	43.	32.	61.	52.	

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAYS = DAYS OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

003671

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 18 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - INDIVIDUAL DATA

RAT #	VIABLE FETUSES					DEAD FETUSES			EARLY RESORPTIONS		LATE RESORPTIONS		IMPLANTATION SITES			CORPORA LUTEA				
	SEX		RIGHT	LEFT	TOTAL	RIGHT	LEFT	TOTAL	RIGHT	LEFT	TOTAL	RIGHT	LEFT	TOTAL	RIGHT	LEFT	TOTAL	RIGHT	LEFT	TOTAL
	M	F	HORN			HORN			HORN			HORN			HORN			HORN		
DOSAGE GROUP I					0 (VEHICLE) MG/KG/DAY															
12801	9	4	8	5	13	0	0	0	0	1	1	0	0	0	8	6	14	8	9	17
12802	9	5	9	5	14	0	0	0	1	0	1	0	0	0	10	5	15	10	9	19
12803	9	7	8	8	16	0	0	0	0	0	0	0	0	0	8	8	16	9	8	17
12804	5	8	5	8	13	0	0	0	0	0	0	0	0	0	5	8	13	6	11	17
12805	7	8	8	7	15	0	0	0	0	0	0	0	0	0	8	7	15	10	7	17
12806	9	6	9	6	15	0	0	0	0	0	0	0	0	0	9	6	15	9	7	16
12807	6	8	4	10	14	0	0	0	1	1	2	0	0	0	5	11	16	5	12	17
12808	7	5	6	6	12	0	0	0	2	3	5	0	0	0	8	9	17	9	11	20
12809	8	10	10	8	18	0	0	0	0	0	0	0	0	0	10	8	18	10	9	19
12810	6	4	0	10	10	0	0	0	0	0	0	0	0	0	0	10	10	5	10	15
12811	4	10	5	9	14	0	0	0	0	0	0	0	0	0	5	9	14	7	9	16
12812	7	7	8	6	14	0	0	0	1	0	1	0	0	0	9	6	15	10	6	16
12813	NOT PREGNANT																			
12814	7	9	7	9	16	0	0	0	2	1	3	0	0	0	8	10	18	9	10	19
12815	6	9	8	7	15	0	0	0	2	0	2	0	0	0	10	7	17	10	9	19
12816	7	5	5	7	12	0	0	0	2	0	2	0	0	0	7	7	14	7	7	14
12817	8	7	6	9	15	0	0	0	0	0	0	0	0	0	6	9	15	6	9	15
12818	3	10	9	4	13	0	0	0	1	1	2	0	0	0	10	5	15	12	6	18
12819	5	10	10	5	15	0	0	0	0	1	1	0	0	0	10	6	16	11	6	17
12820	6	8	8	6	14	0	0	0	0	1	1	0	0	0	8	7	15	8	7	15
12821	10	5	7	8	15	0	0	0	0	0	0	0	0	0	7	8	15	11	10	21
12822	10	5	7	8	15	0	0	0	0	0	0	0	0	0	7	8	15	7	10	17
12823	8	6	11	3	14	0	0	0	0	1	1	0	0	0	11	4	15	12	5	17
12824	4	8	6	6	12	0	0	0	0	0	0	0	0	0	6	6	12	7	7	14
12825	7	11	8	10	18	0	0	0	0	0	0	0	0	0	8	10	18	8	10	18

M = MALE F = FEMALE

PLACENTAE APPEARED NORMAL UNLESS NOTED OTHERWISE.

003672

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ElFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 18 (PAGE 2): CAESAREAN-SECTIONING OBSERVATIONS - INDIVIDUAL DATA

		VIABLE FETUSES				DEAD FETUSES		EARLY RESORPTIONS		LATE RESORPTIONS		IMPLANTATION SITES		CORPORA LUTEA						
RAT #	SEX		RIGHT LEFT		TOTAL	RIGHT LEFT		TOTAL	RIGHT LEFT		TOTAL	RIGHT LEFT		TOTAL	RIGHT LEFT		TOTAL			
	M	F	HORN			HORN			HORN			HORN			HORN			OVARY		
DOSAGE GROUP II		1 MG/KG/DAY																		
12826	8	6	9	5	14	0	0	0	0	0	0	0	0	0	9	5	14	12	5	17
12827	5	8	7	6	13	0	0	0	0	1	1	0	0	0	7	7	14	8	9	17
12828	10	8	11	7	18	0	0	0	0	0	0	0	0	0	11	7	18	11	8	19
12829	8	6	7	7	14	0	0	0	1	0	1	0	0	0	8	7	15	8	8	16
12830	7	8	8	7	15	0	0	0	0	0	0	0	0	0	8	7	15	9	7	16
12831	6	10	11	5	16	0	0	0	1	0	1	0	0	0	12	5	17	12	5	17
12832	7	7	6	8	14	0	0	0	1	0	1	0	0	0	7	8	15	10	10	20
12833	10	3	7	6	13	0	0	0	1	0	1	0	0	0	8	6	14	8	6	14
12834	9	6	5	10	15	0	0	0	0	0	0	0	0	0	5	10	15	5	10	15
12835	3	6	2	7	9	0	0	0	0	0	0	0	0	0	2	7	9	9	8	17
12836	6	9	7	8	15	0	0	0	1	0	1	0	0	0	8	8	16	8	10	18
12837	4	10	7	7	14	0	0	0	1	0	1	0	0	0	8	7	15	8	8	16
12838	8	7	9	6	15	0	0	0	0	0	0	0	0	0	9	6	15	9	6	15
12839	6	11	7	10	17	0	0	0	0	0	0	0	0	0	7	10	17	7	11	18
12840	11	6	9	8	17	0	0	0	0	0	0	0	0	0	9	8	17	9	10	19
12841	9	8	9	8	17	0	0	0	0	0	0	0	0	0	9	8	17	9	8	17
12842	9	7	10	6	16	0	0	0	0	0	0	0	0	0	10	6	16	10	6	16
12843	5	8	7	6	13	0	0	0	0	1	1	0	0	0	7	7	14	7	8	15
12844	6	11	11	6	17	0	0	0	0	0	0	0	0	0	11	6	17	11	8	19
12845	NOT PREGNANT																			
12846	NOT PREGNANT																			
12847	11	7	14	4	18	0	0	0	0	0	0	0	0	0	14	4	18	15	6	21
12848	7	11	13	5	18	0	0	0	0	0	0	0	0	0	13	5	18	13	7	20
12849	9	6	9	6	15	0	0	0	0	0	0	0	0	0	9	6	15	9	6	15
12850	7	9	7	9	16	0	0	0	0	2	2	0	0	0	7	11	18	7	12	19

M = MALE F = FEMALE

PLACENTAE APPEARED NORMAL UNLESS NOTED OTHERWISE.

003673

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 18 (PAGE 3): CAESAREAN-SECTIONING OBSERVATIONS - INDIVIDUAL DATA

VIABLE FETUSES					DEAD FETUSES			EARLY RESORPTIONS		LATE RESORPTIONS		IMPLANTATION SITES			CORPORA LUTEA					
RAT #	SEX		RIGHT LEFT		TOTAL	RIGHT LEFT		TOTAL	RIGHT LEFT		TOTAL	RIGHT LEFT		TOTAL	RIGHT LEFT		TOTAL	RIGHT LEFT		TOTAL
	M	F	HORN			HORN			HORN			HORN			HORN			OVARY		
DOSAGE GROUP III					5 MG/KG/DAY															
12851	7	8	4	11	15	0	0	0	1	0	1	0	0	0	5	11	16	6	12	18
12852	8	8	6	10	16	0	0	0	0	0	0	0	0	0	6	10	16	6	11	17
12853	5	9	10	4	14	0	0	0	0	1	1	0	0	0	10	5	15	10	7	17
12854	6	10	7	9	16	0	0	0	0	0	0	0	0	0	7	9	16	8	10	18
12855	NOT PREGNANT																			
12856	5	9	5	9	14	0	0	0	0	0	0	0	0	0	5	9	14	5	9	14
12857	11	8	9	10	19	0	0	0	0	0	0	0	0	0	9	10	19	12	11	23
12858	7	7	5	9	14	0	0	0	1	0	1	0	0	0	6	9	15	6	11	17
12859	10	7	10	7	17	0	0	0	0	0	0	0	0	0	10	7	17	10	7	17
12860	7	8	6	9	15	0	0	0	1	0	1	0	0	0	7	9	16	9	11	20
12861	6	6	8	4	12	0	0	0	1	1	2	0	0	0	9	5	14	10	8	18
12862	7	8	8	7	15	0	0	0	0	0	0	0	0	0	8	7	15	8	7	15
12863	5	9	4	10	14	0	0	0	1	0	1	0	0	0	5	10	15	5	10	15
12864	6	8	10	4	14	0	0	0	0	0	0	0	0	0	10	4	14	12	5	17
12865	5	10	7	8	15	0	0	0	1	1	2	0	0	0	8	9	17	8	9	17
12866	9	10	11	8	19	0	0	0	0	0	0	0	0	0	11	8	19	11	11	22
12867	9	5	4	10	14	0	0	0	0	0	0	0	0	0	4	10	14	5	10	15
12868	1	4	2	3	5	0	0	0	0	2	2	0	0	0	2	5	7	7	6	13
12869	9	6	7	8	15	0	0	0	0	0	0	0	0	0	7	8	15	7	8	15
12870	6	10	6	10	16	0	0	0	0	0	0	0	0	0	6	10	16	6	11	17
12871	8	6	6	8	14	0	0	0	0	2	2	0	0	0	6	10	16	6	11	17
12872	9	5	9	5	14	0	0	0	0	0	0	0	0	0	9	5	14	10	6	16
12873	5	9	4	10	14	0	0	0	1	0	1	0	0	0	5	10	15	5	13	18
12874	7	9	7	9	16	0	0	0	0	1	1	0	0	0	7	10	17	7	10	17
12875	8	2	2	8	10	0	0	0	4	1	5	0	0	0	6	9	15	7	9	16

M = MALE F = FEMALE

PLACENTAE APPEARED NORMAL UNLESS NOTED OTHERWISE.

003674

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 18 (PAGE 4): CAESAREAN-SECTIONING OBSERVATIONS - INDIVIDUAL DATA

VIABLE FETUSES					DEAD FETUSES			EARLY RESORPTIONS		LATE RESORPTIONS		IMPLANTATION SITES			CORPORA LUTEA					
RAT #	SEX		RIGHT LEFT		TOTAL	RIGHT LEFT		TOTAL	RIGHT LEFT		TOTAL	RIGHT LEFT		TOTAL	RIGHT LEFT		TOTAL			
	M	F	HORN			HORN			HORN			HORN			HORN			OVARY		
DOSAGE GROUP IV					10 MG/KG/DAY															
12876	9	6	8	7	15	0	0	0	0	0	0	0	0	0	8	7	15	9	8	17
12877	6	8	9	5	14	0	0	0	0	0	0	0	0	0	9	5	14	11	6	17
12878	7	8	3	12	15	0	0	0	0	0	0	0	0	0	3	12	15	4	12	16
12879	9	6	8	7	15	0	0	0	0	0	0	0	0	0	8	7	15	10	9	19
12880	8	7	9	6	15	0	0	0	0	0	0	0	0	0	9	6	15	11	9	20
12881	6	6	8	4	12	0	0	0	0	1	1	2	0	0	9	5	14	10	5	15
12882	6	11	7	10	17	0	0	0	0	0	0	0	0	0	7	10	17	8	11	19
12883	8	6	5	9	14	0	0	0	0	1	2	3	0	0	6	11	17	6	11	17
12884	6	6	9	3	12	0	0	0	0	0	1	1	0	0	9	4	13	9	6	15
12885	9	8	9	8	17	0	0	0	0	0	0	0	0	0	9	8	17	10	9	19
12886	9	4	8	5	13	0	0	0	0	1	0	1	0	0	9	5	14	10	7	17
12887	8	8	6	10	16	0	0	0	0	0	0	0	0	0	6	10	16	6	10	16
12888	6	7	7	6	13	0	0	0	0	0	1	1	0	0	7	7	14	8	10	18
12889	1	2	2	1	3	0	0	0	0	0	0	0	0	0	2	1	3	11	4	15
12890	7	8	4	11	15	0	0	0	0	1	0	1	0	0	5	11	16	5	11	16
12891	8	5	6	7	13	0	0	0	0	0	0	0	0	0	6	7	13	6	7	13
12892	5	10	8	7	15	0	0	0	0	0	0	0	0	0	8	7	15	8	7	15
12893	10	6	11	5	16	0	0	0	0	0	0	0	0	0	11	5	16	14	7	21
12894	7	7	8	6	14	0	0	0	0	1	1	0	0	0	8	7	15	8	7	15
12895	8	6	6	8	14	0	0	0	0	1	0	1	0	0	7	8	15	7	8	15
12896	6	8	5	9	14	0	0	0	0	0	0	0	0	0	5	9	14	5	10	15
12897	7	8	6	9	15	0	0	0	0	0	0	0	0	0	6	9	15	9	9	18
12898	6	12	11	7	18	0	0	0	0	0	0	0	0	0	11	7	18	11	8	19
12899	10	3	7	6	13	0	0	0	0	1	0	1	0	0	8	6	14	8	7	15
12900	9	7	10	6	16	0	0	0	0	0	0	0	0	0	10	6	16	11	6	17

M = MALE F = FEMALE

PLACENTAE APPEARED NORMAL UNLESS NOTED OTHERWISE.

003675

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 18 (PAGE 5): CAESAREAN-SECTIONING OBSERVATIONS - INDIVIDUAL DATA

		VIABLE FETUSES				DEAD FETUSES		EARLY RESORPTIONS		LATE RESORPTIONS		IMPLANTATION SITES		CORPORA LUTEA						
RAT #	SEX		RIGHT LEFT		TOTAL	RIGHT LEFT		TOTAL	RIGHT LEFT		TOTAL	RIGHT LEFT		TOTAL	RIGHT LEFT		TOTAL			
	M	F	HORN			HORN			HORN			HORN			OVARY					
DOSAGE GROUP V			20 MG/KG/DAY																	
12901	11	6	9	8	17	0	0	0	0	0	0	0	0	0	9	8	17	9	8	17
12902	4	8	7	5	12	0	0	0	1	0	1	0	0	0	9	5	14	11	6	17
12903	8	6	8	6	14	0	0	0	1	0	1	0	0	0	9	6	15	10	7	17
12904	2	8	6	4	10	0	0	0	1	2	3	0	0	0	7	6	13	8	7	15
12905	5	7	6	6	12	0	0	0	0	0	0	0	0	0	6	6	12	7	8	15
12906	6	7	7	6	13	0	0	0	1	0	1	0	0	0	8	6	14	8	6	14
12907	6	3	0	9	9	0	0	0	0	1	1	0	0	0	0	10	10	8	10	18
12908	6	8	3	11	14	0	0	0	0	2	2	0	0	0	3	13	16	4	14	18
12909	8	4	7	5	12	0	0	0	0	1	1	0	0	0	7	6	13	9	8	17
12910	NOT PREGNANT																			
12911	9	4	5	8	13	0	0	0	1	0	1	0	0	0	6	8	14	6	8	14
12912	7	6	9	4	13	0	0	0	0	0	0	0	0	0	9	4	13	11	4	15
12913	7	5	5	7	12	0	0	0	1	0	1	0	0	0	6	7	13	9	8	17
12914	8	7	12	3	15	0	0	0	0	0	0	0	0	0	12	3	15	12	4	16
12915	8	6	8	6	14	0	0	0	1	2	3	0	0	0	9	8	17	9	13	22
12916	8	8	8	8	16	0	0	0	0	1	1	0	0	0	8	9	17	8	9	17
12917	10	4	9	5	14	0	0	0	1	0	1	0	0	0	10	5	15	11	6	17
12918	5	10	12	3	15	0	0	0	0	1	1	0	0	0	12	4	16	12	5	17
12919	8	6	6	8	14	0	0	0	0	0	0	0	0	0	6	8	14	6	8	14
12920	8	8	9	7	16	0	0	0	0	0	0	0	0	0	9	7	16	10	9	19
12921	6	8	7	7	14	0	0	0	0	0	0	0	0	0	7	7	14	7	10	17
12922	7	5	7	5	12	0	0	0	1	2	3	0	0	0	8	7	15	8	8	16
12923	7	7	8	6	14	0	0	0	0	0	0	0	0	0	8	6	14	8	6	14
12924	7	8	8	7	15	0	0	0	0	0	0	0	0	0	8	7	15	8	8	16
12925	11	5	9	7	16	0	0	0	0	0	0	0	0	0	9	7	16	9	9	18

M = MALE F = FEMALE

PLACENTAE APPEARED NORMAL UNLESS NOTED OTHERWISE.

003676

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 18 (PAGE 6): CAESAREAN-SECTIONING OBSERVATIONS - INDIVIDUAL DATA

RAT #	VIABLE FETUSES			DEAD FETUSES			EARLY RESORPTIONS			LATE RESORPTIONS			IMPLANTATION SITES			CORPORA LUTEA		
	RIGHT	LEFT	TOTAL	RIGHT	LEFT	TOTAL	RIGHT	LEFT	TOTAL	RIGHT	LEFT	TOTAL	RIGHT	LEFT	TOTAL	RIGHT	LEFT	TOTAL
	HORN			HORN			HORN			HORN			HORN			HORN		
SATELLITE DOSAGE GROUP I							0 (VEHICLE) MG/KG/DAY											
12573	12	3	15	0	0	0	1	0	1	0	0	0	13	3	16	13	3	16
12574	9	9	18	0	0	0	0	0	0	0	0	0	9	9	18	12	12	24
12575	6	1	7	0	0	0	0	0	0	0	0	0	6	1	7	6	6	12
SATELLITE DOSAGE GROUP II							1 MG/KG/DAY											
12576	11	3	14	0	0	0	1	0	1	0	0	0	12	3	15	15	5	20
12577	7	11	18	0	0	0	0	0	0	0	0	0	7	11	18	8	12	20
12578	6	10	16	0	0	0	0	1	1	0	0	0	6	11	17	8	11	19
12579	10	5	15	0	0	0	0	0	0	0	0	0	10	5	15	10	5	15
12580	10	4	14	0	0	0	0	1	1	0	0	0	10	5	15	11	5	16
SATELLITE DOSAGE GROUP III							5 MG/KG/DAY											
12581	6	7	13	0	0	0	0	2	2	0	0	0	6	9	15	6	9	15
12582	13	5	18	0	0	0	0	0	0	0	0	0	13	5	18	14	7	21
12583	13	7	20	0	0	0	0	0	0	0	0	0	13	7	20	13	11	24
SATELLITE DOSAGE GROUP IV							10 MG/KG/DAY											
12584	9	6	15	0	0	0	2	0	2	0	0	0	11	6	17	14	8	22
12585	6	10	16	0	0	0	0	0	0	0	0	0	6	10	16	6	10	16
12586	8	5	13	0	0	0	0	1	1	0	0	0	8	6	14	9	7	16
SATELLITE DOSAGE GROUP V							20 MG/KG/DAY											
12587	9	5	14	0	0	0	0	0	0	0	0	0	9	5	14	9	5	14
12588	9	6	15	0	0	0	0	0	0	0	0	0	9	6	15	9	6	15
12589	7	7	14	0	0	0	0	0	0	0	0	0	7	7	14	7	7	14
12590	11	3	14	0	0	0	1	1	2	0	0	0	12	4	16	12	4	16
12591	9	7	16	0	0	0	1	0	1	0	0	0	10	7	17	10	9	19

PLACENTAE APPEARED NORMAL UNLESS NOTED OTHERWISE.

003677

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ElFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 19 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - INDIVIDUAL DATA

RAT #	NUMBER OF LIVE FETUSES			AVERAGE FETAL BODY WEIGHT (G)			----- CONCEPTUSES ----- RESORBED		
	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL a	N	N	%
DOSAGE GROUP I									
0 (VEHICLE) MG/KG/DAY									
12801	9	4	13	3.62	3.37	3.54	14	1	7.1
12802	9	5	14	2.03	1.89	1.98	15	1	6.7
12803	9	7	16	3.49	3.46	3.48	16	0	0.0
12804	5	8	13	3.63	3.44	3.51	13	0	0.0
12805	7	8	15	3.64	3.55	3.59	15	0	0.0
12806	9	6	15	3.64	3.36	3.53	15	0	0.0
12807	6	8	14	3.39	3.51	3.46	16	2	12.5
12808	7	5	12	3.70	3.42	3.58	17	5	29.4
12809	8	10	18	5.25	5.11	5.17	18	0	0.0
12810	6	4	10	3.58	3.14	3.40	10	0	0.0
12811	4	10	14	3.78	3.51	3.59	14	0	0.0
12812	7	7	14	3.54	3.24	3.39	15	1	6.7
12813	NOT PREGNANT								
12814	7	9	16	3.77	3.45	3.59	18	2	11.1
12815	6	9	15	3.56	3.43	3.48	17	2	11.8
12816	7	5	12	3.62	3.35	3.51	14	2	14.3
12817	8	7	15	3.44	2.85	3.17	15	0	0.0
12818	3	10	13	3.76	3.49	3.55	15	2	13.3
12819	5	10	15	3.27	3.01	3.10	16	1	6.2
12820	6	8	14	3.52	3.38	3.44	15	1	6.7
12821	10	5	15	3.31	3.14	3.25	15	0	0.0
12822	10	5	15	3.54	3.16	3.41	15	0	0.0
12823	8	6	14	3.84	3.87	3.85	15	1	6.7
12824	4	8	12	3.87	3.42	3.57	12	0	0.0
12825	7	11	18	3.96	3.66	3.78	18	0	0.0

a. TOTAL = SUM OF FETAL WEIGHTS/NUMBER OF LIVE FETUSES.

003678

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 19 (PAGE 2): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - INDIVIDUAL DATA

RAT #	NUMBER OF LIVE FETUSES			AVERAGE FETAL BODY WEIGHT (G)			----- CONCEPTUSES ----- RESORBED		
	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL a	N	N	%
DOSAGE GROUP II				1 MG/KG/DAY					
12826	8	6	14	3.33	2.94	3.16	14	0	0.0
12827	5	8	13	3.39	3.21	3.28	14	1	7.1
12828	10	8	18	3.53	3.27	3.41	18	0	0.0
12829	8	6	14	3.00	3.03	3.01	15	1	6.7
12830	7	8	15	3.77	3.60	3.68	15	0	0.0
12831	6	10	16	3.48	3.18	3.30	17	1	5.9
12832	7	7	14	3.12	2.98	3.05	15	1	6.7
12833	10	3	13	3.30	3.27	3.30	14	1	7.1
12834	9	6	15	3.48	3.35	3.43	15	0	0.0
12835	3	6	9	3.68	3.49	3.55	9	0	0.0
12836	6	9	15	3.48	3.20	3.32	16	1	6.2
12837	4	10	14	3.85	3.67	3.72	15	1	6.7
12838	8	7	15	3.48	3.21	3.35	15	0	0.0
12839	6	11	17	3.42	3.22	3.29	17	0	0.0
12840	11	6	17	3.23	2.85	3.10	17	0	0.0
12841	9	8	17	3.46	3.18	3.33	17	0	0.0
12842	9	7	16	3.78	3.56	3.68	16	0	0.0
12843	5	8	13	3.74	3.58	3.64	14	1	7.1
12844	6	11	17	3.90	3.63	3.72	17	0	0.0
12845	NOT PREGNANT								
12846	NOT PREGNANT								
12847	11	7	18	3.29	2.96	3.16	18	0	0.0
12848	7	11	18	3.36	3.08	3.19	18	0	0.0
12849	9	6	15	3.52	3.24	3.41	15	0	0.0
12850	7	9	16	3.34	3.05	3.18	18	2	11.1

a. TOTAL = SUM OF FETAL WEIGHTS/NUMBER OF LIVE FETUSES.

003679

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 19 (PAGE 3): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - INDIVIDUAL DATA

RAT #	NUMBER OF LIVE FETUSES			AVERAGE FETAL BODY WEIGHT (G)			----- CONCEPTUSES ----- RESORBED		
	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL a	N	N	%
DOSAGE GROUP III			5 MG/KG/DAY						
12851	7	8	15	3.69	3.36	3.51	16	1	6.2
12852	8	8	16	3.34	3.20	3.27	16	0	0.0
12853	5	9	14	3.78	3.65	3.70	15	1	6.7
12854	6	10	16	3.52	3.07	3.24	16	0	0.0
12855	NOT PREGNANT								
12856	5	9	14	3.55	3.24	3.35	14	0	0.0
12857	11	8	19	3.34	3.16	3.26	19	0	0.0
12858	7	7	14	3.55	3.43	3.49	15	1	6.7
12859	10	7	17	3.20	3.20	3.20	17	0	0.0
12860	7	8	15	3.82	3.55	3.67	16	1	6.2
12861	6	6	12	3.12	2.98	3.04	14	2	14.3
12862	7	8	15	2.95	2.91	2.93	15	0	0.0
12863	5	9	14	3.67	3.37	3.48	15	1	6.7
12864	6	8	14	3.76	3.52	3.62	14	0	0.0
12865	5	10	15	3.67	3.44	3.52	17	2	11.8
12866	9	10	19	3.42	3.21	3.31	19	0	0.0
12867	9	5	14	3.44	3.15	3.34	14	0	0.0
12868	1	4	5	3.35	3.16	3.19	7	2	28.6
12869	9	6	15	3.35	3.20	3.29	15	0	0.0
12870	6	10	16	3.69	3.40	3.51	16	0	0.0
12871	8	6	14	3.46	3.26	3.37	16	2	12.5
12872	9	5	14	3.32	3.19	3.27	14	0	0.0
12873	5	9	14	3.54	3.41	3.45	15	1	6.7
12874	7	9	16	3.66	3.54	3.59	17	1	5.9
12875	8	2	10	3.68	3.38	3.62	15	5	33.3

a. TOTAL = SUM OF FETAL WEIGHTS/NUMBER OF LIVE FETUSES.

003680

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ElFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 19 (PAGE 4): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - INDIVIDUAL DATA

RAT #	NUMBER OF LIVE FETUSES			AVERAGE FETAL BODY WEIGHT (G)			----- CONCEPTUSES ----- RESORBED		
	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL a	N	N	%
DOSAGE GROUP IV				10 MG/KG/DAY					
12876	9	6	15	3.67	3.59	3.64	15	0	0.0
12877	6	8	14	3.27	3.08	3.16	14	0	0.0
12878	7	8	15	3.53	3.34	3.43	15	0	0.0
12879	9	6	15	3.39	3.46	3.42	15	0	0.0
12880	8	7	15	3.32	3.08	3.21	15	0	0.0
12881	6	6	12	3.12	2.82	2.97	14	2	14.3
12882	6	11	17	3.69	3.43	3.52	17	0	0.0
12883	8	6	14	3.40	3.30	3.36	17	3	17.6
12884	6	6	12	3.18	3.14	3.16	13	1	7.7
12885	9	8	17	3.26	2.86	3.07	17	0	0.0
12886	9	4	13	3.60	3.45	3.55	14	1	7.1
12887	8	8	16	3.21	2.95	3.08	16	0	0.0
12888	6	7	13	3.01	2.98	3.00	14	1	7.1
12889	1	2	3	3.47	3.66	3.60	3	0	0.0
12890	7	8	15	3.24	3.04	3.14	16	1	6.2
12891	8	5	13	3.82	3.52	3.70	13	0	0.0
12892	5	10	15	3.60	3.43	3.49	15	0	0.0
12893	10	6	16	3.39	3.26	3.34	16	0	0.0
12894	7	7	14	3.55	3.69	3.62	15	1	6.7
12895	8	6	14	3.25	3.18	3.22	15	1	6.7
12896	6	8	14	3.48	3.34	3.40	14	0	0.0
12897	7	8	15	3.38	3.41	3.40	15	0	0.0
12898	6	12	18	3.22	3.23	3.22	18	0	0.0
12899	10	3	13	3.31	3.24	3.29	14	1	7.1
12900	9	7	16	3.22	3.25	3.24	16	0	0.0

a. TOTAL = SUM OF FETAL WEIGHTS/NUMBER OF LIVE FETUSES.

003681

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 19 (PAGE 5): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - INDIVIDUAL DATA

RAT #	NUMBER OF LIVE FETUSES			AVERAGE FETAL BODY WEIGHT (G)			----- CONCEPTUSES ----- RESORBED		
	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL a	N	N	%
DOSAGE GROUP V									
20 MG/KG/DAY									
12901	11	6	17	3.28	3.07	3.21	17	0	0.0
12902	4	8	12	3.23	3.05	3.11	14	2	14.3
12903	8	6	14	3.21	3.00	3.12	15	1	6.7
12904	2	8	10	3.20	3.01	3.04	13	3	23.1
12905	5	7	12	3.34	3.28	3.31	12	0	0.0
12906	6	7	13	3.41	3.24	3.32	14	1	7.1
12907	6	3	9	2.96	2.86	2.93	10	1	10.0
12908	6	8	14	3.15	2.98	3.05	16	2	12.5
12909	8	4	12	3.12	2.68	2.97	13	1	7.7
12910	NOT PREGNANT								
12911	9	4	13	3.27	2.95	3.17	14	1	7.1
12912	7	6	13	3.74	3.34	3.55	13	0	0.0
12913	7	5	12	2.97	2.99	2.98	13	1	7.7
12914	8	7	15	3.43	3.20	3.32	15	0	0.0
12915	8	6	14	3.59	3.20	3.42	17	3	17.6
12916	8	8	16	3.05	2.85	2.95	17	1	5.9
12917	10	4	14	3.18	2.82	3.07	15	1	6.7
12918	5	10	15	3.27	3.05	3.12	16	1	6.2
12919	8	6	14	3.24	2.99	3.13	14	0	0.0
12920	8	8	16	3.35	3.09	3.22	16	0	0.0
12921	6	8	14	3.36	3.27	3.31	14	0	0.0
12922	7	5	12	3.18	3.07	3.14	15	3	20.0
12923	7	7	14	3.44	3.25	3.35	14	0	0.0
12924	7	8	15	3.39	3.13	3.25	15	0	0.0
12925	11	5	16	2.91	2.91	2.91	16	0	0.0

a. TOTAL = SUM OF FETAL WEIGHTS/NUMBER OF LIVE FETUSES.

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ElFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 19 (PAGE 6): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - INDIVIDUAL DATA

RAT #	NUMBER OF LIVE FETUSES	AVERAGE FETAL BODY WEIGHT (G)	----- CONCEPTUSES -----		
			RESORBED		
	TOTAL	TOTAL a	N	N	%
SATELLITE DOSAGE GROUP I		0 (VEHICLE) MG/KG/DAY			
12573	15	1.15	16	1	6.2
12574	18	1.19	18	0	0.0
12575	7	1.43	7	0	0.0
SATELLITE DOSAGE GROUP II		1 MG/KG/DAY			
12576	14	1.31	15	1	6.7
12577	18	1.38	18	0	0.0
12578	16	1.28	17	1	5.9
12579	15	1.37	15	0	0.0
12580	14	1.46	15	1	6.7
SATELLITE DOSAGE GROUP III		5 MG/KG/DAY			
12581	13	1.43	15	2	13.3
12582	18	1.30	18	0	0.0
12583	20	1.34	20	0	0.0
SATELLITE DOSAGE GROUP IV		10 MG/KG/DAY			
12584	15	1.22	17	2	11.8
12585	16	1.17	16	0	0.0
12586	13	1.26	14	1	7.1
SATELLITE DOSAGE GROUP V		20 MG/KG/DAY			
12587	14	1.16	14	0	0.0
12588	15	1.35	15	0	0.0
12589	14	1.32	14	0	0.0
12590	14	1.41	16	2	12.5
12591	16	1.32	17	1	5.9

a. TOTAL = SUM OF FETAL WEIGHTS/NUMBER OF LIVE FETUSES.

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 20 (PAGE 1): FETAL SEX, VITAL STATUS AND BODY WEIGHT - INDIVIDUAL DATA

FETUS #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
DOSAGE GROUP I										0 (VEHICLE) MG/KG/DAY													
RAT #	CLs																						
12801	8/ 9	MA	MA	FA	FA	MA	MA	MA	MA / MA	FA	MA	E	FA	MA									
		3.54	3.90	3.31	3.15	3.41	3.58	3.64	3.84	3.48	3.51	3.36		3.51	3.80								
12802	10/ 9	MA	FA	FA	FA	MA	MA	E	FA	MA	MA / MA	MA	MA	FA	MA								
		2.01	1.70	1.94	1.83	1.89	2.01		1.82	2.06	2.14	1.95	2.12	2.05	2.15	2.08							
12803	9/ 8	MA	MA	MA	FA	FA	MA	FA	MA / MA	FA	FA	FA	MA	MA	MA	FA							
		3.28	3.60	3.72	3.44	3.66	3.82	3.24	3.40	3.26	3.88	3.51	3.08	3.39	3.30	3.65	3.43						
12804	6/11	MA	FA	MA	FA	FA / FA	FA	FA	FA	MA	MA	FA	MA										
		3.44	3.50	3.72	3.43	3.18	3.53	3.46	3.41	3.53	3.59	3.51	3.45	3.88									
12805	10/ 7	FA	MA	FA	FA	FA	FA	FA	FA / MA	MA	MA	MA	FA	MA	MA								
		3.47	3.84	3.62	3.48	3.30	3.49	3.59	3.91	3.42	3.99	3.41	3.51	3.52	3.63	3.72							
12806	9/ 7	MA	FA	MA	MA	MA	MA	FA	FA	FA / MA	FA	MA	MA	MA	FA								
		3.65	3.36	3.67	3.62	3.81	3.31	3.18	3.27	3.49	3.62	3.50	3.46	3.76	3.85	3.34							
12807	5/12	MA	FA	FA	E	MA / MA	FA	FA	FA	MA	MA	FA	MA	E	FA	FA							
		3.41	3.64	3.62		3.02	3.63	3.81	3.30	3.09	3.60	3.27	3.68	3.41		3.50	3.47						
12808	9/11	FA	E	E	FA	MA	FA	MA	MA / FA	FA	FA	E	MA	MA	MA	E	E	MA					
		3.43			3.75	3.91	3.35	3.58	3.82	3.18	3.38		3.57	3.80	3.65		3.57						
12809	10/ 9	FA	FA	FA	FA	FA	MA	FA	FA	MA	MA / FA	FA	FA	MA	MA	MA	MA	MA					
		5.33	5.24	4.95	5.36	5.03	5.52	4.86	5.06	5.08	5.47	4.83	5.05	5.41	4.91	5.32	4.84	5.43	5.43				
12810	5/10 /	FA	FA	FA	MA	MA	MA	MA	MA	MA	FA												
		2.95	3.21	2.96	3.84	3.81	3.34	3.55	3.54	3.39	3.46												
12811	7/ 9	FA	FA	FA	FA	MA / FA	FA	FA	FA	FA	MA	FA	MA	MA									
		3.46	3.38	3.72	3.30	3.81	3.61	3.75	3.56	3.45	3.46	3.86	3.43	3.77	3.68								
12812	10/ 6	FA	MA	MA	MA	FA	E	MA	MA	FA / FA	MA	FA	FA	MA									
		3.61	3.40	3.33	3.47	3.41		3.40	3.56	3.23	3.32	3.66	2.68	3.19	3.26	4.00							
12813	NOT PREGNANT																						

M = MALE F = FEMALE A = ALIVE E = EARLY RESORPTION "/" DENOTES POSITION OF CERVIX
CLs = CORPORA LUTEA/OVARY FETAL BODY WEIGHTS WERE RECORDED IN GRAMS (G).

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 20 (PAGE 2): FETAL SEX, VITAL STATUS AND BODY WEIGHT - INDIVIDUAL DATA

FETUS #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
DOSAGE GROUP I	0 (VEHICLE) MG/KG/DAY																						
RAT # CLs																							
12814 9/10	FA	E	MA	FA	MA	FA	FA	MA / MA	FA	FA	FA	FA	E	FA	MA	MA	FA	MA					
	3.37		3.77	3.65	3.80	3.55	3.44	4.03	3.61	3.22	3.36	3.46		3.62	3.76	3.78	3.39	3.65					
12815 10/ 9	E	E	FA	FA	MA	MA	FA	MA	FA	FA / FA	FA	FA	FA	MA	MA	MA	FA						
			3.32	3.78	3.52	3.35	3.36	3.45	3.57	3.43	3.57	3.04	3.41	3.80	3.62	3.65	3.36						
12816 7/ 7	E	MA	FA	MA	FA	MA	E / FA	FA	FA	FA	MA	MA	MA	MA	MA								
		3.85	3.53	3.40	3.45	3.36		3.09	3.28	3.38	3.81	3.76	3.64	3.54									
12817 6/ 9	MA	MA	MA	FA	FA	FA / FA	FA	FA	FA	MA	MA	MA	FA	MA	MA								
	3.67	3.78	3.25	2.99	1.82	3.25	3.13	2.93	3.22	3.35	3.29	3.73	2.63	3.16	3.31								
12818 12/ 6	FA	FA	FA	MA	FA	E	FA	MA	MA	FA / E	FA	FA	FA	FA	FA								
	3.14	3.29	3.80	3.60	3.43		3.30	3.90	3.77	3.71		3.54	3.35	3.56	3.77								
12819 11/ 6	FA	FA	FA	MA	FA	FA	MA	FA	FA	MA / FA	MA	FA	FA	FA	E	MA							
	2.91	3.30	2.77	3.13	3.37	2.90	3.01	2.70	2.85	3.29	3.07	3.53	3.02	3.21		3.41							
12820 8/ 7	FA	MA	FA	MA	FA	MA	FA	FA / MA	FA	FA	FA	E	MA	FA	MA								
	3.36	3.46	3.80	3.27	3.55	3.63	3.30	3.27	3.42	3.22	3.22		3.72	3.31	3.60								
12821 11/10	MA	MA	MA	FA	MA	MA	MA / MA	MA	MA	MA	FA	FA	FA	MA	FA								
	3.13	3.15	3.43	3.22	3.80	3.08	3.27	3.19	3.32	3.40	3.06	3.18	3.09	3.32	3.13								
12822 7/10	MA	FA	FA	MA	MA	MA	FA / MA	MA	MA	MA	FA	FA	FA	MA	MA								
	3.46	3.17	2.71	3.78	3.89	3.58	3.34	3.45	3.19	3.38	3.34	3.31	3.27	3.48	3.80								
12823 12/ 5	MA	MA	FA	MA	MA	MA	FA	FA	FA	MA	MA / MA	FA	E	FA									
	3.68	3.45	3.60	3.56	4.20	3.86	4.40	3.97	3.52	4.28	3.97	3.68	3.65		4.09								
12824 7/ 7	FA	MA	MA	FA	MA	MA / FA	FA	FA	FA	FA	FA	FA											
	3.59	4.00	3.86	3.91	4.00	3.63	2.99	3.20	3.38	3.40	3.52	3.37											
12825 8/10	FA	FA	MA	FA	FA	MA	MA	FA / FA	MA	MA	FA	FA	FA	MA	FA	MA	FA	MA	FA				
	3.67	3.59	3.97	3.74	3.54	4.08	4.05	3.59	3.61	3.98	3.75	3.69	3.58	3.69	3.80	3.78	4.12	3.75					

M = MALE F = FEMALE A = ALIVE E = EARLY RESORPTION "/" DENOTES POSITION OF CERVIX
CLs = CORPORA LUTEA/OVARY FETAL BODY WEIGHTS WERE RECORDED IN GRAMS (G).

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ElFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 20 (PAGE 3): FETAL SEX, VITAL STATUS AND BODY WEIGHT - INDIVIDUAL DATA

FETUS #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
DOSAGE GROUP II	1 MG/KG/DAY																						
RAT # CLs	FA	MA	FA	MA	MA	MA	MA	MA	FA / FA	MA	MA	FA	FA										
12826 12/ 5	2.26	3.30	3.22	3.42	3.14	3.31	3.46	3.56	3.16	2.89	3.33	3.12	2.95	3.19									
12827 8/ 9	FA	MA	FA	FA	FA	FA	MA / MA	MA	MA	FA	MA	FA	E	FA									
	2.95	3.39	3.12	3.55	3.21	3.16	3.30	3.60	3.40	3.09	3.24	3.30		3.32									
12828 11/ 8	FA	MA	MA	MA	MA	MA	FA	MA	MA	MA	FA / FA	FA	FA	MA	FA	FA	MA	FA					
	3.29	3.57	3.53	3.26	3.59	3.50	3.47	3.65	3.35	3.23	3.23	3.08	3.05	3.63	3.49	3.12	3.98	3.44					
12829 8/ 8	MA	E	FA	MA	FA	MA	MA	FA / MA	MA	FA	FA	FA	FA	MA	MA								
	2.88		3.13	3.05	3.16	3.45	3.03	3.14	2.79	2.72	2.99	2.86	2.89	3.07	3.01								
12830 9/ 7	MA	FA	FA	FA	FA	FA	FA	MA / FA	FA	FA	MA	MA	MA	MA	MA								
	3.85	3.60	3.58	3.76	3.63	3.77	3.59	3.80	3.19	3.65	3.33	3.48	4.14	3.88	3.92								
12831 12/ 5	FA	MA	FA	FA	FA	MA	E	FA	FA	FA	FA	FA / MA	MA	FA	MA	MA							
	3.32	3.22	3.25	2.89	3.26	3.22		3.29	3.23	2.95	3.07	3.41	3.34	3.49	3.18	3.76	3.85						
12832 10/10	MA	FA	E	FA	MA	FA	MA / FA	MA	MA	FA	FA	MA	MA	FA									
	3.24	3.00		2.79	3.13	3.20	3.16	3.03	3.36	2.93	2.91	2.98	3.04	3.02	2.93								
12833 8/ 6	FA	MA	MA	E	MA	MA	MA	MA / MA	MA	MA	FA	MA	FA										
	3.46	3.40	3.42		3.07	3.20	3.45	3.09	3.56	2.95	3.33	3.08	3.56	3.27									
12834 5/10	FA	FA	FA	MA	FA / FA	MA	MA	MA	MA	MA	MA	MA	FA	MA	MA								
	3.49	3.41	3.14	3.41	3.40	3.42	3.38	3.34	3.70	3.72	3.57	3.52	3.25	3.18	3.49								
12835 9/ 8	MA	FA / FA	FA	FA	FA	MA	FA	MA	FA														
	3.52	3.60	3.73	3.80	2.36	3.77	3.92	3.76	3.52														
12836 8/10	FA	E	FA	FA	FA	MA	FA	FA / MA	MA	MA	FA	MA	FA	MA	FA								
	2.84		3.06	3.19	3.18	3.47	3.63	3.30	3.39	3.20	3.91	3.36	3.64	3.06	3.29	3.23							
12837 8/ 8	FA	FA	MA	E	FA	FA	FA	FA / FA	FA	FA	MA	MA	FA	FA	MA								
	3.54	3.49	3.74		3.80	3.69	3.78	3.64	3.58	3.74	3.84	3.91	4.26	3.14	3.92								
12838 9/ 6	MA	FA	FA	MA	MA	FA	MA	MA	FA / FA	MA	MA	FA	FA	MA									
	3.12	3.25	3.43	3.60	3.46	3.51	3.67	3.23	2.40	3.26	3.84	3.51	3.17	3.46	3.39								

M = MALE F = FEMALE A = ALIVE E = EARLY RESORPTION "/" DENOTES POSITION OF CERVIX
CLs = CORPORA LUTEA/OVARY FETAL BODY WEIGHTS WERE RECORDED IN GRAMS (G).

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ELFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 20 (PAGE 4): FETAL SEX, VITAL STATUS AND BODY WEIGHT - INDIVIDUAL DATA

FETUS #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
DOSAGE GROUP II	1 MG/KG/DAY																						
RAT # CLs																							
12839 7/11	FA	FA	MA	FA	FA	MA	FA / MA	FA	MA	FA	FA	FA	FA	MA	FA	FA	MA						
	2.69	3.32	3.40	2.91	3.16	3.37	3.23	3.49	3.27	3.09	3.11	3.33	3.23	3.63	3.36	3.87	3.51						
12840 9/10	FA	MA	MA	MA	MA	FA	MA	MA	FA / MA	MA	FA	FA	FA	FA	MA	MA	MA						
	2.90	3.19	3.33	3.11	3.68	2.96	3.19	3.13	3.03	3.31	3.07	2.56	2.86	2.79	3.24	3.17	3.12						
12841 9/ 8	FA	MA	FA	MA	MA	FA	MA	FA	MA / MA	MA	FA	FA	FA	MA	FA	FA	MA						
	3.39	3.69	3.14	3.56	3.25	3.13	3.31	2.62	3.53	3.60	3.13	3.29	3.32	3.43	3.11	3.44	3.68						
12842 10/ 6	FA	MA	MA	MA	MA	FA	MA	MA	FA	FA / MA	MA	FA	MA	FA	FA								
	3.18	3.54	3.81	4.17	3.97	3.60	3.84	3.70	3.82	3.66	3.51	3.81	3.52	3.65	3.77	3.39							
12843 7/ 8	FA	MA	FA	FA	MA	FA	MA / FA	FA	FA	FA	MA	E	MA										
	3.66	3.34	3.57	3.51	3.99	3.40	3.39	3.58	3.41	3.62	3.91	3.98	4.02										
12844 11/ 8	MA	FA	FA	FA	FA	FA	MA	MA	MA	FA	MA / FA	FA	FA	MA	FA	FA							
	3.70	3.94	3.49	3.75	3.65	3.74	3.73	3.93	3.88	3.55	4.22	3.36	3.58	3.43	3.93	3.92	3.51						
12845	NOT PREGNANT																						
12846	NOT PREGNANT																						
12847 15/ 6	MA	MA	MA	MA	MA	MA	MA	FA	MA	FA	FA	FA	FA	FA / MA	MA	MA	FA						
	3.63	2.80	3.07	2.97	3.28	3.62	2.80	3.03	3.28	3.24	2.74	2.92	2.92	2.65	3.78	3.45	3.52	3.21					
12848 13/ 7	MA	MA	FA	MA	FA	MA	FA	MA	FA	FA	FA	FA	FA / MA	FA	MA	FA	FA						
	3.19	3.31	2.99	3.78	3.08	3.40	3.18	3.27	3.26	2.86	3.09	3.15	3.06	3.16	3.01	3.43	3.04	3.12					
12849 9/ 6	MA	FA	MA	MA	FA	FA	FA	MA	MA / MA	FA	FA	MA	MA	MA									
	3.72	3.31	3.45	3.60	3.40	3.07	3.36	3.58	3.49	3.35	3.30	3.03	3.65	3.46	3.39								
12850 7/12	FA	MA	MA	FA	MA	FA	MA / MA	FA	FA	E	E	FA	FA	FA	MA	FA	MA						
	3.39	3.66	3.32	3.45	3.14	3.14	3.37	3.25	2.95	2.91			3.23	3.00	3.07	3.46	2.33	3.18					

M = MALE F = FEMALE A = ALIVE E = EARLY RESORPTION "/" DENOTES POSITION OF CERVIX
CLs = CORPORA LUTEA/OVARY FETAL BODY WEIGHTS WERE RECORDED IN GRAMS (G).

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 20 (PAGE 5): FETAL SEX, VITAL STATUS AND BODY WEIGHT - INDIVIDUAL DATA

FETUS #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
DOSAGE GROUP III																							
5 MG/KG/DAY																							
RAT #	CLs																						
12851	6/12	FA	MA	E	MA	MA / FA	FA	MA	FA	FA	FA	MA	MA	FA	FA	MA							
		3.42	3.57		3.55	3.80	3.25	3.13	3.77	3.34	3.20	3.54	3.84	3.48	3.52	3.48	3.82						
12852	6/11	FA	FA	MA	FA	MA	MA / MA	MA	FA	FA	MA	FA	MA	MA	FA	FA							
		3.09	3.31	3.29	3.22	3.23	3.58	3.12	3.44	3.10	2.98	3.36	3.21	3.30	3.39	3.29	3.38						
12853	10/ 7	MA	FA	MA	FA	FA	FA	FA	FA	MA	FA / MA	MA	E	FA	FA								
		3.26	3.52	3.87	3.65	3.48	3.76	3.82	3.50	3.66	3.35	4.00	4.09	4.03	3.75								
12854	8/10	MA	FA	FA	MA	FA	MA	MA / FA	FA	FA	FA	MA	FA	MA	FA	FA							
		3.57	2.90	3.21	3.44	2.98	3.43	3.50	2.96	2.29	3.24	3.24	3.59	3.50	3.56	3.18	3.24						
12855		NOT PREGNANT																					
12856	5/ 9	FA	MA	FA	FA	MA / FA	MA	FA	FA	FA	FA	MA	FA	MA									
		3.35	3.57	3.10	3.56	3.61	3.16	3.47	3.47	2.68	3.43	3.16	3.61	3.21	3.49								
12857	12/11	MA	MA	FA	MA	MA	MA	MA	FA / MA	FA	MA	MA	MA	MA	FA	FA	FA	FA	FA				
		3.31	3.30	3.34	3.50	3.28	3.49	3.40	3.31	3.45	3.18	3.13	3.19	3.21	3.56	3.14	2.61	3.24	2.93	3.44			
12858	6/11	MA	FA	MA	E	FA	FA / MA	MA	MA	FA	FA	MA	FA	MA	FA	MA							
		3.59	3.83	3.88		3.50	3.73	3.25	3.73	3.13	3.34	3.38	3.47	3.32	2.99	3.70							
12859	10/ 7	MA	MA	FA	FA	FA	MA	MA	MA	FA / MA	MA	FA	FA	FA	MA	MA	FA						
		3.21	3.19	3.15	3.26	3.24	3.31	3.29	3.21	3.22	3.28	2.97	3.22	3.21	3.12	3.26	3.15	3.17					
12860	9/11	MA	E	MA	MA	FA	MA	MA / FA	MA	FA	FA	MA	FA	FA	FA	FA							
		3.54		3.43	3.64	3.70	4.31	4.00	3.50	3.85	3.47	3.55	3.95	3.51	3.53	3.36	3.76						
12861	10/ 8	MA	MA	E	FA	FA	FA	MA	MA / MA	FA	E	FA	FA										
		2.84	3.13		2.91	2.92	3.26	2.89	3.07	3.40	2.99	2.87	3.06	3.20									
12862	8/ 7	MA	FA	FA	FA	MA	MA	FA	MA / FA	MA	MA	FA	FA	MA	FA								
		2.93	2.77	3.02	3.13	2.96	3.13	2.81	2.70	2.77	3.04	2.89	2.99	3.00	3.02	2.76							
12863	5/10	MA	MA	FA	FA	E / FA	MA	MA	FA	FA	FA	FA	FA	FA	MA								
		3.65	3.48	3.40	3.37		3.64	3.78	3.75	3.19	3.24	3.47	3.56	3.14	3.29	3.69							

M = MALE F = FEMALE A = ALIVE E = EARLY RESORPTION "/" DENOTES POSITION OF CERVIX
CLs = CORPORA LUTEA/OVARY FETAL BODY WEIGHTS WERE RECORDED IN GRAMS (G).

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 20 (PAGE 6): FETAL SEX, VITAL STATUS AND BODY WEIGHT - INDIVIDUAL DATA

FETUS #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
DOSAGE GROUP III											5 MG/KG/DAY												
RAT #	CLs																						
12864	12/ 5	FA	FA	MA	MA	FA	FA	FA	FA	MA	MA / FA	MA	MA	FA									
		3.51	3.46	3.54	3.77	3.60	3.49	3.67	3.73	3.97	3.91	3.36	3.48	3.90	3.37								
12865	8/ 9	FA	FA	FA	E	MA	FA	FA	MA / FA	FA	MA	FA	FA	MA	FA	E	MA						
		3.32	3.22	3.86		3.87	3.42	3.30	3.28	3.49	3.50	3.65	3.77	3.38	3.84	3.18	3.72						
12866	11/11	FA	FA	FA	FA	FA	FA	MA	MA	FA	FA / MA	FA	MA	MA	MA	MA	MA	MA	MA	MA			
		2.70	3.08	3.15	2.84	3.18	3.38	3.30	3.41	3.46	3.35	3.43	3.39	3.57	3.34	3.52	3.44	3.30	3.44	3.68			
12867	5/10	MA	MA	FA	MA / MA	MA	MA	MA	MA	FA	MA	FA	FA	MA	FA								
		4.00	3.53	3.25	3.46	3.21	3.10	3.53	3.16	3.03	3.53	3.00	3.38	3.44	3.08								
12868	7/ 6	FA	FA / FA	FA	MA	E	E																
		3.22	3.46	3.13	2.81	3.35																	
12869	7/ 8	MA	FA	MA	FA	MA	FA	MA / FA	MA	FA	MA	MA	MA	MA	FA								
		3.50	3.38	3.30	3.30	3.22	3.20	3.35	3.01	3.19	3.21	3.44	3.41	3.55	3.20	3.07							
12870	6/11	FA	MA	MA	FA	FA	FA / MA	MA	MA	FA	FA	MA	FA	FA	FA	FA							
		3.48	3.92	3.91	3.28	3.32	3.09	3.64	3.61	3.37	3.63	3.22	3.68	3.49	3.75	3.33	3.45						
12871	6/11	MA	FA	FA	MA	MA	FA / FA	FA	E	MA	FA	MA	MA	E	MA	MA							
		3.26	3.46	3.33	3.62	3.72	3.55	2.66	3.34		3.29	3.21	3.58	3.19	3.54	3.46							
12872	10/ 6	FA	MA	MA	MA	FA	MA	FA	MA	FA / MA	FA	MA	MA	MA									
		3.21	3.36	3.34	3.45	3.15	3.25	3.29	3.50	3.16	3.11	3.12	3.37	3.44	3.07								
12873	5/13	FA	E	FA	MA	FA / FA	FA	FA	FA	FA	MA	MA	MA	MA	FA								
		3.55		3.78	3.71	3.26	3.34	3.02	2.90	3.59	3.57	3.56	3.57	3.18	3.68	3.65							
12874	7/10	MA	MA	MA	MA	MA	FA	MA / FA	E	FA	FA	FA	FA	MA	FA	FA	FA						
		3.67	3.53	3.75	3.67	3.79	3.62	3.66	3.43		3.36	3.53	3.39	3.77	3.58	3.28	3.54	3.92					
12875	7/ 9	E	E	E	MA	FA	E / MA	FA	MA	E	MA	MA	MA	MA	MA								
					4.04	3.51		3.73	3.25	3.76		3.56	3.71	3.43	3.62	3.57							
M = MALE F = FEMALE A = ALIVE E = EARLY RESORPTION "/" DENOTES POSITION OF CERVIX CLs = CORPORA LUTEA/OVARY FETAL BODY WEIGHTS WERE RECORDED IN GRAMS (G).																							

M = MALE F = FEMALE A = ALIVE E = EARLY RESORPTION "/" DENOTES POSITION OF CERVIX
CLs = CORPORA LUTEA/OVARY FETAL BODY WEIGHTS WERE RECORDED IN GRAMS (G).

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 20 (PAGE 7): FETAL SEX, VITAL STATUS AND BODY WEIGHT - INDIVIDUAL DATA

FETUS #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
DOSAGE GROUP IV		10 MG/KG/DAY																					
RAT #	CLs																						
12876	9/ 8	MA	FA	FA	MA	FA	MA	MA	MA / FA	MA	MA	MA	FA	MA	FA								
		3.48	3.62	3.64	3.79	3.21	3.55	3.49	3.91	3.63	3.46	3.62	3.84	3.62	3.89	3.81							
12877	11/ 6	FA	MA	FA	MA	MA	FA	FA	FA	FA / MA	MA	MA	MA	FA	FA								
		2.93	3.13	3.07	3.28	3.23	2.88	3.28	2.95	3.27	3.40	3.44	3.14	3.08	3.16								
12878	4/12	MA	FA	MA / MA	MA	MA	FA	FA	FA	MA	MA	MA	FA	FA	FA	FA							
		3.80	3.88	3.82	3.36	3.44	3.20	3.30	3.63	3.31	3.40	3.60	3.34	3.15	3.00	3.18							
12879	10/ 9	FA	FA	MA	FA	FA	FA	MA	MA / MA	MA	MA	MA	MA	MA	FA								
		3.21	3.83	3.61	3.34	3.49	3.44	3.08	3.60	3.41	3.20	3.55	3.10	3.62	3.31	3.45							
12880	11/ 9	FA	MA	MA	FA	MA	FA	FA	MA / FA	MA	MA	MA	MA	FA	MA								
		3.01	3.40	3.65	3.01	3.19	3.30	3.16	3.25	3.21	2.83	3.17	3.35	3.23	3.11	3.28							
12881	10/ 5	FA	E	MA	FA	MA	MA	MA	FA	FA / MA	FA	FA	E	MA									
		2.31		3.03	2.91	3.03	3.07	3.27	2.88	2.93	2.95	2.89	3.00		3.39								
12882	8/11	MA	FA	FA	FA	MA	FA	FA / MA	MA	FA	MA	FA	FA	FA	FA	FA	MA						
		3.39	3.64	3.86	3.57	3.60	3.61	3.15	3.85	3.56	3.23	3.79	3.19	3.06	3.66	3.44	3.28	3.93					
12883	6/11	FA	FA	MA	MA	MA	E / MA	FA	MA	FA	MA	MA	FA	E	FA	E	MA						
		3.38	3.23	3.89	3.20	3.28		3.46	3.42	3.69	3.34	3.31	3.19	3.12		3.29		3.18					
12884	9/ 6	FA	MA	FA	MA	FA	MA	MA	FA	MA / MA	FA	E	FA										
		3.02	3.41	3.23	2.97	3.02	3.24	3.09	3.00	3.52	2.84	3.19		3.40									
12885	10/ 9	FA	FA	MA	MA	MA	MA	FA	MA	FA / FA	MA	MA	MA	MA	FA	FA	FA						
		3.02	3.15	3.52	3.38	3.22	3.24	3.17	3.44	3.01	2.87	3.36	2.10	3.76	3.32	1.67	3.00	3.03					
12886	10/ 7	MA	FA	FA	MA	MA	MA	E	MA	FA / MA	FA	MA	MA	MA									
		3.61	3.21	3.61	3.71	3.53	3.47		3.80	3.82	3.16	3.15	3.41	4.00	3.72								
12887	6/10	FA	FA	MA	MA	MA	MA / MA	FA	FA	MA	FA	FA	MA	FA	FA	MA							
		3.08	2.88	3.28	2.95	3.26	3.16	3.38	3.04	3.19	3.17	2.71	2.91	3.27	2.90	2.90	3.23						
12888	8/10	MA	FA	FA	FA	MA	MA	MA / FA	FA	E	FA	FA	MA	MA									
		3.03	3.01	3.16	2.88	3.05	2.90	2.85	2.83	3.07		2.99	2.95	2.96	3.27								

M = MALE F = FEMALE A = ALIVE E = EARLY RESORPTION "/" DENOTES POSITION OF CERVIX
CLs = CORPORA LUTEA/OVARY FETAL BODY WEIGHTS WERE RECORDED IN GRAMS (G).

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 20 (PAGE 8): FETAL SEX, VITAL STATUS AND BODY WEIGHT - INDIVIDUAL DATA

FETUS #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
DOSAGE GROUP IV																							
10 MG/KG/DAY																							
RAT #	CLs																						
12889	11/ 4	FA	MA / FA																				
		3.54	3.47	3.79																			
12890	5/11	MA	MA	FA	FA	E / MA	MA	FA	MA	FA	FA	FA	FA	MA	MA	FA							
		3.25	3.55	3.44	2.99	3.04	3.18	3.20	3.34	2.15	3.39	3.09	3.26	3.20	3.16	2.84							
12891	6/ 7	MA	FA	MA	MA	FA / MA	MA	MA	MA	MA	FA	FA											
		3.46	3.49	3.88	3.87	3.82	3.39	3.74	3.98	4.06	3.93	3.63	3.29	3.59									
12892	8/ 7	FA	FA	FA	FA	FA	FA	MA / FA	MA	FA	MA	MA	MA	FA									
		3.31	3.41	3.56	3.43	3.38	3.41	3.21	3.75	3.71	3.52	3.50	3.63	3.58	3.52	3.42							
12893	14/ 7	FA	MA	FA	FA	MA	FA	FA	MA	FA	MA	MA / MA	MA	MA	MA	MA							
		3.24	3.27	3.30	3.42	3.48	3.34	3.16	3.48	3.08	3.51	3.37	3.31	3.02	3.52	3.45	3.49						
12894	8/ 7	FA	FA	FA	MA	MA	FA	FA	MA / MA	MA	FA	E	MA	FA	MA								
		3.24	3.74	3.72	3.55	3.58	3.72	3.60	3.66	3.32	3.52	4.16	3.50	3.68	3.73								
12895	7/ 8	MA	MA	MA	MA	MA	MA	E / MA	MA	FA	FA	FA	FA	FA	FA								
		3.00	3.17	3.43	3.16	3.27	3.35	3.35	3.26	3.04	3.25	3.20	2.92	3.11	3.55								
12896	5/10	FA	MA	FA	MA	MA / FA	FA	MA	FA	FA	MA	MA	FA	FA									
		3.07	3.65	3.41	3.53	3.12	3.39	3.19	3.56	3.40	3.44	3.36	3.69	3.54	3.29								
12897	9/ 9	MA	FA	FA	FA	MA	FA / FA	MA	FA	FA	FA	MA	MA	MA	MA								
		3.19	3.53	3.51	3.63	3.59	3.54	3.53	3.29	3.08	3.30	3.18	3.65	3.18	3.41	3.33							
12898	11/ 8	FA	MA	MA	FA	FA	FA	FA	FA	MA	MA	FA / MA	FA	FA	FA	FA	MA	FA					
		3.00	3.18	2.77	3.15	3.03	3.19	3.24	3.14	3.46	3.26	3.25	3.16	3.19	3.44	3.38	3.36	3.47	3.36				
12899	8/ 7	MA	FA	FA	MA	FA	MA	MA	E / MA	MA	MA	MA	MA	MA									
		3.34	3.12	3.23	3.47	3.36	3.44	3.18	3.20	3.03	3.37	3.68	3.11	3.29									
12900	11/ 6	MA	MA	MA	FA	MA	FA	FA	FA	MA / MA	MA	MA	FA	FA	MA								
		2.96	2.95	3.47	3.39	3.00	3.05	3.35	3.59	3.37	3.31	3.56	3.12	3.22	2.66	3.33	3.43						

M = MALE F = FEMALE A = ALIVE E = EARLY RESORPTION "/" DENOTES POSITION OF CERVIX
CLs = CORPORA LUTEA/OVARY FETAL BODY WEIGHTS WERE RECORDED IN GRAMS (G).

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 20 (PAGE 9): FETAL SEX, VITAL STATUS AND BODY WEIGHT - INDIVIDUAL DATA

FETUS #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
DOSAGE GROUP V	20 MG/KG/DAY																						
RAT # CLs																							
12901 9/ 8	MA	MA	MA	MA	MA	FA	FA	FA	MA / FA	FA	FA	MA	MA	MA	MA	MA	MA	MA	MA	MA	MA	MA	MA
	3.17	3.37	3.23	3.11	3.06	2.94	3.03	2.82	3.16	3.25	3.12	3.27	3.40	3.59	3.40	3.26	3.38						
12902 11/ 6	FA	E	FA	FA	MA	MA	FA	E	FA / MA	MA	FA	FA	FA	FA									
	2.93		3.01	3.00	3.31	3.07	2.70		3.07	3.16	3.37	3.18	3.41	3.09									
12903 10/ 7	FA	MA	MA	E	MA	MA	FA	MA	FA / FA	MA	MA	FA	FA	MA									
	3.08	3.48	3.37		3.27	3.32	2.85	2.80	3.12	3.04	3.16	3.09	2.84	3.07	3.18								
12904 8/ 7	FA	FA	MA	FA	E	FA	FA / FA	E	E	MA	FA	FA											
	3.01	3.16	3.10	2.99		2.92	2.86	3.09			3.30	3.13	2.89										
12905 7/ 8	MA	FA	FA	MA	FA	MA / FA	FA	FA	FA	FA	MA	MA											
	3.37	3.10	3.37	3.76	3.37	3.24	3.04	3.44	3.22	3.46	3.12	3.19											
12906 8/ 6	FA	MA	MA	FA	MA	FA	E	MA / MA	FA	FA	FA	MA	FA										
	3.10	3.44	3.48	3.11	3.49	3.37		3.38	2.96	3.17	3.34	3.24	3.71	3.37									
12907 8/10 /	MA	FA	MA	MA	FA	MA	E	MA	MA	FA													
	2.50	2.43	2.85	3.20	2.90	3.17		3.11	2.94	3.25													
12908 4/14	FA	MA	FA / MA	FA	MA	FA	FA	MA	FA	MA	FA	MA	E	MA	FA	E							
	3.09	3.49	3.01	3.02	3.05	3.08	2.80	2.61	3.16	3.22	3.12	3.17		2.99	2.92								
12909 9/ 8	FA	FA	MA	MA	MA	FA	MA / MA	E	MA	MA	FA	MA											
	2.47	3.13	3.31	3.18	3.01	2.38	2.88	3.32		3.23	2.97	2.76	3.03										
12910	NOT PREGNANT																						
12911 6/ 8	E	FA	MA	MA	MA	FA / MA	MA	FA	MA	FA	MA	MA	MA	MA									
	3.15	3.12	3.29	2.97	3.07	3.37	3.40	2.54	3.22	3.05	3.25	3.47	3.32										
12912 11/ 4	FA	FA	FA	MA	FA	FA	MA	MA	MA / MA	MA	FA	MA											
	3.06	3.34	3.15	3.82	3.98	3.49	3.62	3.57	4.10	3.52	3.64	2.99	3.89										
12913 9/ 8	MA	MA	E	MA	FA	FA / MA	MA	FA	MA	MA	FA	FA											
	2.94	3.26		3.39	3.08	3.06	2.41	2.98	3.11	2.93	2.91	2.72	2.98										

M = MALE F = FEMALE A = ALIVE E = EARLY RESORPTION "/" DENOTES POSITION OF CERVIX
CLs = CORPORA LUTEA/OVARY FETAL BODY WEIGHTS WERE RECORDED IN GRAMS (G).

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 20 (PAGE 10): FETAL SEX, VITAL STATUS AND BODY WEIGHT - INDIVIDUAL DATA

FETUS #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
DOSAGE GROUP V		20 MG/KG/DAY																					
RAT #	CLs																						
12914	12/ 4	FA	MA	MA	FA	FA	FA	MA	FA	MA	MA	MA	FA /	FA	MA	MA							
		3.06	3.16	3.59	3.37	2.79	3.27	3.40	3.35	3.32	3.35	3.71	3.32	3.24	3.37	3.53							
12915	9/13	FA	MA	FA	E	MA	MA	FA	FA	MA /	MA	FA	E	E	MA	MA	MA	FA					
		2.94	3.58	3.41		3.43	3.65	2.98	2.99	3.72	3.27	3.21			3.87	3.38	3.81	3.66					
12916	8/ 9	FA	MA	MA	FA	MA	MA	MA	MA /	FA	E	FA	MA	FA	FA	FA	FA	MA					
		2.58	3.03	3.11	2.94	3.33	3.16	2.76	3.02	2.64		2.90	3.15	3.34	3.05	2.63	2.75	2.86					
12917	11/ 6	MA	MA	MA	E	MA	MA	MA	FA	FA	MA /	FA	FA	MA	MA	MA							
		3.13	3.07	3.07		3.39	3.22	3.24	2.79	2.77	3.12	2.76	2.94	3.14	3.37	3.02							
12918	12/ 5	FA	FA	FA	FA	MA	FA	MA	FA	FA	MA	FA	MA /	E	FA	MA	FA						
		2.57	3.22	2.89	3.08	3.10	2.87	3.34	3.25	3.26	3.30	3.02	3.11		2.99	3.50	3.35						
12919	6/ 8	MA	FA	MA	MA	MA	MA /	MA	FA	MA	FA	MA	FA	FA	FA								
		3.05	2.87	3.15	3.61	3.26	3.17	3.22	3.07	3.28	2.97	3.14	3.00	3.05	2.97								
12920	10/ 9	FA	MA	MA	MA	MA	MA	FA	FA	MA /	FA	MA	FA	MA	FA	FA	FA						
		3.25	3.52	3.31	3.32	3.43	3.23	2.91	3.17	3.43	3.03	3.28	3.16	3.26	2.93	3.15	3.14						
12921	7/10	MA	FA	FA	FA	MA	MA	MA /	FA	MA	FA	FA	MA	FA	FA								
		3.66	3.26	3.14	3.28	3.39	2.71	3.44	3.20	3.23	3.31	3.34	3.73	3.34	3.27								
12922	8/ 8	MA	FA	MA	E	MA	FA	FA	MA /	E	E	MA	MA	FA	MA	FA							
		2.80	2.95	3.36		3.58	3.35	2.96	2.96			3.16	3.06	3.07	3.38	3.01							
12923	8/ 6	MA	MA	MA	FA	FA	FA	FA	FA /	FA	MA	MA	MA	MA	FA								
		3.54	3.39	3.16	3.08	3.58	3.24	3.38	2.94	3.12	3.55	3.55	3.31	3.58	3.44								
12924	8/ 8	MA	MA	FA	MA	MA	FA	FA	MA /	FA	FA	FA	MA	MA	FA	FA							
		3.27	2.92	3.45	3.68	3.61	2.98	2.93	3.59	3.10	3.03	3.26	3.04	3.63	3.47	2.85							
12925	9/ 9	MA	FA	FA	FA	MA	MA	MA	MA	FA /	MA	MA	FA	MA	MA	MA	MA						
		2.45	2.65	3.04	3.17	3.17	2.79	2.74	2.93	2.93	2.86	3.06	2.76	2.82	3.08	3.06	3.06						

M = MALE F = FEMALE A = ALIVE E = EARLY RESORPTION "/" DENOTES POSITION OF CERVIX
CLs = CORPORA LUTEA/OVARY FETAL BODY WEIGHTS WERE RECORDED IN GRAMS (G).

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 20 (PAGE 11): FETAL SEX, VITAL STATUS AND BODY WEIGHT - INDIVIDUAL DATA

FETUS #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
SATELLITE DOSAGE GROUP I											0 (VEHICLE) MG/KG/DAY												
RAT #	CLs																						
12573	13/ 3	E	A	A	A	A	A	A	A	A	A	A	A	A	A / A	A	A						
		0.80	1.08	1.15	1.07	1.16	1.34	1.23	1.28	1.11	1.32	1.26	1.09	0.08a	1.22	1.05							
12574	12/12	A	A	A	A	A	A	A	A	A / A	A	A	A	A	A	A	A	A	A				
		1.12	1.21	1.27	1.17	1.29	1.20	1.12	1.20	1.19	1.09	1.24	1.31	1.32	1.10	1.18	1.19	1.12	1.18				
12575	6/ 6	A	A	A	A	A	A / A																
		1.36	1.49	1.43	1.27	1.45	1.44	1.57															
SATELLITE DOSAGE GROUP II											1 MG/KG/DAY												
12576	15/ 5	A	A	A	A	A	A	A	A	A	A	A	E / A	A	A	A							
		1.17	1.05	1.17	1.21	1.30	1.29	1.36	1.36	1.38	1.32	1.42		1.46	1.42	1.46							
12577	8/12	A	A	A	A	A	A	A / A	A	A	A	A	A	A	A	A	A	A	A				
		1.08	1.38	1.51	1.40	1.45	1.39	1.47	1.36	1.45	1.39	1.42	1.49	1.31	1.44	1.45	1.30	1.29	1.29				
12578	8/11	A	A	A	A	A	A / A	A	A	A	A	A	E	A	A	A	A	A	A				
		1.17	1.35	1.28	1.27	1.28	1.29	1.23	1.24	1.28	1.30	1.36		1.23	1.30	1.30	1.18	1.38					
12579	10/ 5	A	A	A	A	A	A	A	A	A	A / A	A	A	A	A	A							
		1.32	1.32	1.23	1.39	1.34	1.46	1.50	1.36	1.26	1.26	1.52	1.51	1.34	1.28	1.50							
12580	11/ 5	A	A	A	A	A	A	A	A	A	A / A	A	A	E	A	A							
		1.23	1.39	1.49	1.50	1.51	1.46	1.52	1.49	1.39	1.54	1.48	1.36		1.55	1.54							
SATELLITE DOSAGE GROUP III											5 MG/KG/DAY												
12581	6/ 9	A	A	A	A	A	A / A	A	A	A	A	A	E	E	A	A							
		1.24	1.42	1.55	1.54	1.37	1.47	1.32	1.31	1.47	1.51	1.45			1.44	1.52							
12582	14/ 7	A	A	A	A	A	A	A	A	A	A	A	A	A / A	A	A	A	A	A				
		1.10	1.12	1.34	1.21	1.37	1.23	1.40	1.43	1.50	1.29	1.26	1.22	1.32	1.29	1.43	1.32	1.02	1.49				
12583	13/11	A	A	A	A	A	A	A	A	A	A	A	A	A / A	A	A	A	A	A	A			
		1.49	1.26	1.27	1.48	1.26	1.45	1.30	1.35	1.19	1.30	1.52	1.29	1.05	1.30	1.43	1.44	1.38	1.45	1.34	1.31		

A = ALIVE E = EARLY RESORPTION "/" DENOTES POSITION OF CERVIX

CLs = CORPORA LUTEA/OVARY FETAL BODY WEIGHTS WERE RECORDED IN GRAMS (G).

a. Value presumed incorrectly recorded; value excluded from group averages.

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 20 (PAGE 12): FETAL SEX, VITAL STATUS AND BODY WEIGHT - INDIVIDUAL DATA

FETUS #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
SATELLITE DOSAGE GROUP IV											10 MG/KG/DAY												
RAT #	CLs																						
12584	14/ 8	E	A	A	E	A	A	A	A	A	A	A /	A	A	A	A	A	A					
		1.28	1.18		1.29	1.17	1.39	1.30	1.26	1.17	1.24	1.04	1.12	1.26	1.18	1.15	1.21						
12585	6/10	A	A	A	A	A	A /	A	A	A	A	A	A	A	A	A	A						
		1.18	1.32	1.25	1.30	1.19	1.07	1.17	1.10	0.71	1.21	1.17	1.30	1.20	1.13	1.24	1.17						
12586	9/ 7	A	A	A	A	A	A	A /	A	E	A	A	A	A	A								
		1.25	1.25	1.35	0.99	1.44	1.30	1.26	1.13	1.27		1.27	1.23	1.35	1.35								
SATELLITE DOSAGE GROUP V											20 MG/KG/DAY												
12587	9/ 5	A	A	A	A	A	A	A	A /	A	A	A	A	A	A								
		1.03	1.15	1.16	1.25	1.17	1.07	1.13	1.12	1.19	1.05	1.23	1.32	1.17	1.26								
12588	9/ 6	A	A	A	A	A	A	A	A /	A	A	A	A	A	A	A							
		1.25	1.27	1.32	1.28	1.47	1.11	1.42	1.35	1.28	1.40	1.36	1.37	1.47	1.47	1.38							
12589	7/ 7	A	A	A	A	A	A	A /	A	A	A	A	A	A	A	A							
		1.25	1.26	1.30	1.31	1.34	1.30	1.32	1.11	1.35	1.29	1.40	1.32	1.49	1.38								
12590	12/ 4	A	A	A	A	A	A	A	E	A	A	A	A /	E	A	A	A						
		1.25	1.37	1.56	1.38	1.38	1.43	1.31		1.25	1.41	1.32	1.52		1.65	1.50	1.46						
12591	10/ 9	A	A	A	A	A	A	A	A	A	E /	A	A	A	A	A	A	A					
		1.20	1.28	1.36	1.36	1.37	1.17	1.22	1.35	1.36		1.31	1.41	1.30	1.40	1.34	1.29	1.32					
A = ALIVE E = EARLY RESORPTION "/ " DENOTES POSITION OF CERVIX CLs = CORPORA LUTEA/OVARY FETAL BODY WEIGHTS WERE RECORDED IN GRAMS (G).																							

A = ALIVE E = EARLY RESORPTION "/" DENOTES POSITION OF CERVIX
CLs = CORPORA LUTEA/OVARY FETAL BODY WEIGHTS WERE RECORDED IN GRAMS (G).

003695

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 21 (PAGE 1): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP I		0 (VEHICLE) MG/KG/DAY					
RAT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION		SOFT TISSUE EXAMINATION		SKELETAL EXAMINATION	
		N/N	DESCRIPTION	N/N	DESCRIPTION	N/N	DESCRIPTION
12801	1 (7.7)	0/13		1/ 6	FETUS 10 VESSELS: UMBILICAL ARTERY DESCENDS TO THE LEFT OF URINARY BLADDER	0/ 7	
12802	6 (42.8)	0/14		1/ 7	FETUS 11 KIDNEYS: PELVIS, SLIGHT DILATION, right	5/ 7	FETUS 1 STERNAL CENTRA: 1ST, NOT OSSIFIED PELVIS: PUBIS, INCOMPLETELY OSSIFIED, bilateral FETUS 3 PELVIS: PUBIS, INCOMPLETELY OSSIFIED, left FETUS 5 STERNAL CENTRA: 1ST, NOT OSSIFIED FETUS 8 PELVIS: PUBIS, INCOMPLETELY OSSIFIED, bilateral FETUS 10 STERNAL CENTRA: 1ST, NOT OSSIFIED
12803	1 (6.2)	0/16		1/ 8	FETUS 2 KIDNEYS: PELVIS, SLIGHT DILATION, bilateral	0/ 8	

N/N = NUMBER OF SPECIMENS WITH ALTERATIONS/NUMBER OF SPECIMENS EXAMINED

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 21 (PAGE 2): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP I		0 (VEHICLE) MG/KG/DAY					
RAT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION		SOFT TISSUE EXAMINATION		SKELETAL EXAMINATION	
		N/N	DESCRIPTION	N/N	DESCRIPTION	N/N	DESCRIPTION
12804	0(0.0)	0/13		0/ 6		0/ 7	
12805	0(0.0)	0/15		0/ 7		0/ 8	
12806	0(0.0)	0/15		0/ 7		0/ 8	
12807	0(0.0)	0/14		0/ 7		0/ 7	
12808	0(0.0)	0/12		0/ 6		0/ 6	
12809	0(0.0)	0/18		0/ 9		0/ 9	
12810	1(10.0)	0/10		1/ 5	FETUS 10 VESSELS: UMBILICAL ARTERY DESCENDS TO THE LEFT OF URINARY BLADDER	0/ 5	
12811	0(0.0)	0/14		0/ 7		0/ 7	
12812	0(0.0)	0/14		0/ 7		0/ 7	
12813	NOT PREGNANT						
12814	0(0.0)	0/16		0/ 8		0/ 8	
12815	0(0.0)	0/15		0/ 7		0/ 8	
12816	0(0.0)	0/12		0/ 6		0/ 6	
12817	0(0.0)	0/15		0/ 7		0/ 8	
12818	0(0.0)	0/13		0/ 6		0/ 7	
12819	0(0.0)	0/15		0/ 7		0/ 8	

N/N = NUMBER OF SPECIMENS WITH ALTERATIONS/NUMBER OF SPECIMENS EXAMINED

003697

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 21 (PAGE 3): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP I		0 (VEHICLE) MG/KG/DAY					
RAT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION		SOFT TISSUE EXAMINATION		SKELETAL EXAMINATION	
		N/N	DESCRIPTION	N/N	DESCRIPTION	N/N	DESCRIPTION
12820	0 (0.0)	0/14		0/ 7		0/ 7	
12821	4 (26.7)	0/15		1/ 7	FETUS 6 VESSELS: UMBILICAL ARTERY DESCENDS TO THE LEFT OF URINARY BLADDER	3/ 8	FETUS 7 STERNAL CENTRA: 1ST, INCOMPLETELY OSSIFIED FETUS 11 STERNAL CENTRA: 1ST, INCOMPLETELY OSSIFIED FETUS 15 STERNAL CENTRA: 1ST, INCOMPLETELY OSSIFIED
12822	2 (13.3)	0/15		1/ 7	FETUS 4 LUNGS: APICAL LOBE, ABSENT	1/ 8	FETUS 9 STERNAL CENTRA: 1ST, INCOMPLETELY OSSIFIED
12823	0 (0.0)	0/14		0/ 7		0/ 7	
12824	0 (0.0)	0/12		0/ 6		0/ 6	
12825	0 (0.0)	0/18		0/ 9		0/ 9	

N/N = NUMBER OF SPECIMENS WITH ALTERATIONS/NUMBER OF SPECIMENS EXAMINED

003698

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 21 (PAGE 4): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP II		1 MG/KG/DAY					
RAT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION		SOFT TISSUE EXAMINATION		SKELETAL EXAMINATION	
		N/N	DESCRIPTION	N/N	DESCRIPTION	N/N	DESCRIPTION
12826	1 (7.1)	0/14		1/ 7	FETUS 12 VESSELS: INNOMINATE, ABSENT	0/ 7	
12827	0 (0.0)	0/13		0/ 6		0/ 7	
12828	0 (0.0)	0/18		0/ 8		0/10	
12829	0 (0.0)	0/14		0/ 7		0/ 7	
12830	0 (0.0)	0/15		0/ 7		0/ 8	
12831	0 (0.0)	0/16		0/ 8		0/ 8	
12832	2 (14.3)	0/14		0/ 7		2/ 7	FETUS 4 CERVICAL VERTEBRAE: CERVICAL RIB PRESENT AT 7TH CERVICAL VERTEBRA, right FETUS 6 CERVICAL VERTEBRAE: CERVICAL RIB PRESENT AT 7TH CERVICAL VERTEBRA, right
12833	0 (0.0)	0/13		0/ 6		0/ 7	
12834	1 (6.7)	0/15		1/ 7	FETUS 14 VESSELS: UMBILICAL ARTERY DESCENDS TO THE LEFT OF URINARY BLADDER	0/ 8	

N/N = NUMBER OF SPECIMENS WITH ALTERATIONS/NUMBER OF SPECIMENS EXAMINED

003699

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 21 (PAGE 5): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP II		1 MG/KG/DAY					
RAT NUMBER	SPECIMENS WITH ANY ALTERATIONS N (%)	GROSS EXTERNAL EXAMINATION		SOFT TISSUE EXAMINATION		SKELETAL EXAMINATION	
		N/N	DESCRIPTION	N/N	DESCRIPTION	N/N	DESCRIPTION
12835	0 (0.0)	0/ 9		0/ 4		0/ 5	
12836	0 (0.0)	0/15		0/ 7		0/ 8	
12837	1 (7.1)	0/14		1/ 7	FETUS 9 VESSELS: INNOMINATE, ABSENT	0/ 7	
12838	0 (0.0)	0/15		0/ 7		0/ 8	
12839	0 (0.0)	0/17		0/ 8		0/ 9	
12840	1 (5.9)	0/17		0/ 8		1/ 9	FETUS 13 STERNAL CENTRA: 1ST, INCOMPLETELY OSSIFIED
12841	0 (0.0)	0/17		0/ 8		0/ 9	
12842	1 (6.2)	0/16		0/ 8		1/ 8	FETUS 15 CERVICAL VERTEBRAE: CERVICAL RIB PRESENT AT 7TH CERVICAL VERTEBRA, right
12843	0 (0.0)	0/13		0/ 6		0/ 7	
12844	0 (0.0)	0/17		0/ 8		0/ 9	
12845	NOT PREGNANT						

N/N = NUMBER OF SPECIMENS WITH ALTERATIONS/NUMBER OF SPECIMENS EXAMINED

003700

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 21 (PAGE 6): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP II		1 MG/KG/DAY					
RAT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION		SOFT TISSUE EXAMINATION		SKELETAL EXAMINATION	
		N/N	DESCRIPTION	N/N	DESCRIPTION	N/N	DESCRIPTION
12846	NOT PREGNANT						
12847	0(0.0)	0/18		0/ 9		0/ 9	
12848	1(5.6)	0/18		0/ 9		1/ 9	FETUS 1 RIBS: WAVY, right 7th - 10th
12849	0(0.0)	0/15		0/ 7		0/ 8	
12850	2(12.5)	0/16		1/ 8	FETUS 16 LUNGS: DIAPHRAGMATIC LOBE, ABSENT	1/ 8	FETUS 17 STERNAL CENTRA: 1ST, NOT OSSIFIED

N/N = NUMBER OF SPECIMENS WITH ALTERATIONS/NUMBER OF SPECIMENS EXAMINED

003701

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 21 (PAGE 7): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP III		5 MG/KG/DAY					
RAT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION		SOFT TISSUE EXAMINATION		SKELETAL EXAMINATION	
		N/N	DESCRIPTION	N/N	DESCRIPTION	N/N	DESCRIPTION
12851	0 (0.0)	0/15		0/ 7		0/ 8	
12852	0 (0.0)	0/16		0/ 8		0/ 8	
12853	0 (0.0)	0/14		0/ 7		0/ 7	
12854	0 (0.0)	0/16		0/ 8		0/ 8	
12855	NOT PREGNANT						
12856	0 (0.0)	0/14		0/ 6		0/ 8	
12857	0 (0.0)	0/19		0/ 9		0/10	
12858	0 (0.0)	0/14		0/ 7		0/ 7	
12859	2 (11.8)	0/17		0/ 8		2/ 9	FETUS 11 PELVIS: ISCHIUM, INCOMPLETELY OSSIFIED, right FETUS 15 PELVIS: ISCHIUM, INCOMPLETELY OSSIFIED, right
12860	2 (13.3)	0/15		2/ 7	FETUS 5 VESSELS: UMBILICAL ARTERY DESCENDS TO THE LEFT OF URINARY BLADDER FETUS 9 VESSELS: UMBILICAL ARTERY DESCENDS TO THE LEFT OF URINARY BLADDER	0/ 8	

N/N = NUMBER OF SPECIMENS WITH ALTERATIONS/NUMBER OF SPECIMENS EXAMINED

003702

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 21 (PAGE 8): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP III		5 MG/KG/DAY					
RAT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION		SOFT TISSUE EXAMINATION		SKELETAL EXAMINATION	
		N/N	DESCRIPTION	N/N	DESCRIPTION	N/N	DESCRIPTION
12861	0 (0.0)	0/12		0/ 6		0/ 6	
12862	0 (0.0)	0/15		0/ 7		0/ 8	
12863	1 (7.1)	0/14		0/ 8		1/ 6	FETUS 14 STERNAL CENTRA: 1ST, INCOMPLETELY OSSIFIED
12864	0 (0.0)	0/14		0/ 7		0/ 7	
12865	1 (6.7)	0/15		0/ 7		1/ 8	FETUS 6 CERVICAL VERTEBRAE: CERVICAL RIB PRESENT AT 7TH CERVICAL VERTEBRA, left
12866	0 (0.0)	0/19		0/ 9		0/10	
12867	0 (0.0)	0/14		0/ 7		0/ 7	
12868	0 (0.0)	0/ 5		0/ 2		0/ 3	
12869	0 (0.0)	0/15		0/ 7		0/ 8	
12870	0 (0.0)	0/16		0/ 8		0/ 8	
12871	0 (0.0)	0/14		0/ 7		0/ 7	
12872	0 (0.0)	0/14		0/ 7		0/ 7	
12873	0 (0.0)	0/14		0/ 7		0/ 7	
12874	0 (0.0)	0/16		0/ 8		0/ 8	
12875	0 (0.0)	0/10		0/ 5		0/ 5	

N/N = NUMBER OF SPECIMENS WITH ALTERATIONS/NUMBER OF SPECIMENS EXAMINED

003703

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 21 (PAGE 9): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP IV		10 MG/KG/DAY					
RAT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION		SOFT TISSUE EXAMINATION		SKELETAL EXAMINATION	
		N/N	DESCRIPTION	N/N	DESCRIPTION	N/N	DESCRIPTION
12876	0(0.0)	0/15		0/ 7		0/ 8	
12877	1(7.1)	0/14		1/ 7	FETUS 14 KIDNEYS: PELVIS, MODERATE DILATION, right	0/ 7	
12878	0(0.0)	0/15		0/ 7		0/ 8	
12879	0(0.0)	0/15		0/ 7		0/ 8	
12880	0(0.0)	0/15		0/ 7		0/ 8	
12881	0(0.0)	0/12		0/ 6		0/ 6	
12882	1(5.9)	0/17		0/ 8		1/ 9	FETUS 3 CERVICAL VERTEBRAE: CERVICAL RIB PRESENT AT 7TH CERVICAL VERTEBRA, left
12883	0(0.0)	0/14		0/ 7		0/ 7	
12884	0(0.0)	0/12		0/ 6		0/ 6	

N/N = NUMBER OF SPECIMENS WITH ALTERATIONS/NUMBER OF SPECIMENS EXAMINED

003704

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 21 (PAGE 10): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP IV		10 MG/KG/DAY					
RAT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION		SOFT TISSUE EXAMINATION		SKELETAL EXAMINATION	
		N/N	DESCRIPTION	N/N	DESCRIPTION	N/N	DESCRIPTION
12885	1(5.9)	1/17	FETUS 15 BODY: TRUNK SHORT TAIL: ABSENT	0/ 8		1/ 9	FETUS 15 CERVICAL VERTEBRAE: 4 PRESENT a THORACIC VERTEBRAE: 0 PRESENT a ARCH, NOT OSSIFIED, bilateral 1st - 13th; CENTRUM, NOT OSSIFIED, 1st - 13th LUMBAR VERTEBRAE: 0 PRESENT a ARCH, NOT OSSIFIED, bilateral 1st - 6th; CENTRUM, NOT OSSIFIED, 1st - 6th SACRAL VERTEBRAE: 0 PRESENT a ARCH, NOT OSSIFIED, bilateral 1st - 3rd; CENTRUM, NOT OSSIFIED, 1st - 3rd CAUDAL VERTEBRAE: 0 PRESENT a PELVIS: PUBIS, NOT OSSIFIED, bilateral RIBS: 0 PRESENT a, NOT OSSIFIED, bilateral 1st - 13th

N/N = NUMBER OF SPECIMENS WITH ALTERATIONS/NUMBER OF SPECIMENS EXAMINED
a. Excluded from ossification site group averages and statistical analyses.

003705

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 21 (PAGE 11): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP IV		10 MG/KG/DAY					
RAT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION		SOFT TISSUE EXAMINATION		SKELETAL EXAMINATION	
		N/N	DESCRIPTION	N/N	DESCRIPTION	N/N	DESCRIPTION
12886	0 (0.0)	0/13		0/ 6		0/ 7	
12887	0 (0.0)	0/16		0/ 8		0/ 8	
12888	2 (15.4)	0/13		0/ 6		2/ 7	FETUS 1 PELVIS: PUBIS, INCOMPLETELY OSSIFIED, left FETUS 14 STERNAL CENTRA: 1ST, INCOMPLETELY OSSIFIED
12889	0 (0.0)	0/ 3		0/ 1		0/ 2	
12890	1 (6.7)	0/15		0/ 7		1/ 8	FETUS 10 CERVICAL VERTEBRAE: CERVICAL RIB PRESENT AT 7TH CERVICAL VERTEBRA, left
12891	0 (0.0)	0/13		0/ 6		0/ 7	
12892	0 (0.0)	0/15		0/ 7		0/ 8	

N/N = NUMBER OF SPECIMENS WITH ALTERATIONS/NUMBER OF SPECIMENS EXAMINED

003706

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 21 (PAGE 12): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP IV		10 MG/KG/DAY					
RAT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION		SOFT TISSUE EXAMINATION		SKELETAL EXAMINATION	
		N/N	DESCRIPTION	N/N	DESCRIPTION	N/N	DESCRIPTION
12893	1 (6.2)	0/16		0/ 8		1/ 8	FETUS 13 SKULL: NASAL - FRONTAL, SUTURE LARGE
12894	0 (0.0)	0/14		0/ 7		0/ 7	
12895	0 (0.0)	0/14		0/ 7		0/ 7	
12896	0 (0.0)	0/14		0/ 7		0/ 7	
12897	0 (0.0)	0/15		0/ 7		0/ 8	
12898	1 (5.6)	0/18		0/ 9		1/ 9	FETUS 15 CERVICAL VERTEBRAE: CERVICAL RIB PRESENT AT 7TH CERVICAL VERTEBRA, right
12899	0 (0.0)	0/13		0/ 6		0/ 7	
12900	0 (0.0)	0/16		0/ 8		0/ 8	

N/N = NUMBER OF SPECIMENS WITH ALTERATIONS/NUMBER OF SPECIMENS EXAMINED

003707

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 21 (PAGE 13): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP V		20 MG/KG/DAY					
RAT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION		SOFT TISSUE EXAMINATION		SKELETAL EXAMINATION	
		N/N	DESCRIPTION	N/N	DESCRIPTION	N/N	DESCRIPTION
12901	0 (0.0)	0/17		0/ 7		0/10	
12902	0 (0.0)	0/12		0/ 6		0/ 6	
12903	0 (0.0)	0/14		0/ 7		0/ 7	
12904	1 (10.0)	0/10		0/ 5		1/ 5	FETUS 1 RIBS: WAVY, right 5th - 7th and 10th
12905	0 (0.0)	0/12		0/ 6		0/ 6	
12906	0 (0.0)	0/13		0/ 6		0/ 7	
12907	1 (11.1)	0/ 9		0/ 4		1/ 5	FETUS 1 STERNAL CENTRA: 1ST, NOT OSSIFIED
12908	1 (7.1)	0/14		0/ 7		1/ 7	FETUS 5 CERVICAL VERTEBRAE: CERVICAL RIB PRESENT AT 7TH CERVICAL VERTEBRA, left
12909	4 (33.3)	0/12		0/ 6		4/ 6	FETUS 5 RIBS: WAVY, bilateral 4th - 11th

N/N = NUMBER OF SPECIMENS WITH ALTERATIONS/NUMBER OF SPECIMENS EXAMINED

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PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 21 (PAGE 14): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP V		20 MG/KG/DAY					
RAT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION		SOFT TISSUE EXAMINATION		SKELETAL EXAMINATION	
		N/N	DESCRIPTION	N/N	DESCRIPTION	N/N	DESCRIPTION
12909 (CONT)							FETUS 7 RIBS: WAVY, right 4th - 12th, left 3rd - 12th; INCOMPLETELY OSSIFIED (HYPOPLASTIC), right 9th - 12th, left 10th - 12th FETUS 10 RIBS: WAVY, right 6th - 11th, left 6th, 7th and 10th FETUS 12 RIBS: WAVY, right 4th - 11th, left 6th - 9th
12910	NOT PREGNANT						
12911	0(0.0)	0/13		0/ 6		0/ 7	
12912	1(7.7)	0/13		0/ 6		1/ 7	FETUS 5 CERVICAL VERTEBRAE: CERVICAL RIB PRESENT AT 7TH CERVICAL VERTEBRA, left
12913	0(0.0)	0/12		0/ 6		0/ 6	
12914	0(0.0)	0/15		0/ 7		0/ 8	
12915	0(0.0)	0/14		0/ 7		0/ 7	
12916	0(0.0)	0/16		0/ 8		0/ 8	

N/N = NUMBER OF SPECIMENS WITH ALTERATIONS/NUMBER OF SPECIMENS EXAMINED

003709

PROTOCOL 418-011: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: T-6316.7)

TABLE 21 (PAGE 15): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP V		20 MG/KG/DAY					
RAT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION		SOFT TISSUE EXAMINATION		SKELETAL EXAMINATION	
		N/N	DESCRIPTION	N/N	DESCRIPTION	N/N	DESCRIPTION
12917	0 (0.0)	0/14		0/ 7		0/ 7	
12918	0 (0.0)	0/15		0/ 7		0/ 8	
12919	2 (14.3)	0/14		0/ 7		2/ 7	FETUS 3 RIBS: WAVY, bilateral 4th - 12th FETUS 9 RIBS: WAVY, bilateral 4th - 12th
12920	1 (6.2)	0/16		0/ 8		1/ 8	FETUS 1 CERVICAL VERTEBRAE: CERVICAL RIB PRESENT AT 7TH CERVICAL VERTEBRA, left
12921	0 (0.0)	0/14		0/ 7		0/ 7	
12922	0 (0.0)	0/12		0/ 6		0/ 6	
12923	1 (7.1)	0/14		0/ 7		1/ 7	FETUS 7 CERVICAL VERTEBRAE: CERVICAL RIB PRESENT AT 7TH CERVICAL VERTEBRA, bilateral
12924	0 (0.0)	0/15		0/ 7		0/ 8	
12925	0 (0.0)	0/16		0/ 8		0/ 8	

N/N = NUMBER OF SPECIMENS WITH ALTERATIONS/NUMBER OF SPECIMENS EXAMINED

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APPENDIX C
PROTOCOL AND AMENDMENTS



Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, PA 19044
Telephone: (215) 443-8710
Telefax: (215) 443-8587

PROTOCOL 418-011

SPONSOR'S STUDY NUMBER: T-6316.7

STUDY TITLE: Oral (Gavage) Developmental Toxicity Study of N-EtFOSE in Rats

PURPOSE: The purpose of this study is to detect adverse effects of N-EtFOSE on Crl:CD®BR VAF/Plus® presumed pregnant female rats and development of the embryo and fetus consequent to exposure of the dam from implantation to closure of the hard palate. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.

TESTING FACILITY: Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, Pennsylvania 19044-1297
Telephone: (215) 443-8710
Telefax: (215) 443-8587

STUDY DIRECTOR: Raymond G. York, Ph.D., DABT
Associate Director of Research

SPONSOR: 3M Toxicology Services
3M Center, Building 220-2E-02
St. Paul, Minnesota 55144-1000

STUDY MONITOR: Marvin T. Case, D.V.M., Ph.D.
Telephone: (651) 733-5180
Telefax: (651) 733-1773

**ALTERNATE
STUDY MONITOR:** Andrew M. Seacat, Ph.D.
Telephone: (651) 575-3161
Telefax: (651) 733-1773

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REGULATORY CITATIONS:

U.S. Food and Drug Administration (1994). International Conference on Harmonisation; Guideline on detection of toxicity to reproduction for medicinal products. *Federal Register*, September 22, 1994, Vol. 59, No. 183.

U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58.

Japanese Ministry of Health and Welfare (1997). *Good Laboratory Practice Standard for Safety Studies on Drugs*, MHW Ordinance Number 21, March 26, 1997.

European Economic Community (1989). *Council decision on 28 July 1989 on the acceptance by the European Economic Community of an OECD decision/recommendation on compliance with principles of good laboratory practice*. Official Journal of the European Communities: Legislation. 32(No. L 315; 28 October): 1-17.

REGULATORY COMPLIANCE:

This study will be conducted in compliance with the Good Laboratory Practice (GLP) regulations cited above.

All changes or revisions of this protocol shall be documented, signed by the Study Director and the Sponsor, dated and maintained with the protocol.

The Quality Assurance Unit (QAU) will audit the protocol, the raw data and the report, and will inspect critical phases of the study in accordance with the Standard Operating Procedures of Argus Research Laboratories, Inc.

The final report will include a statement signed by the Study Director that the report accurately reflects the raw data obtained during the performance of the study and that all applicable GLP regulations were followed in the conduct of the study. Should significant deviations from GLP regulations occur, each will be described in detail, together with how the deviation might affect the quality or integrity of the study.

SCHEMATIC OF STUDY DESIGN AND STUDY SCHEDULE:

See ATTACHMENT 1 to the protocol.

TEST ARTICLE AND VEHICLE:**Identification:****Test Article:**

Name:	N-EtFOSE.
Physical Description:	Waxy solid.
Lot/Batch Number:	FM-3929 (30035, 30037, 30039).
Specific Gravity:	~1.7.
Purity:	99.1%.
Expiration Date:	May, 2000.

Information on the identity, composition, strength and purity of the test article is on file with the Sponsor.

Vehicle:

2% Tween® 80 in Reverse Osmosis Membrane Processed Deionized Water (R.O. Deionized Water). Supplier and lot identification of Tween® 80 will be documented in the raw data.

Neither the Sponsor nor the Study Director is aware of any potential contaminants likely to be present in the vehicle that would interfere with the results of this study. Therefore, no analyses other than those mentioned in this protocol will be conducted.

Safety Precautions:

Gloves, mask, appropriate eye protection and a uniform/lab coat are to be worn during formulation preparation and administration. The Material Safety Data Sheet (MSDS) is attached to the protocol (see ATTACHMENT 2).

Storage:

Bulk Test Article:	Room Temperature.
Vehicle Components:	Room Temperature.
Prepared Vehicle:	Room Temperature.
Prepared Formulations:	Refrigerated (samples to be frozen).

All test article shipments to the Testing Facility should be addressed to the attention of Julian Gulbinski, Manager of Formulations, at the previously cited address and telephone number.

Shipments should include information concerning storage conditions and shipping cartons should be labeled appropriately. The recipient should be notified in advance of shipment.

FORMULATION:**Frequency of Preparation:**

Formulations suspensions will be prepared weekly at the Testing Facility.

Detailed preparation procedures are attached to this protocol (ATTACHMENT 3).

Adjustment for Purity:

The test article will be considered 100% pure for the purpose of dosage calculations.

Testing Facility Reserve Samples:

The Testing Facility will reserve a sample (1 g) of each lot of bulk test article used during the course of this study. The Testing Facility will reserve a sample (5 ml) of each lot of vehicle components used during the course of the study. Samples will be stored under the previously cited conditions.

ANALYSES:

Samples additional to those described below may be taken if deemed necessary during the course of the study.

Bulk Test Article Sampling:

No analyses of the bulk test article will be conducted during the course of this study. Information on the stability of the bulk test article is on file with the Sponsor.

Analyses of Prepared Formulations:

At the request of the Sponsor, no analyses of prepared test article formulations will be conducted during the course of the study. Homogeneity and stability information is on file with the Sponsor. However, records will be maintained to document how the test article formulations were prepared.

Concentration of Test Article Formulations:

Concentration of the prepared formulations will be verified during the course of this study. Duplicate samples (2 mL each) will be taken from the first and last preparation on the day prepared. One sample of each set will be shipped for analysis; the remaining samples will be retained at the Testing Facility as backup samples. Backup samples will be stored under the previously cited conditions and discarded at the Testing Facility upon request of the Sponsor.

Shipping Instructions:

Samples to be analyzed will be shipped (frozen on dry ice) to:

Kris J. Hansen, Ph.D.
3M Environmental Technology and Safety Services
935 Bush Avenue
Building 2-3E-09
St. Paul, Minnesota 55133-3331
Telephone: (612) 778-6018
Telefax: (612) 778-6176

The recipient will be notified in advance of sample shipment.

DISPOSITION:

Prepared formulations will be discarded at the Testing Facility. All remaining bulk test article will be returned to the Study Monitor at the previously cited address.

TEST SYSTEM:**Species/Strain and Reason for Selection:**

The CrI:CD®BR VAF/Plus® (Sprague-Dawley) rat was selected as the Test System because: 1) it is one mammalian species accepted and widely used throughout industry for nonclinical studies of developmental toxicity (embryo-fetal toxicity/teratogenicity); 2) this strain has been demonstrated to be sensitive to developmental toxins; 3) historical data and experience exist at the Testing Facility⁽¹⁻³⁾; and 4) the test article is pharmacologically active in this species and strain.

Number:

Initial population acclimated:	190 virgin female rats.
Population selected for study:	125 mated female rats (25 per dosage group).
Population assigned to satellite study:	19 mated female rats (five per Groups II and V and three per Groups I, III and IV) assigned to toxicokinetic evaluation.

Body Weight and Age:

Female rats will be ordered to have body weights of 200 g to 225 g each at receipt, at which time they will be expected to be at least 60 days of age. Actual body weights will be recorded the day after receipt and will be documented in the raw data. The weight range will be included in the final report.

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Sex:

Female rats will be given the test article. Male rats of the same source and strain will be used only as breeders and are not considered part of the Test System.

Source:

Charles River Laboratories, Inc.

The rats will be shipped in filtered cartons by air freight and/or truck from Charles River Laboratories, Inc., to the Testing Facility.

Identification:

Rats are permanently identified using Monel® self-piercing ear tags (Gey Band and Tag Co., Inc., No. MSPT 20101). Male rats are given unique permanent identification numbers upon assignment to the Testing Facility's breeder male rat population. Female rats are assigned temporary numbers at receipt and given unique permanent identification numbers when assigned to the study on the basis of day 0 of presumed gestation body weights.

ANIMAL HUSBANDRY:

All cage sizes and housing conditions are in compliance with the *Guide for the Care and Use of Laboratory Animals*⁽⁴⁾.

Housing:

The rats will be individually housed in stainless steel, wire-bottomed cages except during the cohabitation period. During cohabitation, each pair of rats will be housed in the male rat's cage. No nesting materials will be supplied because the female rats will be sacrificed before parturition is expected.

Room Air, Temperature and Humidity:

The animal room is independently supplied with at least ten changes per hour of 100% fresh air that has been passed through 99.97% HEPA filters (Airo Clean® room). Room temperature will be maintained at 64°F (18°C) to 79°F (26°C) and monitored constantly. Room humidity will also be monitored constantly and maintained at 30% to 70%.

Light

An automatically controlled 12-hour light:12-hour dark fluorescent light cycle will be maintained. Each dark period will begin at 1900 hours EST.

Diet:

Rats will be given Certified Rodent Diet® #5002 (PMI Nutrition International) available *ad libitum* from individual feeders.

Water:

Water will be available *ad libitum* from individual bottles attached to the cages or from an automatic watering access system. All water will be from a local source and passed through a reverse osmosis membrane before use. Chlorine will be added to the processed water as a bacteriostat; processed water is expected to contain no more than 1.2 ppm chlorine at the time of analysis. Water is analyzed monthly for possible bacterial contamination and twice annually for possible chemical contamination.

Contaminants:

Neither the Sponsor nor the Study Director is aware of any potential contaminants likely to be present in the certified diet or in the drinking water at levels that would interfere with the results of this study. Therefore, no analyses other than those routinely performed by the feed supplier or those mentioned in this protocol will be conducted.

RANDOMIZATION AND COHABITATION:

Upon arrival, male and female rats will be assigned to individual housing on the basis of computer-generated random units. After acclimation, virgin female rats will be cohoused with breeder male rats, one male rat per female rat. The cohabitation period will consist of a maximum of five days. Female rats with spermatozoa observed in a smear of the vaginal contents and/or a copulatory plug observed *in situ* will be considered to be at day 0 of presumed gestation and assigned to individual housing.

Healthy mated female rats will be assigned to dosage groups based on computer-generated (weight-ordered) randomization procedures.

ADMINISTRATION:**Route and Reason for Choice:**

The oral (gavage) route was selected for use because: 1) in comparison with the dietary route, the exact dosage can be accurately administered; and 2) it is one of the proposed routes for clinical use.

Method and Frequency:

Female rats will be given the test article once daily on days 6 through 17 of presumed gestation, the period of organogenesis. Dosages will be adjusted for the most recently recorded body weight and given at approximately the same time each day.

Rationale for Dosage Selection:

Dosages were selected on the basis of a dosage-range study (Argus Research Laboratories, Inc., Protocol 418-011P) that tested 0, 1, 5, 10, 25 and 35 mg/kg/day. In that study, body weight gain was decreased at 10 mg/kg/day and higher dosages, and feed consumption values were reduced at all dosages tested.

Dosage Levels, Concentrations and Volumes:

Dosage Group	Number of Rats	Dosage (mg/kg/day)	Concentration (mg/mL)	Dosage Volume (mL/kg)	Argus Batch Number
I	25 + 3*	0 (Vehicle)	0	5	B-418-011-A(Day.Month.Year)
II	25 + 5*	1	0.2	5	B-418-011-B(Day.Month.Year)
III	25 + 3*	5	1	5	B-418-011-B(Day.Month.Year)
IV	25 + 3*	10	2	5	B-418-011-C(Day.Month.Year)
V	25 + 5*	20	4	5	B-418-011-D(Day.Month.Year)

The test article will be considered 100% pure for the purpose of dosage calculations.

*. Rats assigned to the satellite group for blood collection.

TESTS, ANALYSES AND MEASUREMENTS:**Viability:**

All Periods: At least twice daily.

Clinical Observations and/or General Appearance:

Acclimation Period: Weekly.

Predosage Period: Day 0 of presumed gestation.

Dosage Period: Twice daily. Prior to dosage administration and once approximately one hour postdosage.

Postdosage Period: Once daily.

Clinical observations may be recorded more frequently than cited above, if deemed appropriate by the Study Director and/or Study Monitor.

Body Weights:

Acclimation Period: Weekly.

Predosage Period: Day 0 and 4 of presumed gestation.

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Dosage Period: Daily.

Postdosage Period: Daily.

Feed Consumption Values (recorded and tabulated):

Predosage Period: Day 0 and 4 of presumed gestation.

Dosage Period: Days 6, 8, 10, 12, 14 and 16 of presumed gestation.

Postdosage Period: Days 18 and 20 of presumed gestation.

Feed consumption values may be recorded more frequently if it is necessary to replenish the feed. These intervals will not be tabulated.

Mating Performance:

Mating will be evaluated daily during the cohabitation period and confirmed by observation of spermatozoa in a smear of the vaginal contents and/or a copulatory plug observed *in situ*.

Caesarean-Sectioning Observations:

Rats will be Caesarean-sectioned on day 20 of presumed gestation. The fetuses will be removed from the uterus and placed in individual containers. The rats will be examined for number and distribution of:

Corpora Lutea.

Implantation Sites.

[Placentae appearance (size, color or shape if abnormal) will be noted in the raw data].

Live and Dead Fetuses.

(A live fetus is defined as one that responds to stimuli; a dead fetus is defined as a term fetus that does not respond to stimuli and that is not markedly autolyzed; dead fetuses demonstrating marked to extreme autolysis are considered to be late resorptions.)

Early and Late Resorptions.

(A conceptus is defined as a late resorption if it is grossly evident that organogenesis has occurred; if this is not the case, the conceptus is defined as an early resorption.)

Fetal Observations:**Gross External Alterations and Sex:**

Fetuses will be examined for sex and for gross external alterations. Late resorptions and dead fetuses also will be examined for sex and for gross external alterations to the extent possible but such observations will not be included in either data summarization or statistical analyses.

Body Weights and Identification:

The body weight of each fetus will be recorded. Only body weights of live fetuses will be used to determine litter fetal body weight averages. Fetuses will be tagged with identification noting study number, litter number, uterine distribution and fixative.

Soft Tissue Examination:

Approximately one-half of the fetuses in each litter will be examined for soft tissue alterations by using an adaptation of Wilson's sectioning technique⁽⁵⁾. The fetuses will be initially fixed in Bouin's solution; sections will be retained in alcohol.

Skeletal Examination:

The remaining fetuses (approximately one-half of the fetuses in each litter) will be examined for skeletal alterations after staining with alizarin red S⁽⁶⁾. The fetuses will be initially fixed in alcohol; skeletal preparations will be retained in glycerin with thymol added as a preservative.

Representative photographs of fetal gross, soft tissue and skeletal alterations will be taken.

METHOD OF SACRIFICE:

Rats will be sacrificed by carbon dioxide asphyxiation. Live fetuses will be sacrificed by an intraperitoneal injection of euthanasia solution (Beuthanasia®-D Special, manufactured by Schering-Plough Animal Health).

NECROPSY:

Gross lesions will be retained in neutral buffered 10% formalin for possible future evaluation (a table of random units will be used to select one control group rat from which all tissues examined at necropsy will be retained, in order to provide control tissues for any possible histopathological evaluations of gross lesions). Unless specifically cited below, all other tissues will be discarded.

Satellite Rats Assigned to Toxicokinetic Sample Collection:

On day 18 of presumed gestation (the day following the last dosage), rats assigned to the toxicokinetic evaluation will be sacrificed and the following samples collected. Blood samples (approximately 4 mL per rat) will be collected from the inferior vena cava into serum separator tubes and centrifuged. The resulting serum (approximately 2 mL) will be immediately frozen on dry ice and maintained frozen (-70°C) until shipment to the Sponsor for analysis. The liver will be excised, weighed, and a sample section (lateral lobe) will be frozen and retained at -70°C until shipment to the Sponsor for analysis.

Rats will be Caesarean-sectioned and fetuses will be examined grossly to the extent possible as described above for rats assigned to the main study. Fetuses and placentae will be pooled per litter and retained frozen (-70°C) until shipment to the Sponsor for analysis

After completion of sample collection, serum, liver section (lateral lobe), fetal and placental samples will be shipped (frozen on dry ice) to Kris J. Hansen, Ph.D., at the previously cited address for analysis. Both the recipient and the Study Monitor will be notified in advance of sample shipment.

Scheduled Sacrifice:

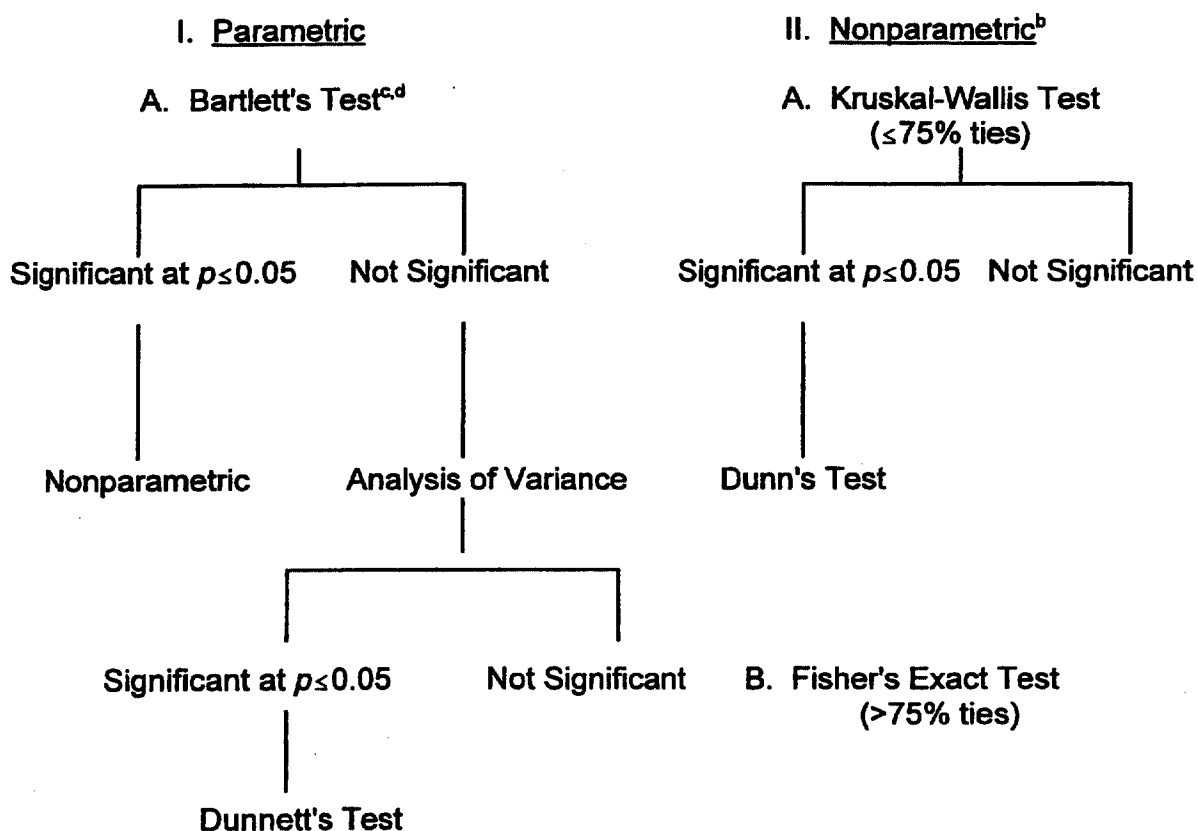
On day 20 of presumed gestation, female rats will be Caesarean-sectioned, and a gross necropsy of the thoracic, abdominal and pelvic viscera will be performed. Uteri of apparently nonpregnant rats will be stained with 10% ammonium sulfide to confirm the absence of implantation sites⁽⁷⁾.

Rats Found Dead or Moribund:

Rats that die or are sacrificed because of moribund condition, abortion or premature delivery will be examined for the cause of death or moribund condition on the day the observation is made. The rats will be examined for gross lesions. Pregnancy status and uterine contents of female rats will be recorded. Aborted fetuses and/or delivered pups will be examined to the extent possible, using the same methods described for fetuses. Uteri of apparently nonpregnant rats will be stained with 10% ammonium sulfide to confirm the absence of implantation sites⁽⁷⁾.

PROPOSED STATISTICAL METHODS⁽⁸⁻¹⁴⁾

Averages and percentages will be calculated. Litter values will be used where appropriate. Additional procedures and/or analyses may be performed, if appropriate.

Type of Test^a**III. Test for Proportion Data**

Variance Test for Homogeneity
of the Binomial Distribution

-
- a. Statistically significant probabilities are reported as either $p \leq 0.05$ or $p \leq 0.01$.
 b. Proportion data are not included in this category.
 c. Used only to analyze data with homogeneity of variance.
 d. Test for homogeneity of variance.

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DATA ACQUISITION, VERIFICATION AND STORAGE:

Data will be hand- and/or computer-recorded. Records will be reviewed by the Study Director and/or appropriate management personnel within 21 days after generation. All original records will be stored in the archives of the Testing Facility. All original data will be bound and indexed. A copy of all raw data will be supplied to the Sponsor upon request. Preserved tissues will be stored at the Testing Facility at no charge for one year after mailing of the draft final report, after which time the Sponsor will be contacted to determine the disposition of these materials.

RECORDS TO BE MAINTAINED:

Protocol and Amendments.
Test Article, Vehicle and/or Reagent Receipt, Preparation and Use.
Animal Acquisition.
Randomization Schedules.
Mating History.
Treatment (if prescribed by Staff Veterinarian).
General Comments.
Clinical Observations and/or General Appearance.
Blood and Tissue Sample Collection, Processing and Shipment.
Body Weights.
Feed Consumption Values.
Caesarean-Sectioning and Fetal Observations.
Gross Necropsy Observations.
Organ Weights.
Photographs (if required).
Study Maintenance (room and environmental records).
Feed and Water Analyses.
Packing and/or Shipment Lists.

KEY PERSONNEL:

Executive Director of Research: Mildred S. Christian, Ph.D., Fellow, ATS
Director of Research: Alan M. Hoberman, Ph.D., DABT
Associate Director of Research and Study Director: Raymond G. York, Ph.D., DABT
Director of Laboratory Operations: John F. Barnett, B.S.
Manager of Study Coordination: Valerie A. Sharper, M.S.
Manager of Animal Operations and Member, Institutional Animal Care and Use Committee: Dena C. Lebo, V.M.D.
Manager of Regulatory Compliance: Kathleen A. Moran, M.S.
Consultant, Veterinary Pathology: W. Ray Brown, D.V.M., Ph.D., ACVP

FINAL REPORT:

A comprehensive draft final report will be prepared on completion of the study and will be finalized following consultation with the Sponsor. The report will include the following:

Summary and Conclusion.

Experimental Design and Method.

Evaluation of Test Results.

Appendices: Figures, Summary and Individual Tables Summarizing the Above Data, Protocol and Associated Amendments and Deviations, Study Director's GLP Compliance Statement, Reports of Supporting Data (if appropriate) and QAU Statement.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE STATEMENT:

The procedures described in this protocol have been reviewed by the Testing Facility's Institutional Animal Care and Use Committee. All procedures described in this protocol that involve study animals will be conducted in a manner to avoid or minimize discomfort, distress or pain to the animals.

The Sponsor's signature below documents the fact that information concerning the necessity for conducting this study and the fact that this is not an unnecessarily duplicative study may be obtained from the Sponsor. No alternative (*in vitro*) procedures were available for meeting the stated purposes of the study.

REFERENCES:

1. Christian, M.S. and Voytek, P.E. (1982). *In Vivo Reproductive and Mutagenicity Tests*. Environmental Protection Agency, Washington, D.C. National Technical Information Service, U.S. Department of Commerce, Springfield, VA 22161.
2. Christian, M.S. (1984). Reproductive toxicity and teratology evaluations of naltrexone (Proceedings of Naltrexone Symposium, New York Academy of Sciences, November 7, 1983), *J. Clin. Psychiat.* 45(9):7-10.
3. Lang, P.L. (1988). *Embryo and Fetal Developmental Toxicity (Teratology) Control Data in the Charles River CrI:CD@BR Rat*. Charles River Laboratories, Inc., Wilmington, MA 01887-0630. (Data base provided by Argus Research Laboratories, Inc.)
4. Institute of Laboratory Animal Resources (1996). *Guide for the Care and Use of Laboratory Animals*. National Academy Press, Washington, D.C.

5. Wilson, J.G. (1965). Methods for administering agents and detecting malformations in experimental animals. *Teratology: Principles and Techniques* (Wilson, J.G. and Warkany, J., eds.), University of Chicago Press, pp. 262-277.
6. Staples, R.E. and Schnell, V.L. (1964). Refinement in rapid clearing technique in the KOH-alizarin red S method for fetal bone. *Stain Technol.* 39:61-63.
7. Salewski, E. (1964). Färbemethode zum makroskopischen Nachweis von Implantationsstellen am Uterus der Ratte. *Arch. Pathol. Exp. Pharmacol.* 247:367.
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9. Sokal, R.R. and Rohlf, F.J. (1969). Bartlett's test of homogeneity of variances. *Biometry*, W.H. Freeman and Co., San Francisco, pp. 370-371.
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13. Dunn, O.J. (1964). Multiple comparisons using rank sums. *Technometrics* 6(3):241-252.
14. Siegel, S. (1956). *Nonparametric Statistics for the Behavioral Sciences*, McGraw-Hill, New York, pp. 96-104.

PROTOCOL APPROVAL:

FOR THE TESTING FACILITY



Alan M. Hoberman, Ph.D., DABT
Director of Research

29 JUL -98

Date



Raymond G. York, Ph.D., DABT
Associate Director of Research
Study Director

31-JUL-98

Date



Dena C. Lebo, V.M.D.
Member, Institutional Animal Care and
Use Committee

29 Jul 98

Date

FOR THE SPONSOR



Marvin T. Case, D.V.M., Ph.D.
Study Monitor

3 Aug 1998

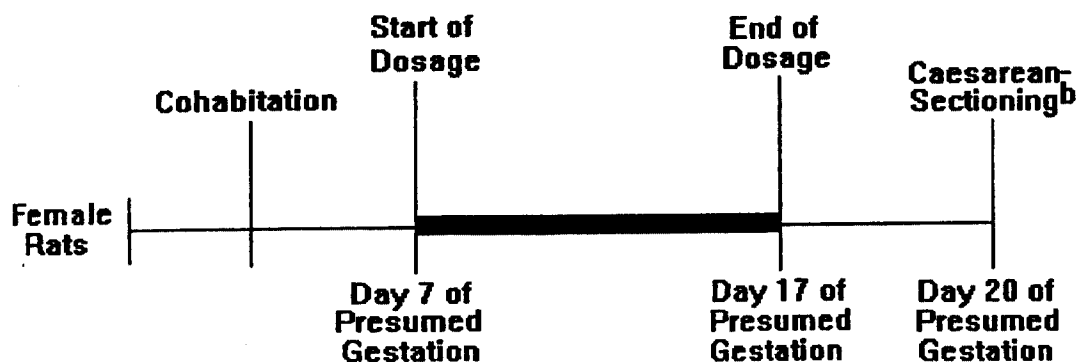
Date

ATTACHMENT 1

SCHEMATIC OF STUDY DESIGN AND STUDY SCHEDULE

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STUDY SCHEMATIC
DEVELOPMENTAL TOXICITY STUDY^a



■ = Dosage Period

a = For additional details see "Tests, Analyses and Measurements" section of the protocol

b = Fetal evaluations (all - external, 1/2 per litter - soft tissue or skeletal)

ATTACHMENT 1

Protocol 418-011
Page 2 of 2**SCHEDULE^a**

11 AUG 98	Arrival Date - Acclimation Begins.
18 AUG 98 PM - 23 AUG 98 AM	Cohabitation Period.
19 AUG 98	First Possible Day 0 of Presumed Gestation.
23 AUG 98	Last Possible Day 0 of Presumed Gestation
25 AUG 98 - 09 SEP 98	Dosage Period (Days 6 through 17 of presumed gestation).
08 SEP 98 - 12 SEP 98	Caesarean-Sectioning Period (Day 20 of presumed gestation).
02 DEC 98	Draft Final Report.

-
- a. The study initiation date is the date the Study Director signs the protocol.

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ATTACHMENT 2
MATERIAL SAFETY DATA SHEET

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MATERIAL SAFETY
DATA SHEET

3M
3M Center
St. Paul, Minnesota
55144-1000
1-800-364-3577 or (612) 737-6501 (24 hours)

N-E+FOSE

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distributed with the intention of earning a profit thereon.

DIVISION: 3M CHEMICALS

TRADE NAME:

FC-10 FLUORAD Brand Fluorochemical Alcohol

ID NUMBER/U.P.C.:

98-0211-1113-7 00-51135-09495-2 98-0211-1183-0 00-51135-09542-3
98-0211-1575-7 00-51135-02145-3 98-0211-6620-6 00-51135-10439-2
ZF-0002-0572-2

ISSUED: January 29, 1998

SUPERSEDES: November 05, 1997

DOCUMENT: 10-3778-7

1. INGREDIENT	C.A.S. NO.	PERCENT
PERFLUOROOCTANESULFONAMIDO ALCOHOL.....	1691-99-2	80.0 - 90.0
PERFLUOROHXANESULFONAMIDO ALCOHOL.....	34455-03-3	3.0 - 7.0
PERFLUOROHEPTANESULFONAMIDO ALCOHOL.....	68555-73-7	2.0 - 6.0
PERFLUOROBUTANESULFONAMIDO ALCOHOL.....	34449-89-3	2.0 - 6.0
PERFLUOROPENTANESULFONAMIDO ALCOHOL.....	68555-72-6	1.0 - 3.0

2. PHYSICAL DATA

BOILING POINT:..... ca. 118 C
@ 1 mm Hg
VAPOR PRESSURE:..... < 10 mmHg
Calc @ 20 C
VAPOR DENSITY:..... > 1.0 Air=1
Calc @ 20 C.
EVAPORATION RATE:..... < 1.0 BuOAc=1
SOLUBILITY IN WATER:..... neglig.
SPECIFIC GRAVITY:..... ca. 1.7 Water=1
(of melt)
PERCENT VOLATILE:..... 0 %
pH:..... N/A
VISCOSITY:..... N/D
MELTING POINT:..... N/D

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2. PHYSICAL DATA (continued)

APPEARANCE AND ODOR:
Amber waxy solid

3. FIRE AND EXPLOSION HAZARD DATA

FLASH POINT:..... > 148 C Setflash
FLAMMABLE LIMITS - LEL:..... N/A
FLAMMABLE LIMITS - UEL:..... N/A
AUTOIGNITION TEMPERATURE:..... N/A

EXTINGUISHING MEDIA:
Water, Carbon dioxide, Dry chemical, Foam

SPECIAL FIRE FIGHTING PROCEDURES:
Wear full protective clothing, including helmet, self-contained,
positive pressure or pressure demand breathing apparatus, bunker coat
and pants, bands around arms, waist and legs, face mask, and
protective covering for exposed areas of the head.

UNUSUAL FIRE AND EXPLOSION HAZARDS:
See Hazardous Decomposition section for products of combustion.

4. REACTIVITY DATA

STABILITY: Stable

INCOMPATIBILITY - MATERIALS/CONDITIONS TO AVOID:
Not applicable.

HAZARDOUS POLYMERIZATION: Hazardous polymerization will not occur.

HAZARDOUS DECOMPOSITION PRODUCTS:
Carbon Monoxide and Carbon Dioxide, Oxides of Nitrogen, Oxides of
Sulfur, Hydrogen Fluoride, Toxic Vapors, Gases or Particulates.

5. ENVIRONMENTAL INFORMATION

SPILL RESPONSE:
Refer to other sections of this MSDS for information regarding
physical and health hazards, respiratory protection, ventilation, and
personal protective equipment. Collect spilled material. Clean up
residue. Place in a U.S. DOT-approved container. 003733

MSDS: FC-10 FLUORAD Brand Fluorochemical Alcohol
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5. ENVIRONMENTAL INFORMATION (continued)

RECOMMENDED DISPOSAL:

Incinerate in a permitted hazardous waste incinerator in the presence of a combustible material. Combustion products will include HF. Dispose of waste product in a facility permitted to accept chemical waste.

ENVIRONMENTAL DATA:

Laboratory tests showed no biodegradation. 96-Hr. LD50 Fathead Minnow (*Pimephales promelas*) - No mortality at water saturation. No statistically significant effect on % hatch, % survival, weight, and length in 30 day Fathead Minnow egg fry study. Lab tests showed 200 fold bioconcentration of FC-10 into muscle fillets of channel catfish.

REGULATORY INFORMATION:

Volatile Organic Compounds: N/A.
VOC Less H2O & Exempt Solvents: N/A.

This product complies with the chemical registration requirements of TSCA, EINECS, CDSL, AICS and Korea.

EPCRA HAZARD CLASS:

FIRE HAZARD: No PRESSURE: No REACTIVITY: No ACUTE: Yes CHRONIC: Yes

6. SUGGESTED FIRST AID

EYE CONTACT:

Immediately flush eyes with large amounts of water. Get immediate medical attention.

SKIN CONTACT:

Immediately wash skin with soap and large amounts of water. Remove contaminated clothing. If signs/symptoms occur, call a physician. Wash contaminated clothing before reuse and dispose of contaminated shoes.

INHALATION:

If signs/symptoms occur, remove person to fresh air. If signs/symptoms continue, call a physician.

IF SWALLOWED:

Call a physician IMMEDIATELY. If swallowed, induce vomiting immediately as directed by medical personnel. Never give anything by mouth to an unconscious person.

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7. PRECAUTIONARY INFORMATION

EYE PROTECTION:

Avoid eye contact. Wear safety glasses with side shields.

SKIN PROTECTION:

Avoid skin contact. Wear appropriate gloves when handling this material. A pair of gloves made from the following material(s) are recommended: butyl rubber. Use one or more of the following personal protection items as necessary to prevent skin contact: coveralls.

RECOMMENDED VENTILATION:

Use with appropriate local exhaust ventilation. Provide sufficient ventilation to maintain emissions below recommended exposure limits. If exhaust ventilation is not adequate, use appropriate respiratory protection.

RESPIRATORY PROTECTION:

Avoid breathing of airborne material. Select one of the following NIOSH approved respirators based on airborne concentration of contaminants and in accordance with OSHA regulations: half-mask dust respirator, full-face supplied air respirator.

PREVENTION OF ACCIDENTAL INGESTION:

Do not eat, drink or smoke when using this product. Wash exposed areas thoroughly with soap and water. Wash hands after handling and before eating.

RECOMMENDED STORAGE:

Store away from heat. Keep container closed when not in use.

FIRE AND EXPLOSION AVOIDANCE:

Nonflammable.

OTHER PRECAUTIONARY INFORMATION:

No smoking: Smoking while using this product can result in contamination of the tobacco and/or smoke and lead to the formation of the hazardous decomposition products mentioned in section 4 of this MSDS.

HMIS HAZARD RATINGS: HEALTH: 1 FLAMMABILITY: 1 REACTIVITY: 0
PERSONAL PROTECTION: X (See precautions, section 7.)

EXPOSURE LIMITS

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INGREDIENT	VALUE	UNIT	TYPE	AUTH	SKIN*
PERFLUOROOCETANESULFONAMIDO ALCOHOL...	0.1	MG/M3	TWA	3M	Y
PERFLUOROHEXANESULFONAMIDO ALCOHOL...	0.1	MG/M3	TWA	3M	Y
PERFLUOROHEPTANESULFONAMIDO ALCOHOL.....	0.1	MG/M3	TWA	3M	Y

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January 29, 1998

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EXPOSURE LIMITS (continued)

INGREDIENT	VALUE	UNIT	TYPE	AUTH	SKIN*
PERFLUOROBUTANESULFONAMIDO ALCOHOL...	0.1	MG/M3	TWA	3M	Y
PERFLUOROPENTANESULFONAMIDO ALCOHOL.....	0.1	MG/M3	TWA	3M	Y

* SKIN NOTATION: Listed substances indicated with 'Y' under SKIN refer to the potential contribution to the overall exposure by the cutaneous route including mucous membrane and eye, either by airborne or, more particularly, by direct contact with the substance. Vehicles can alter skin absorption.

SOURCE OF EXPOSURE LIMIT DATA:

- 3M: 3M Recommended Exposure Guidelines

8. HEALTH HAZARD DATA

EYE CONTACT:

No adverse health effects are expected from eye contact.

SKIN CONTACT:

Product is not expected to be irritating to the skin.

May be absorbed through the skin and persist in the body for an extended time.

INHALATION:

May be absorbed by inhalation and persist in the body for an extended time.

IF SWALLOWED:

Ingestion is not a likely route of exposure to this product.

Illness may occur after a single swallowing of relatively large quantities of this material.

MUTAGENICITY:

Not mutagenic in in-vitro assays.

REPRODUCTIVE/DEVELOPMENTAL TOXINS:

Substance was not teratogenic in the rat at doses as high as 30 milligrams per kilogram per day via oral route.

OTHER HEALTH HAZARD INFORMATION:

This product is not known to contain any substances regulated under California Proposition 65.

A Product Toxicity Summary Sheet is available.

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January 29, 1998

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SECTION CHANGE DATES

HEADING

SECTION CHANGED SINCE November 05, 1997 ISSUE

Abbreviations: N/D - Not Determined N/A - Not Applicable CA - Approximately

The information in this Material Safety Data Sheet (MSDS) is believed to be correct as of the date issued. 3M MAKES NO WARRANTIES, EXPRESSED OR IMPLIED, INCLUDING, BUT NOT LIMITED TO, ANY IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE OR COURSE OF PERFORMANCE OR USAGE OF TRADE. User is responsible for determining whether the 3M product is fit for a particular purpose and suitable for user's method of use or application. Given the variety of factors that can affect the use and application of a 3M product, some of which are uniquely within the user's knowledge and control, it is essential that the user evaluate the 3M product to determine whether it is fit for a particular purpose and suitable for user's method of use or application.

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ATTACHMENT 3
TEST ARTICLE PREPARATION PROCEDURE

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ATTACHMENT 3

Protocol 418-011
Version: 418-011 (28 JUL 98)
Page 1 of 3

TEST ARTICLE AND CONTROL ARTICLE PREPARATION PROCEDURE

Test Article: N-EtFOSE

Vehicle: 2% Tween® 80, in R.O. Water

A. Purpose: The purpose of this procedure is to provide a method for the preparation of dosage suspensions of N-EtFOSE and the control article for oral administration to rats on Argus Study 418-011.

B. General Information:

1. All suspension containers will be labeled and color coded. Each label will specify the protocol number, test article identification, Argus batch number, concentration, dosage level, preparation date, expiration date and storage conditions.
- 2a. Suspensions will be prepared:
___ Daily X Weekly ___ For ___ days of use
- 2b. Vehicle will be prepared:
___ Daily X Weekly ___ For ___ days of use
3. Suspensions will be prepared at a final dosage volume of 5 mL/kg.
4. Safety:
X Gloves, lab coat, goggles or safety glasses and faceshield
X Dust-Mist Respirator
___ Half-Face Respirator
___ Full-Face Respirator/Positive Pressure Hood
___ Tyvek Suit/Apron
5. Dosage suspensions adjusted for Free base and % Purity.
___ Yes X No (Calculations based on 100%)
___ Free Base ___ Purity
6. Sampling requirements: Cited in protocol.
7. Storage: Cited in protocol.

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ATTACHMENT 3

Protocol 418-011
Version: 418-011 (28 JUL 98)
Page 2 of 3

TEST ARTICLE AND CONTROL ARTICLE PREPARATION PROCEDURE

NOTE: Test article will be prepared as a serial dilution from the high dosage to the low dosage. Once the final volumes are achieved, stir bars are to be added to the containers; mixing should occur during sampling and/or administration.

C. Preparation of Vehicle

1. Add the required amount of R.O. deionized water to an appropriately labeled container. Heat the water to $50 \pm 5^{\circ}\text{C}$, add the required amount of Tween® 80 and mix until uniform (See TEST ARTICLE CALCULATIONS).

D. Test Article Suspension Preparation:

1. To prepare the 4.0-mg/mL, Group V suspension, add the required amount of test article (See TEST ARTICLE CALCULATIONS) into an appropriately sized, labeled container. Add the required amount of vehicle and heat the mixture to $80 \pm 5^{\circ}\text{C}$ for approximately 30 minutes.
2. Once the test article has dissolved; spin over night while the solution cools. (Be sure there is a visible vortex, this will achieve the desired emulsion.)
3. To prepare the 2.0-mg/mL, Group IV suspension, remove the required amount of stock suspension (Group V) (See TEST ARTICLE CALCULATIONS), add the required amount of vehicle and mix.
4. To prepare the 1.0-mg/mL, Group III suspension, remove the required amount of stock suspension (Group IV) (See TEST ARTICLE CALCULATIONS), add the required amount of vehicle and mix.

ATTACHMENT 3

Protocol 418-011
Version: 418-011 (28 JUL 98)
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TEST ARTICLE AND CONTROL ARTICLE PREPARATION PROCEDURE

5. To prepare the 0.2-mg/mL, Group II suspension, remove the required amount of stock suspension (Group III) (See TEST ARTICLE CALCULATIONS), add the required amount of vehicle and mix.

Written by: *Stephen J. Jellinek*Approved by: *Raymond H. Hagan* Date: 31-JUL-98Clarification: ☒ No ☐ Yes (See attached clarification form.)Initials/Date : HC 9-21-98

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Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, PA 19044
Telephone: (215) 443-8710
Telefax: (215) 443-8587

PROTOCOL 418-011

ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS

SPONSOR'S STUDY NUMBER: T-6316.7

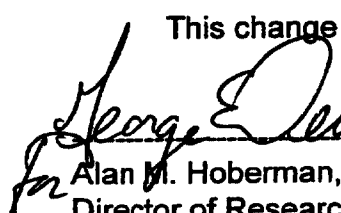
Amendment 1 - 12 August 1998

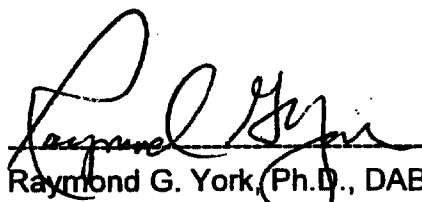
1. Frequency of Preparation (page 4 and page 1 of Attachment 3 to the protocol):

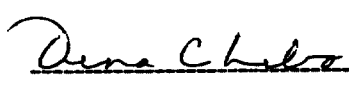
Formulations (suspensions) will be prepared daily at the Testing Facility, rather than weekly.

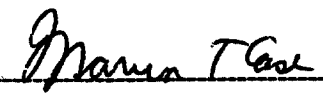
Reason for Change:

This change corrects the protocol.

 12-AUG-98
Alan M. Hoberman, Ph.D., DABT Date
Director of Research

 12-AUG-98
Raymond G. York, Ph.D., DABT Date
Associate Director of Research
Study Director

 12 Aug 98
Dena C. Lebo, V.M.D. Date
Member, Institutional Animal Care and
Use Committee

 13 Aug 1998
Marvin T. Case, D.V.M., Ph.D. Date
Study Monitor

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Argus Research Laboratories, Inc.
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Telefax: (215) 443-8587

PROTOCOL 418-011

ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RATS

SPONSOR'S STUDY NUMBER: T-6316.7

Amendment 2 - 11 December 1998

1. Sponsor (page 1 of the protocol):

The Sponsor is 3M Corporate Toxicology, rather than 3M Toxicology Services.

Reason for Change:

This change was made at the request of the Sponsor.

2. Species/Strain and Reason for Selection (page 5 of the protocol):

The test article is biologically active, rather than pharmacologically active in this strain.

Reason for Change:

This change was made at the request of the Sponsor to correct the protocol.

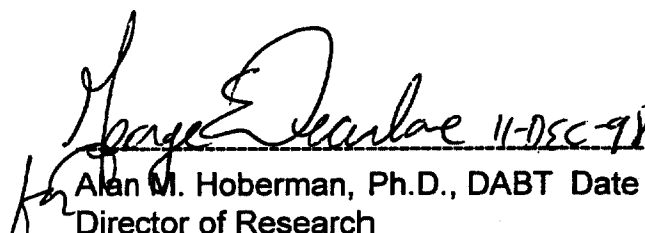
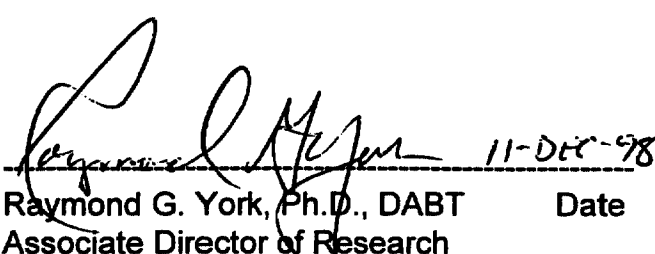
3. Route and Reason for Choice (page 7 of the protocol):

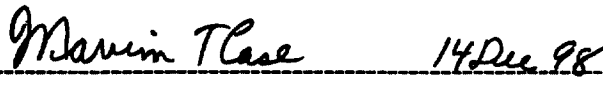
The oral (gavage) route is a possible route of human exposure, rather than the one proposed for clinical use.

003743

Reason for Change:

This change was made at the request of the Sponsor to correct the protocol.

	11-DEC-98		11-DEC-98
Alan M. Hoberman, Ph.D., DABT	Date	Raymond G. York, Ph.D., DABT	Date
Director of Research		Associate Director of Research	
		Study Director	

	11-Dec-98		14 Dec 98
Dena C. Lebo, V.M.D.	Date	Marvin T. Case, D.V.M., Ph.D.	Date
Member, Institutional Animal Care and		Study Monitor	
Use Committee			

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APPENDIX D

**DEVIATIONS FROM THE PROTOCOL AND THE STANDARD OPERATING
PROCEDURES OF THE TESTING FACILITY**

003745

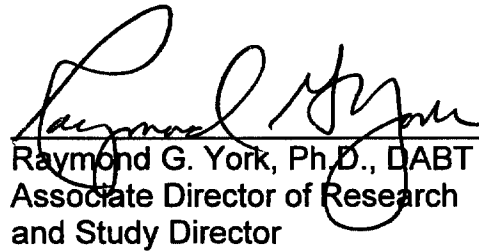
DEVIATIONS FROM THE PROTOCOL AND
STANDARD OPERATING PROCEDURES OF THE TESTING FACILITY

1. 26 AUG 98 (Day 4 of presumed gestation): Clinical observations and body weights were not recorded for the following rats:

<u>Dosage Group</u>	<u>Dosage (mg/kg/day)</u>	<u>Assigned Numbers</u>
I	0 (Vehicle)	12814 - 12816
II	1	12839 - 12847
III	5	12864 - 12872
IV	10	12883 - 12897
V	20	12912 - 12922

This deviation did not adversely affect the outcome of the study because it occurred before initiation of the dosage period and represents a small loss of data across all dosage groups.

All deviations are documented in the raw data.


Raymond G. York, Ph.D., DABT
Associate Director of Research
and Study Director

17-Dec-98
Date

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APPENDIX E

TEMPERATURE AND RELATIVE HUMIDITY REPORTS

ARGUS

Temperature and Relative Humidity Report Location: Room 04 Protocol Number: 418-011			
Range of Dates: 11-Aug-1998 13:45 to 12-Sep-1998 10:26			
Target Range: Species: Rat	Temperature 64°F to 79°F	Relative Humidity 30% to 70%	
Total Number of Days:	33	33	
Total Number of Hours:	764.49	764.49	
Total Number of Data Points:	766	766	
Mean (± SD):	69.3 (± 0.4)	47.7	(± 2.4)
Maximum:	70.2	54.1	
Median:	69.3	47.7	
Minimum:	67.7	41.3	
Number of Points in Range (%):	766 (100.0)	766	(100.0)
Number of Points High (%):	0 (0.0)	0	(0.0)
Number of Points Low (%):	0 (0.0)	0	(0.0)

Report Generated: 23-Oct-1998 at 09:15

COMMENTS: _____

REVIEWED BY: DATE:

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APPENDIX F
PILOT REPORT

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