FINAL REPORT

PROTOCOL 418-010

ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS

SPONSOR'S STUDY NUMBER: 6316.8

FINAL REPORT DATE: 11 JANUARY 1999

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ARGUS RESEARCH LABORATORIES, INC.
PROTOCOL NUMBER: 418-010
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I. SUMMARY AND CONCLUSION

A. Methods[a]

Twenty-two New Zealand White [Hra:(NZW)SPF] timed-pregnant female rabbits were assigned to each of five dosage groups (Groups I through V). Nineteen additional female rabbits were assigned to one of five dosage groups for the satellite study (three, five, three, three and five rabbits 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 orally (via stomach tube) once daily to these naturally-bred rabbits on days 7 through 20 of presumed gestation (DGs 7 through 20). Dosages of 0 (Vehicle), 0.1, 1.0, 2.5 and 3.75 mg/kg/day were administered at a dosage volume of 5 mL/kg, adjusted daily on the basis of the individual body weights.

The female rabbits were observed for viability at least twice each day of the study. The rabbits were also examined for clinical observations of effects of the test article, abortions, premature deliveries and deaths before and approximately 60 minutes after dosage and once daily during the postdosage period. Body weights were recorded on DG 0, the day of arrival at the Testing Facility and on DGs 7 through 29. Feed consumption values were recorded daily after arrival at the Testing Facility.

On DG 21, toxicokinetic samples were collected from the satellite rabbits assigned to the toxicokinetic evaluation. Blood samples were collected from the inferior vena cava and centrifuged. The resulting serum was shipped to the

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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).

Sponsor for analysis. The liver was excised, weighed and a sample was taken from the right lateral lobe and shipped to the Sponsor for analysis. Rabbits were Caesarean-sectioned and fetuses were examined grossly to the extent possible as described for rabbits assigned to the main study. Fetuses and placentae were pooled by litter shipped to the Sponsor for analysis.

On DG 29, rabbits in the main study were sacrificed, Caesarean-sectioned 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 was excised and examined for pregnancy, number and distribution of implantations, early and late resorptions and live and dead fetuses. Each fetus was identified, weighed and examined for gross external alterations. All fetuses were examined internally to identify sex and visceral alterations; cavitated organs were evaluated by dissection; and the brain was cross-sectioned and examined *in situ*. All fetuses were examined for skeletal alterations after staining with alizarin red S.

B. Results

No compound-related deaths occurred during the study. One, two and five does aborted and were sacrificed in the 0 (Vehicle), 2.5 and 3.75 mg/kg/day dosage groups, respectively. These abortions occurred at the end of or after the completion of the dosing period. The abortions in the 2.5 and 3.75 mg/kg/day dosage groups were considered related to the test article because they occurred at dosage-dependent incidences in the two highest dosage groups. All other rabbits survived until scheduled sacrifice on gestation day 29 (DG 29).

Increased numbers of does in the 0.1, 1.0, 2.5 and 3.75 mg/kg/day dosage groups had observations of abnormal stool (no, scant, and soft or liquid feces). All other adverse clinical observations were considered unrelated to the test article.

One 3.75 mg/kg/day dosage doe had a pale liver that was considered possibly related to the test article because it occurred in a high dosage group.

Groups administered the 1.0, 2.5 and 3.75 mg/kg/day dosages of the test article had statistically significant reductions in body weight gain or body weight losses on DGs 7 to 10 and 10 to 13. Reflecting these effects of the test article, body weight gains were significantly reduced in the 2.5 and 3.75 mg/kg/day dosage groups for the entire dosage period. The 2.5 and 3.75 mg/kg/day dosage groups had significantly reduced body weights on DGs 14 through 25.

Absolute and relative feed consumption values were significantly reduced at several tabulated intervals during the dosage period in the 2.5 and/or 3.75 mg/kg/day dosage groups. Reflecting these effects of the test article, the 3.75 mg/kg/day dosage group had significantly reduced absolute and relative feed consumption values for the entire dosage period.

The litter averages for late resorptions were increased in the 2.5 and 3.75 mg/kg/day dosage groups. These increases in the number of late resorptions were considered treatment-related because they occurred at the two highest dosages. No gross external, soft tissue or skeletal fetal alterations (malformations or variations) were caused by dosages of the test article as high as 3.75 mg/kg/day.

C. Conclusion

On the basis of these data, the maternal no-observable-effect-level (NOEL) of N-EtFOSE is 0.1 mg/kg/day (the 1.0 mg/kg/day and higher dosages caused statistically significant reductions in body weight gains or weight losses and the 2.5 and 3.75 mg/kg/day dosages also significantly reduced absolute and relative feed consumption values). The developmental NOEL is 1.0 mg/kg/day (the 2.5 and 3.75 mg/kg/day dosages caused increased incidences of late resorptions and abortions). Based on these data, N-EtFOSE should not be identified as a selective developmental toxicant; the compound was not found to be teratogenic in the rabbit.

11-JAN-99

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

11-JAN-99

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

11-JAN-99

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:

418-010

A.4. Sponsor's Study Number:

6316.8

A.5. Purpose of the Study:

The purpose of this study was to detect adverse effects of N-EtFOSE on New Zealand White [Hra:(NZW)SPF] presumed pregnant female rabbits and development of the embryo and fetus consequent to exposure of the doe from implantation to closure of the hard palate. This study was designed to evaluate ICH Harmonised Tripartite Guideline stages C and D of the reproductive process in a nonrodent species.

A.6. Study Design:

The requirements of the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline[1] were used as the basis for 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 deviations from the GLP regulations that affected the quality of 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)
Joseph W. Lech, B.S. (Team Leader - General Laboratory)
Betsy J. Kerns, B.S. (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. (Report Administrator)

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:

11 August 1998

A.16. Dates of Technical Performance:

Rabbit Arrival Date	28 AUG 98
Dosage Period [Days 7 through 20 of presumed gestation (DGs 7 through 20)]	30 AUG 98 - 16 SEP 98
Toxicokinetic Sample Collection (DG 21)	17 SEP 98
Caesarean-Sectioning Period (DG 29)	21 SEP 98 - 25 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. All unused test article suspensions were discarded at the Testing Facility. Unused bulk test article will be returned to the Study Monitor upon completion of all work with the test article.

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.

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 suspensions.

B.5. Analysis of Purity:

Information regarding the identity, composition, strength, purity and stability 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 Numbers:

M03H05 and L06662

C.3. Date Received and Storage Conditions:

The Tween® 80 was received on 22 May 1998 and 8 July 1998 (lot M03H05) and 1 September 1998 (lot L06662), 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, 0.02, 0.2, 0.5 and 0.75 mg/mL. Prepared formulations were stored at room temperature.

D.1. Sample Information:

Sample Type	Components	Size	Date Retained	Storage Conditions	Shipped To	Date Shipped
Concentration (all levels)	N/A	2 mL[a]	30 AUG 98[b] 16 SEP 98[c]	Frozen (dry ice)	Sponsor	31 AUG 98 16 SEP 98
Bulk Test Article Reserve	N/A	1 g	03 SEP 98	Room temperature	Testing Facility Archives	01 OCT 98
Vehicle Reserve	Tween® 80 (lot M03H05)	5 mL	03 SEP 98	Room temperature	Testing Facility Archives	01 OCT 98
	Tween® 80 (lot L06662)	5 mL	09 SEP 98	Room temperature	Testing Facility Archives	01 OCT 98
	R.O. Deionized Water	5 mL	03 SEP 98	Room temperature	Testing Facility Archives	01 OCT 98

N/A = Not applicable
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 backups.
b. First preparation.
c. Last 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 suspensions were prepared. Analyses were performed by 3M Environmental Technology and Safety Services. The results of these analyses have not yet been forwarded to the Testing Facility.

E. Test System:

E.1. Species:

Rabbit

E.2. Strain:

New Zealand White [Hra:(NZW)SPF]

E.3. Supplier (Source):

Covance Research Products Inc., Denver, Pennsylvania

E.4. Sex:

Timed-pregnant female

E.5. Rationale for Test System:

The New Zealand White [Hra:(NZW)SPF] rabbit was selected as the Test System because: 1) it is one non-rodent mammalian species accepted and widely used throughout the industry for nonclinical studies of developmental toxicity (embryo-fetal toxicity/teratogenicity); 2) this strain of rabbit 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 pharmacologically active in the species and strain.

E.6. Test System Data:

Number of Rabbits	129
Approximate Date of Birth	28 FEB 98, 07 MAR 98, 28 MAR 98
Approximate Age at Arrival	5 - 6 months
Weight (kg) on DG 0	2.8 - 4.4
Weight (kg) at Arrival	2.9 - 4.2

E.7. Method of Randomization:

Upon arrival, rabbits were assigned to individual housing on the basis of computer-generated random units. Rabbits were assigned to one of five dosage groups (Groups I through V), 22 rabbits per dosage group, for the main portion of the study. An additional 19 satellite rabbits were assigned for toxicokinetic evaluation; five rabbits were assigned to each of the low and high dosage groups (Groups II and V), and three rabbits were assigned to each of the remaining dosage groups (Groups I, III and IV). Rabbits were assigned to dosage groups using a computer-generated (weight-ordered) randomization procedure based on body weights recorded by and at the Supplier (Covance Research Products, Inc.) on DG 0.

E.8. System of Identification:

Each rabbit was individually identified with a Monel® self-piercing ear tag (Gey Band and Tag Co., Inc., No. MSPT 20103) inscribed with the rabbit's designated unique permanent number. Cage tags were marked with the study number, permanent rabbit number, sex, test article identification and dosage level.

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® rooms). Room temperature and humidity were monitored constantly throughout the study. Room temperature was targeted at 61°F to 72°F (16°C to 22°C); relative humidity was targeted at 30% to 70%. See APPENDIX E (TEMPERATURE AND RELATIVE HUMIDITY REPORTS).

F.3. Housing:

Rabbits were individually housed. All cage sizes and housing conditions are 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:

Approximately 150 g of Certified Rabbit Chow® #5322 (PMI Nutrition International, St. Louis, Missouri) was available to each rabbit each day until the first day of dosage, at which time approximately 180 g of the same certified feed was offered to each rabbit each day. The certified feed was available from individual stainless steel "J-type" feeders attached to each cage.

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 Sponsor nor the Study Director 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 rabbits *ad libitum* from an automatic watering system (individual sipper tubes). 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 Sponsor nor the Study Director 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 Rabbits	Dosage (mg/kg/day)	Concentration (mg/mL)	Dosage Volume (mL/kg)	Assigned Rabbit Numbers	
					Main Study	Satellite Study[a]
I	22+3[a]	0 (Vehicle)	0	5	8572 - 8593	8682 - 8684
II	22+5[a]	0.1	0.02	5	8594 - 8615	8685 - 8689
III	22+3[a]	1.0	0.2	5	8616 - 8637	8690 - 8692
IV	22+3[a]	2.5	0.5	5	8638 - 8659	8693 - 8695
V	22+5[a]	3.75	0.75	5	8660 - 8681	8696 - 8700

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

a. Rabbits assigned to toxicokinetic evaluation.

G.2. Rationale for Dosage Selection:

Dosages were selected on the basis of a dosage-range study [Argus Research Laboratories, Inc., Protocol 418-010P (see APPENDIX F)].

In the 418-010P study, severe maternal body weight loss occurred in the 10, 25, 50 and 75 mg/kg/day dosage groups; there were no surviving rabbits in these groups. Abortions occurred in the 5 and 10 mg/kg/day dosage groups. Caesarean-section observations revealed increased late resorptions and reduced fetal body weights at 5 mg/kg/day. Increases in early resorptions were found at 1 mg/kg/day; however, there was no decrease in mean litter size.

G.3. Route of Administration:

Oral (stomach tube)

G.4. Rationale for Route of Administration:

The oral (stomach tube) 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 possible routes of human exposure.

G.5. Frequency of Administration:

Appropriate dosages of the test article or vehicle were administered orally (via stomach tube) once daily to naturally-bred rabbits on DGs 7 through 20[a]. Dosages of 0 (Vehicle), 0.1, 1.0, 2.5 and 3.75 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 intubation. The rabbits were intubated at approximately the same time each day.

G.6. Length of Study:

Approximately 4 weeks

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a. See APPENDIX D (DEVIATIONS FROM THE PROTOCOL AND THE STANDARD OPERATING PROCEDURES OF THE TESTING FACILITY), item 1.

G.7. **Method of Study Performance**:

The female rabbits were naturally bred by breeder male rabbits of the same source and strain before shipment to the Testing Facility. The rabbits were mated on five consecutive days and shipped to the Testing Facility on the day after the last day of mating. The day of mating was considered to be DG 0. A computer-generated (weight-ordered) randomization procedure was used to assign the rabbits to five dosage groups based on body weights recorded on DG 0 and supplied by Covance Research Products, Inc.

All rabbits were observed for viability at least twice each day of the study and for general appearance at least once during acclimation. Additional examinations for clinical observations of effects of the test article, abortions, premature deliveries and deaths were made before each daily intubation (DGs 7 through 20) and approximately 60 minutes after intubation during the dosage period. These observations were also made once daily during the postdosage period (DG 21 through 29).

Body weights were recorded on DG 0, the day of arrival at the Testing Facility and on DGs 7 through 29. Feed consumption values were recorded daily after arrival at the Testing Facility.

G.8. **Gross Necropsy**:

G.8.a. **Satellite Rabbits Assigned to Toxicokinetic Sample Collection**:

On DG 21 (the day following the last dosage), toxicokinetic samples were collected from the rabbits assigned to the toxicokinetic evaluation. Following anesthesia with pentobarbital, blood samples (approximately 4 mL per rabbit) 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 was taken from the right lateral lobe, frozen and retained at -70°C until shipment to the Sponsor for analysis.

Rabbits were Caesarean-sectioned and fetuses were examined grossly to the extent possible, as described for rabbits assigned to the main study. Fetuses and placentae were pooled by litter and retained frozen (-70°C) until shipment to the Sponsor for analysis.

After completion of sample collection, serum, liver sections, fetal and placental samples were shipped (frozen on dry ice) to 3M Environmental Technology and Safety Services, St. Paul, Minnesota.

G.8.b. Scheduled Sacrifice:

All surviving rabbits were sacrificed by intravenous injection of Beuthanasia®-D Special euthanasia solution on DG 29. The rabbits were Caesarean-sectioned and a gross necropsy of the thoracic, abdominal and pelvic viscera was performed. Gross lesions were preserved in neutral buffered 10% formalin for possible future evaluation (with the exception of parovarian cysts, which are common, spontaneous lesions in rabbits); all other tissues were discarded.

The number of corpora lutea in each ovary was recorded. The uterus was excised and examined for pregnancy, number and distribution of implantations, early and late resorptions and live and dead fetuses. Uteri from does that appeared nonpregnant were stained with 10% ammonium sulfide to confirm the absence of implantation sites[9]. 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 mechanical 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.

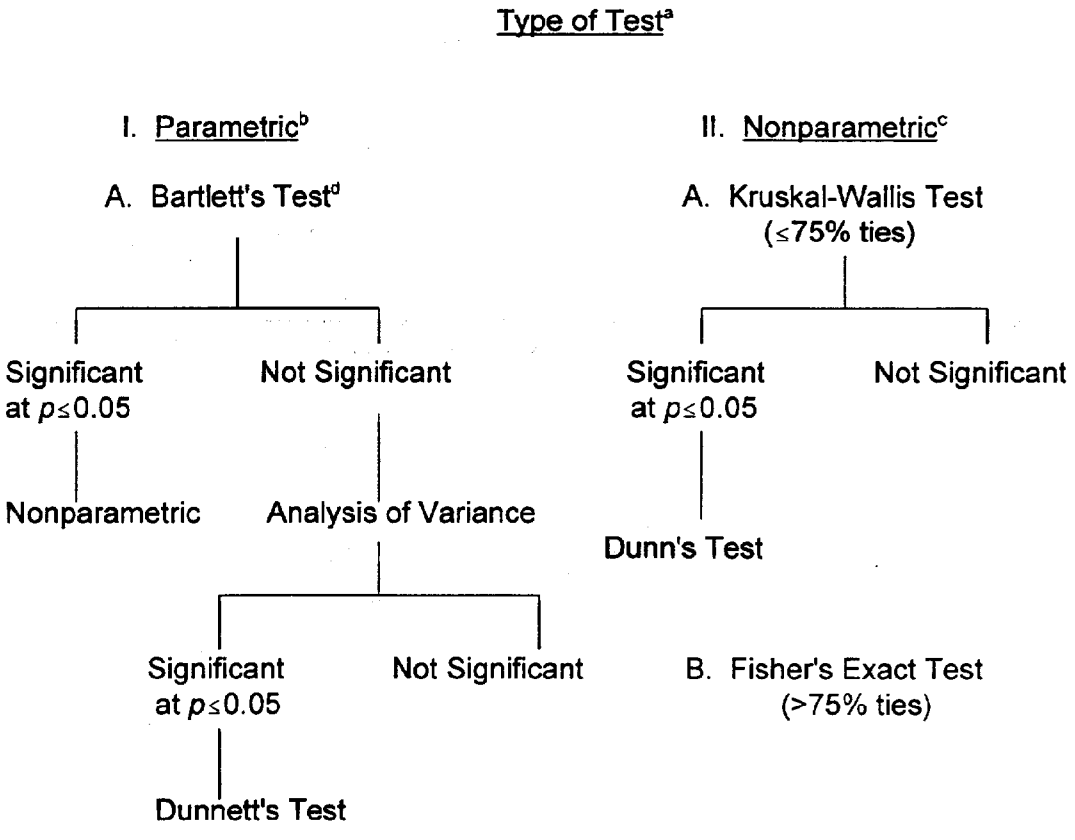
Each Caesarean-delivered fetus was weighed, examined for gross external alterations and individually identified with a tag noting study number, litter number, and uterine distribution. Live fetuses were sacrificed by an intraperitoneal injection of Beuthanasia®-D Special. All fetuses were examined internally to identify sex and visceral alterations; cavitated organs were evaluated by dissection[10]; and the brain was cross-sectioned (a single cross-section was made between the parietal and the frontal bones) and examined *in situ*. Fetal gross lesions were preserved in neutral buffered 10% formalin for possible future evaluation.

All fetuses were examined for skeletal alterations after staining with alizarin red S[11]. Skeletal preparations were retained in glycerin with thymol added as a preservative. Late resorptions were examined to the extent possible. Representative photographs of fetal alterations are available in the raw data.

Rabbits that died or were sacrificed because of abortion or premature delivery were examined for cause of death on the day the observation was made. Pregnancy status and uterine contents were recorded. Aborted fetuses and/or delivered pups were examined to the extent possible, using the same methods described for fetuses.

G.9. Statistical Analyses:

The following schematic represents the statistical analyses of the data:



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a. Statistically significant probabilities are reported as either $p \leq 0.05$ or $p \leq 0.01$.
b. Used only to analyze data with homogeneity of variance.
c. Proportion data are not included in this category.
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 ($p\leq0.05$), 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 ($p\leq0.05$)], the Kruskal-Wallis Test[16] was used, when less than or equal to 75% ties were present; when more than 75% ties were present, Fisher's Exact Test[17] was used. In cases in which the Kruskal-Wallis Test was statistically significant ($p\leq0.05$), Dunn's Method of Multiple Comparisons[18] was used to identify the statistical significance of the individual groups.

Count data obtained at Caesarean-sectioning were evaluated using the procedures previously described for the Kruskal-Wallis Test[16].

III. RESULTS

A. Mortality, Abortions, Clinical and Necropsy Observations (Summaries - Tables 1 and 3; Individual Data - Tables 2, 15 and 16)

A.1. Mortality

No deaths were attributable to EtFOSE. The only death occurred in a vehicle control group doe, an event attributable to an intubation accident. Vehicle control group doe 8587 was found dead approximately one hour after the seventh daily dosage on gestation day 13 (DG 13). No other adverse clinical observations occurred in this doe. This doe lost weight after DG 9 and its feed consumption was reduced after DG 10. Necropsy of the doe revealed a perforation (0.5 cm x 0.1 cm) in the right diaphragmatic lung lobe; all other tissues appeared normal. The litter consisted of eight fetuses that appeared normal for their developmental ages at gross external examination.

A.2. Abortions

One, two and five** does aborted at the end of or after the completion of the dosage period (on DGs 19, 20, 21, 23, 26 or 29) in the 0 (Vehicle), 2.5 and 3.75 mg/kg/day dosage groups, respectively. The abortions in the 2.5 and 3.75 mg/kg/day dosage groups were considered effects of the test article because the incidences were dosage-dependent.

0 (Vehicle) mg/kg/day

Doe 8581 aborted on DG 26, six days after the last dosage was administered. No other adverse clinical observations occurred in this doe, and its body weight gain and feed consumption were comparable to other control group does. No gross lesions were revealed by necropsy of the doe. The litter consisted of nine late resorptions; autolysis of these specimens precluded further evaluation.

2.5 mg/kg/day

Doe 8647 aborted on DG 21, one day after the last dosage was administered. Additional adverse clinical observations in this doe included scant feces (DGs 14 to 21), soft or liquid feces (DGs 16 to 20) and red substance in cage pan (DG 21). This doe generally lost weight and had severely reduced feed consumption after DG 7. No gross lesions were revealed by necropsy of the doe. The litter consisted of two late resorptions, and two dead and nine live fetuses. Autolysis precluded evaluation of the late resorptions. The live and dead fetuses

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

appeared normal for their developmental ages at gross external and soft tissue examination. Ten of the eleven fetuses had not ossified pubes at skeletal examination.

Doe 8652 aborted on DG 26, six days after the last dosage was administered. Additional adverse clinical observations in this doe included a red perioral substance (DG 8) that was probably associated with an intubation problem, no feces in cage pan (DGs 12, 22 and 24), soft or liquid feces (DGs 13 to 21), scant feces (DGs 13 to 21, 23, 25 and 26) and ungroomed coat (DGs 14 to 15 and 20 to 21). This doe lost weight and had severely reduced feed consumption after DG 10. No gross lesions were revealed by necropsy of the doe. The litter consisted of two live fetuses, one dead fetus and one late resorption. The fetuses and the late resorption appeared normal for their developmental ages at gross external, soft tissue and skeletal examinations.

3.75 mg/kg/day

Doe 8660 aborted on DG 20 before administration of the 14th daily dosage. Additional adverse clinical observations in this doe included soft or liquid feces (DGs 8 to 10), ungroomed coat (DGs 8 to 11), scant feces (DGs 11 to 14 and 16), no feces in cage pan (DGs 15 and 17 to 19), tan perianal substance (DG 19) and red substance in cage pan (DG 20). This doe generally lost weight and had severely reduced feed consumption after DG 7. No gross lesions were revealed by necropsy. The litter consisted of three dead and seven live fetuses. All fetuses appeared normal for their developmental ages at gross external examination. Soft tissue and skeletal examinations were not performed due to the early developmental ages of the fetuses.

Doe 8661 aborted on DG 23, three days after the last dosage was administered. Additional adverse clinical observations in this doe included soft or liquid feces (DGs 10 to 12), scant feces (DGs 11 to 15 and 21 to 23), localized alopecia on the underside (DGs 11 to 23), no feces in cage pan (DGs 16 to 20), ungroomed coat (DGs 20 to 23) and red substance in cage pan (DG 23). This doe generally lost weight and had severely reduced feed consumption after DG 7. No gross lesions were revealed by necropsy of the doe. The litter consisted of six live fetuses, one dead fetus and two late resorptions. One fetus was edematous at gross external examination; all other fetuses appeared normal for their developmental ages at gross external examination. All fetuses appeared normal at soft tissue examination. All fetuses had not ossified pubes and one of these fetuses also had split ribs at skeletal examination.

Doe 8663 aborted on DG 26, six days after the last dosage was administered Additional adverse clinical observations in this doe included soft or liquid feces (DGs 11 and 13 to 15), scant feces (DGs 11 to 19, 21 and 25), ungroomed coat (DGs 13 to 15 and 25) and no feces in cage pan (DGs 20 and 22 to 24). This

doe generally lost weight and had severely reduced feed consumption. After DG 7. No gross lesions were revealed by necropsy of the doe. The litter consisted of nine dead fetuses and one late resorption. Autolysis precluded evaluation of the late resorption. All aborted fetuses were partially cannibalized but, within the limits of evaluation, appeared normal for their developmental ages at gross external and soft tissue examinations. Seven of the fetuses had not ossified pubes and one of these fetuses also had split ribs at skeletal examination.

Doe 8667 aborted on DG 19, after the 13th daily dosage was administered. Additional adverse clinical observations in this doe included scant feces (DGs 12 and 14 to 19) and red substance in cage pan (DG 19). This doe generally lost weight after DG 7, and its feed consumption was severely reduced after DG 10. No gross lesions were revealed by necropsy of the doe. The litter consisted of four fetuses that appeared normal for their developmental ages at gross external examination. Soft tissue and skeletal examinations were not performed due to the early developmental ages of the fetuses.

Doe 8669 aborted on DG 29, nine days after the last dosage was administered. Additional adverse clinical observations in this doe included scant feces (DGs 11 to 17, 20 and 23 to 26), soft or liquid feces (DGs 13 and 15 to 16) and no feces in cage pan (DGs 18 to 19, 21 to 22 and 27 to 28). This doe generally lost weight throughout the study and feed consumption was severely reduced after DG 9. No gross lesions were revealed by necropsy. The litter consisted of ten late resorptions that were too autolyzed for further evaluation.

A.3. Clinical Observations

The incidences of scant, or soft or liquid fetuses were increased in does in the 0.1, 1.0, 2.5 and 3.75 mg/kg/day dosage groups; the incidence of scant feces was significant ($p \leq 0.01$) in these four dosage groups. No feces in the cage pan also occurred in one, one and six** does in the 1.0, 2.5 and 3.75 mg/kg/day dosage groups, respectively. Additional adverse clinical observations attributable to the test article occurred in does that aborted and included red substance in the can pan in one doe in the 2.5 mg/kg/day and three does in the 3.75 mg/kg/day dosage group and a tan perianal substance in one doe in the 3.75 mg/kg/day dosage group.

All other adverse clinical observations were considered unrelated to the test article because the incidences were not dosage-dependent. These observations included a red perioral substance, localized alopecia on the limbs, neck and/or underside, ungroomed coat, lacrimation and a scab or mass on the hindpaws.

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

A.4. Necropsy Observations

One 3.75 mg/kg/day dosage doe (8662) that had a pale liver that was considered possibly related to the test article because it occurred in a high dosage group rabbit. Control rabbit 8587 had a perforation in the right diaphragmatic lung lobe as the result of an intubation error, as previously described.

B. Maternal Body Weights and Body Weight Changes (Figure 1; Summaries - Tables 4 and 5; Individual Data - Table 17)

Groups administered the 1.0, 2.5 and 3.75 mg/kg/day dosages of the test article had statistically significant ($p \leq 0.05$ or $p \leq 0.01$) reductions in body weight gains or body weight losses on DGs 7 to 10 and 10 to 13 (2.5 and 3.75 mg/kg/day only), as compared to the control group values. Reflecting these effects of the test article, body weight gains were significantly reduced ($p \leq 0.01$) in the 2.5 and 3.75 mg/kg/day dosage groups for the entire dosage period (calculated as DGs 7 to 21).

The 2.5 and 3.75 mg/kg/day dosage groups had significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) body weights on DGs 14 through 25, as compared with the control group values.

Body weights and body weight gains were unaffected by the 0.1 mg/kg/day dosage of the test article.

C. Maternal Absolute (g/day) and Relative (g/kg/day) Feed Consumption Values (Summaries - Tables 6 and 7; Individual Data - Table 18)

Absolute (g/day) and relative (g/kg/day) feed consumption values were reduced during the dosage period in the 2.5 and/or 3.75 mg/kg/day dosage groups. These reductions were significant ($p \leq 0.05$ or $p \leq 0.01$) for absolute feed consumption values on DGs 10 to 13 and 13 to 16 in the 2.5 mg/kg/day dosage group and DGs 7 to 10, 10 to 13 and 13 to 16 in the 3.75 mg/kg/day dosage group. Significant reductions ($p \leq 0.05$ or $p \leq 0.01$) in relative feed consumption values occurred on DGs 10 to 13 and 13 to 16 in the 3.75 mg/kg/day dosage group.

Reflecting these effects of the test article, the 3.75 mg/kg/day dosage group had significantly reduced ($p \leq 0.01$) absolute and relative feed consumption values for the entire dosage period (calculated as DGs 7 to 21).

Feed consumption values were unaffected by dosages of the test article as high as 1.0 mg/kg/day.

D. Caesarean-Sectioning and Litter Observations (Summaries - Tables 8 and 9; Individual Data - Tables 19 through 21)

Pregnancy occurred in 18 (81.8%), 20 (90.9%), 20 (90.9%), 21 (95.4%) and 21 (95.4%) rabbits in each dosage group. Caesarean-sectioning observations on DG 29 were based on 16, 20, 20, 19 and 16 pregnant rabbits in each of the five respective dosage groups. One, two and five does aborted in the 0 (Vehicle), 2.5 and 3.75 mg/kg/day dosage groups, respectively, and one vehicle control group rabbit was found dead on DG 13.

The litter averages for late resorptions were increased in the 2.5 and 3.75 mg/kg/day dosage groups. These increases in the number of late resorptions were considered treatment-related because they occurred at the two highest dosages.

No biologically important or statistically significant differences occurred in the litter averages for corpora lutea, implantations, live fetuses, total or early resorptions and fetal body weights. There were no dead fetuses, no does with all conceptuses resorbed. All placentae appeared normal.

E. Fetal Alterations (Summaries - Tables 10 through 14; Individual Data - Table 22)

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 133, 167, 165, 141 and 129 DG 29 Caesarean-delivered live fetuses in 16, 20, 20, 19 and 16 litters in the 0 (Vehicle), 0.1, 1.0, 2.5 and 3.75 mg/kg/day dosage groups, respectively. Each fetus was examined for gross external, soft tissue and skeletal alterations and fetal ossification site averages.

E.1. Summary of Fetal Alterations (Summary - Table 10; Individual Data - Table 22)

Combination of malformations and variations resulted in the following incidences for fetal alterations. In the 0 (Vehicle), 0.1, 1.0, 2.5 and 3.75 mg/kg/day dosage groups, respectively, 10 (62.5%), 11 (55.0%), 10 (50.0%), 12 (63.2%) and 9 (56.2%) litters had fetuses with one or more alterations observed. In these same respective dosage groups, the total numbers of fetuses with any identified alterations were 23 (17.3%), 22 (13.2%), 29 (17.6%), 23 (16.3%) and 14 (10.8%). One or more alterations occurred in averages of 17.0%, 13.6%,

16.5%, 16.1% and 11.7% of the fetuses per litter in the five respective dosage groups.

No gross external, soft tissue or skeletal fetal alterations (malformations or variations) were caused by dosages of the test article as high as 3.75 mg/kg/day. There were no dosage-dependent or significant differences in the litter or fetal incidences of any gross external, soft tissue or skeletal alterations.

E.2. Fetal Gross External Alterations (Summary - Table 11; Individual Data - Table 22)

E.2.a. Malformations

Control group fetus 8586-8 had a short trunk and absent tail at gross external examination. Soft tissue examination revealed fused, displaced and small kidneys and *situs inversus*. Skeletal examination of this fetus revealed fused 1st through 4th sternal centra, fusion of the xiphoid and 4th sternal centrum, only six thoracic vertebrae present, no ossification of the centra and arches of the 5th and 6th thoracic vertebrae, fused 4th and 5th left ribs, an extra ossification site attached to the 6th ribs and absence of all lumbar, sacral and caudal vertebrae.

One fetus in the 2.5 mg/kg/day dosage group (8644-5) had a short snout with a protruding tongue as the only alteration.

High dosage group (3.75 mg/kg/day) fetus 8665-8 had an edematous neck, a short snout with a protruding tongue and small ears at gross external examination. Soft tissue examination revealed no additional alterations. Skeletal examination of this fetus revealed fused 3rd and 4th sternal centra and angulated alae of the hyoid.

E.2.b. Variations

One 0.1 mg/kg/day dosage group fetus (8600-11) had a distended abdomen. Soft tissue and skeletal examinations revealed no other additional alterations.

E.3. Fetal Soft Tissue Alterations (Summary - Table 12; Individual Data - Table 22)

E.3.a. Malformations

Externally malformed control group fetus 8586-8 had fused, displaced and small kidneys and *situs inversus*. This fetus had a short trunk and absent tail at gross external examination and associated skeletal malformations, as previously described.

Small and fused lung lobes occurred in one 2.5 mg/kg/day dosage group fetus (8646-1). This fetus had common truncus arterious as the only other alteration.

All other soft tissue malformations have been previously described.

E.3.b. Variations

E.3.b.1. Eyes

One control group fetus (8579-4), one 0.1 mg/kg/day dosage group fetus (8597-8) and one 2.5 mg/kg/day dosage group fetus (8646-2) had a circumcorneal hemorrhage of one or both eyes, a variation generally attributable to trauma during processing. Fetus 8597-8 also had absence of the intermediate lobe of the lungs. No other alterations occurred in these fetuses.

E.3.b.2. Vessels

Common truncus arteriosus occurred in one 2.5 mg/kg/day dosage group fetus (8646-1). This fetus also had lung malformations, as previously described.

E.3.b.3. Lungs

Absence of the intermediate lobe of the lungs occurred in 2, 5, 1, 1 and 4 fetuses from 2, 4, 1, 1 and 4 litters in the 0 (Vehicle), 0.1, 1.0, 2.5 and 3.75 mg/kg/day dosage groups, respectively. One of the 0.1 mg/kg/day dosage group fetuses (8597-8) also had circumcorneal hemorrhage of the right eye, as previously described. One of the 3.75 mg/kg/day dosage group fetuses (8672-6) also had a variation in skull ossification (internasal), fused sternal centra and misaligned caudal vertebrae.

E.3.b.4. Kidneys

The left kidney was displaced caudally in 12, 1, 17 and 5 fetuses from 2, 1, 2, and 2 litters in the 0 (Vehicle), 0.1, 1.0 and 2.5 mg/kg/day dosage groups. The externally malformed vehicle control group fetus also had fused and small kidneys, as previously described. Another vehicle control group fetus (8590-8) also had a variation in skull ossification (internasal).

E.3.b.5. Hindlimb

The skin was constricted on the right hindlimb of one 3.75 mg/kg/day dosage group fetus (8673-3). No additional alterations occurred in this fetus.

E.4. Fetal Skeletal Alterations (Summaries - Tables 13 and 14; Individual Data - Table 22)

E.4.a. Malformations

E.4.a.1. Vertebrae/Ribs/Sternum

Externally malformed vehicle control group fetus 8586-8 had skeletal malformations of the sternum, vertebrae and ribs related to the observations of a short trunk and absent tail at gross external examination. The 1st through 4th sternal centra were fused, fusion of the xiphoid and 4th sternal centrum, only six thoracic vertebrae present, absent ossification of the centra and arches of the 5th and 6th thoracic vertebrae, fused 4th and 5th left ribs, an extra ossification site attached to 6th ribs and absence of all lumbar, sacral and caudal vertebrae.

E.4.a.2. Thoracic Vertebrae/Ribs

Interrelated vertebral/rib malformation or malformations of the thoracic vertebrae and ribs occurred in one 0 (Vehicle) mg/kg/day, two 1.0 mg/kg/day and one 3.75 mg/kg/day dosage group fetuses. These types of vertebral/rib malformations are relatively common at maternally toxic dosages in rabbits and generally considered to be secondary to maternal stress[19]. Each of these fetuses is described below.

Fetus 8582-8 (vehicle control group) had a small left arch and unilateral ossification (left) of the centrum of the 10th thoracic vertebra and fusion of the 10th and 11th ribs

Fetus 8625-5 (1.0 mg/kg/day dosage group) had fused centra of the 8th and 9th thoracic vertebrae, a bifid centrum in the 9th thoracic vertebra and fused 8th and 9th right ribs.

Fetus 8628-8 (1.0 mg/kg/day dosage group) had only 11 thoracic vertebrae and 11 ribs present; the 7th right rib and the 8th left rib were split.

Fetus 8670-1 (3.75 mg/kg/day dosage group) had a right hemivertebra present as the 12th thoracic vertebra and a split 10th left rib.

E.4.a.3. Lumbar Vertebrae

One 0.1 mg/kg/day dosage group fetus (8612-6) had a right hemivertebra, present between the 6th and 7th lumbar vertebrae, as the only alteration.

E.4.a.4. Caudal Vertebrae

Misaligned caudal vertebrae occurred in three 0.1 mg/kg/day dosage group fetuses and 1 3.75 mg/kg/day dosage group fetus. One 0.1 mg/kg/day dosage group fetus and the 3.75 mg/kg/day dosage group fetus had additional skeletal alterations, as previously described.

E.4.b. Variations

E.4.b.1. Skull

Common small irregularities in ossification of the skull[20] [the presence of small ossification sites within the sutures or calvaria (nasal, frontal or parietal bones) and/or irregular shaping or fusion of the bones] occurred in 5, 4, 4, 5 and 2 fetuses in 5, 3, 4, 4 and 2 litters in the 0 (Vehicle), 0.1, 1.0, 2.5 and 3.75 mg/kg/day dosage groups, respectively. Irregular ossification of the nasal bones (midline suture displaced or internasal ossification site) were the most common of these small irregularities in ossification patterns, occurring in 3, 4, 3, 4 and 2 fetuses in 3, 3, 3, 3 and 2 litters in the five respective dosage groups. One of the 2.5 mg/kg/day dosage group fetuses (8648-18) also had fused sternal centra and one 3.5 mg/kg/day dosage group fetus also had fused sternal centra and misaligned caudal vertebrae. No other skeletal alterations occurred in these fetuses.

E.4.b.2. Hyoid

One or both alae of the hyoid were angulated in 3, 4, 1, 2 and 6 fetuses in 2, 4, 1, 1 and 4 litters in the 0 (Vehicle), 0.1, 1.0, 2.5 and 3.75 mg/kg/day dosage groups, respectively. One 0.1 mg/kg/day dosage group fetus (8596-1) and two 3.75 mg/kg/day dosage group fetuses (8665-8; 8678-7) also had fused sternal centra. Another 0.1 mg/kg/day dosage group fetus (8614-4) also had short hyoid alae and a misaligned caudal vertebra.

E.4.b.3. Vertebrae

One 0.1 mg/kg/day dosage group fetus (8601-5) had unilateral ossification of the centrum of the 13th thoracic vertebra as the only alteration.

The centrum of the 12th thoracic vertebra was fused to the centrum of the 1st lumbar vertebra; the centrum of the 1st lumbar vertebra was bifid in one 1.0 mg/kg/day dosage group fetus (8628-6).

E.4.b.4. Sternum

Fused 3rd and 4th sternal centra occurred in 1, 4, 3, 5 and 4 fetuses from 1, 4, 1, 3 and 3 litters in the five respective dosage groups. Additional alterations in these fetuses were described previously.

E.4.b.5. Pelvis

Three fetuses from two 2.5 mg/kg/day dosage group litters had unossified pubes as the only alteration. The significant increase ($p \leq 0.01$) in the fetal incidence of this alteration was considered unrelated to the test article because it was not dosage-dependent.

E.4.b.6. Fetal Ossification Site Averages

The average numbers of ossification sites in the hyoid, vertebrae (cervical, thoracic, lumbar, sacral and caudal), 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 and did not significantly differ.

F. Satellite Rabbits (Individual Data – Tables 15 through 20)

One satellite doe in the 1.0 mg/kg/day dosage group and another satellite doe in the 3.75 mg/kg/day dosage group aborted and were sacrificed.

Satellite doe 8691 aborted on DG 18 after the 12th daily dosage was administered. No other adverse clinical observations occurred in this doe. This doe lost weight after DG 16; its feed consumption values were unremarkable. No gross lesions were revealed by necropsy of the doe. The litter consisted of three early resorptions.

Satellite doe 8700 aborted on DG 19 after 12 daily dosages had been administered. Additional adverse clinical observations in this doe included scant feces (DGs 7, 11, 13 and 17 to 18), no feces in cage pan (DGs 12 and 14 to 16), localized alopecia on the underside (DGs 12 to 18) and soft or liquid feces (DG 13). Body weight loss occurred in this doe after DG 8, and its feed consumption was severely reduced after DG 10. No gross lesions were revealed by necropsy of the doe. The litter consisted of four dead fetuses and two conceptuses that were presumed cannibalized.

Adverse clinical observations in the satellite groups were similar to those in the main study groups. Observations of scant feces and soft or liquid feces occurred in the 0.1, 1, 2.5 and/or 3.75 mg/kg/day dosage groups. One doe in the 3.75 mg/kg/day dosage group had observations of no feces in cage pan.

Patterns of body weight gain and feed consumption were generally comparable to the rabbits in the main study at the same dosage levels. Only one rabbit in the 2.5 mg/kg/day dosage group was not pregnant at Caesarean-sectioning on DG 21. Caesarean-sectioning and litter parameters were comparable among the five dosage groups. One doe in the 0.1 mg/kg/day dosage group had black and brown mottling of the lungs at necropsy; all other does appeared normal. Average liver weights for pregnant does on DG 21 were 134.4 ± 10.0, 128.9 ± 4.2, 106.6 ± 42.2, 117.8 ± 35.5 and 109.0 ± 37.5 in the 0 (Vehicle), 0.1, 1.0, 2.5 and 3.75 mg/kg/day dosage groups, respectively. The data for rabbits assigned to the satellite portion of the study are provided in individual tables only.

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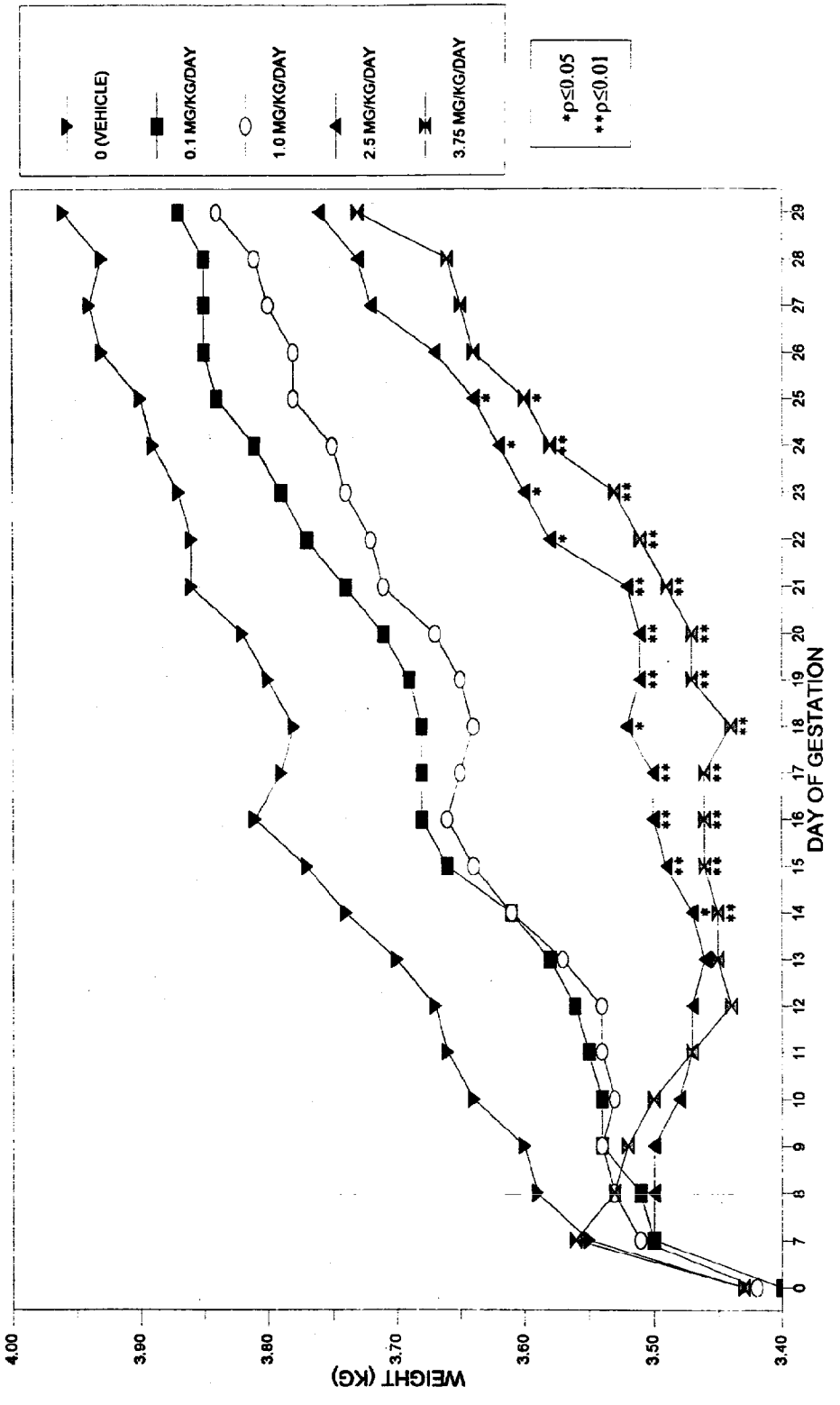
APPENDIX A

REPORT FIGURE

MATERNAL BODY WEIGHTS

Figure 1



APPENDIX B

REPORT TABLES

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 1 (PAGE 1): CLINICAL OBSERVATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 0.1	III 1.0	IV 2.5	V 3.75
MAXIMUM POSSIBLE INCIDENCE		487/ 22	506/ 22	506/22	495/ 22	478/ 22
FOUND DEAD		1b	0	0	0	0
ABORTED		1c	0	0	2d,e	5**f-j
SCANT FECES		16/ 6	58/ 13**	62/ 15**	108/ 16**d,e	122/ 17**f-j
SOFT OR LIQUID FECES		14/ 4	40/ 10	36/ 10	51/ 8d,e	41/ 12f-h,j
NO FECES IN CAGE PAN		0/ 0	0/ 0	1/ 1	3/ 1e	34/ 6**f-h,j
LOCALIZED ALOPECIA:	TOTAL	6/ 4	14/ 2	11/ 3	33/ 4	67/ 6
	LIMBS	5/ 3	0/ 0	2/ 1	12/ 2	31/ 4
	NECK	0/ 0	0/ 0	2/ 1	1/ 1	23/ 1
	UNDERSIDE	4/ 3	14/ 2	7/ 1	21/ 2	13/ 1g
UNGROOMED COAT		11/ 5	14/ 5	27/ 4	10/ 3e	15/ 4f-h
RED SUBSTANCE IN CAGE PAN		0/ 0	0/ 0	0/ 0	1/ 1d	3/ 3f,g,i
TAN PERIANAL SUBSTANCE		0/ 0	0/ 0	0/ 0	0/ 0	1/ 1f
RED PERIORAL SUBSTANCE		0/ 0	0/ 0	0/ 0	1/ 1e	1/ 1
LACRIMATION		0/ 0	2/ 1	0/ 0	2/ 1	0/ 0

STATISTICAL ANALYSES OF CLINICAL OBSERVATION DATA WERE RESTRICTED TO THE NUMBER OF RABBITS WITH OBSERVATIONS.
MAXIMUM POSSIBLE INCIDENCE = (DAYS x RABBITS)/NUMBER OF RABBITS EXAMINED PER GROUP ON DAYS 7 THROUGH 29 OF PRESUMED GESTATION.
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RABBITS WITH OBSERVATION.

a. Dosage occurred on days 7 through 20 of presumed gestation.
b. Doe 8587 was found dead on day 13 of gestation.
c. Doe 8581 aborted on day 26 of gestation.
d. Doe 8647 aborted on day 21 of gestation.
e. Doe 8652 aborted on day 26 of gestation.
f. Doe 8660 aborted on day 20 of gestation.
g. Doe 8661 aborted on day 23 of gestation.
h. Doe 8663 aborted on day 26 of gestation.
i. Doe 8667 aborted on day 19 of gestation.
j. Doe 8669 aborted on day 29 of gestation.
** Significantly different from the vehicle control group value ($p \leq 0.01$).

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 1 (PAGE 2): CLINICAL OBSERVATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a	I 0 (VEHICLE)	II 0.1	III 1.0	IV 2.5	V 3.75
MAXIMUM POSSIBLE INCIDENCE	487/ 22	506/ 22	506/22	495/ 22	478/ 22
FOUND DEAD	1b	0	0	0	0
ABORTED	1c	0	0	2d,e	5**f-j
HINDPAWS: SCAB	0/ 0	0/ 0	7/ 1	0/ 0	0/ 0
HINDPAWS: MASS	0/ 0	0/ 0	4/ 1	0/ 0	0/ 0

STATISTICAL ANALYSES OF CLINICAL OBSERVATION DATA WERE RESTRICTED TO THE NUMBER OF RABBITS WITH OBSERVATIONS.
MAXIMUM POSSIBLE INCIDENCE = (DAYS x RABBITS)/NUMBER OF RABBITS EXAMINED PER GROUP ON DAYS 7 THROUGH 29 OF PRESUMED GESTATION.
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RABBITS WITH OBSERVATION.

a. Dosage occurred on days 7 through 20 of presumed gestation.
b. Doe 8587 was found dead on day 13 of gestation.
c. Doe 8581 aborted on day 26 of gestation.
d. Doe 8647 aborted on day 21 of gestation.
e. Doe 8652 aborted on day 26 of gestation.
f. Doe 8660 aborted on day 20 of gestation.
g. Doe 8661 aborted on day 23 of gestation.
h. Doe 8663 aborted on day 26 of gestation.
i. Doe 8667 aborted on day 19 of gestation.
j. Doe 8669 aborted on day 29 of gestation.

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 2 (PAGE 1): UTERINE CONTENTS AND LITTER DATA FOR RABBITS THAT DIED OR ABORTED

DOSAGE GROUP DOSAGE (MG/KG/DAY)a	RABBIT NUMBER	DAY OF DEATH	CORPORA LUTEA R	L	T	IMPLANTATIONS R	L	T	EMBRYOS OR FETUSES b R	L	A	T	RESORPTIONS c R	L	A	T
I 0 (VEHICLE)	8581	ABORTED ON DAY 26 OF GESTATION	5	4	9	5	4	9	0	0	0	0	5	3	1	9
	8587	FOUND DEAD ON DAY 13 OF GESTATION	5	4	9	4	4	8	4	4	0	8d	0	0	0	0
II 0.1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
III 1.0	8691e	ABORTED ON DAY 18 OF GESTATION	3	5	8	0	3	3	0	0	0	0	0	2	1	3
IV 2.5	8647	ABORTED ON DAY 21 OF GESTATION	6	7	13	6	7	13	4	6	1	11f	1	0	1	2
	8652	ABORTED ON DAY 26 OF GESTATION	8	6	14	2	2	4	1	1	1	3g	0	1	0	1
V 3.75	8660	ABORTED ON DAY 20 OF GESTATION	6	4	10	6	4	10	4	3	3	10h	0	0	0	0
	8661	ABORTED ON DAY 23 OF GESTATION	8	3	11	6	3	9	5	1	1	7i	1	1	0	2

R = RIGHT L = LEFT A = ABORTED T = TOTAL

a. Dosage occurred on day 7 through 20 of gestation.
b. Conceptuses appeared normal for developmental ages.
c. Late resorptions unless otherwise noted.
d. Viability of fetuses unable to be determined because of maternal death.
e. Doe 8691 was a satellite animal.
f. Litter 8647 had two dead fetuses.
g. Litter 8652 had one dead fetus.
h. Litter 8660 had three dead fetuses.
i. Fetus 8661-6 had edema on the dorsal and ventral neck.

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TABLE 2 (PAGE 2): UTERINE CONTENTS AND LITTER DATA FOR RABBITS THAT DIED OR ABORTED

DOSAGE GROUP DOSAGE (MG/KG/DAY)a	RABBIT NUMBER	DAY OF DEATH	CORPORA LUTEA R	L	T	IMPLANTATIONS R	L	T	EMBRYOS OR FETUSES b R	L	A	T	RESORPTIONS c R	L	A	T
V 3.75	8663	ABORTED ON DAY 26 OF GESTATION	8	4	12	7	3	10	0	0	9	9d	0	0	1	1
	8667	ABORTED ON DAY 19 OF GESTATION	2	3	5	2	2	4	1	1	2	4	0	0	0	0
	8669	ABORTED ON DAY 29 OF GESTATION	5	6	11	4	6	10	0	0	0	0	4	1	5	10
	8700e	ABORTED ON DAY 19 OF GESTATION	6	1	7	5	1	6	0	0	4	4f	0	0	0	0

R = RIGHT L = LEFT A = ABORTED T = TOTAL

a. Dosage occurred on day 7 through 20 of gestation.
b. Conceptuses appeared normal for developmental ages.
c. Late resorptions unless otherwise noted.
d. All fetuses were partially cannibalized.
e. Doe 8700 was a satellite animal.
f. Two aborted conceptuses were presumed to have been cannibalized.

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TABLE 3 (PAGE 1): NECROPSY OBSERVATIONS - SUMMARY

DOSAGE GROUP		I	II	III	IV	V
DOSAGE (MG/KG/DAY)a		0 (VEHICLE)	0.1	1.0	2.5	3.75
RABBITS EXAMINED b	N	22	22	22	22	22
FOUND DEAD	N	1c	0	0	0	0
ABORTED	N	1d	0	0	2e,f	5**g-k
APPEARED NORMAL	N	21	22	22	22	21
LUNGS: RIGHT DIAPHRAGMATIC LOBE, PERFORATION	N	1c	0	0	0	0
LIVER: PALE	N	0	0	0	0	1

a. Dosage occurred on days 7 through 20 of presumed gestation.
b. Refer to the individual clinical observations table (Table 15) for external observations confirmed at necropsy.
c. Doe 8587 was found dead on day 13 of gestation.
d. Doe 8581 aborted on day 26 of gestation.
e. Doe 8647 aborted on day 21 of gestation.
f. Doe 8652 aborted on day 26 of gestation.
g. Doe 8660 aborted on day 20 of gestation.
h. Doe 8661 aborted on day 23 of gestation.
i. Doe 8663 aborted on day 26 of gestation.
j. Doe 8667 aborted on day 19 of gestation.
k. Doe 8669 aborted on day 29 of gestation.
** Significantly different from the vehicle control group value ($p \leq 0.01$).

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TABLE 4 (PAGE 1): MATERNAL BODY WEIGHTS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 0.1	III 1.0	IV 2.5	V 3.75
RABBITS TESTED	N	22	22	22	22	22
PREGNANT	N	18	20	20	21	21
MATERNAL BODY WEIGHT (KG)						
DAY 0	MEAN±S.D.	3.43 ± 0.33	3.40 ± 0.27	3.42 ± 0.30	3.40 ± 0.32	3.43 ± 0.32
DAY 7	MEAN±S.D.	3.55 ± 0.34	3.50 ± 0.29	3.51 ± 0.26	3.50 ± 0.30	3.56 ± 0.26
DAY 8	MEAN±S.D.	3.59 ± 0.33	3.51 ± 0.25	3.53 ± 0.27	3.50 ± 0.31	3.53 ± 0.25
DAY 9	MEAN±S.D.	3.60 ± 0.32	3.54 ± 0.26	3.54 ± 0.28	3.50 ± 0.30	3.52 ± 0.26
DAY 10	MEAN±S.D.	3.64 ± 0.32	3.54 ± 0.27	3.53 ± 0.29	3.48 ± 0.31	3.50 ± 0.26
DAY 11	MEAN±S.D.	3.66 ± 0.34	3.55 ± 0.26	3.54 ± 0.28	3.47 ± 0.32	3.47 ± 0.25
DAY 12	MEAN±S.D.	3.67 ± 0.35	3.56 ± 0.27	3.54 ± 0.28	3.47 ± 0.31	3.44 ± 0.25
DAY 13	MEAN±S.D.	3.70 ± 0.36	3.58 ± 0.29	3.57 ± 0.29	3.46 ± 0.30	3.45 ± 0.25
DAY 14	MEAN±S.D.	3.74 ± 0.37 [17]b	3.61 ± 0.28	3.61 ± 0.28	3.47 ± 0.30*	3.45 ± 0.29**
DAY 15	MEAN±S.D.	3.77 ± 0.39 [17]b	3.66 ± 0.28	3.64 ± 0.29	3.49 ± 0.30**	3.46 ± 0.28**
DAY 16	MEAN±S.D.	3.81 ± 0.38 [17]b	3.68 ± 0.26	3.66 ± 0.30	3.50 ± 0.32**	3.46 ± 0.28**
DAY 17	MEAN±S.D.	3.79 ± 0.36 [17]b	3.68 ± 0.28	3.65 ± 0.28	3.50 ± 0.30**	3.46 ± 0.29**
DAY 18	MEAN±S.D.	3.78 ± 0.36 [17]b	3.68 ± 0.28	3.64 ± 0.29	3.52 ± 0.30*	3.44 ± 0.31**
DAY 19	MEAN±S.D.	3.80 ± 0.35 [17]b	3.69 ± 0.28	3.65 ± 0.29	3.51 ± 0.30**	3.47 ± 0.29** [20]b
DAY 20	MEAN±S.D.	3.82 ± 0.35 [17]b	3.71 ± 0.28	3.67 ± 0.28	3.51 ± 0.32**	3.47 ± 0.31** [19]b

DAY = DAY OF GESTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 20 of gestation.
b. Excludes values for rabbits that died or aborted.
* 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 4 (PAGE 2): MATERNAL BODY WEIGHTS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 0.1	III 1.0	IV 2.5	V 3.75
RABBITS TESTED	N	22	22	22	22	22
PREGNANT	N	18	20	20	21	21
INCLUDED IN ANALYSES	N	17b	20	20	21	19b
MATERNAL BODY WEIGHT (KG)						
DAY 21	MEAN±S.D.	3.86 ± 0.33	3.74 ± 0.28	3.71 ± 0.28	3.52 ± 0.34**	3.49 ± 0.30**
DAY 22	MEAN±S.D.	3.86 ± 0.35	3.77 ± 0.29	3.72 ± 0.29	3.58 ± 0.30*	3.51 ± 0.32**
DAY 23	MEAN±S.D.	3.87 ± 0.35	3.79 ± 0.30	3.74 ± 0.29	3.60 ± 0.31*	3.53 ± 0.34**
DAY 24	MEAN±S.D.	3.89 ± 0.35	3.81 ± 0.31	3.75 ± 0.29	3.62 ± 0.32*	3.58 ± 0.34**
DAY 25	MEAN±S.D.	3.90 ± 0.36	3.84 ± 0.32	3.78 ± 0.30	3.64 ± 0.32*	3.60 ± 0.35*
DAY 26	MEAN±S.D.	3.93 ± 0.35	3.85 ± 0.34	3.78 ± 0.31	3.67 ± 0.33	3.64 ± 0.37
DAY 27	MEAN±S.D.	3.94 ± 0.36	3.85 ± 0.35	3.80 ± 0.33	3.72 ± 0.29	3.65 ± 0.38
DAY 28	MEAN±S.D.	3.93 ± 0.36	3.85 ± 0.36	3.81 ± 0.33	3.73 ± 0.29	3.66 ± 0.40
DAY 29	MEAN±S.D.	3.96 ± 0.35	3.87 ± 0.37	3.84 ± 0.33	3.76 ± 0.29	3.73 ± 0.39

DAY = DAY OF GESTATION
a. Dosage occurred on days 7 through 20 of gestation.
b. Excludes values for rabbits that died or aborted.
* 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 BODY WEIGHT CHANGES - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 0.1	III 1.0	IV 2.5	V 3.75
RABBITS TESTED	N	22	22	22	22	22
PREGNANT	N	18	20	20	21	21
MATERNAL BODY WEIGHT CHANGE (KG)						
DAYS 0 - 7	MEAN±S.D.	+0.13 ± 0.17	+0.10 ± 0.15	+0.10 ± 0.11	+0.10 ± 0.09	+0.13 ± 0.10
DAYS 7 - 10	MEAN±S.D.	+0.08 ± 0.08	+0.05 ± 0.10	+0.01 ± 0.08*	-0.03 ± 0.11*	-0.07 ± 0.16**
DAYS 10 - 13	MEAN±S.D.	+0.06 ± 0.07	+0.03 ± 0.07	+0.04 ± 0.06	-0.01 ± 0.11**	-0.04 ± 0.10**
DAYS 13 - 16	MEAN±S.D.	+0.10 ± 0.06 [17]b	+0.10 ± 0.05	+0.09 ± 0.07	+0.03 ± 0.10	+0.00 ± 0.13
DAYS 16 - 19	MEAN±S.D.	+0.00 ± 0.07 [17]b	+0.01 ± 0.06	+0.00 ± 0.09	+0.01 ± 0.11	-0.01 ± 0.06 [20]b
DAYS 19 - 21	MEAN±S.D.	+0.05 ± 0.10 [17]b	+0.05 ± 0.03	+0.05 ± 0.04	+0.01 ± 0.06	+0.01 ± 0.06 [19]b
DAYS 21 - 24	MEAN±S.D.	+0.04 ± 0.10 [17]b	+0.07 ± 0.07	+0.04 ± 0.07	+0.06 ± 0.07 [20]b	+0.07 ± 0.10 [18]b
DAYS 24 - 29	MEAN±S.D.	+0.05 ± 0.14 [16]b	+0.06 ± 0.12	+0.08 ± 0.12	+0.11 ± 0.07 [19]b	+0.12 ± 0.10 [16]b
DAYS 7 - 21	MEAN±S.D.	+0.31 ± 0.17 [17]b	+0.24 ± 0.14	+0.20 ± 0.17	+0.01 ± 0.32**	-0.07 ± 0.33** [19]b
DAYS 21 - 29	MEAN±S.D.	+0.09 ± 0.18 [16]b	+0.14 ± 0.14	+0.13 ± 0.17	+0.18 ± 0.09 [19]b	+0.21 ± 0.17 [16]b
DAYS 7 - 29	MEAN±S.D.	+0.39 ± 0.19 [16]b	+0.38 ± 0.21	+0.32 ± 0.23	+0.26 ± 0.26 [19]b	+0.22 ± 0.37 [16]b
DAYS 0 - 29	MEAN±S.D.	+0.49 ± 0.19 [16]b	+0.48 ± 0.27	+0.42 ± 0.26	+0.36 ± 0.26 [19]b	+0.34 ± 0.38 [16]b

DAYS = DAYS OF GESTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 20 of gestation.
b. Excludes values for rabbits that died or aborted.
* 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 ABSOLUTE FEED CONSUMPTION VALUES (G/DAY) - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 0.1	III 1.0	IV 2.5	V 3.75
RABBITS TESTED	N	22	22	22	22	22
PREGNANT	N	18	20	20	21	21
MATERNAL FEED CONSUMPTION (G/DAY)						
DAYS 7 - 10	MEAN±S.D.	163.5 ± 28.2	165.1 ± 24.6	147.8 ± 45.3	135.8 ± 52.6	109.9 ± 69.9*
DAYS 10 - 13	MEAN±S.D.	158.7 ± 22.2 [17]b	153.8 ± 27.2	131.7 ± 46.4 [19]c	103.4 ± 65.9*	71.2 ± 66.4**
DAYS 13 - 16	MEAN±S.D.	162.2 ± 22.3 [17]b	156.4 ± 35.6	139.4 ± 54.9	97.1 ± 73.6*	82.6 ± 73.4*
DAYS 16 - 19	MEAN±S.D.	146.5 ± 40.1 [17]b	148.6 ± 50.8	144.5 ± 61.6	117.5 ± 74.8	94.5 ± 81.1 [20]b
DAYS 19 - 21	MEAN±S.D.	149.2 ± 32.4 [17]b	155.4 ± 39.7	147.1 ± 52.9	130.4 ± 65.0 [20]b	106.0 ± 73.0 [19]b
DAYS 21 - 24	MEAN±S.D.	138.2 ± 28.3 [17]b	148.7 ± 36.1	134.7 ± 51.3	130.7 ± 55.9 [20]b	126.2 ± 64.2 [18]b
DAYS 24 - 29	MEAN±S.D.	116.6 ± 48.2 [16]b	117.4 ± 41.4	117.8 ± 45.4	128.1 ± 33.6 [18]b,c	140.7 ± 45.8 [15]b,c
DAYS 7 - 21	MEAN±S.D.	157.0 ± 24.4 [17]b	156.0 ± 28.8	142.4 ± 45.0	119.7 ± 58.1 [20]b	96.5 ± 64.2* [19]b
DAYS 21 - 29	MEAN±S.D.	124.7 ± 36.8 [16]b	129.1 ± 35.5	124.3 ± 45.0	130.9 ± 37.7 [18]b,c	141.0 ± 45.2 [15]b,c
DAYS 7 - 29	MEAN±S.D.	144.9 ± 19.9 [16]b	146.2 ± 26.6	135.8 ± 41.1	124.5 ± 46.6 [18]b,c	121.0 ± 49.0 [15]b,c

DAYS = DAYS OF GESTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 20 of gestation.
b. Excludes values for rabbits that died or aborted.
c. Excludes values that were associated with spillage or wet feed.
* 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): MATERNAL RELATIVE FEED CONSUMPTION VALUES (G/KG/DAY) - SUMMARY

DOSAGE GROUP		I	II	III	IV	V
DOSAGE (MG/KG/DAY)a		0 (VEHICLE)	0.1	1.0	2.5	3.75
RABBITS TESTED	N	22	22	22	22	22
PREGNANT	N	18	20	20	21	21
MATERNAL FEED CONSUMPTION (G/KG/DAY)						
DAYS 7 - 10	MEAN±S.D.	45.8 ± 9.0	47.2 ± 8.0	41.8 ± 12.2	39.0 ± 15.0	31.6 ± 20.1
DAYS 10 - 13	MEAN±S.D.	43.3 ± 5.9 [17]b	43.2 ± 6.8	37.1 ± 12.6 [19]c	29.8 ± 18.9	20.3 ± 18.8**
DAYS 13 - 16	MEAN±S.D.	43.4 ± 6.6 [17]b	43.4 ± 10.3	38.5 ± 15.0	27.4 ± 20.5	23.5 ± 20.3*
DAYS 16 - 19	MEAN±S.D.	38.8 ± 11.1 [17]b	40.4 ± 13.4	39.6 ± 16.8	33.3 ± 21.3	26.4 ± 22.3 [20]b
DAYS 19 - 21	MEAN±S.D.	39.2 ± 8.7 [17]b	41.8 ± 10.0	39.9 ± 14.4	36.4 ± 18.2 [20]]b	29.6 ± 19.8 [19]b
DAYS 21 - 24	MEAN±S.D.	36.0 ± 8.1 [17]b	39.3 ± 8.8	35.9 ± 13.5	35.9 ± 14.8 [20]b	35.0 ± 17.7 [18]b
DAYS 24 - 29	MEAN±S.D.	29.7 ± 12.3 [16]b	30.0 ± 9.6	30.7 ± 11.1	34.6 ± 8.5 [18]b,c	38.0 ± 12.6 [15]b,c
DAYS 7 - 21	MEAN±S.D.	42.4 ± 7.2 [17]b	43.3 ± 7.8	39.6 ± 12.2	34.1 ± 16.3 [20]b	27.4 ± 17.7* [19]b
DAYS 21 - 29	MEAN±S.D.	32.0 ± 9.8 [16]b	33.5 ± 8.1	32.7 ± 11.2	35.6 ± 9.5 [18]b,c	38.6 ± 12.4 [15]b,c
DAYS 7 - 29	MEAN±S.D.	38.3 ± 6.0 [16]b	39.6 ± 6.4	37.0 ± 10.8	34.8 ± 12.6 [18]b,c	33.8 ± 13.1 [15]b,c

DAYS = DAYS OF GESTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 20 of gestation.
b. Excludes values for rabbits that died or aborted.
c. Excludes values that were associated with spillage or wet feed.
* 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 8 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 0.1	III 1.0	IV 2.5	V 3.75
RABBITS TESTED	N	22	22	22	22	22
PREGNANT	N(%)	18(81.8)	20(90.9)	20(90.9)	21(95.4)	21(95.4)
FOUND DEAD	N(%)	1(5.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
ABORTED	N(%)	1(5.6)	0(0.0)	0(0.0)	2(9.5)	5(23.8)
RABBITS PREGNANT AND CAESAREAN-SECTIONED ON DAY 29 OF GESTATION	N	16	20	20	19	16
CORPORA LUTEA	MEAN±S.D.	10.9 ± 2.3	10.8 ± 2.0	10.3 ± 2.3	9.4 ± 3.8	10.4 ± 2.4
IMPLANTATIONS	MEAN±S.D.	9.0 ± 1.8	8.6 ± 2.0	8.6 ± 1.9	7.8 ± 3.1	8.9 ± 1.8
LITTER SIZES	MEAN±S.D.	8.3 ± 2.2	8.4 ± 2.0	8.2 ± 1.9	7.4 ± 2.2	8.1 ± 2.1
LIVE FETUSES	N	133	167	165	141	129
	MEAN±S.D.	8.3 ± 2.2	8.4 ± 2.0	8.2 ± 1.9	7.4 ± 2.2	8.1 ± 2.1
DEAD FETUSES	N	0	0	0	0	0
RESORPTIONS	MEAN±S.D.	0.7 ± 1.8	0.3 ± 0.9	0.3 ± 0.7	0.4 ± 1.2	0.8 ± 1.2
EARLY RESORPTIONS	N	10	4	3	1	2
	MEAN±S.D.	0.6 ± 1.8	0.2 ± 0.7	0.2 ± 0.4	0.0 ± 0.2	0.1 ± 0.3
LATE RESORPTIONS	N	1	2	3	6	11
	MEAN±S.D.	0.1 ± 0.2	0.1 ± 0.4	0.2 ± 0.7	0.3 ± 1.0	0.7 ± 1.1
DOES WITH ANY RESORPTIONS	N(%)	3(18.8)	2(10.0)	4(20.0)	2(10.5)	6(37.5)
DOES WITH ALL CONCEPTUSES RESORBED	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
DOES WITH VIABLE FETUSES	N(%)	16(100.0)	20(100.0)	20(100.0)	19(100.0)	16(100.0)
PLACENTAE APPEARED NORMAL	N(%)	16(100.0)	20(100.0)	20(100.0)	19(100.0)	16(100.0)

a. Dosage occurred on days 7 through 20 of gestation.

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TABLE 9 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 0.1	III 1.0	IV 2.5	V 3.75
LITTERS WITH ONE OR MORE LIVE FETUSES	N	16	20	20	19	16
IMPLANTATIONS	MEAN±S.D.	9.0 ± 1.8	8.6 ± 2.0	8.6 ± 1.9	7.8 ± 3.1	8.9 ± 1.8
LIVE FETUSES	N	133	167	165	141	129
	MEAN±S.D.	8.3 ± 2.2	8.4 ± 2.0	8.2 ± 1.9	7.4 ± 2.2	8.1 ± 2.1
LIVE MALE FETUSES	N	65	85	77	76	62
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	46.6 ± 20.0	51.0 ± 11.8	48.3 ± 16.3	52.9 ± 21.2	45.8 ± 15.1
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	40.17 ± 12.51	43.37 ± 5.25	42.54 ± 4.50	41.54 ± 7.87	39.90 ± 8.54
MALE FETUSES	MEAN±S.D.	40.37 ± 12.68 [15]b	43.36 ± 5.51	43.70 ± 5.08	41.07 ± 7.08 [18]c	40.91 ± 8.47
FEMALE FETUSES	MEAN±S.D.	39.50 ± 12.77	43.55 ± 5.26	42.02 ± 4.70	41.66 ± 8.18	39.48 ± 8.98
% RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	6.9 ± 18.3	3.1 ± 9.8	3.3 ± 8.8	2.6 ± 7.7	9.3 ± 14.4

[ ] = NUMBER OF VALUES AVERAGED

a. Dosage occurred on days 7 through 20 of gestation.

b. Litter 8582 had no male fetuses.

c. Litter 8655 had no male fetuses.

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TABLE 10 (PAGE 1): FETAL ALTERATIONS - SUMMARY

DOSAGE GROUP		I	II	III	IV	V
DOSAGE (MG/KG/DAY)a		0 (VEHICLE)	0.1	1.0	2.5	3.75
LITTERS EVALUATED	N	16	20	20	19	16
FETUSES EVALUATED	N	133	167	165	141	129
LIVE	N	133	167	165	141	129
LITTERS WITH FETUSES WITH ANY ALTERATION OBSERVED	N(%)	10(62.5)	11(55.0)	10(50.0)	12(63.2)	9(56.2)
FETUSES WITH ANY ALTERATION OBSERVED	N(%)	23(17.3)	22(13.2)	29(17.6)	23(16.3)	14(10.8)
% FETUSES WITH ANY ALTERATION/LITTER	MEAN±S.D.	17.0 ± 25.2	13.6 ± 16.5	16.5 ± 29.8	16.1 ± 18.2	11.7 ± 13.3

a. Dosage occurred on days 7 through 20 of gestation.

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TABLE 11 (PAGE 1): FETAL GROSS EXTERNAL ALTERATIONS - SUMMARY

DOSAGE GROUP		I	II	III	IV	V
DOSAGE (MG/KG/DAY)a		0 (VEHICLE)	0.1	1.0	2.5	3.75
LITTERS EVALUATED	N	16	20	20	19	16
FETUSES EVALUATED	N	133	167	165	141	129
LIVE	N	133	167	165	141	129
SNOUT: SHORT						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.3)	1(6.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.7)	1(0.8)b
ABDOMEN: DISTENDED						
LITTER INCIDENCE	N(%)	0(0.0)	1(5.0)	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)
TRUNK: SHORT						
LITTER INCIDENCE	N(%)	1(6.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.8)c	0(0.0)	0(0.0)	0(0.0)	0(0.0)
TAIL: ABSENT						
LITTER INCIDENCE	N(%)	1(6.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.8)c	0(0.0)	0(0.0)	0(0.0)	0(0.0)
BODY: EDEMA						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(6.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.8)b
EARS: SMALL						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(6.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.8)b

a. Dosage occurred on days 7 through 20 of gestation.
b. Fetus 8665-8 had other gross external alterations.
c. Fetus 8586-8 had other gross external alterations.

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TABLE 12 (PAGE 1): FETAL SOFT TISSUE 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)	0.1	1.0	2.5	3.75
LITTERS EVALUATED	N	16	20	20	19	16
FETUSES EVALUATED	N	133	167	165	141	129
LIVE	N	133	167	165	141	129
EYES: CIRCUMCORNEAL HEMORRHAGE						
LITTER INCIDENCE	N(%)	1(6.2)	1(5.0)	0(0.0)	1(5.3)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.8)	1(0.6)b	0(0.0)	1(0.7)	0(0.0)
VESSELS: COMMON TRUNCUS ARTERIOSUS						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.3)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.7)c	0(0.0)
LUNGS: SMALL						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.3)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.7)c	0(0.0)
LUNGS: FUSED						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.3)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.7)c	0(0.0)
LUNGS: INTERMEDIATE LOBE ABSENT						
LITTER INCIDENCE	N(%)	2(12.5)	4(20.0)	1(5.0)	1(5.3)	4(25.0)
FETAL INCIDENCE	N(%)	2(1.5)	5(3.0)b	1(0.6)	1(0.7)	4(3.1)
KIDNEYS: DISPLACED						
LITTER INCIDENCE	N(%)	2(12.5)	1(5.0)	2(10.0)	2(10.5)	0(0.0)
FETAL INCIDENCE	N(%)	12(9.0)d	1(0.6)**	17(10.3)	5(3.5)*	0(0.0)**
KIDNEYS: SMALL						
LITTER INCIDENCE	N(%)	1(6.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.8)d	0(0.0)	0(0.0)	0(0.0)	0(0.0)
KIDNEYS: FUSED						
LITTER INCIDENCE	N(%)	1(6.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.8)d	0(0.0)	0(0.0)	0(0.0)	0(0.0)

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TABLE 12 (PAGE 2): FETAL SOFT TISSUE ALTERATIONS - SUMMARY

DOSAGE GROUP		I	II	III	IV	V
DOSAGE (MG/KG/DAY)a		0 (VEHICLE)	0.1	1.0	2.5	3.75
LITTERS EVALUATED	N	16	20	20	19	16
FETUSES EVALUATED	N	133	167	165	141	129
LIVE	N	133	167	165	141	129
ABDOMEN: SITUS INVERSUS						
LITTER INCIDENCE	N(%)	1(6.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.8)d	0(0.0)	0(0.0)	0(0.0)	0(0.0)
HINDLIMB: SKIN CONSTRICTED						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(6.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.8)

a. Dosage occurred on days 7 through 20 of gestation.
b. Fetus 8597-8 had other soft tissue alterations.
c. Fetus 8646-1 had other soft tissue alterations.
d. Fetus 8586-8 had other soft tissue alterations.
* 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 13 (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)	0.1	1.0	2.5	3.75
LITTERS EVALUATED	N	16	20	20	19	16
FETUSES EVALUATED	N	133	167	165	141	129
LIVE	N	133	167	165	141	129
SKULL - IRREGULAR OSSIFICATION:b (SUMMARIZATION OF ALL IRREGULAR OSSIFICATION OF THE SKULL c; INDIVIDUAL SUBCATEGORIES CITED BELOW)						
LITTER INCIDENCE	N(%)	5(31.0)	3(15.0)	4(20.0)	4(21.0)	2(12.5)
FETAL INCIDENCE	N(%)	5(3.8)	4(2.4)	4(2.4)	5(3.5)	2(1.6)
SKULL: NASAL(S), IRREGULAR OSSIFICATION (SUMMARIZATION OF INTERNASAL; MIDLINE SUTURE DISPLACED)						
LITTER INCIDENCE	N(%)	3(18.8)	3(15.0)	3(15.0)	3(15.8)	2(12.5)
FETAL INCIDENCE	N(%)	3(2.2)	4(2.4)	3(1.8)	4(2.8)	2(1.6)
SKULL: NASALS, MIDLINE SUTURE DISPLACED						
LITTER INCIDENCE	N(%)	1(6.2)	2(10.0)	1(5.0)	2(10.5)	1(6.2)
FETAL INCIDENCE	N(%)	1(0.8)	3(1.8)	1(0.6)	3(2.1)k	1(0.8)
SKULL: NASALS, CONTAIN AN INTERNASAL						
LITTER INCIDENCE	N(%)	2(12.5)	1(5.0)	2(10.0)	1(5.3)	1(6.2)
FETAL INCIDENCE	N(%)	2(1.5)	1(0.6)	2(1.2)	1(0.7)	1(0.8)n
SKULL: FRONTALS, CONTAIN AN INTERFRONTAL						
LITTER INCIDENCE	N(%)	2(12.5)	1(5.0)	1(5.0)	1(5.3)	0(0.0)
FETAL INCIDENCE	N(%)	2(1.5)	1(0.6)	1(0.6)	1(0.7)	0(0.0)
SKULL - OTHER ALTERATIONS:b						
HYOID: ALA, ANGULATED						
LITTER INCIDENCE	N(%)	2(12.5)	4(20.0)	1(5.0)	1(5.3)	4(25.0)
FETAL INCIDENCE	N(%)	3(2.2)	4(2.4)f,g	1(0.6)	2(1.4)	6(4.6)l,o
HYOID: ALA, SHORT						
LITTER INCIDENCE	N(%)	0(0.0)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)g	0(0.0)	0(0.0)	0(0.0)

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TABLE 13 (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)	0.1	1.0	2.5	3.75
LITTERS EVALUATED	N	16	20	20	19	16
FETUSES EVALUATED	N	133	167	165	141	129
LIVE	N	133	167	165	141	129
THORACIC VERTEBRAE: HEMIVERTEBRA						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(6.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.8)m
THORACIC VERTEBRAE: CENTRA, FUSED						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	2(10.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	2(1.2)h,i	0(0.0)	0(0.0)
THORACIC VERTEBRAE: CENTRUM, BIFID						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(5.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.6)h	0(0.0)	0(0.0)
THORACIC VERTEBRAE: 11 PRESENT						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(5.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.6)j	0(0.0)	0(0.0)
THORACIC VERTEBRAE: CENTRUM, UNILATERAL OSSIFICATION						
LITTER INCIDENCE	N(%)	1(6.2)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.8)d	1(0.6)	0(0.0)	0(0.0)	0(0.0)
THORACIC VERTEBRAE: 6 PRESENT						
LITTER INCIDENCE	N(%)	1(6.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.8)e	0(0.0)	0(0.0)	0(0.0)	0(0.0)
THORACIC VERTEBRAE: CENTRUM, NOT OSSIFIED						
LITTER INCIDENCE	N(%)	1(6.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.8)e	0(0.0)	0(0.0)	0(0.0)	0(0.0)
THORACIC VERTEBRAE: ARCH, NOT OSSIFIED						
LITTER INCIDENCE	N(%)	1(6.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.8)e	0(0.0)	0(0.0)	0(0.0)	0(0.0)
THORACIC VERTEBRAE: ARCH, SMALL						
LITTER INCIDENCE	N(%)	1(6.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.8)d	0(0.0)	0(0.0)	0(0.0)	0(0.0)

TABLE 13 (PAGE 3): 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)	0.1	1.0	2.5	3.75
LITTERS EVALUATED	N	16	20	20	19	16
FETUSES EVALUATED	N	133	167	165	141	129
LIVE	N	133	167	165	141	129
LUMBAR VERTEBRAE: CENTRUM, BIFID						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(5.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.6)i	0(0.0)	0(0.0)
LUMBAR VERTEBRAE: HEMIVERTEBRA						
LITTER INCIDENCE	N(%)	0(0.0)	1(5.0)	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)
LUMBAR VERTEBRAE: 0 PRESENT						
LITTER INCIDENCE	N(%)	1(6.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.8)e	0(0.0)	0(0.0)	0(0.0)	0(0.0)
SACRAL VERTEBRAE: 0 PRESENT						
LITTER INCIDENCE	N(%)	1(6.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.8)e	0(0.0)	0(0.0)	0(0.0)	0(0.0)
CAUDAL VERTEBRAE: MISALIGNED						
LITTER INCIDENCE	N(%)	0(0.0)	2(10.0)	0(0.0)	0(0.0)	1(6.2)
FETAL INCIDENCE	N(%)	0(0.0)	3(1.8)g	0(0.0)	0(0.0)	1(0.8)n
CAUDAL VERTEBRAE: 0 PRESENT						
LITTER INCIDENCE	N(%)	1(6.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.8)e	0(0.0)	0(0.0)	0(0.0)	0(0.0)
RIBS: SPLIT						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(5.0)	0(0.0)	1(6.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.6)j	0(0.0)	1(0.8)m
RIBS: FUSED						
LITTER INCIDENCE	N(%)	2(12.5)	0(0.0)	1(5.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	2(1.5)d,e	0(0.0)	1(0.6)h	0(0.0)	0(0.0)
RIBS: 11 PRESENT						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(5.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.6)j	0(0.0)	0(0.0)

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TABLE 13 (PAGE 4): 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)	0.1	1.0	2.5	3.75
LITTERS EVALUATED	N	16	20	20	19	16
FETUSES EVALUATED	N	133	167	165	141	129
LIVE	N	133	167	165	141	129
RIBS: EXTRA OSSIFICATION						
LITTER INCIDENCE	N(%)	1(6.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.8)e	0(0.0)	0(0.0)	0(0.0)	0(0.0)
STERNAL CENTRA: FUSED						
LITTER INCIDENCE	N(%)	1(6.2)	4(20.0)	1(5.0)	3(15.8)	3(18.8)
FETAL INCIDENCE	N(%)	1(0.8)e	4(2.4)f	3(1.8)	5(3.5)k	4(3.1)l,n,o
XIPHOID: FUSED						
LITTER INCIDENCE	N(%)	1(6.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.8)e	0(0.0)	0(0.0)	0(0.0)	0(0.0)
PELVIS: PUBIS, NOT OSSIFIED						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	2(10.5)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	3(2.1)**	0(0.0)

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TABLE 13 (PAGE 5): FETAL SKELETAL ALTERATIONS - SUMMARY

FOOTNOTES:

a. Dosage occurred on days 7 through 20 of gestation.
b. Fetuses with alterations of the skull and/or hyoid are not separately identified in this summary table, except when alterations of other ossification sites were also present.
c. Includes all alterations noted for the skull except hyoid, ala, angulated and ala, short. These categories are excluded because these alterations do not result from irregular ossification.
d. Fetus 8582-8 had other skeletal alterations.
e. Fetus 8586-8 had other skeletal alterations.
f. Fetus 8596-1 had other skeletal alterations.
g. Fetus 8614-4 had other skeletal alterations.
h. Fetus 8625-5 had other skeletal alterations.
i. Fetus 8628-6 had other skeletal alterations.
j. Fetus 8628-8 had other skeletal alterations.
k. Fetus 8648-18 had other skeletal alterations.
l. Fetus 8665-8 had other skeletal alterations.
m. Fetus 8670-1 had other skeletal alterations.
n. Fetus 8672-6 had other skeletal alterations.
o. Fetus 8678-7 had other skeletal alterations.
** Significantly different from the vehicle control group value ($p \leq 0.01$).

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TABLE 14 (PAGE 1): FETAL OSSIFICATION SITES - CAESAREAN-DELIVERED LIVE FETUSES (DAY 29 OF GESTATION) - SUMMARY

DOSAGE GROUP		I	II	III	IV	V
DOSAGE (MG/KG/DAY)a		0 (VEHICLE)	0.1	1.0	2.5	3.75
LITTERS EXAMINED	N	16	20	20	19	16
FETUSES EXAMINED	N	133	167	165	141	129
LIVE	N	133	167	165	141	129
OSSIFICATION SITES PER FETUS PER LITTER						
HYOID	MEAN±S.D.	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	0.97 ± 0.14	0.99 ± 0.05
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.	12.77 ± 0.19	12.68 ± 0.30	12.60 ± 0.26	12.73 ± 0.26	12.58 ± 0.30
LUMBAR	MEAN±S.D.	6.22 ± 0.20	6.32 ± 0.30	6.38 ± 0.26	6.27 ± 0.26	6.42 ± 0.30
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.	17.04 ± 0.45	17.00 ± 0.37	16.90 ± 0.31	16.78 ± 0.37	16.82 ± 0.39
RIBS (PAIRS)	MEAN±S.D.	12.68 ± 0.25	12.62 ± 0.28	12.50 ± 0.33	12.67 ± 0.30	12.53 ± 0.31
STERNUM						
MANUBRIUM	MEAN±S.D.	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
STERNAL CENTERS	MEAN±S.D.	3.95 ± 0.10	3.94 ± 0.09	3.88 ± 0.16	3.92 ± 0.14	3.92 ± 0.10
XIPHOID	MEAN±S.D.	0.89 ± 0.14	0.96 ± 0.06	0.96 ± 0.14	0.83 ± 0.26	0.94 ± 0.18
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.	4.99 ± 0.02	4.98 ± 0.04	4.96 ± 0.16	4.95 ± 0.14	4.92 ± 0.25
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.	13.86 ± 0.25	13.91 ± 0.17	13.90 ± 0.24	13.84 ± 0.26	13.95 ± 0.12
HINDLIMB b						
TARSALS	MEAN±S.D.	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00	1.98 ± 0.05	1.94 ± 0.20
METATARSALS	MEAN±S.D.	4.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.00
DIGITS	MEAN±S.D.	4.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.00
PHALANGES	MEAN±S.D.	12.00 ± 0.00	12.00 ± 0.00	11.99 ± 0.04	11.97 ± 0.08	11.98 ± 0.05

a. Dosage occurred on days 7 through 20 of gestation.
b. Calculated as average per limb.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

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

RABBIT #		DESCRIPTION
DOSAGE GROUP I		0 (VEHICLE) MG/KG/DAY
8572	DG(16- 18)	UNGROOMED COAT
	DG(17- 19)	SOFT OR LIQUID FECES
	DG(17- 20)	SCANT FECES
	DG(23)	SCANT FECES
	DG(23- 24)	SOFT OR LIQUID FECES
	DG(28- 29)	LOCALIZED ALOPECIA: UNDERSIDE a
	DG(28- 29)	LOCALIZED ALOPECIA: LIMBS a
8573	DG(29)	LOCALIZED ALOPECIA: UNDERSIDE a
8574		NO ADVERSE FINDINGS
8575		NO ADVERSE FINDINGS
8576		NO ADVERSE FINDINGS
8577		NO ADVERSE FINDINGS
8578		NO ADVERSE FINDINGS
8579		NO ADVERSE FINDINGS
8580	DG(26- 27)	SCANT FECES
8581	DG(26)	ABORTED AND SACRIFICED
8582		NO ADVERSE FINDINGS
8583		NO ADVERSE FINDINGS
8584		NO ADVERSE FINDINGS
8585	DG(27- 29)	SCANT FECES
	DG(28)	UNGROOMED COAT
	DG(28- 29)	SOFT OR LIQUID FECES
8586	DG(28- 29)	LOCALIZED ALOPECIA: LIMBS a
	DG(29)	SCANT FECES
8587	DG(13)	FOUND DEAD
8588	DG(29)	UNGROOMED COAT a
8589	DG(25- 26)	SCANT FECES
	DG(27- 29)	UNGROOMED COAT a
	DG(28- 29)	SOFT OR LIQUID FECES
	DG(28- 29)	SCANT FECES
	DG(29)	LOCALIZED ALOPECIA: UNDERSIDE a
	DG(29)	LOCALIZED ALOPECIA: LIMBS a
8590		NO ADVERSE FINDINGS
8591	DG(23- 27)	SOFT OR LIQUID FECES
	DG(25- 27)	UNGROOMED COAT
	DG(28)	SCANT FECES
8592		NO ADVERSE FINDINGS
8593		NO ADVERSE FINDINGS

DG = DAY OF PRESUMED GESTATION
a. Observation confirmed at necropsy.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

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

RABBIT #		DESCRIPTION
DOSAGE GROUP II		0.1 MG/KG/DAY
8594	DG(16- 23)	SCANT FECES
	DG(21- 23)	SOFT OR LIQUID FECES
	DG(28- 29)	UNGROOMED COAT a
	DG(29)	SOFT OR LIQUID FECES
	DG(29)	SCANT FECES
8595	DG(21- 25)	SOFT OR LIQUID FECES
	DG(22- 29)	SCANT FECES
	DG(29)	SOFT OR LIQUID FECES
8596		NO ADVERSE FINDINGS
8597		NO ADVERSE FINDINGS
8598		NO ADVERSE FINDINGS
8599	DG(28- 29)	SCANT FECES
8600	DG(12- 14)	SOFT OR LIQUID FECES
	DG(21- 29)	SOFT OR LIQUID FECES
8601	DG(24- 29)	SCANT FECES
8602	DG(17)	SCANT FECES
	DG(28- 29)	LOCALIZED ALOPECIA: UNDERSIDE a
	DG(28- 29)	SCANT FECES
8603	DG(19)	SOFT OR LIQUID FECES
	DG(27- 28)	UNGROOMED COAT
	DG(27- 29)	SOFT OR LIQUID FECES
	DG(27- 29)	SCANT FECES
8604	DG(7- 8)	UNGROOMED COAT
	DG(14)	SOFT OR LIQUID FECES
	DG(18)	SOFT OR LIQUID FECES
	DG(21- 22)	LACRIMATION
	DG(26)	UNGROOMED COAT
	DG(27- 29)	SCANT FECES
8605	DG(25- 29)	SCANT FECES
8606	DG(21- 22)	SOFT OR LIQUID FECES
8607	DG(27- 28)	SOFT OR LIQUID FECES
	DG(27- 28)	SCANT FECES
8608	DG(19)	SOFT OR LIQUID FECES
	DG(20)	SCANT FECES
	DG(26- 29)	SOFT OR LIQUID FECES
	DG(26- 29)	SCANT FECES

DG = DAY OF PRESUMED GESTATION
a. Observation confirmed at necropsy.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

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

RABBIT #		DESCRIPTION
DOSAGE GROUP II		0.1 MG/KG/DAY
8609	DG(15)	SCANT FECES
	DG(26- 27)	SCANT FECES
8610		NO ADVERSE FINDINGS
8611	DG(24- 29)	SCANT FECES
8612		NO ADVERSE FINDINGS
8613	DG(16- 18)	UNGROOMED COAT
	DG(17- 19)	SCANT FECES
	DG(18- 29)	LOCALIZED ALOPECIA: UNDERSIDE a
	DG(27- 29)	UNGROOMED COAT
	DG(28- 29)	SOFT OR LIQUID FECES
8614	DG(24)	UNGROOMED COAT
	DG(24)	SOFT OR LIQUID FECES
8615		NO ADVERSE FINDINGS

DG = DAY OF PRESUMED GESTATION
a. Observation confirmed at necropsy.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

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

RABBIT #		DESCRIPTION
DOSAGE GROUP III		1.0 MG/KG/DAY
8616	DG(17- 23)	SCANT FECES
	DG(18- 24)	SOFT OR LIQUID FECES
	DG(28- 29)	LOCALIZED ALOPECIA: LIMBS a
	DG(29)	SOFT OR LIQUID FECES
	DG(29)	SCANT FECES
8617	DG(17- 19)	SOFT OR LIQUID FECES
	DG(17- 24)	SCANT FECES
	DG(29)	SOFT OR LIQUID FECES
8618	DG(16- 18)	SCANT FECES
	DG(23- 24)	SOFT OR LIQUID FECES
8619	DG(16- 17)	SOFT OR LIQUID FECES
	DG(16- 17)	SCANT FECES
	DG(18)	NO FECES IN CAGE PAN
	DG(19- 22)	SOFT OR LIQUID FECES
	DG(19- 29)	SCANT FECES
	DG(23- 29)	LOCALIZED ALOPECIA: UNDERSIDE a
8620		NO ADVERSE FINDINGS
8621	DG(11)	SCANT FECES
8622	DG(24)	SCANT FECES
8623		NO ADVERSE FINDINGS
8624	DG(28)	SOFT OR LIQUID FECES
8625	DG(14)	SOFT OR LIQUID FECES
	DG(14- 21)	UNGROOMED COAT
	DG(23- 29)	UNGROOMED COAT
	DG(23- 29)	SOFT OR LIQUID FECES
	DG(23- 29)	SCANT FECES
	DG(28- 29)	LOCALIZED ALOPECIA: NECK a
8626	DG(27- 28)	SCANT FECES
8627	DG(27)	SOFT OR LIQUID FECES
	DG(27- 28)	SCANT FECES
	DG(27- 29)	UNGROOMED COAT a
8628	DG(27- 29)	SCANT FECES
8629	DG(26)	SOFT OR LIQUID FECES
	DG(26- 28)	SCANT FECES
8630		NO ADVERSE FINDINGS
8631	DG(10)	UNGROOMED COAT
	DG(14)	UNGROOMED COAT

DG = DAY OF PRESUMED GESTATION
a. Observation confirmed at necropsy.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

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

RABBIT #		DESCRIPTION
DOSAGE GROUP III		1.0 MG/KG/DAY
8632	DG(16)	SCANT FECES
8633	DG(22- 29)	SCANT FECES
	DG(23)	SOFT OR LIQUID FECES
	DG(28)	SOFT OR LIQUID FECES
8634	DG(28)	SCANT FECES
8635	DG(9- 10)	SOFT OR LIQUID FECES
	DG(9- 13)	UNGROOMED COAT
	DG(18)	UNGROOMED COAT
	DG(18)	SOFT OR LIQUID FECES
	DG(19- 22)	HINDPAWS: MASS (1.0 CM X 1.0 CM X 0.5 CM)
	DG(23- 29)	HINDPAWS: SCAB (0.5 CM X 0.5 CM X 0.5 CM)a
	DG(24)	UNGROOMED COAT
8636		NO ADVERSE FINDINGS
8637	DG(28)	SCANT FECES

DG = DAY OF PRESUMED GESTATION
a. Observation confirmed at necropsy.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

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

RABBIT #		DESCRIPTION
DOSAGE GROUP IV		2.5 MG/KG/DAY
8638	DG(10- 11)	UNGROOMED COAT
	DG(10- 29)	LOCALIZED ALOPECIA: UNDERSIDE a
	DG(11- 12)	SCANT FECES
	DG(16- 19)	SOFT OR LIQUID FECES
	DG(16- 22)	SCANT FECES
	DG(17)	UNGROOMED COAT
	DG(22- 24)	SOFT OR LIQUID FECES
	DG(24)	UNGROOMED COAT
	DG(29)	SCANT FECES
8639	DG(11- 29)	SCANT FECES
	DG(17- 22)	SOFT OR LIQUID FECES
	DG(27- 29)	SOFT OR LIQUID FECES
8640	DG(11- 22)	SCANT FECES
	DG(19- 20)	SOFT OR LIQUID FECES
	DG(22- 23)	LACRIMATION
	DG(25)	SOFT OR LIQUID FECES
8641	DG(16- 29)	SCANT FECES
	DG(17- 18)	UNGROOMED COAT
	DG(17- 22)	SOFT OR LIQUID FECES
	DG(26- 29)	LOCALIZED ALOPECIA: LIMBS a
	DG(29)	LOCALIZED ALOPECIA: NECK a
8642	DG(17)	SOFT OR LIQUID FECES
	DG(19)	SOFT OR LIQUID FECES
	DG(21- 23)	SOFT OR LIQUID FECES
	DG(25- 29)	SOFT OR LIQUID FECES
	DG(29)	SCANT FECES
8643		NO ADVERSE FINDINGS
8644		NO ADVERSE FINDINGS
8645		NO ADVERSE FINDINGS
8646	DG(10- 16)	SCANT FECES
	DG(22)	SCANT FECES
8647	DG(14- 21)	SCANT FECES
	DG(16- 20)	SOFT OR LIQUID FECES
	DG(21)	RED SUBSTANCE IN CAGE PAN
	DG(21)	ABORTED AND SACRIFICED
8648	DG(14- 16)	SCANT FECES

DG = DAY OF PRESUMED GESTATION
a. Observation confirmed at necropsy.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 15 (PAGE 7): CLINICAL OBSERVATIONS - INDIVIDUAL DATA

RABBIT #		DESCRIPTION
DOSAGE GROUP IV		2.5 MG/KG/DAY
8649	DG(15- 16)	SCANT FECES
	DG(26- 27)	SCANT FECES
8650	DG(27)	SCANT FECES
8651	DG(26- 27)	SCANT FECES
	DG(29)	LOCALIZED ALOPECIA: UNDERSIDE a
8652	DG(8)	RED PERIORAL SUBSTANCE
	DG(12)	NO FECES IN CAGE PAN
	DG(13- 21)	SOFT OR LIQUID FECES
	DG(13- 21)	SCANT FECES
	DG(14- 15)	UNGROOMED COAT
	DG(20- 21)	UNGROOMED COAT
	DG(22)	NO FECES IN CAGE PAN
	DG(23)	SCANT FECES
	DG(24)	NO FECES IN CAGE PAN
	DG(25- 26)	SCANT FECES
	DG(26)	ABORTED AND SACRIFICED
8653	DG(15- 16)	SCANT FECES
	DG(27)	SCANT FECES
	DG(29)	SCANT FECES
8654	DG(16)	SCANT FECES
8655	DG(28)	SCANT FECES
8656	DG(22- 29)	LOCALIZED ALOPECIA: LIMBS a
8657		NO ADVERSE FINDINGS
8658		NO ADVERSE FINDINGS
8659	DG(12- 17)	SCANT FECES
	DG(16- 17)	SOFT OR LIQUID FECES
	DG(28- 29)	SCANT FECES

DG = DAY OF PRESUMED GESTATION
a. Observation confirmed at necropsy.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 15 (PAGE 8): CLINICAL OBSERVATIONS - INDIVIDUAL DATA

RABBIT #		DESCRIPTION
DOSAGE GROUP V		3.75 MG/KG/DAY
8660	DG(8- 10)	SOFT OR LIQUID FECES
	DG(8- 11)	UNGROOMED COAT
	DG(11- 14)	SCANT FECES
	DG(15)	NO FECES IN CAGE PAN
	DG(16)	SCANT FECES
	DG(17- 19)	NO FECES IN CAGE PAN
	DG(19)	TAN PERIANAL SUBSTANCE
	DG(20)	RED SUBSTANCE IN CAGE PAN
	DG(20)	ABORTED AND SACRIFICED
8661	DG(10- 12)	SOFT OR LIQUID FECES
	DG(11- 15)	SCANT FECES
	DG(11- 23)	LOCALIZED ALOPECIA: UNDERSIDE a
	DG(16- 20)	NO FECES IN CAGE PAN
	DG(20- 23)	UNGROOMED COAT
	DG(21- 23)	SCANT FECES
	DG(23)	RED SUBSTANCE IN CAGE PAN
	DG(23)	ABORTED AND SACRIFICED
8662	DG(9- 12)	SCANT FECES
	DG(10- 12)	UNGROOMED COAT
	DG(12)	SOFT OR LIQUID FECES
	DG(13- 19)	NO FECES IN CAGE PAN
	DG(20- 22)	SOFT OR LIQUID FECES
	DG(20- 22)	SCANT FECES
	DG(23- 29)	NO FECES IN CAGE PAN
8663	DG(11)	SOFT OR LIQUID FECES
	DG(11- 19)	SCANT FECES
	DG(13- 15)	UNGROOMED COAT
	DG(13- 15)	SOFT OR LIQUID FECES
	DG(20)	NO FECES IN CAGE PAN
	DG(21)	SCANT FECES
	DG(22- 24)	NO FECES IN CAGE PAN
	DG(25)	UNGROOMED COAT
	DG(25)	SCANT FECES
	DG(26)	ABORTED AND SACRIFICED

DG = DAY OF PRESUMED GESTATION
a. Observation confirmed at necropsy.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 15 (PAGE 9): CLINICAL OBSERVATIONS - INDIVIDUAL DATA

RABBIT #		DESCRIPTION
DOSAGE GROUP V		3.75 MG/KG/DAY
8664	DG(7- 29)	LOCALIZED ALOPECIA: NECK a
	DG(9- 23)	SCANT FECES
	DG(17- 19)	SOFT OR LIQUID FECES
	DG(27- 29)	SOFT OR LIQUID FECES
	DG(29)	SCANT FECES
8665	DG(11- 15)	SCANT FECES
	DG(18)	SCANT FECES
	DG(27- 29)	LOCALIZED ALOPECIA: LIMBS
8666		NO ADVERSE FINDINGS
8667	DG(12)	SCANT FECES
	DG(14- 19)	SCANT FECES
	DG(19)	RED SUBSTANCE IN CAGE PAN
	DG(19)	ABORTED AND SACRIFICED
8668	DG(15- 29)	LOCALIZED ALOPECIA: LIMBS a
8669	DG(11- 17)	SCANT FECES
	DG(13)	SOFT OR LIQUID FECES
	DG(15- 16)	SOFT OR LIQUID FECES
	DG(18- 19)	NO FECES IN CAGE PAN
	DG(20)	SCANT FECES
	DG(21- 22)	NO FECES IN CAGE PAN
	DG(23- 26)	SCANT FECES
	DG(27- 28)	NO FECES IN CAGE PAN
	DG(29)	ABORTED AND SACRIFICED
8670	DG(28)	SCANT FECES
8671	DG(7- 8)	SOFT OR LIQUID FECES
	DG(10)	SCANT FECES
	DG(27)	SCANT FECES
8672	DG(8)	RED PERIORAL SUBSTANCE
	DG(10- 11)	SCANT FECES
	DG(12)	NO FECES IN CAGE PAN
	DG(13- 16)	SCANT FECES
	DG(27)	SCANT FECES
8673	DG(12- 25)	SCANT FECES
	DG(19- 25)	SOFT OR LIQUID FECES

DG = DAY OF PRESUMED GESTATION
a. Observation confirmed at necropsy.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 15 (PAGE 10): CLINICAL OBSERVATIONS - INDIVIDUAL DATA

RABBIT #		DESCRIPTION
DOSAGE GROUP V		3.75 MG/KG/DAY
8673	DG(27)	SOFT OR LIQUID FECES
8674		NO ADVERSE FINDINGS
8675	DG(12- 19)	SCANT FECES
	DG(26)	SCANT FECES
	DG(28- 29)	SCANT FECES
8676	DG(14)	SOFT OR LIQUID FECES
	DG(14- 15)	SCANT FECES
	DG(29)	LOCALIZED ALOPECIA: LIMBS a
8677	DG(18- 29)	LOCALIZED ALOPECIA: LIMBS a
8678	DG(19)	SOFT OR LIQUID FECES
	DG(19)	SCANT FECES
8679		NO ADVERSE FINDINGS
8680	DG(14- 15)	SCANT FECES
	DG(15)	SOFT OR LIQUID FECES
	DG(18- 19)	SOFT OR LIQUID FECES
8681	DG(14- 22)	SCANT FECES
	DG(18- 20)	SOFT OR LIQUID FECES
	DG(26)	SCANT FECES

DG = DAY OF PRESUMED GESTATION
a. Observation confirmed at necropsy.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 15 (PAGE 11): CLINICAL OBSERVATIONS - INDIVIDUAL DATA

RABBIT #		DESCRIPTION
SATELLITE DOSAGE GROUP I		0 (VEHICLE) MG/KG/DAY
8682		NO ADVERSE FINDINGS
8683		NO ADVERSE FINDINGS
8684		NO ADVERSE FINDINGS
SATELLITE DOSAGE GROUP II		0.1 MG/KG/DAY
8685	DG(14)	SOFT OR LIQUID FECES
	DG(14- 15)	SCANT FECES
8686		NO ADVERSE FINDINGS
8687	DG(21)	SCANT FECES
8688		NO ADVERSE FINDINGS
8689		NO ADVERSE FINDINGS
SATELLITE DOSAGE GROUP III		1.0 MG/KG/DAY
8690		NO ADVERSE FINDINGS
8691		NO ADVERSE FINDINGS
	DG(18)	ABORTED AND SACRIFICED
8692	DG(13- 16)	SCANT FECES
	DG(19)	SOFT OR LIQUID FECES

DG = DAY OF PRESUMED GESTATION

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 15 (PAGE 12): CLINICAL OBSERVATIONS - INDIVIDUAL DATA

RABBIT #		DESCRIPTION
SATELLITE DOSAGE GROUP IV		2.5 MG/KG/DAY
8693		NO ADVERSE FINDINGS
8694	DG(14)	SCANT FECES
8695		NO ADVERSE FINDINGS
SATELLITE DOSAGE GROUP V		3.75 MG/KG/DAY
8696	DG(14- 21)	LOCALIZED ALOPECIA: UNDERSIDE a
	DG(15)	SOFT OR LIQUID FECES
	DG(18- 19)	SOFT OR LIQUID FECES
8697	DG(7- 10)	UNGROOMED COAT
	DG(12- 18)	SCANT FECES
8698	DG(14- 21)	SCANT FECES
	DG(17- 20)	SOFT OR LIQUID FECES
	DG(19- 21)	LOCALIZED ALOPECIA: UNDERSIDE a
8699		NO ADVERSE FINDINGS
8700	DG(7)	SCANT FECES
	DG(11)	SCANT FECES
	DG(12)	NO FECES IN CAGE PAN
	DG(12- 18)	LOCALIZED ALOPECIA: UNDERSIDE
	DG(13)	SCANT FECES
	DG(13)	SOFT OR LIQUID FECES
	DG(14- 16)	NO FECES IN CAGE PAN
	DG(17- 18)	SCANT FECES
	DG(19)	ABORTED AND SACRIFICED

DG = DAY OF PRESUMED GESTATION
a. Observation confirmed at necropsy.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 16 (PAGE 1): NECROPSY OBSERVATIONS - INDIVIDUAL DATA

DOSAGE GROUP DOSAGE (MG/KG/DAY)	RABBIT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
I 0 (VEHICLE)	8572	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8573	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8574	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8575	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8576	DG 29	NP	14	ALL TISSUES APPEARED NORMAL.
	8577	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8578	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8579	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8580	DG 29	NP	14	ALL TISSUES APPEARED NORMAL.
	8581	DG 26	P	14	ABORTED ON DAY 26 OF GESTATION. ALL TISSUES APPEARED NORMAL.
	8582	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8583	DG 29	NP	14	ALL TISSUES APPEARED NORMAL.
	8584	DG 29	NP	14	ALL TISSUES APPEARED NORMAL.
	8585	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8586	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8587	DG 13	P	7	FOUND DEAD ON DAY 13 OF GESTATION (57 MINUTES AFTER DOSAGE). LUNGS: RIGHT DIAPHRAGMATIC LOBE, PERFORATION (0.5 CM X 0.1 CM). ALL OTHER TISSUES APPEARED NORMAL.
	8588	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8589	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8590	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8591	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8592	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8593	DG 29	P	14	ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION
a. Refer to the individual clinical observations table (Table 15) for external observations confirmed at necropsy.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 16 (PAGE 2): NECROPSY OBSERVATIONS - INDIVIDUAL DATA

DOSAGE GROUP DOSAGE (MG/KG/DAY)	RABBIT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
II					
0.1	8594	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8595	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8596	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8597	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8598	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8599	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8600	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8601	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8602	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8603	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8604	DG 29	NP	14	ALL TISSUES APPEARED NORMAL.
	8605	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8606	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8607	DG 29	NP	14	ALL TISSUES APPEARED NORMAL.
	8608	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8609	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8610	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8611	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8612	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8613	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8614	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8615	DG 29	P	14	ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION
a. Refer to the individual clinical observations table (Table 15) for external observations confirmed at necropsy.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 16 (PAGE 3): NECROPSY OBSERVATIONS - INDIVIDUAL DATA

DOSAGE GROUP DOSAGE (MG/KG/DAY)	RABBIT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
III					
1.0	8616	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8617	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8618	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8619	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8620	DG 29	NP	14	ALL TISSUES APPEARED NORMAL.
	8621	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8622	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8623	DG 29	NP	14	ALL TISSUES APPEARED NORMAL.
	8624	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8625	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8626	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8627	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8628	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8629	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8630	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8631	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8632	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8633	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8634	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8635	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8636	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8637	DG 29	P	14	ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION
a. Refer to the individual clinical observations table (Table 15) for external observations confirmed at necropsy.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 16 (PAGE 4): NECROPSY OBSERVATIONS - INDIVIDUAL DATA

DOSAGE GROUP DOSAGE (MG/KG/DAY)	RABBIT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
IV					
2.5	8638	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8639	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8640	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8641	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8642	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8643	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8644	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8645	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8646	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8647	DG 21	P	14	ABORTED ON DAY 21 OF GESTATION. ALL TISSUES APPEARED NORMAL.
	8648	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8649	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8650	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8651	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8652	DG 26	P	14	ABORTED ON DAY 26 OF GESTATION. ALL TISSUES APPEARED NORMAL.
	8653	DG 29	NP	14	ALL TISSUES APPEARED NORMAL.
	8654	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8655	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8656	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8657	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8658	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8659	DG 29	P	14	ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION
a. Refer to the individual clinical observations table (Table 15) for external observations confirmed at necropsy.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtPOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 16 (PAGE 5): NECROPSY OBSERVATIONS - INDIVIDUAL DATA

DOSAGE GROUP DOSAGE (MG/KG/DAY)	RABBIT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
V 3.75	8660	DG 20	P	13	ABORTED ON DAY 20 OF GESTATION. ALL TISSUES APPEARED NORMAL.
	8661	DG 23	P	14	ABORTED ON DAY 23 OF GESTATION. ALL TISSUES APPEARED NORMAL.
	8662	DG 29	P	14	LIVER: PALE ALL OTHER TISSUES APPEARED NORMAL.
	8663	DG 26	P	14	ABORTED ON DAY 26 OF GESTATION. ALL TISSUES APPEARED NORMAL.
	8664	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8665	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8666	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8667	DG 19	P	13	ABORTED ON DAY 19 OF GESTATION. ALL TISSUES APPEARED NORMAL.
	8668	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8669	DG 29	P	14	ABORTED ON DAY 29 OF GESTATION. ALL TISSUES APPEARED NORMAL.
	8670	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8671	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8672	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8673	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8674	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8675	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8676	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8677	DG 29	NP	14	ALL TISSUES APPEARED NORMAL.
	8678	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8679	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8680	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8681	DG 29	P	14	ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION
a. Refer to the individual clinical observations table (Table 15) for external observations confirmed at necropsy.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 16 (PAGE 6): NECROPSY OBSERVATIONS - INDIVIDUAL DATA

SATELLITE DOSAGE GROUP DOSAGE (MG/KG/DAY)	RABBIT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a	LIVER WEIGHT (G)
I						
0 (VEHICLE)	8682	DG 21	P	14	ALL TISSUES APPEARED NORMAL.	145.7
	8683	DG 21	P	14	ALL TISSUES APPEARED NORMAL.	130.8
	8684	DG 21	P	14	ALL TISSUES APPEARED NORMAL.	126.7
II						
0.1	8685	DG 21	P	14	LUNGS: ALL LOBES, MOTTLED BLACK AND BROWN (PINPOINT TO 1.0 CM IN DIAMETER). ALL OTHER TISSUES APPEARED NORMAL.	123.6
	8686	DG 21	P	14	ALL TISSUES APPEARED NORMAL.	165.9
	8687	DG 21	P	14	ALL TISSUES APPEARED NORMAL.	110.0
	8688	DG 21	P	14	ALL TISSUES APPEARED NORMAL.	138.6
	8689	DG 21	P	14	ALL TISSUES APPEARED NORMAL.	106.5
III						
1.0	8690	DG 21	P	14	ALL TISSUES APPEARED NORMAL.	136.5
	8691	DG 18	P	12	ABORTED ON DAY 18 OF GESTATION. ALL TISSUES APPEARED NORMAL.	105.1
	8692	DG 21	P	14	ALL TISSUES APPEARED NORMAL.	76.8
IV						
2.5	8693	DG 21	NP	14	ALL TISSUES APPEARED NORMAL.	100.9
	8694	DG 21	P	14	ALL TISSUES APPEARED NORMAL.	142.9
	8695	DG 21	P	14	ALL TISSUES APPEARED NORMAL.	92.7
V						
3.75	8696	DG 21	P	14	ALL TISSUES APPEARED NORMAL.	145.2
	8697	DG 21	P	14	ALL TISSUES APPEARED NORMAL.	81.9
	8698	DG 21	P	14	ALL TISSUES APPEARED NORMAL.	71.8
	8699	DG 21	P	14	ALL TISSUES APPEARED NORMAL.	137.3
	8700	DG 19	P	12	ABORTED ON DAY 19 OF GESTATION. ALL TISSUES APPEARED NORMAL.	60.0

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION
a. Refer to the individual clinical observations table (Table 15) for external observations confirmed at necropsy.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 17 (PAGE 1): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS	DAY 0	7	8	9	10	11	12	13	14	15	16	17	18
RABBIT #	DOSAGE GROUP I				0 (VEHICLE) MG/KG/DAY								
8572 P	3.60	3.42	3.36	3.44	3.49	3.54	3.55	3.58	3.63	3.68	3.59	3.53	3.48
8573 P	3.95	4.12	4.14	4.18	4.14	4.14	4.20	4.23	4.26	4.28	4.28	4.26	4.24
8574 P	3.89	4.22	4.18	4.15	4.12	4.19	4.25	4.33	4.35	4.38	4.39	4.29	4.32
8575 P	3.58	3.76	3.78	3.82	3.83	3.85	3.82	3.84	3.88	3.91	3.97	3.95	3.96
8576 NP	3.34	3.22	3.47	3.53	3.55	3.51	3.55	3.62	3.62	3.60	3.61	3.60	3.56
8577 P	2.92	3.11	3.10	3.16	3.18	3.18	3.20	3.21	3.24	3.26	3.30	3.30	3.36
8578 P	2.85	3.06	3.11	3.12	3.12	3.09	3.10	3.14	3.20	3.23	3.27	3.27	3.29
8579 P	3.23	3.07	3.27	3.28	3.34	3.33	3.34	3.39	3.36	3.34	3.51	3.56	3.57
8580 NP	3.29	3.52	3.44	3.48	3.44	3.42	3.45	3.50	3.53	3.56	3.53	3.47	3.52
8581 P	3.11	3.23	3.27	3.30	3.36	3.37	3.43	3.45	3.50	3.52	3.53	3.59	3.48
8582 P	3.32	3.29	3.30	3.35	3.37	3.40	3.36	3.35	3.38	3.39	3.39	3.38	3.38
8583 NP	3.17	3.34	3.34	3.34	3.25	3.30	3.32	3.40	3.42	3.44	3.49	3.48	3.46
8584 NP	3.41	3.56	3.51	3.69	3.59	3.60	3.65	3.64	3.77	3.74	3.81	3.73	3.73
8585 P	3.57	3.64	3.72	3.77	3.84	3.81	3.82	3.82	3.88	3.96	3.98	3.98	3.99
8586 P	3.36	3.42	3.44	3.48	3.47	3.53	3.57	3.58	3.61	3.53	3.66	3.58	3.60
8587 P	3.02	3.61	3.56	3.60	3.59	3.58	3.51	3.50	FOUND DEAD ON DAY 13 OF GESTATION				
8588 P	3.72	3.80	3.86	3.76	3.89	3.89	3.90	3.96	4.02	4.07	4.06	4.06	4.06
8589 P	3.51	3.70	3.73	3.74	3.80	3.83	3.84	3.85	3.90	3.93	3.95	3.99	4.00
8590 P	3.82	3.95	4.04	4.07	4.17	4.28	4.29	4.35	4.40	4.50	4.62	4.52	4.47
8591 P	3.65	3.68	3.70	3.72	3.76	3.78	3.83	3.85	3.85	3.88	3.91	3.91	3.94
8592 P	3.17	3.39	3.45	3.40	3.42	3.47	3.51	3.50	3.57	3.63	3.66	3.58	3.56
8593 P	3.40	3.51	3.58	3.53	3.54	3.54	3.60	3.65	3.60	3.64	3.68	3.66	3.66

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 17 (PAGE 2): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS	DAY 19	20	21	22	23	24	25	26	27	28	29
RABBIT #	DOSAGE GROUP I				0 (VEHICLE) MG/KG/DAY						
8572 P	3.55	3.62	3.64	3.70	3.67	3.64	3.71	3.80	3.83	3.84	3.85
8573 P	4.20	4.24	4.19	4.18	4.21	4.26	4.32	4.34	4.34	4.33	4.37
8574 P	4.34	4.35	4.21	4.25	4.34	4.34	4.38	4.38	4.44	4.45	4.49
8575 P	4.01	4.01	4.00	4.03	4.03	4.00	4.04	4.02	4.05	4.00	4.07
8576 NP	3.57	3.58	3.62	3.68	3.70	3.71	3.73	3.73	3.76	3.77	3.76
8577 P	3.41	3.35	3.40	3.38	3.39	3.43	3.51	3.56	3.57	3.54	3.65
8578 P	3.29	3.31	3.34	3.31	3.36	3.35	3.34	3.33	3.31	3.35	3.36
8579 P	3.58	3.61	3.64	3.70	3.72	3.76	3.81	3.86	3.89	3.88	3.92
8580 NP	3.56	3.59	3.54	3.56	3.58	3.53	3.48	3.39	3.45	3.51	3.50
8581 P	3.60	3.66	3.66	3.68	3.57	3.67	3.49	ABORTED ON DAY 26 OF GESTATION			
8582 P	3.38	3.37	3.42	3.42	3.47	3.55	3.54	3.53	3.52	3.54	3.58
8583 NP	3.47	3.46	3.47	3.46	3.49	3.54	3.58	3.54	3.56	3.59	3.58
8584 NP	3.89	3.83	3.90	3.89	3.88	3.96	4.10	3.98	3.97	3.92	3.98
8585 P	3.98	3.98	4.05	4.08	4.09	4.12	4.10	3.96	3.87	3.79	3.77
8586 P	3.59	3.62	3.64	3.66	3.70	3.75	3.75	3.73	3.78	3.81	3.80
8587 P	FOUND DEAD ON DAY 13 OF GESTATION										
8588 P	4.10	4.06	4.11	4.16	4.18	4.24	4.25	4.27	4.30	4.29	4.37
8589 P	4.02	4.00	4.04	4.04	4.07	4.09	4.08	4.09	4.04	3.96	3.92
8590 P	4.47	4.50	4.52	4.59	4.60	4.65	4.67	4.68	4.68	4.72	4.66
8591 P	3.97	4.02	4.05	4.07	4.05	3.98	3.91	3.88	3.92	3.93	3.94
8592 P	3.58	3.64	3.99	3.72	3.70	3.70	3.69	3.71	3.73	3.74	3.80
8593 P	3.62	3.65	3.70	3.70	3.71	3.68	3.69	3.78	3.77	3.78	3.87

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 17 (PAGE 3): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS	DAY 0	7	8	9	10	11	12	13	14	15	16	17	18
RABBIT #	DOSAGE GROUP II					0.1 MG/KG/DAY							
8594 P	3.91	3.95	3.86	3.92	3.93	3.96	3.95	3.93	3.90	3.91	3.88	3.88	3.83
8595 P	3.43	3.48	3.52	3.54	3.50	3.50	3.52	3.51	3.55	3.58	3.60	3.56	3.56
8596 P	3.10	3.31	3.31	3.32	3.35	3.41	3.43	3.43	3.45	3.48	3.54	3.55	3.55
8597 P	3.28	3.61	3.68	3.69	3.69	3.71	3.72	3.73	3.82	3.83	3.87	3.92	3.88
8598 P	3.22	3.44	3.43	3.48	3.49	3.49	3.46	3.53	3.53	3.56	3.66	3.62	3.65
8599 P	3.37	3.61	3.58	3.60	3.64	3.66	3.71	3.81	3.84	3.87	3.90	3.89	3.90
8600 P	3.34	3.55	3.58	3.66	3.73	3.65	3.66	3.70	3.67	3.71	3.75	3.77	3.71
8601 P	3.26	3.03	3.26	3.30	3.38	3.39	3.37	3.36	3.37	3.44	3.49	3.47	3.47
8602 P	2.89	3.00	3.01	2.99	2.98	2.99	2.96	2.98	3.00	3.04	3.07	3.02	3.08
8603 P	3.73	3.79	3.76	3.83	3.83	3.85	3.90	3.96	3.97	3.99	4.03	4.02	4.01
8604 NP	3.99	4.04	4.01	3.94	3.97	4.01	4.06	4.03	3.98	3.96	3.98	4.01	4.02
8605 P	3.58	3.65	3.64	3.63	3.70	3.66	3.65	3.70	3.81	3.85	3.87	3.87	3.86
8606 P	3.76	3.81	3.83	3.84	3.80	3.79	3.83	3.87	3.95	4.00	3.93	3.99	4.01
8607 NP	3.03	3.24	3.29	3.32	3.30	3.33	3.35	3.38	3.42	3.40	3.43	3.42	3.43
8608 P	2.91	3.08	3.11	3.06	3.03	3.03	3.07	3.12	3.19	3.20	3.24	3.21	3.09
8609 P	3.32	3.42	3.52	3.52	3.55	3.56	3.55	3.47	3.45	3.48	3.59	3.63	3.65
8610 P	3.16	3.16	3.18	3.29	3.29	3.32	3.36	3.18	3.28	3.42	3.36	3.42	3.50
8611 P	3.53	3.20	3.22	3.23	3.19	3.16	3.19	3.22	3.27	3.33	3.36	3.36	3.38
8612 P	3.47	3.72	3.72	3.74	3.69	3.69	3.74	3.73	3.82	3.87	3.90	3.92	3.96
8613 P	3.59	3.80	3.77	3.76	3.72	3.72	3.68	3.74	3.79	3.86	3.80	3.67	3.66
8614 P	3.70	3.80	3.72	3.76	3.81	3.82	3.87	3.88	3.88	3.96	3.95	3.97	3.98
8615 P	3.40	3.53	3.48	3.59	3.56	3.58	3.65	3.69	3.69	3.75	3.73	3.78	3.83

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 17 (PAGE 4): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS	DAY 19	20	21	22	23	24	25	26	27	28	29
RABBIT #	DOSAGE GROUP II					0.1 MG/KG/DAY					
8594 P	3.80	3.79	3.84	3.88	3.99	4.05	4.11	4.17	4.13	4.09	4.02
8595 P	3.65	3.65	3.68	3.63	3.63	3.61	3.60	3.60	3.60	3.55	3.46
8596 P	3.57	3.58	3.63	3.64	3.63	3.69	3.75	3.75	3.77	3.75	3.78
8597 P	3.92	3.98	3.98	4.02	4.06	4.02	4.02	4.01	3.98	4.02	4.05
8598 P	3.66	3.68	3.72	3.73	3.71	3.74	3.74	3.75	3.75	3.78	3.81
8599 P	3.90	3.94	3.96	3.98	4.00	3.99	4.04	4.05	4.04	4.03	4.07
8600 P	3.76	3.74	3.83	3.86	3.81	3.84	3.90	3.93	3.96	3.97	4.07
8601 P	3.48	3.53	3.52	3.56	3.58	3.58	3.60	3.61	3.63	3.63	3.69
8602 P	3.05	3.03	3.05	3.07	3.08	3.09	3.06	3.07	3.08	3.05	3.05
8603 P	4.02	4.01	4.09	4.14	4.17	4.24	4.26	4.28	4.20	4.20	4.16
8604 NP	4.05	4.04	4.06	4.12	4.16	4.16	4.20	4.26	4.11	4.06	4.09
8605 P	3.86	3.87	3.91	3.95	3.98	4.06	4.08	4.07	4.09	4.10	4.16
8606 P	4.02	4.06	4.03	4.04	4.07	4.15	4.16	4.17	4.18	4.22	4.31
8607 NP	3.49	3.51	3.53	3.54	3.57	3.56	3.61	3.68	3.51	3.50	3.48
8608 P	3.12	3.16	3.24	3.31	3.32	3.36	3.38	3.28	3.22	3.18	3.16
8609 P	3.63	3.65	3.66	3.75	3.71	3.73	3.71	3.78	3.79	3.82	3.81
8610 P	3.48	3.51	3.54	3.57	3.62	3.64	3.66	3.67	3.70	3.74	3.80
8611 P	3.37	3.41	3.40	3.36	3.41	3.37	3.42	3.33	3.25	3.29	3.38
8612 P	3.94	3.95	3.98	4.00	4.03	4.01	4.12	4.11	4.16	4.20	4.28
8613 P	3.69	3.72	3.76	3.73	3.78	3.82	3.89	3.96	4.03	3.95	3.98
8614 P	4.02	4.00	4.04	4.14	4.15	4.18	4.24	4.28	4.32	4.30	4.30
8615 P	3.84	3.89	3.91	3.97	4.00	4.04	4.08	4.05	4.06	4.08	4.15

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 17 (PAGE 5): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS	DAY 0	7	8	9	10	11	12	13	14	15	16	17	18
RABBIT #	DOSAGE GROUP III					1.0 MG/KG/DAY							
8616 P	3.70	3.95	3.94	3.99	3.92	3.94	3.87	3.92	3.90	3.93	3.96	3.86	3.79
8617 P	3.76	3.73	3.78	3.80	3.74	3.81	3.80	3.84	3.83	3.80	3.76	3.69	3.69
8618 P	3.64	3.55	3.52	3.55	3.47	3.42	3.41	3.44	3.47	3.48	3.50	3.51	3.55
8619 P	3.52	3.53	3.57	3.58	3.58	3.56	3.53	3.48	3.49	3.44	3.41	3.33	3.33
8620 NP	3.07	3.31	3.32	3.34	3.36	3.36	3.32	3.32	3.27	3.30	3.38	3.36	3.36
8621 P	2.84	3.21	3.12	3.15	3.03	3.07	3.04	3.05	3.16	3.14	3.18	3.27	3.23
8622 P	3.45	3.59	3.62	3.66	3.65	3.71	3.68	3.73	3.75	3.81	3.85	3.70	3.74
8623 NP	3.33	3.53	3.62	3.58	3.59	3.61	3.63	3.65	3.69	3.67	3.71	3.68	3.72
8624 P	3.07	3.16	3.24	3.25	3.29	3.30	3.32	3.34	3.32	3.36	3.36	3.34	3.39
8625 P	3.60	3.63	3.70	3.74	3.78	3.76	3.77	3.72	3.65	3.73	3.82	3.83	3.85
8626 P	3.12	3.29	3.35	3.30	3.22	3.26	3.30	3.35	3.45	3.49	3.52	3.51	3.36
8627 P	2.96	3.15	3.03	3.02	3.07	3.11	3.14	3.10	3.13	3.16	3.20	3.23	3.22
8628 P	3.26	3.34	3.46	3.50	3.51	3.57	3.54	3.61	3.69	3.71	3.71	3.71	3.72
8629 P	3.36	3.48	3.49	3.51	3.51	3.56	3.56	3.60	3.63	3.66	3.70	3.72	3.72
8630 P	3.31	3.48	3.46	3.47	3.46	3.47	3.47	3.53	3.62	3.67	3.70	3.69	3.69
8631 P	3.18	3.27	3.29	3.29	3.21	3.25	3.26	3.31	3.37	3.47	3.48	3.50	3.49
8632 P	3.59	3.73	3.70	3.75	3.78	3.78	3.78	3.85	3.93	3.95	4.00	3.96	3.94
8633 P	3.23	3.22	3.21	3.21	3.22	3.19	3.14	3.18	3.20	3.21	3.22	3.24	3.26
8634 P	3.83	3.92	3.96	3.95	3.97	3.98	4.03	4.06	4.09	4.11	4.18	4.20	4.16
8635 P	3.57	3.71	3.71	3.66	3.72	3.73	3.76	3.81	3.82	3.86	3.84	3.87	3.89
8636 P	3.40	3.44	3.50	3.45	3.47	3.50	3.53	3.52	3.57	3.64	3.63	3.64	3.68
8637 P	3.96	3.91	3.94	3.97	3.93	3.92	3.94	3.97	4.07	4.15	4.13	4.15	4.18

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 17 (PAGE 6): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS	DAY 19	20	21	22	23	24	25	26	27	28	29
RABBIT #	DOSAGE GROUP III					1.0 MG/KG/DAY					
8616 P	3.73	3.68	3.86	3.86	3.89	3.91	3.93	3.96	3.99	3.96	3.93
8617 P	3.67	3.69	3.70	3.72	3.73	3.74	3.80	3.84	3.85	3.86	3.88
8618 P	3.55	3.61	3.64	3.64	3.66	3.66	3.65	3.68	3.67	3.70	3.73
8619 P	3.28	3.24	3.27	3.28	3.19	3.24	3.34	3.29	3.32	3.38	3.46
8620 NP	3.39	3.41	3.44	3.48	3.49	3.51	3.53	3.53	3.58	3.58	3.59
8621 P	3.29	3.36	3.36	3.41	3.42	3.49	3.48	3.39	3.41	3.46	3.48
8622 P	3.77	3.79	3.80	3.80	3.77	3.80	3.83	3.83	3.87	3.85	3.87
8623 NP	3.70	3.72	3.74	3.81	3.81	3.82	3.86	3.94	3.92	3.94	4.04
8624 P	3.39	3.40	3.43	3.45	3.52	3.51	3.52	3.54	3.62	3.65	3.64
8625 P	3.90	3.91	3.92	3.80	3.78	3.73	3.70	3.62	3.55	3.49	3.47
8626 P	3.38	3.42	3.46	3.47	3.52	3.50	3.51	3.52	3.53	3.59	3.62
8627 P	3.22	3.26	3.28	3.30	3.31	3.33	3.32	3.28	3.19	3.17	3.23
8628 P	3.77	3.75	3.84	3.88	3.93	3.91	3.94	3.98	3.96	3.96	3.95
8629 P	3.74	3.78	3.81	3.85	3.88	3.92	3.92	3.90	3.90	3.90	3.90
8630 P	3.67	3.67	3.71	3.76	3.78	3.76	3.80	3.89	3.95	3.99	4.00
8631 P	3.50	3.55	3.58	3.64	3.65	3.66	3.70	3.71	3.79	3.84	3.83
8632 P	3.97	4.00	4.02	4.04	4.02	4.04	4.04	3.91	3.99	4.03	4.09
8633 P	3.28	3.31	3.36	3.31	3.39	3.40	3.44	3.44	3.46	3.47	3.48
8634 P	4.19	4.20	4.20	4.22	4.25	4.26	4.35	4.36	4.43	4.43	4.45
8635 P	3.90	3.89	3.91	3.96	4.00	4.03	4.08	4.13	4.17	4.21	4.24
8636 P	3.66	3.72	3.78	3.80	3.78	3.86	3.87	3.94	3.99	3.99	4.05
8637 P	4.21	4.20	4.23	4.28	4.28	4.32	4.38	4.34	4.32	4.36	4.42

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 17 (PAGE 7): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS	DAY 0	7	8	9	10	11	12	13	14	15	16	17	18
RABBIT #	DOSAGE GROUP IV					2.5 MG/KG/DAY							
8638 P	3.42	3.45	3.42	3.34	3.26	3.22	3.26	3.34	3.44	3.39	3.37	3.32	3.30
8639 P	3.73	4.02	4.00	3.90	3.79	3.76	3.78	3.67	3.72	3.64	3.65	3.61	3.56
8640 P	3.92	4.08	4.07	3.97	3.90	3.85	3.84	3.77	3.75	3.66	3.70	3.68	3.69
8641 P	3.46	3.40	3.38	3.35	3.34	3.33	3.34	3.35	3.39	3.42	3.42	3.36	3.33
8642 P	4.09	4.05	4.07	4.07	4.09	4.06	4.07	4.02	4.00	3.96	3.94	3.90	3.94
8643 P	3.39	3.52	3.58	3.53	3.58	3.52	3.53	3.50	3.56	3.62	3.64	3.64	3.66
8644 P	3.22	3.41	3.36	3.39	3.40	3.40	3.42	3.36	3.35	3.42	3.47	3.39	3.44
8645 P	3.31	3.48	3.44	3.52	3.51	3.55	3.57	3.59	3.61	3.68	3.65	3.69	3.76
8646 P	2.91	3.01	3.00	2.98	2.90	2.87	2.77	2.79	2.72	2.74	2.68	2.80	2.93
8647 P	3.13	3.36	3.30	3.41	3.33	3.23	3.28	3.06	3.08	3.10	2.94	2.96	2.91
8648 P	3.53	3.71	3.74	3.66	3.75	3.77	3.77	3.69	3.61	3.62	3.70	3.71	3.77
8649 P	3.36	3.51	3.48	3.39	3.29	3.32	3.37	3.42	3.46	3.50	3.63	3.70	3.71
8650 P	3.10	3.22	3.19	3.10	3.14	3.14	3.16	3.18	3.19	3.25	3.26	3.27	3.30
8651 P	3.26	3.38	3.42	3.47	3.42	3.47	3.45	3.47	3.49	3.60	3.61	3.68	3.67
8652 P	3.60	3.66	3.68	3.72	3.74	3.74	3.63	3.56	3.47	3.45	3.43	3.35	3.32
8653 NP	3.64	3.73	3.73	3.78	3.77	3.80	3.64	3.59	3.58	3.62	3.62	3.66	3.74
8654 P	2.87	3.01	3.00	3.01	3.01	2.92	2.95	3.01	3.08	3.07	3.06	3.12	3.14
8655 P	3.59	3.56	3.62	3.62	3.62	3.63	3.65	3.71	3.72	3.75	3.74	3.74	3.74
8656 P	3.80	3.81	3.88	3.88	3.95	3.96	3.95	3.99	4.01	4.07	4.10	4.08	4.08
8657 P	3.25	3.36	3.34	3.43	3.44	3.45	3.47	3.55	3.53	3.58	3.62	3.60	3.64
8658 P	3.05	3.19	3.20	3.27	3.26	3.28	3.32	3.34	3.42	3.46	3.48	3.50	3.51
8659 P	3.41	3.36	3.39	3.40	3.30	3.33	3.37	3.39	3.27	3.29	3.31	3.42	3.47

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
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BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 17 (PAGE 8): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS	DAY 19	20	21	22	23	24	25	26	27	28	29
RABBIT #	DOSAGE GROUP IV					2.5 MG/KG/DAY					
8638 P	3.30	3.30	3.34	3.38	3.41	3.48	3.55	3.61	3.65	3.68	3.67
8639 P	3.57	3.58	3.54	3.48	3.48	3.48	3.51	3.51	3.44	3.52	3.59
8640 P	3.55	3.57	3.61	3.68	3.75	3.83	3.89	3.95	3.94	3.98	3.96
8641 P	3.29	3.22	3.17	3.16	3.18	3.24	3.29	3.32	3.37	3.37	3.39
8642 P	3.94	3.92	3.97	3.96	4.00	4.03	4.03	4.02	4.03	4.02	4.06
8643 P	3.70	3.71	3.76	3.77	3.82	3.84	3.88	3.89	3.92	3.94	3.97
8644 P	3.42	3.44	3.47	3.50	3.51	3.52	3.51	3.52	3.50	3.50	3.49
8645 P	3.73	3.72	3.75	3.78	3.80	3.83	3.88	3.92	3.92	3.92	3.95
8646 P	2.98	3.02	3.03	3.00	3.02	3.02	3.05	3.07	3.10	3.10	3.15
8647 P	2.82	2.70	2.66	ABORTED ON DAY 21 OF GESTATION							
8648 P	3.75	3.76	3.79	3.85	3.88	3.83	3.89	3.89	3.90	3.91	3.99
8649 P	3.72	3.74	3.75	3.78	3.80	3.81	3.82	3.84	3.86	3.87	3.88
8650 P	3.29	3.31	3.35	3.32	3.33	3.36	3.39	3.42	3.45	3.50	3.47
8651 P	3.67	3.70	3.71	3.73	3.75	3.78	3.72	3.73	3.70	3.78	3.77
8652 P	3.27	3.20	3.17	3.14	3.08	3.04	3.01	2.97	ABORTED ON DAY 26 OF GESTATION		
8653 NP	3.74	3.72	3.80	3.80	3.85	3.84	3.81	3.89	3.92	3.94	4.00
8654 P	3.18	3.20	3.18	3.24	3.26	3.26	3.30	3.35	3.39	3.40	3.42
8655 P	3.72	3.74	3.76	3.80	3.83	3.82	3.86	3.89	3.91	3.87	3.91
8656 P	4.08	4.08	4.10	4.15	4.18	4.22	4.24	4.33	4.35	4.35	4.41
8657 P	3.64	3.71	3.68	3.72	3.74	3.76	3.77	3.78	3.80	3.80	3.83
8658 P	3.55	3.56	3.57	3.63	3.64	3.69	3.72	3.73	3.75	3.71	3.73
8659 P	3.47	3.46	3.52	3.53	3.54	3.56	3.53	3.58	3.63	3.67	3.76

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
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BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 17 (PAGE 9): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS	DAY 0	7	8	9	10	11	12	13	14	15	16	17	18
RABBIT #	DOSAGE GROUP V					3.75 MG/KG/DAY							
8660 P	3.76	3.92	3.63	3.69	3.42	3.54	3.41	3.50	3.52	3.56	3.40	3.52	3.54
8661 P	3.44	3.55	3.47	3.35	3.29	3.31	3.17	3.24	3.17	3.18	3.12	3.14	3.09
8662 P	3.49	3.68	3.55	3.51	3.41	3.39	3.34	3.33	3.23	3.22	3.21	3.15	3.13
8663 P	3.95	4.04	4.00	3.84	3.84	3.83	3.68	3.68	3.69	3.60	3.63	3.65	3.53
8664 P	4.18	4.12	4.04	3.99	3.98	3.86	3.86	3.79	3.81	3.73	3.64	3.74	3.73
8665 P	2.99	3.24	3.19	3.11	3.12	3.09	2.96	2.97	2.87	3.01	3.13	3.16	3.13
8666 P	3.58	3.78	3.71	3.73	3.89	3.82	3.86	3.80	3.93	3.99	3.99	4.00	4.00
8667 P	2.97	3.26	3.20	3.17	3.22	3.11	3.14	3.07	3.03	3.01	2.93	2.87	2.81
8668 P	2.89	3.26	3.20	3.29	3.35	3.30	3.30	3.35	3.44	3.48	3.49	3.52	3.50
8669 P	3.70	3.81	3.78	3.76	3.72	3.66	3.55	3.59	3.54	3.54	3.49	3.44	3.41
8670 P	3.12	3.24	3.28	3.32	3.22	3.25	3.23	3.27	3.31	3.36	3.38	3.36	3.38
8671 P	3.35	3.41	3.44	3.33	3.36	3.38	3.42	3.50	3.56	3.60	3.62	3.62	3.67
8672 P	3.21	3.40	3.31	3.23	3.11	3.09	3.09	3.05	3.03	3.09	3.21	3.30	3.27
8673 P	3.23	3.38	3.40	3.39	3.44	3.38	3.33	3.28	3.19	3.12	3.10	3.05	3.04
8674 P	3.55	3.57	3.55	3.61	3.58	3.56	3.58	3.62	3.66	3.67	3.64	3.63	3.62
8675 P	3.26	3.30	3.29	3.24	3.21	3.22	3.25	3.27	3.31	3.33	3.32	3.28	3.27
8676 P	3.70	3.71	3.75	3.80	3.76	3.76	3.78	3.80	3.79	3.82	3.79	3.80	3.85
8677 NP	3.09	3.12	3.15	3.18	3.26	3.22	3.22	3.21	3.22	3.23	3.23	3.21	3.21
8678 P	3.37	3.58	3.61	3.60	3.59	3.61	3.63	3.66	3.70	3.73	3.77	3.74	3.78
8679 P	3.61	3.64	3.72	3.86	3.67	3.65	3.62	3.66	3.69	3.70	3.83	3.86	3.82
8680 P	3.31	3.39	3.43	3.43	3.53	3.51	3.49	3.48	3.48	3.46	3.48	3.48	3.50
8681 P	3.39	3.54	3.54	3.61	3.69	3.62	3.60	3.56	3.50	3.40	3.40	3.29	3.29

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 17 (PAGE 10): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS	DAY 19	20	21	22	23	24	25	26	27	28	29
RABBIT #	DOSAGE GROUP V					3.75 MG/KG/DAY					
8660 P	3.37	ABORTED ON DAY 20 OF GESTATION									
8661 P	3.07	3.03	3.10	3.12	3.02	ABORTED ON DAY 23 OF GESTATION					
8662 P	3.07	3.05	3.05	2.97	2.96	2.90	2.90	2.86	2.81	2.76	2.74
8663 P	3.56	3.57	3.48	3.48	3.54	3.47	3.42	ABORTED ON DAY 26 OF GESTATION			
8664 P	3.63	3.62	3.63	3.71	3.82	3.90	3.89	3.93	3.92	3.95	4.00
8665 P	3.14	3.13	3.17	3.22	3.24	3.29	3.27	3.28	3.31	3.31	3.35
8666 P	4.00	4.00	4.05	4.08	4.12	4.17	4.22	4.25	4.28	4.27	4.32
8667 P	ABORTED ON DAY 19 OF GESTATION										
8668 P	3.57	3.61	3.48	3.55	3.52	3.60	3.62	3.63	3.65	3.64	3.75
8669 P	3.41	3.37	3.35	3.30	3.25	3.23	3.20	3.18	3.17	3.11	a
8670 P	3.37	3.34	3.35	3.42	3.48	3.48	3.54	3.56	3.53	3.58	3.62
8671 P	3.68	3.71	3.74	3.75	3.75	3.77	3.82	3.91	3.92	3.94	3.92
8672 P	3.25	3.28	3.35	3.37	3.38	3.39	3.42	3.49	3.57	3.54	3.60
8673 P	3.05	2.98	3.01	3.01	3.06	3.10	3.18	3.25	3.32	3.37	3.36
8674 P	3.63	3.63	3.63	3.66	3.69	3.71	3.71	3.77	3.80	3.84	3.87
8675 P	3.29	3.33	3.39	3.38	3.39	3.40	3.41	3.42	3.40	3.42	3.44
8676 P	3.87	3.88	3.91	3.92	3.97	4.02	3.97	4.01	4.02	4.06	4.14
8677 NP	3.26	3.26	3.29	3.38	3.41	3.38	3.40	3.41	3.44	3.48	3.53
8678 P	3.88	3.83	3.81	3.89	3.84	3.88	3.96	3.95	3.98	4.02	4.10
8679 P	3.81	3.84	3.91	3.90	3.97	4.01	4.05	4.10	4.12	4.16	4.11
8680 P	3.52	3.54	3.62	3.61	3.62	3.63	3.63	3.66	3.67	3.69	3.70
8681 P	3.32	3.26	3.31	3.29	3.43	3.55	3.63	3.64	3.64	3.66	3.71

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.
a. Doe 8669 aborted on day 29 of gestation.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 17 (PAGE 11): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS	DAY 0	7	8	9	10	11	12	13	14	15	16	17	18
RABBIT #	SATELLITE DOSAGE GROUP I					0 (VEHICLE) MG/KG/DAY							
8682 P	3.66	3.78	3.81	3.84	3.86	3.94	3.96	3.96	3.98	4.04	4.02	4.03	4.12
8683 P	3.44	3.59	3.65	3.65	3.69	3.71	3.77	3.80	3.86	3.91	3.91	3.94	3.88
8684 P	3.26	3.49	3.56	3.55	3.58	3.60	3.62	3.66	3.63	3.72	3.77	3.77	3.75

	DAY 19	20	21
8682 P	4.12	4.12	4.20
8683 P	3.96	3.98	4.10
8684 P	3.76	3.80	3.86

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 17 (PAGE 12): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS	DAY 0	7	8	9	10	11	12	13	14	15	16	17	18
RABBIT #	SATELLITE DOSAGE GROUP II					0.1 MG/KG/DAY							
8685 P	3.68	3.75	3.75	3.76	3.75	3.77	3.72	3.76	3.73	3.74	3.86	3.90	3.96
8686 P	3.48	3.44	3.46	3.50	3.55	3.54	3.60	3.62	3.62	3.70	3.70	3.73	3.76
8687 P	3.51	3.67	3.70	3.70	3.72	3.74	3.83	3.85	3.85	3.91	3.92	3.95	3.96
8688 P	3.57	3.61	3.67	3.68	3.71	3.68	3.64	3.64	3.67	3.74	3.73	3.76	3.80
8689 P	3.27	3.47	3.48	3.53	3.50	3.46	3.44	3.51	3.54	3.64	3.70	3.66	3.69

	DAY 19	20	21
8685 P	3.94	3.94	3.99
8686 P	3.79	3.80	3.90
8687 P	4.00	4.09	3.97
8688 P	3.84	3.86	3.94
8689 P	3.71	3.73	3.74

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 17 (PAGE 13): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS	DAY 0	7	8	9	10	11	12	13	14	15	16	17	18
RABBIT #	SATELLITE DOSAGE GROUP III					1.0 MG/KG/DAY							
8690 P	4.05	4.03	4.00	4.04	4.01	3.99	4.07	4.15	4.21	4.21	4.26	4.28	4.28
8691 P	3.46	3.59	3.57	3.54	3.61	3.65	3.64	3.68	3.69	3.74	3.80	3.73	3.72
8692 P	3.01	3.30	3.33	3.29	3.22	3.17	3.19	3.17	3.18	3.20	3.23	3.28	3.29

STATUS	DAY 19	20	21
8690 P	4.28	4.30	4.35
8691 P	ABORTED ON DAY 18 OF GESTATION		
8692 P	3.30	3.34	3.26

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 17 (PAGE 14): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS	DAY 0	7	8	9	10	11	12	13	14	15	16	17	18
RABBIT #	SATELLITE DOSAGE GROUP IV					2.5 MG/KG/DAY							
8693 NP	3.70	3.79	3.81	3.84	3.84	3.85	3.89	3.87	3.92	3.98	3.81	3.76	3.74
8694 P	3.42	3.47	3.48	3.55	3.56	3.56	3.54	3.56	3.61	3.68	3.64	3.62	3.64
8695 P	2.88	3.03	3.06	3.02	2.99	3.04	3.05	3.04	3.10	3.11	3.14	3.14	3.18

STATUS	DAY 19	20	21
8693 NP	3.74	3.78	3.86
8694 P	3.70	3.73	3.84
8695 P	3.18	3.18	3.25

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 17 (PAGE 15): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS	DAY 0	7	8	9	10	11	12	13	14	15	16	17	18
RABBIT #	SATELLITE DOSAGE GROUP V					3.75 MG/KG/DAY							
8696 P	4.18	4.12	4.13	4.17	4.21	4.20	4.20	4.28	4.31	4.32	4.34	4.35	4.37
8697 P	3.42	3.34	3.31	3.24	3.27	3.24	3.26	3.23	3.24	3.20	3.22	3.24	3.28
8698 P	3.53	3.76	3.77	3.75	3.80	3.84	3.82	3.85	3.80	3.80	3.73	3.64	3.54
8699 P	3.63	3.71	3.73	3.73	3.76	3.72	3.74	3.79	3.90	3.95	3.93	3.92	3.94
8700 P	3.24	3.25	3.42	3.39	3.35	3.26	3.27	3.24	3.12	3.27	3.21	3.26	3.14

STATUS	DAY 19	20	21
8696 P	4.42	4.38	4.50
8697 P	3.29	3.28	3.34
8698 P	3.50	3.46	3.51
8699 P	3.94	3.98	4.03
8700 P	ABORTED ON DAY 19 OF GESTATION		

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 18 (PAGE 1): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS	DAYS	7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13	13 - 14	14 - 15	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20
RABBIT #	DOSAGE GROUP I					0 (VEHICLE) MG/KG/DAY								
8572	P	8.	86.	126.	96.	110.	141.	125.	145.	67.	13.	31.	60.	115.
8573	P	184.	185.	144.	123.	160.	179.	182.	181.	183.	181.	162.	98.	139.
8574	P	124.	a	158.	184.	166.	166.	141.	162.	162.	72.	156.	159.	126.
8575	P	152.	173.	169.	164.	113.	160.	151.	180.	174.	153.	167.	164.	166.
8576	NP	182.	182.	185.	180.	185.	185.	185.	185.	180.	178.	164.	171.	150.
8577	P	183.	177.	174.	159.	185.	145.	175.	180.	185.	184.	185.	181.	141.
8578	P	185.	181.	176.	134.	163.	135.	183.	182.	173.	175.	163.	184.	183.
8579	P	184.	173.	139.	133.	185.	136.	156.	127.	182.	183.	182.	182.	183.
8580	NP	180.	176.	124.	164.	165.	182.	181.	157.	143.	128.	169.	182.	157.
8581	P	180.	185.	182.	185.	175.	180.	153.	162.	179.	167.	67.	182.	164.
8582	P	142.	171.	151.	121.	92.	112.	103.	110.	137.	113.	97.	95.	99.
8583	NP	161.	160.	0.	147.	170.	181.	185.	183.	178.	162.	114.	139.	134.
8584	NP	182.	181.	181.	181.	184.	180.	182.	183.	185.	183.	183.	184.	167.
8585	P	185.	184.	185.	182.	181.	180.	181.	185.	185.	183.	184.	166.	161.
8586	P	182.	167.	176.	166.	176.	134.	133.	158.	162.	102.	133.	110.	128.
8587	P	112.	133.	121.	78.	51.	FOUND DEAD ON DAY 13 OF GESTATION							
8588	P	185.	181.	180.	181.	180.	182.	185.	184.	182.	182.	181.	184.	184.
8589	P	168.	181.	185.	170.	171.	152.	174.	164.	180.	182.	180.	184.	183.
8590	P	181.	180.	185.	185.	183.	181.	183.	184.	155.	141.	142.	149.	182.
8591	P	184.	184.	180.	180.	185.	182.	185.	181.	182.	182.	185.	183.	181.
8592	P	130.	158.	163.	185.	162.	153.	185.	163.	120.	87.	116.	127.	165.
8593	P	182.	162.	180.	185.	100.	155.	141.	130.	149.	141.	141.	152.	149.

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.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 18 (PAGE 2): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS	DAYS 20 - 21	21 - 22	22 - 23	23 - 24	24 - 25	25 - 26	26 - 27	27 - 28	28 - 29
RABBIT #	DOSAGE GROUP I				0 (VEHICLE) MG/KG/DAY				
8572 P	126.	139.	74.	65.	104.	134.	161.	136.	160.
8573 P	73.	86.	124.	170.	146.	152.	124.	131.	129.
8574 P	10.	53.	101.	157.	102.	132.	146.	131.	135.
8575 P	132.	128.	104.	95.	84.	51.	84.	85.	111.
8576 NP	143.	177.	180.	164.	154.	166.	174.	182.	133.
8577 P	156.	181.	181.	181.	182.	183.	184.	183.	181.
8578 P	148.	142.	136.	109.	89.	58.	61.	114.	70.
8579 P	173.	176.	183.	162.	138.	146.	123.	148.	95.
8580 NP	123.	167.	111.	32.	16.	80.	156.	165.	111.
8581 P	151.	162.	a	114.	51.	ABORTED ON DAY 26 OF GESTATION			
8582 P	118.	145.	149.	183.	180.	182.	182.	164.	106.
8583 NP	142.	130.	115.	143.	147.	135.	168.	151.	93.
8584 NP	180.	182.	184.	185.	182.	183.	182.	183.	181.
8585 P	184.	163.	145.	113.	81.	11.	0.	0.	1.
8586 P	146.	122.	138.	124.	135.	140.	110.	103.	87.
8587 P	FOUND DEAD ON DAY 13 OF GESTATION								
8588 P	184.	184.	a	184.	185.	183.	182.	181.	147.
8589 P	148.	116.	119.	136.	91.	114.	34.	4.	6.
8590 P	184.	184.	185.	181.	181.	185.	183.	172.	152.
8591 P	184.	153.	144.	93.	6.	73.	78.	89.	43.
8592 P	166.	131.	122.	108.	111.	108.	86.	109.	119.
8593 P	142.	122.	128.	133.	103.	155.	122.	130.	124.

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.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 18 (PAGE 3): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

RABBIT #	PREGNANCY STATUS	DAYS 7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13	13 - 14	14 - 15	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20
DOSAGE GROUP II						0.1 MG/KG/DAY								
8594	P	95.	147.	157.	177.	113.	185.	63.	64.	26.	30.	15.	11.	32.
8595	P	136.	168.	101.	133.	140.	149.	142.	171.	126.	77.	a	127.	154.
8596	P	184.	181.	182.	181.	182.	183.	185.	183.	185.	184.	184.	183.	181.
8597	P	182.	184.	182.	182.	182.	180.	185.	180.	181.	184.	185.	185.	183.
8598	P	183.	184.	166.	140.	183.	185.	183.	180.	180.	185.	185.	185.	184.
8599	P	182.	184.	184.	180.	181.	185.	180.	180.	184.	185.	185.	182.	181.
8600	P	184.	174.	161.	148.	154.	116.	180.	168.	148.	164.	137.	145.	101.
8601	P	183.	184.	184.	176.	170.	145.	180.	182.	182.	183.	121.	110.	126.
8602	P	180.	150.	125.	105.	126.	111.	151.	150.	157.	68.	149.	163.	80.
8603	P	184.	181.	183.	181.	180.	185.	126.	90.	127.	119.	118.	114.	158.
8604	NP	51.	86.	89.	162.	138.	183.	130.	124.	172.	162.	141.	144.	119.
8605	P	183.	183.	164.	185.	126.	169.	185.	184.	183.	183.	185.	185.	185.
8606	P	182.	122.	100.	129.	122.	143.	157.	159.	168.	185.	182.	180.	178.
8607	NP	181.	184.	180.	184.	182.	185.	184.	184.	182.	181.	184.	185.	185.
8608	P	181.	160.	152.	119.	147.	153.	142.	161.	155.	110.	7.	76.	127.
8609	P	182.	174.	180.	146.	132.	87.	62.	109.	158.	181.	181.	180.	182.
8610	P	183.	180.	169.	170.	184.	92.	156.	183.	180.	184.	185.	180.	183.
8611	P	170.	141.	114.	73.	125.	135.	104.	164.	168.	185.	184.	172.	162.
8612	P	185.	183.	182.	182.	181.	183.	185.	184.	182.	184.	181.	183.	182.
8613	P	95.	100.	94.	97.	93.	121.	140.	148.	46.	18.	89.	83.	123.
8614	P	182.	182.	182.	185.	181.	181.	185.	183.	181.	183.	180.	180.	184.
8615	P	181.	180.	184.	184.	180.	182.	185.	185.	184.	181.	182.	181.	184.

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.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 18 (PAGE 4): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS	RABBIT #	DOSAGE GROUP II	20 - 21	21 - 22	22 - 23	23 - 24	24 - 25	25 - 26	26 - 27	27 - 28	28 - 29
			DAYS				0.1 MG/KG/DAY				
P	8594		53.	74.	124.	164.	182.	167.	165.	142.	100.
P	8595		150.	106.	90.	73.	67.	71.	76.	41.	9.
P	8596		180.	184.	184.	181.	164.	149.	151.	152.	109.
P	8597		182.	184.	182.	119.	103.	104.	82.	134.	107.
P	8598		180.	184.	182.	181.	172.	183.	182.	183.	122.
P	8599		180.	181.	180.	141.	145.	139.	136.	141.	100.
P	8600		142.	175.	173.	121.	151.	147.	132.	176.	95.
P	8601		110.	134.	152.	73.	83.	86.	88.	122.	103.
P	8602		74.	101.	130.	110.	37.	66.	67.	101.	25.
P	8603		176.	184.	157.	159.	182.	145.	49.	71.	56.
NP	8604		163.	159.	165.	161.	159.	169.	97.	94.	69.
P	8605		180.	185.	184.	166.	102.	112.	116.	118.	100.
P	8606		184.	3.	158.	158.	155.	143.	166.	144.	121.
NP	8607		184.	184.	183.	184.	183.	184.	83.	132.	91.
P	8608		184.	146.	143.	146.	99.	43.	19.	9.	29.
P	8609		180.	181.	159.	147.	92.	132.	130.	113.	90.
P	8610		181.	181.	185.	172.	150.	146.	123.	128.	141.
P	8611		124.	43.	98.	45.	63.	9.	6.	55.	88.
P	8612		181.	182.	183.	184.	184.	180.	184.	181.	172.
P	8613		141.	49.	160.	183.	185.	183.	183.	117.	109.
P	8614		180.	183.	185.	184.	183.	172.	151.	118.	96.
P	8615		182.	181.	182.	183.	184.	117.	99.	110.	125.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAYS = DAYS OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 18 (PAGE 5): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS	DAYS	7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13	13 - 14	14 - 15	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20
RABBIT #	DOSAGE GROUP III					1.0 MG/KG/DAY								
8616	P	149.	173.	150.	95.	34.	79.	57.	72.	76.	35.	1.	2.	17.
8617	P	154.	144.	92.	138.	126.	111.	81.	99.	21.	10.	22.	29.	57.
8618	P	37.	2.	0.	0.	60.	49.	30.	40.	66.	77.	109.	135.	132.
8619	P	121.	129.	104.	69.	4.	34.	11.	8.	2.	0.	0.	2.	6.
8620	NP	182.	182.	182.	98.	145.	135.	106.	167.	185.	176.	184.	180.	180.
8621	P	182.	175.	46.	a	79.	95.	180.	180.	183.	185.	184.	185.	183.
8622	P	185.	185.	183.	180.	184.	185.	180.	180.	181.	126.	115.	150.	168.
8623	NP	183.	184.	126.	185.	181.	178.	174.	182.	184.	185.	181.	185.	182.
8624	P	185.	180.	172.	174.	160.	171.	112.	127.	135.	160.	182.	185.	182.
8625	P	180.	183.	185.	167.	130.	113.	59.	133.	164.	183.	182.	183.	167.
8626	P	156.	89.	35.	133.	159.	113.	163.	144.	174.	185.	147.	98.	113.
8627	P	52.	92.	126.	156.	134.	114.	110.	94.	148.	162.	157.	122.	133.
8628	P	184.	182.	181.	183.	182.	180.	185.	174.	185.	185.	184.	180.	180.
8629	P	185.	181.	181.	180.	154.	125.	134.	151.	185.	185.	184.	182.	184.
8630	P	184.	172.	168.	141.	122.	120.	154.	182.	182.	182.	185.	180.	184.
8631	P	182.	5.	135.	143.	145.	149.	185.	185.	184.	180.	183.	180.	180.
8632	P	183.	183.	183.	184.	180.	184.	185.	185.	185.	180.	182.	183.	183.
8633	P	146.	125.	149.	86.	109.	117.	101.	107.	117.	149.	135.	147.	158.
8634	P	185.	181.	182.	185.	180.	182.	184.	185.	180.	180.	185.	181.	180.
8635	P	182.	163.	143.	155.	151.	181.	184.	185.	183.	182.	185.	183.	185.
8636	P	184.	183.	162.	183.	150.	b	176.	185.	184.	180.	181.	181.	185.
8637	P	182.	183.	183.	146.	144.	164.	182.	181.	181.	182.	185.	184.	177.

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.
b. Wet feed precluded the calculation of this value.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 18 (PAGE 6): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS DAYS 20 - 21	21 - 22	22 - 23	23 - 24	24 - 25	25 - 26	26 - 27	27 - 28	28 - 29
RABBIT # DOSAGE GROUP III				1.0 MG/KG/DAY				
8616 P 74.	43.	76.	103.	95.	109.	133.	100.	71.
8617 P 53.	56.	65.	111.	104.	100.	99.	87.	114.
8618 P 127.	131.	122.	117.	80.	109.	91.	112.	109.
8619 P 3.	1.	3.	17.	8.	35.	66.	96.	106.
8620 NP 174.	170.	182.	166.	156.	154.	170.	185.	128.
8621 P 182.	182.	183.	180.	156.	a	102.	154.	118.
8622 P 145.	140.	139.	109.	116.	122.	135.	160.	139.
8623 NP 184.	184.	183.	183.	183.	183.	181.	181.	184.
8624 P 182.	184.	158.	150.	129.	93.	167.	154.	86.
8625 P 137.	93.	39.	13.	15.	2.	2.	7.	2.
8626 P 126.	143.	116.	134.	125.	140.	167.	151.	96.
8627 P 135.	157.	119.	93.	54.	34.	3.	82.	63.
8628 P 182.	175.	174.	159.	146.	166.	129.	89.	87.
8629 P 184.	172.	163.	173.	140.	112.	89.	47.	88.
8630 P 183.	174.	153.	161.	171.	180.	183.	159.	132.
8631 P 182.	169.	184.	182.	184.	184.	185.	165.	126.
8632 P 181.	181.	184.	185.	181.	184.	183.	a	180.
8633 P 166.	43.	128.	130.	116.	108.	68.	54.	51.
8634 P 180.	183.	185.	184.	184.	183.	169.	160.	142.
8635 P 184.	183.	183.	185.	184.	149.	143.	139.	120.
8636 P 177.	181.	180.	184.	183.	182.	174.	153.	142.
8637 P 146.	3.	181.	184.	169.	98.	86.	112.	113.

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.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 18 (PAGE 7): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

RABBIT #	PREGNANCY STATUS	DAYS 7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13	13 - 14	14 - 15	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20
DOSAGE GROUP IV						2.5 MG/KG/DAY								
8638	P	59.	10.	5.	2.	48.	84.	83.	5.	23.	16.	21.	63.	55.
8639	P	154.	60.	2.	0.	3.	2.	4.	2.	0.	1.	0.	3.	1.
8640	P	146.	54.	7.	0.	1.	3.	5.	3.	2.	3.	0.	2.	79.
8641	P	71.	57.	52.	48.	59.	62.	55.	49.	24.	2.	0.	3.	0.
8642	P	184.	185.	174.	158.	139.	151.	120.	113.	89.	101.	100.	115.	108.
8643	P	181.	182.	183.	131.	122.	124.	165.	180.	182.	185.	184.	180.	182.
8644	P	182.	169.	183.	109.	128.	80.	82.	130.	168.	154.	165.	157.	155.
8645	P	185.	181.	185.	184.	183.	162.	168.	169.	182.	185.	185.	185.	182.
8646	P	180.	114.	18.	1.	3.	1.	3.	1.	36.	127.	183.	179.	163.
8647	P	104.	99.	2.	42.	14.	1.	1.	2.	0.	4.	1.	12.	0.
8648	P	180.	155.	137.	136.	101.	37.	14.	49.	84.	109.	152.	97.	101.
8649	P	139.	76.	36.	113.	151.	130.	133.	131.	182.	185.	183.	180.	175.
8650	P	152.	63.	132.	124.	169.	112.	102.	102.	130.	123.	122.	114.	136.
8651	P	184.	180.	185.	180.	185.	162.	162.	181.	154.	174.	184.	169.	162.
8652	P	183.	178.	181.	119.	0.	1.	2.	0.	2.	0.	10.	0.	0.
8653	NP	185.	182.	174.	118.	26.	73.	87.	129.	127.	184.	173.	152.	170.
8654	P	184.	161.	144.	183.	138.	140.	141.	142.	127.	176.	181.	157.	172.
8655	P	185.	144.	183.	182.	180.	181.	184.	182.	183.	170.	148.	159.	182.
8656	P	185.	184.	181.	185.	183.	183.	185.	183.	180.	185.	184.	184.	183.
8657	P	181.	178.	165.	152.	136.	140.	185.	161.	181.	185.	180.	184.	181.
8658	P	184.	168.	159.	185.	182.	184.	185.	180.	181.	182.	185.	180.	185.
8659	P	183.	185.	69.	101.	59.	57.	4.	2.	55.	114.	150.	181.	184.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAYS = DAYS OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 18 (PAGE 9): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS	DAYS	7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13	13 - 14	14 - 15	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20
RABBIT #	DOSAGE GROUP V					3.75 MG/KG/DAY								
8660	P	0.	0.	1.	0.	1.	3.	10.	3.	0.	0.	0.	1.	a
8661	P	23.	1.	1.	1.	2.	2.	2.	4.	0.	0.	0.	0.	0.
8662	P	14.	0.	0.	0.	1.	1.	0.	1.	1.	1.	0.	0.	0.
8663	P	38.	2.	0.	1.	0.	0.	2.	5.	1.	1.	0.	1.	0.
8664	P	20.	2.	0.	2.	1.	1.	4.	2.	1.	1.	0.	1.	12.
8665	P	183.	97.	41.	2.	12.	3.	6.	111.	154.	148.	133.	124.	110.
8666	P	183.	182.	183.	163.	181.	132.	184.	184.	185.	184.	184.	185.	181.
8667	P	181.	162.	141.	1.	64.	41.	23.	17.	1.	0.	3.	b	
8668	P	183.	185.	185.	183.	182.	184.	183.	180.	185.	184.	181.	181.	185.
8669	P	158.	109.	12.	4.	1.	2.	116.	0.	0.	4.	1.	7.	0.
8670	P	184.	181.	1.	124.	74.	110.	113.	110.	133.	153.	127.	115.	106.
8671	P	182.	1.	72.	88.	160.	181.	185.	185.	183.	184.	183.	180.	181.
8672	P	95.	2.	6.	7.	8.	0.	4.	119.	168.	182.	156.	123.	145.
8673	P	184.	152.	174.	59.	48.	1.	1.	0.	1.	0.	9.	0.	0.
8674	P	180.	185.	163.	147.	168.	185.	156.	169.	164.	165.	155.	116.	111.
8675	P	184.	138.	97.	81.	52.	80.	96.	120.	133.	94.	86.	100.	130.
8676	P	184.	143.	111.	118.	101.	93.	43.	53.	120.	158.	169.	167.	169.
8677	NP	181.	181.	182.	184.	182.	150.	155.	180.	181.	120.	139.	152.	184.
8678	P	183.	165.	125.	154.	123.	140.	163.	185.	182.	183.	183.	184.	181.
8679	P	183.	182.	104.	69.	63.	111.	156.	183.	184.	182.	180.	183.	184.
8680	P	182.	181.	180.	177.	123.	99.	78.	72.	138.	143.	146.	143.	180.
8681	P	183.	182.	168.	170.	110.	90.	34.	7.	2.	0.	0.	1.	1.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAYS = DAYS OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).
a. Doe 8660 aborted on day 20 of gestation.
b. Doe 8667 aborted on day 19 of gestation.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 18 (PAGE 8): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS	DAYS 20 - 21	21 - 22	22 - 23	23 - 24	24 - 25	25 - 26	26 - 27	27 - 28	28 - 29
RABBIT #	DOSAGE GROUP IV				2.5 MG/KG/DAY				
8638 P	74.	86.	89.	120.	109.	117.	110.	91.	105.
8639 P	5.	2.	4.	12.	11.	24.	44.	93.	96.
8640 P	105.	147.	167.	182.	174.	184.	184.	154.	112.
8641 P	3.	37.	33.	89.	75.	74.	100.	115.	121.
8642 P	123.	123.	129.	156.	111.	107.	114.	31.	71.
8643 P	184.	185.	185.	181.	176.	165.	159.	184.	147.
8644 P	147.	152.	164.	116.	113.	106.	101.	110.	58.
8645 P	185.	182.	184.	182.	184.	183.	165.	182.	142.
8646 P	146.	113.	134.	100.	122.	109.	115.	162.	134.
8647 P	ABORTED ON DAY 21 OF GESTATION								
8648 P	112.	122.	112.	89.	97.	95.	135.	95.	73.
8649 P	163.	129.	124.	130.	119.	160.	132.	127.	121.
8650 P	150.	107.	108.	127.	145.	169.	134.	118.	111.
8651 P	182.	139.	123.	143.	54.	101.	138.	132.	130.
8652 P	0.	5.	0.	1.	1.	ABORTED ON DAY 26 OF GESTATION			
8653 NP	183.	149.	157.	159.	180.	184.	185.	166.	129.
8654 P	159.	149.	126.	159.	152.	173.	145.	106.	116.
8655 P	181.	184.	182.	181.	184.	170.	135.	130.	129.
8656 P	181.	170.	180.	185.	183.	185.	178.	168.	164.
8657 P	163.	170.	164.	183.	170.	a	a	a	a
8658 P	185.	182.	183.	185.	181.	150.	130.	119.	96.
8659 P	182.	183.	184.	180.	120.	182.	170.	160.	174.

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.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 18 (PAGE 10): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS	DAYS 20 - 21	21 - 22	22 - 23	23 - 24	24 - 25	25 - 26	26 - 27	27 - 28	28 - 29
RABBIT #	DOSAGE GROUP V				3.75 MG/KG/DAY				
8660 P	ABORTED ON DAY 20 OF GESTATION								
8661 P	7.	0.	ABORTED ON DAY 23 OF GESTATION						
8662 P	7.	0.	0.	1.	0.	0.	5.	0.	0.
8663 P	9.	0.	0.	1.	0.	ABORTED ON DAY 26 OF GESTATION			
8664 P	43.	91.	101.	125.	119.	123.	131.	162.	160.
8665 P	134.	162.	182.	148.	120.	107.	136.	181.	130.
8666 P	185.	183.	185.	181.	185.	174.	168.	182.	157.
8667 P	ABORTED ON DAY 19 OF GESTATION								
8668 P	180.	182.	182.	181.	185.	182.	180.	180.	148.
8669 P	0.	0.	1.	4.	2.	6.	3.	2.	ABORTED ON DAY 29 OF GESTATION
8670 P	129.	181.	172.	170.	180.	170.	182.	185.	114.
8671 P	182.	133.	164.	158.	166.	183.	116.	a	b
8672 P	181.	185.	184.	182.	184.	182.	184.	180.	182.
8673 P	66.	83.	93.	91.	144.	181.	181.	177.	118.
8674 P	120.	115.	151.	164.	154.	185.	168.	155.	164.
8675 P	142.	115.	128.	126.	114.	73.	b	88.	81.
8676 P	134.	116.	127.	131.	96.	151.	131.	136.	150.
8677 NP	181.	183.	184.	182.	185.	180.	183.	184.	185.
8678 P	181.	b	181.	181.	176.	b	b	180.	140.
8679 P	183.	183.	185.	185.	182.	171.	150.	135.	77.
8680 P	155.	133.	131.	143.	127.	121.	118.	129.	108.
8681 P	113.	84.	162.	184.	180.	183.	151.	159.	144.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAYS = DAYS OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).
a. Value was not recorded.
b. Spilled feed precluded the calculation of this value.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 18 (PAGE 11): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS	DAYS 7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13	13 - 14	14 - 15	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20
RABBIT #	SATELLITE DOSAGE GROUP I					0 (VEHICLE) MG/KG/DAY							
8682 P	183.	181.	182.	181.	176.	183.	184.	185.	182.	172.	184.	184.	185.
8683 P	184.	109.	171.	180.	184.	180.	184.	143.	172.	180.	185.	184.	185.
8684 P	184.	184.	180.	181.	184.	155.	140.	181.	184.	181.	156.	143.	181.

	DAYS 20 - 21
8682 P	180.
8683 P	174.
8684 P	162.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAYS = DAYS OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 18 (PAGE 12): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS	DAYS	7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13	13 - 14	14 - 15	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20
RABBIT #	SATELLITE DOSAGE GROUP II						0.1 MG/KG/DAY							
8685 P		180.	180.	150.	157.	113.	112.	55.	67.	168.	181.	157.	154.	149.
8686 P		181.	184.	182.	180.	181.	157.	163.	183.	185.	183.	180.	184.	184.
8687 P		182.	184.	183.	180.	181.	183.	182.	184.	181.	181.	181.	185.	180.
8688 P		181.	184.	153.	154.	123.	92.	150.	181.	181.	180.	181.	180.	183.
8689 P		160.	176.	164.	73.	80.	142.	168.	168.	183.	182.	146.	145.	181.

	DAYS 20 - 21
8685 P	138.
8686 P	184.
8687 P	33.
8688 P	184.
8689 P	131.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAYS = DAYS OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 18 (PAGE 13): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS	DAYS	7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13	13 - 14	14 - 15	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20
RABBIT #	SATELLITE DOSAGE GROUP III						1.0 MG/KG/DAY							
8690 P		180.	181.	182.	184.	182.	184.	183.	184.	183.	184.	180.	184.	182.
8691 P		180.	182.	182.	180.	181.	182.	184.	185.	184.	183.	a		
8692 P		157.	137.	100.	77.	78.	47.	51.	53.	95.	116.	127.	108.	163.

	DAYS 20 - 21
8690 P	180.
8691 P	ABORTED ON DAY 18 OF GESTATION
8692 P	67.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAYS = DAYS OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).
a. Doe 8691 aborted on day 18 of gestation.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 18 (PAGE 14): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS	DAYS	7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13	13 - 14	14 - 15	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20
RABBIT #	SATELLITE DOSAGE GROUP IV						2.5 MG/KG/DAY							
8693 NP		181.	181.	181.	181.	181.	181.	183.	165.	103.	51.	78.	102.	137.
8694 P		181.	180.	172.	161.	115.	127.	183.	185.	181.	185.	183.	184.	184.
8695 P		181.	144.	124.	141.	148.	128.	146.	134.	147.	162.	155.	140.	155.

	DAYS 20 - 21
8693 NP	122.
8694 P	175.
8695 P	144.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAYS = DAYS OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 18 (PAGE 15): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS	DAYS	7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13	13 - 14	14 - 15	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20
RABBIT #	SATELLITE DOSAGE GROUP V						3.75 MG/KG/DAY							
8696 P		181.	185.	136.	180.	163.	156.	184.	185.	164.	180.	177.	181.	182.
8697 P		106.	51.	75.	60.	76.	39.	34.	17.	84.	95.	134.	135.	144.
8698 P		180.	182.	182.	176.	130.	130.	62.	46.	13.	3.	1.	2.	4.
8699 P		183.	181.	156.	156.	109.	128.	183.	182.	181.	184.	184.	181.	184.
8700 P		184.	134.	121.	2.	1.	0.	2.	0.	0.	0.	1.	a	

PREGNANCY STATUS	DAYS 20 - 21
8696 P	181.
8697 P	101.
8698 P	4.
8699 P	182.
8700 P	ABORTED ON DAY 19 OF GESTATION

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAYS = DAYS OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).
a. Doe 8700 aborted on day 19 of gestation.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 19 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - INDIVIDUAL DATA

			VIABLE FETUSES			DEAD FETUSES			EARLY RESORPTIONS			LATE RESORPTIONS			IMPLANTATION SITES			CORPORA LUTEA		
	SEX		RIGHT HORN	LEFT HORN	TOTAL	RIGHT HORN	LEFT HORN	TOTAL	RIGHT HORN	LEFT HORN	TOTAL	RIGHT HORN	LEFT HORN	TOTAL	RIGHT HORN	LEFT HORN	TOTAL	RIGHT OVARY	LEFT OVARY	TOTAL
RABBIT #	M	F																		
DOSAGE GROUP I								0 (VEHICLE) MG/KG/DAY												
8572	1	6	3	4	7	0	0	0	0	0	0	0	0	0	3	4	7	4	5	9
8573	5	2	6	1	7	0	0	0	0	0	0	0	0	0	6	1	7	6	3	9
8574	4	5	6	3	9	0	0	0	0	0	0	0	0	0	6	3	9	7	4	11
8575	5	5	8	2	10	0	0	0	0	0	0	0	0	0	8	2	10	8	3	11
8576	NOT PREGNANT																			
8577	4	3	2	5	7	0	0	0	0	0	0	0	0	0	2	5	7	2	7	9
8578	4	3	2	5	7	0	0	0	0	0	0	0	0	0	2	5	7	3	6	9
8579	5	2	5	2	7	0	0	0	0	0	0	0	0	0	5	2	7	6	3	9
8580	NOT PREGNANT																			
8581	ABORTED ON DAY 26 OF GESTATION																			
8582	0	3	1	2	3	0	0	0	6	1	7	0	0	0	7	3	10	8	4	12
8583	NOT PREGNANT																			
8584	NOT PREGNANT																			
8585	4	4	7	1	8	0	0	0	0	2	2	1	0	1	8	3	11	8	4	12
8586	5	5	8	2	10	0	0	0	0	0	0	0	0	0	8	2	10	9	4	13
8587	FOUND DEAD ON DAY 13 OF GESTATION																			
8588	2	5	4	3	7	0	0	0	0	1	1	0	0	0	4	4	8	4	4	8
8589	5	4	4	5	9	0	0	0	0	0	0	0	0	0	4	5	9	5	5	10
8590	8	3	4	7	11	0	0	0	0	0	0	0	0	0	4	7	11	6	9	15
8591	3	6	2	7	9	0	0	0	0	0	0	0	0	0	2	7	9	6	9	15
8592	6	7	7	6	13	0	0	0	0	0	0	0	0	0	7	6	13	7	7	14
8593	4	5	4	5	9	0	0	0	0	0	0	0	0	0	4	5	9	4	5	9

M = MALE F = FEMALE
PLACENTAE APPEARED NORMAL UNLESS NOTED OTHERWISE.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 19 (PAGE 2): CAESAREAN-SECTIONING OBSERVATIONS - INDIVIDUAL DATA

			VIABLE FETUSES			DEAD FETUSES			EARLY RESORPTIONS			LATE RESORPTIONS			IMPLANTATION SITES			CORPORA LUTEA		
	SEX		RIGHT HORN	LEFT HORN	TOTAL	RIGHT HORN	LEFT HORN	TOTAL	RIGHT HORN	LEFT HORN	TOTAL	RIGHT HORN	LEFT HORN	TOTAL	RIGHT HORN	LEFT HORN	TOTAL	RIGHT OVARY	LEFT OVARY	TOTAL
RABBIT #	M	F																		
DOSAGE GROUP II								0.1 MG/KG/DAY												
8594	2	3	2	3	5	0	0	0	1	2	3	0	0	0	3	5	8	3	8	11
8595	3	2	3	2	5	0	0	0	0	0	0	0	0	0	3	2	5	3	4	7
8596	3	4	3	4	7	0	0	0	0	0	0	0	0	0	3	4	7	5	7	12
8597	5	4	5	4	9	0	0	0	0	0	0	0	0	0	5	4	9	5	4	9
8598	2	1	0	3	3	0	0	0	0	0	0	0	0	0	0	3	3	4	3	7
8599	3	6	4	5	9	0	0	0	0	0	0	0	0	0	4	5	9	5	6	11
8600	3	6	4	5	9	0	0	0	1	0	1	0	2	2	5	7	12	5	8	13
8601	4	5	3	6	9	0	0	0	0	0	0	0	0	0	3	6	9	3	6	9
8602	3	4	0	7	7	0	0	0	0	0	0	0	0	0	0	7	7	3	7	10
8603	6	3	7	2	9	0	0	0	0	0	0	0	0	0	7	2	9	7	4	11
8604	NOT PREGNANT																			
8605	6	4	8	2	10	0	0	0	0	0	0	0	0	0	8	2	10	9	6	15
8606	5	4	3	6	9	0	0	0	0	0	0	0	0	0	3	6	9	4	6	10
8607	NOT PREGNANT																			
8608	6	5	5	6	11	0	0	0	0	0	0	0	0	0	5	6	11	5	7	12
8609	5	4	2	7	9	0	0	0	0	0	0	0	0	0	2	7	9	2	8	10
8610	4	5	5	4	9	0	0	0	0	0	0	0	0	0	5	4	9	6	6	12
8611	3	6	5	4	9	0	0	0	0	0	0	0	0	0	5	4	9	5	4	9
8612	4	4	5	3	8	0	0	0	0	0	0	0	0	0	5	3	8	6	5	11
8613	7	3	5	5	10	0	0	0	0	0	0	0	0	0	5	5	10	6	5	11
8614	6	3	4	5	9	0	0	0	0	0	0	0	0	0	4	5	9	6	7	13
8615	5	6	3	8	11	0	0	0	0	0	0	0	0	0	3	8	11	4	8	12

M = MALE F = FEMALE

PLACENTAE APPEARED NORMAL UNLESS NOTED OTHERWISE.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 19 (PAGE 3): CAESAREAN-SECTIONING OBSERVATIONS - INDIVIDUAL DATA

			VIABLE FETUSES			DEAD FETUSES			EARLY RESORPTIONS			LATE RESORPTIONS			IMPLANTATION SITES			CORPORA LUTEA		
	SEX		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT	
RABBIT #	M	F	HORN		TOTAL	HORN		TOTAL	HORN		TOTAL	HORN		TOTAL	HORN		TOTAL	OVARY		TOTAL
DOSAGE GROUP III								1.0 MG/KG/DAY												
8616	3	2	4	1	5	0	0	0	0	0	0	2	1	3	6	2	8	6	3	9
8617	3	5	4	4	8	0	0	0	1	0	1	0	0	0	5	4	9	7	6	13
8618	5	5	4	6	10	0	0	0	0	0	0	0	0	0	4	6	10	6	8	14
8619	4	3	4	3	7	0	0	0	0	0	0	0	0	0	4	3	7	6	5	11
8620	NOT PREGNANT																			
8621	5	4	3	6	9	0	0	0	0	0	0	0	0	0	3	6	9	4	6	10
8622	3	1	3	1	4	0	0	0	0	0	0	0	0	0	3	1	4	4	3	7
8623	NOT PREGNANT																			
8624	3	6	3	6	9	0	0	0	1	0	1	0	0	0	4	6	10	4	8	12
8625	5	2	3	4	7	0	0	0	0	0	0	0	0	0	3	4	7	4	5	9
8626	4	3	4	3	7	0	0	0	0	0	0	0	0	0	4	3	7	4	3	7
8627	4	6	6	4	10	0	0	0	0	0	0	0	0	0	6	4	10	6	4	10
8628	6	3	5	4	9	0	0	0	0	0	0	0	0	0	5	4	9	5	6	11
8629	5	5	4	6	10	0	0	0	0	0	0	0	0	0	4	6	10	5	6	11
8630	3	5	5	3	8	0	0	0	0	0	0	0	0	0	5	3	8	5	4	9
8631	1	8	7	2	9	0	0	0	0	0	0	0	0	0	7	2	9	8	3	11
8632	3	5	4	4	8	0	0	0	0	0	0	0	0	0	4	4	8	4	4	8
8633	5	3	4	4	8	0	0	0	0	0	0	0	0	0	4	4	8	4	5	9
8634	3	6	5	4	9	0	0	0	0	0	0	0	0	0	5	4	9	6	5	11
8635	5	3	4	4	8	0	0	0	0	0	0	0	0	0	4	4	8	6	5	11
8636	2	5	4	3	7	0	0	0	0	0	0	0	0	0	4	3	7	4	3	7
8637	5	8	9	4	13	0	0	0	1	0	1	0	0	0	10	4	14	12	4	16

M = MALE F = FEMALE
PLACENTAE APPEARED NORMAL UNLESS NOTED OTHERWISE.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 19 (PAGE 4): CAESAREAN-SECTIONING OBSERVATIONS - INDIVIDUAL DATA

			VIABLE FETUSES			DEAD FETUSES			EARLY RESORPTIONS			LATE RESORPTIONS			IMPLANTATION SITES			CORPORA LUTEA		
	SEX		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT	
RABBIT #	M	F	HORN		TOTAL	HORN		TOTAL	HORN		TOTAL	HORN		TOTAL	HORN		TOTAL	OVARY		TOTAL
DOSAGE GROUP IV								2.5 MG/KG/DAY												
8638	2	5	2	5	7	0	0	0	0	0	0	0	0	0	2	5	7	2	5	7
8639	2	5	4	3	7	0	0	0	0	0	0	1	1	2	5	4	9	6	5	11
8640	3	3	0	6	6	0	0	0	0	0	0	0	0	0	0	6	6	1	6	7
8641	7	2	3	6	9	0	0	0	0	0	0	0	0	0	3	6	9	4	6	10
8642	5	3	5	3	8	0	0	0	0	0	0	0	0	0	5	3	8	6	4	10
8643	5	2	5	2	7	0	0	0	0	0	0	0	0	0	5	2	7	5	4	9
8644	6	3	3	6	9	0	0	0	0	0	0	0	0	0	3	6	9	3	6	9
8645	6	1	3	4	7	0	0	0	0	0	0	0	0	0	3	4	7	4	5	9
8646	4	2	3	3	6	0	0	0	0	0	0	0	0	0	3	3	6	3	3	6
8647	ABORTED ON DAY 21 OF GESTATION																			
8648	4	10	7	7	14	0	0	0	0	1	1	0	4	4	7	12	19	9	14	23
8649	2	4	3	3	6	0	0	0	0	0	0	0	0	0	3	3	6	3	3	6
8650	4	2	2	4	6	0	0	0	0	0	0	0	0	0	2	4	6	2	4	6
8651	5	2	3	4	7	0	0	0	0	0	0	0	0	0	3	4	7	4	5	9
8652	ABORTED ON DAY 26 OF GESTATION																			
8653	NOT PREGNANT																			
8654	4	3	2	5	7	0	0	0	0	0	0	0	0	0	2	5	7	3	7	10
8655	0	3	1	2	3	0	0	0	0	0	0	0	0	0	1	2	3	6	4	10
8656	6	4	4	6	10	0	0	0	0	0	0	0	0	0	4	6	10	5	8	13
8657	4	4	4	4	8	0	0	0	0	0	0	0	0	0	4	4	8	4	4	8
8658	4	4	3	5	8	0	0	0	0	0	0	0	0	0	3	5	8	3	5	8
8659	3	3	3	3	6	0	0	0	0	0	0	0	0	0	3	3	6	4	4	8

M = MALE F = FEMALE

PLACENTAE APPEARED NORMAL UNLESS NOTED OTHERWISE.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 19 (PAGE 5): CAESAREAN-SECTIONING OBSERVATIONS - INDIVIDUAL DATA

			VIABLE FETUSES			DEAD FETUSES		EARLY RESORPTIONS		LATE RESORPTIONS		IMPLANTATION SITES			CORPORA LUTEA		
	SEX		RIGHT	LEFT		RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT		RIGHT	LEFT	
RABBIT #	M	F	HORN	HORN	TOTAL	HORN	TOTAL	HORN	TOTAL	HORN	TOTAL	HORN	HORN	TOTAL	OVARY	OVARY	TOTAL
DOSAGE GROUP V							3.75 MG/KG/DAY										
8660	ABORTED ON DAY 20 OF GESTATION																
8661	ABORTED ON DAY 23 OF GESTATION																
8662	1	3	2	2	4	0	0	0	0	0	1	2	3	3	4	7	3	5	8
8663	ABORTED ON DAY 26 OF GESTATION																
8664	3	4	2	5	7	0	0	0	0	0	0	3	3	2	8	10	4	9	13
8665	3	7	6	4	10	0	0	0	0	0	0	0	0	6	4	10	6	5	11
8666	5	6	8	3	11	0	0	0	0	0	0	0	0	8	3	11	9	3	12
8667	ABORTED ON DAY 19 OF GESTATION																
8668	2	4	2	4	6	0	0	0	1	1	1	1	2	3	6	9	5	6	11
8669	ABORTED ON DAY 29 OF GESTATION																
8670	2	3	2	3	5	0	0	0	0	0	0	1	1	2	4	6	2	5	7
8671	5	4	6	3	9	0	0	0	0	0	0	0	0	6	3	9	6	5	11
8672	6	3	2	7	9	0	0	0	1	1	0	1	1	2	9	11	3	9	12
8673	4	4	4	4	8	0	0	0	0	0	0	0	0	4	4	8	5	6	11
8674	2	4	3	3	6	0	0	0	0	0	0	0	0	3	3	6	3	3	6
8675	4	4	5	3	8	0	0	0	0	0	0	0	0	5	3	8	5	3	8
8676	8	3	4	7	11	0	0	0	0	0	1	0	1	5	7	12	6	8	14
8677	NOT PREGNANT																
8678	2	6	3	5	8	0	0	0	0	0	0	0	0	3	5	8	5	6	11
8679	7	4	4	7	11	0	0	0	0	0	0	0	0	4	7	11	6	8	14
8680	3	5	4	4	8	0	0	0	0	0	0	0	0	4	4	8	4	4	8
8681	5	3	4	4	8	0	0	0	0	0	0	0	0	4	4	8	4	5	9

M = MALE F = FEMALE
PLACENTAE APPEARED NORMAL UNLESS NOTED OTHERWISE.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 19 (PAGE 6): CAESAREAN-SECTIONING OBSERVATIONS - INDIVIDUAL DATA

	VIABLE FETUSES			DEAD FETUSES			EARLY RESORPTIONS			LATE RESORPTIONS			IMPLANTATION SITES			CORPORA LUTEA		
RABBIT #	RIGHT HORN	LEFT HORN	TOTAL	RIGHT HORN	LEFT HORN	TOTAL	RIGHT HORN	LEFT HORN	TOTAL	RIGHT HORN	LEFT HORN	TOTAL	RIGHT HORN	LEFT HORN	TOTAL	RIGHT OVARY	LEFT OVARY	TOTAL
SATELLITE DOSAGE GROUP I						0 (VEHICLE) MG/KG/DAY												
8682	5	6	11	0	0	0	0	0	0	0	0	0	5	6	11	5	6	11
8683	3	5	8	0	0	0	0	0	0	0	0	0	3	5	8	3	5	8
8684	9	0	9	0	0	0	0	0	0	0	0	0	9	0	9	9	0	9
SATELLITE DOSAGE GROUP II						0.1 MG/KG/DAY												
8685	9	4	13	0	0	0	0	0	0	0	0	0	9	4	13	9	4	13
8686	6	3	9	0	0	0	0	1	1	0	0	0	6	4	10	6	5	11
8687	6	3	9	0	0	0	0	0	0	0	0	0	6	3	9	6	3	9
8688	5	5	10	0	0	0	0	0	0	0	0	0	5	5	10	5	5	10
8689	4	6	10	0	0	0	0	0	0	1	0	1	5	6	11	6	7	13
SATELLITE DOSAGE GROUP III						1.0 MG/KG/DAY												
8690	7	6	13	0	0	0	0	0	0	0	0	0	7	6	13	7	6	13
8691	ABORTED ON DAY 18 OF GESTATION																	
8692	3	5	8	0	0	0	0	0	0	0	0	0	3	5	8	3	6	9
SATELLITE DOSAGE GROUP IV						2.5 MG/KG/DAY												
8693	NOT PREGNANT																	
8694	3	7	10	0	0	0	0	0	0	0	0	0	3	7	10	3	7	10
8695	5	4	9	0	0	0	0	0	0	0	0	0	5	4	9	6	4	10
SATELLITE DOSAGE GROUP V						3.75 MG/KG/DAY												
8696	6	4	10	0	0	0	0	0	0	0	0	0	6	4	10	6	5	11
8697	2	2	4	0	0	0	0	0	0	0	0	0	2	2	4	2	4	6
8698	4	3	7	0	0	0	0	0	0	0	0	0	4	3	7	5	3	8
8699	5	6	11	0	0	0	0	0	0	0	0	0	5	6	11	6	7	13
8700	ABORTED ON DAY 19 OF GESTATION																	

PLACENTAE APPEARED NORMAL UNLESS NOTED OTHERWISE.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 20 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - INDIVIDUAL DATA

	NUMBER OF LIVE FETUSES			AVERAGE FETAL BODY WEIGHT (G)			---- CONCEPTUSES ------ RESORBED		
RABBIT #	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL a	N	N	%
DOSAGE GROUP I				0 (VEHICLE) MG/KG/DAY					
8572	1	6	7	43.53	49.55	48.69	7	0	0.0
8573	5	2	7	47.62	51.76	48.80	7	0	0.0
8574	4	5	9	46.23	45.97	46.09	9	0	0.0
8575	5	5	10	49.26	49.60	49.43	10	0	0.0
8576	NOT PREGNANT								
8577	4	3	7	47.38	45.97	46.77	7	0	0.0
8578	4	3	7	42.95	41.32	42.25	7	0	0.0
8579	5	2	7	53.07	49.48	52.04	7	0	0.0
8580	NOT PREGNANT								
8581	ABORTED ON DAY 26 OF GESTATION								
8582	0	3	3	----	47.26	47.26	10	7	70.0
8583	NOT PREGNANT								
8584	NOT PREGNANT								
8585	4	4	8	36.96	28.55	32.75	11	3	27.3
8586	5	5	10	36.42	32.98	34.70	10	0	0.0
8587	FOUND DEAD ON DAY 13 OF GESTATION								
8588	2	5	7	50.22	50.92	50.72	8	1	12.5
8589	5	4	9	35.40	35.12	35.27	9	0	0.0
8590	8	3	11	41.82	40.81	41.54	11	0	0.0
8591	3	6	9	38.50	39.62	39.24	9	0	0.0
8592	6	7	13	33.41	31.14	32.19	13	0	0.0
8593	4	5	9	46.37	41.46	43.64	9	0	0.0

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 20 (PAGE 2): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - INDIVIDUAL DATA

	NUMBER OF LIVE FETUSES			AVERAGE FETAL BODY WEIGHT (G)			---- CONCEPTUSES ------ RESORBED		
RABBIT #	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL a	N	N	%
DOSAGE GROUP II				0.1 MG/KG/DAY					
8594	2	3	5	52.83	51.01	51.74	8	3	37.5
8595	3	2	5	50.16	48.91	49.66	5	0	0.0
8596	3	4	7	41.29	40.53	40.86	7	0	0.0
8597	5	4	9	37.25	40.29	38.60	9	0	0.0
8598	2	1	3	50.72	49.07	50.17	3	0	0.0
8599	3	6	9	37.81	39.44	38.90	9	0	0.0
8600	3	6	9	43.30	43.35	43.33	12	3	25.0
8601	4	5	9	43.08	41.06	41.96	9	0	0.0
8602	3	4	7	35.41	37.97	36.87	7	0	0.0
8603	6	3	9	45.86	47.66	46.46	9	0	0.0
8604	NOT PREGNANT								
8605	6	4	10	44.98	49.26	46.69	10	0	0.0
8606	5	4	9	51.78	49.54	50.79	9	0	0.0
8607	NOT PREGNANT								
8608	6	5	11	32.37	33.51	32.89	11	0	0.0
8609	5	4	9	43.88	39.60	41.98	9	0	0.0
8610	4	5	9	40.08	42.68	41.52	9	0	0.0
8611	3	6	9	40.54	34.81	36.72	9	0	0.0
8612	4	4	8	47.92	49.91	48.92	8	0	0.0
8613	7	3	10	40.52	41.04	40.68	10	0	0.0
8614	6	3	9	42.46	46.68	43.86	9	0	0.0
8615	5	6	11	44.92	44.74	44.82	11	0	0.0

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 20 (PAGE 3): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - INDIVIDUAL DATA

	NUMBER OF LIVE FETUSES			AVERAGE FETAL BODY WEIGHT (G)			---- CONCEPTUSES ------		
								RESORBED	
RABBIT #	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL a	N	N	%
DOSAGE GROUP III				1.0 MG/KG/DAY					
8616	3	2	5	40.05	47.74	43.13	8	3	37.5
8617	3	5	8	46.14	48.29	47.48	9	1	11.1
8618	5	5	10	37.87	38.60	38.23	10	0	0.0
8619	4	3	7	30.79	32.05	31.33	7	0	0.0
8620	NOT PREGNANT								
8621	5	4	9	42.08	42.82	42.41	9	0	0.0
8622	3	1	4	45.20	45.02	45.16	4	0	0.0
8623	NOT PREGNANT								
8624	3	6	9	46.70	42.91	44.17	10	1	10.0
8625	5	2	7	36.79	36.38	36.67	7	0	0.0
8626	4	3	7	50.61	46.28	48.75	7	0	0.0
8627	4	6	10	40.45	37.46	38.66	10	0	0.0
8628	6	3	9	43.27	42.23	42.92	9	0	0.0
8629	5	5	10	39.54	35.42	37.48	10	0	0.0
8630	3	5	8	49.55	44.33	46.29	8	0	0.0
8631	1	8	9	50.67	41.77	42.76	9	0	0.0
8632	3	5	8	42.71	42.87	42.81	8	0	0.0
8633	5	3	8	46.72	46.72	46.72	8	0	0.0
8634	3	6	9	45.63	40.56	42.25	9	0	0.0
8635	5	3	8	47.21	44.37	46.14	8	0	0.0
8636	2	5	7	48.70	48.43	48.50	7	0	0.0
8637	5	8	13	43.34	36.16	38.92	14	1	7.1

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 20 (PAGE 4): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - INDIVIDUAL DATA

	NUMBER OF LIVE FETUSES			AVERAGE FETAL BODY WEIGHT (G)			---- CONCEPTUSES ------ RESORBED		
RABBIT #	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL a	N	N	%
DOSAGE GROUP IV				2.5 MG/KG/DAY					
8638	2	5	7	39.30	41.20	40.66	7	0	0.0
8639	2	5	7	28.30	21.15	23.19	9	2	22.2
8640	3	3	6	38.83	36.92	37.88	6	0	0.0
8641	7	2	9	38.93	44.42	40.15	9	0	0.0
8642	5	3	8	29.41	27.29	28.62	8	0	0.0
8643	5	2	7	44.31	47.06	45.09	7	0	0.0
8644	6	3	9	33.66	39.04	35.45	9	0	0.0
8645	6	1	7	46.81	46.20	46.72	7	0	0.0
8646	4	2	6	44.36	41.34	43.35	6	0	0.0
8647	ABORTED ON DAY 21 OF GESTATION								
8648	4	10	14	31.64	32.64	32.35	19	5	26.3
8649	2	4	6	50.56	47.86	48.76	6	0	0.0
8650	4	2	6	39.30	38.74	39.12	6	0	0.0
8651	5	2	7	47.49	47.44	47.48	7	0	0.0
8652	ABORTED ON DAY 26 OF GESTATION								
8653	NOT PREGNANT								
8654	4	3	7	47.50	50.89	48.95	7	0	0.0
8655	0	3	3	----	55.17	55.17	3	0	0.0
8656	6	4	10	35.96	38.16	36.84	10	0	0.0
8657	4	4	8	48.11	47.03	47.57	8	0	0.0
8658	4	4	8	44.99	45.96	45.47	8	0	0.0
8659	3	3	6	49.84	42.97	46.40	6	0	0.0

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 20 (PAGE 5): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - INDIVIDUAL DATA

	NUMBER OF LIVE FETUSES			AVERAGE FETAL BODY WEIGHT (G)			---- CONCEPTUSES ------ RESORBED		
RABBIT #	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL a	N	N	%
DOSAGE GROUP V				3.75 MG/KG/DAY					
8660	ABORTED ON DAY 20 OF GESTATION								
8661	ABORTED ON DAY 23 OF GESTATION								
8662	1	3	4	19.01	15.77	16.58	7	3	42.8
8663	ABORTED ON DAY 26 OF GESTATION								
8664	3	4	7	44.05	30.09	36.07	10	3	30.0
8665	3	7	10	34.61	34.43	34.48	10	0	0.0
8666	5	6	11	42.90	44.00	43.50	11	0	0.0
8667	ABORTED ON DAY 19 OF GESTATION								
8668	2	4	6	47.20	47.91	47.68	9	3	33.3
8669	ABORTED ON DAY 29 OF GESTATION								
8670	2	3	5	50.20	51.33	50.88	6	1	16.7
8671	5	4	9	38.32	41.36	39.67	9	0	0.0
8672	6	3	9	29.33	34.07	30.91	11	2	18.2
8673	4	4	8	35.84	33.07	34.46	8	0	0.0
8674	2	4	6	52.72	50.08	50.96	6	0	0.0
8675	4	4	8	42.89	36.69	39.79	8	0	0.0
8676	8	3	11	39.19	39.02	39.14	12	1	8.3
8677	NOT PREGNANT								
8678	2	6	8	50.63	46.32	47.40	8	0	0.0
8679	7	4	11	42.01	47.04	43.84	11	0	0.0
8680	3	5	8	43.71	41.13	42.10	8	0	0.0
8681	5	3	8	41.90	39.44	40.98	8	0	0.0

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 20 (PAGE 6): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - INDIVIDUAL DATA

	NUMBER OF LIVE FETUSES	AVERAGE FETAL BODY WEIGHT (G)	---- CONCEPTUSES ------ RESORBED		
RABBIT #	TOTAL	TOTAL	N	N	%
SATELLITE DOSAGE GROUP I		0 (VEHICLE) MG/KG/DAY			
8682	11	4.65	11	0	0.0
8683	8	4.59	8	0	0.0
8684	9	4.41	9	0	0.0
SATELLITE DOSAGE GROUP II		0.1 MG/KG/DAY			
8685	13	5.50	13	0	0.0
8686	9	4.81	10	1	10.0
8687	9	4.52	9	0	0.0
8688	10	5.17	10	0	0.0
8689	10	4.76	11	1	9.1
SATELLITE DOSAGE GROUP III		1.0 MG/KG/DAY			
8690	13	5.11	13	0	0.0
8691	ABORTED ON DAY 18 OF GESTATION				
8692	8	4.69	8	0	0.0
SATELLITE DOSAGE GROUP IV		2.5 MG/KG/DAY			
8693	NOT PREGNANT				
8694	10	4.81	10	0	0.0
8695	9	5.45	9	0	0.0
SATELLITE DOSAGE GROUP V		3.75 MG/KG/DAY			
8696	10	4.74	10	0	0.0
8697	4	5.15	4	0	0.0
8698	7	4.18	7	0	0.0
8699	11	5.16	11	0	0.0
8700	ABORTED ON DAY 19 OF GESTATION				

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 21 (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
DOSAGE GROUP I							0 (VEHICLE) MG/KG/DAY													
RABBIT #	CLs																			
8572	4/ 5	MA	FA	FA /	FA	FA	FA	FA												
		43.53	50.14	49.78	54.40	50.22	47.14	45.60												
8573	6/ 3	FA	MA	FA	MA	MA	MA /	MA												
		52.56	51.49	50.96	47.26	51.38	38.53	49.44												
8574	7/ 4	MA	MA	FA	MA	FA	FA /	FA	MA	FA										
		40.53	45.04	50.45	53.16	44.29	47.55	50.74	46.20	36.84										
8575	8/ 3	FA	MA	MA	MA	MA	FA	FA	FA /	MA	FA									
		54.15	54.58	51.71	49.10	38.16	32.73	48.47	55.37	52.75	57.31									
8576		NOT PREGNANT																		
8577	2/ 7	MA	MA /	FA	FA	MA	FA	MA												
		52.03	50.09	46.67	44.60	41.97	46.65	45.41												
8578	3/ 6	FA	FA /	MA	MA	MA	MA	FA												
		38.84	42.66	44.36	45.46	42.37	39.60	42.45												
8579	6/ 3	MA	MA	MA	FA	MA /	FA	MA												
		56.80	52.82	55.31	43.40	47.53	55.55	52.91												
8580		NOT PREGNANT																		
8581		ABORTED ON DAY 26 OF GESTATION																		
8582	8/ 4	E	E	E	E	E	E	FA /	FA	FA	E									
								46.39	46.23	49.15										
8583		NOT PREGNANT																		
8584		NOT PREGNANT																		

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 21 (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
DOSAGE GROUP I	0 (VEHICLE) MG/KG/DAY																		
RABBIT # CLs																			
8585 8/ 4	MA	MA	L	FA	MA	FA	FA	FA /	E	E	MA								
	44.74	32.38	6.56	34.83	33.94	25.22	22.73	31.43			36.77								
8586 9/ 4	MA	FA	FA	FA	MA	MA	MA	FA /	MA	FA									
	44.88	42.44	31.76	25.46	37.67	27.94	32.46	26.05	39.15	39.19									
8587	FOUND DEAD ON DAY 13 OF GESTATION																		
8588 4/ 4	FA	FA	FA	MA /	FA	MA	FA	E											
	51.46	48.08	52.60	50.53	51.20	49.91	51.26												
8589 5/ 5	FA	FA	MA	FA /	MA	MA	MA	MA	FA										
	39.63	33.12	37.70	37.56	37.35	35.47	32.25	34.21	30.17										
8590 6/ 9	MA	FA	FA	FA /	MA	MA	MA	MA	MA	MA	MA								
	50.64	43.50	36.13	42.80	40.31	39.34	44.89	41.01	34.61	37.65	46.09								
8591 6/ 9	FA	FA /	FA	FA	MA	MA	MA	FA	FA										
	43.91	44.15	41.70	39.60	36.33	40.91	38.25	33.96	34.37										
8592 7/ 7	FA	FA	FA	MA	MA	FA	FA /	MA	FA	MA	FA	MA	MA						
	33.92	29.84	32.76	34.39	23.52	27.72	33.05	41.56	35.46	36.32	25.25	32.26	32.43						
8593 4/ 5	MA	FA	MA	FA /	MA	MA	FA	FA	FA										
	50.75	44.57	43.60	39.79	46.34	44.78	44.80	37.41	40.74										

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 21 (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
DOSAGE GROUP II						0.1 MG/KG/DAY													
RABBIT # CLs																			
8594 3/ 8	FA	FA	E /	MA	E	FA	MA	E											
	51.81	50.44		53.16		50.79	52.50												
8595 3/ 4	MA	FA	FA /	MA	MA														
	53.84	52.62	45.20	42.19	54.46														
8596 5/ 7	FA	MA	MA /	FA	MA	FA	FA												
	41.24	39.09	42.15	45.46	42.63	38.59	36.84												
8597 5/ 4	MA	FA	MA	FA	MA /	FA	MA	FA	MA										
	40.80	44.99	26.59	32.16	37.79	43.76	41.54	40.26	39.52										
8598 4/ 3 /	MA	MA	FA																
	52.37	49.06	49.07																
8599 5/ 6	FA	FA	MA	FA /	FA	FA	FA	MA	MA										
	38.27	38.66	42.15	40.74	38.85	36.72	43.38	35.19	36.10										
8600 5/ 8	FA	MA	FA	E	FA /	FA	MA	FA	ML	FL	FA	MA							
	53.78	48.89	50.99		38.27	46.74	41.57	34.23	20.58	23.54	36.08	39.45							
8601 3/ 6	FA	MA	MA /	FA	FA	FA	FA	MA	MA										
	47.44	46.88	45.46	35.75	42.16	38.11	41.86	35.18	44.78										
8602 3/ 7 /	FA	MA	FA	FA	MA	FA	MA												
	44.17	43.13	42.87	39.54	28.66	25.30	34.45												
8603 7/ 4	FA	FA	MA	MA	MA	MA	FA /	MA	MA										
	54.44	49.57	47.59	46.87	39.59	30.92	38.97	58.13	52.04										
8604	NOT PREGNANT																		
8605 9/ 6	MA	MA	MA	MA	MA	FA	MA	FA /	FA	FA									
	53.06	44.45	45.12	38.74	45.05	46.61	43.45	47.60	52.98	49.83									
8606 4/ 6	FA	MA	FA /	MA	MA	FA	MA	MA	FA										
	48.63	54.94	50.24	55.13	48.58	50.38	48.18	52.08	48.92										

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 21 (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
DOSAGE GROUP II						0.1 MG/KG/DAY													
RABBIT # CLs																			
8607	NOT PREGNANT																		
8608 5/ 7	FA	MA	MA	FA	MA /	MA	MA	FA	FA	FA	MA								
	43.30	31.39	33.84	31.67	30.93	35.26	34.20	36.33	32.75	23.52	28.58								
8609 2/ 8	MA	MA /	FA	MA	FA	MA	FA	MA	FA										
	44.13	44.89	39.28	44.56	41.78	44.34	42.98	41.48	34.34										
8610 6/ 6	FA	FA	MA	MA	FA /	MA	MA	FA	FA										
	36.34	42.52	27.21	40.71	42.69	47.04	45.35	45.61	46.26										
8611 5/ 4	FA	MA	FA	MA	FA /	MA	FA	FA	FA										
	40.66	43.12	40.79	35.11	35.66	43.40	28.02	27.52	36.19										
8612 6/ 5	MA	MA	FA	FA	FA /	MA	FA	MA											
	51.69	50.94	49.90	44.28	53.91	41.29	51.55	47.76											
8613 6/ 5	MA	MA	MA	MA	FA /	MA	FA	MA	FA	MA									
	42.83	44.11	40.54	37.12	41.99	43.20	44.29	38.29	36.84	37.57									
8614 6/ 7	MA	FA	MA	MA /	FA	FA	MA	MA	MA										
	40.11	47.24	46.33	33.10	45.92	46.89	50.85	40.71	43.63										
8615 4/ 8	FA	MA	FA /	MA	FA	MA	FA	MA	FA	FA	MA								
	53.71	51.10	47.25	49.38	50.56	44.52	48.24	39.77	34.76	33.95	39.83								

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 21 (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
DOSAGE GROUP III						1.0 MG/KG/DAY													
RABBIT # CLs																			
8616 6/ 3	FA	L	MA	MA	L	MA /	FA	L											
	48.33	1.92	45.61	38.05	10.57	36.49	47.16	4.50											
8617 7/ 6	FA	FA	MA	FA	E /	MA	FA	FA	MA										
	54.55	48.00	42.79	42.87		54.77	47.12	48.89	40.87										
8618 6/ 8	MA	FA	FA	MA /	MA	FA	FA	FA	MA	MA									
	40.04	40.05	45.18	36.97	40.35	32.58	38.95	36.22	35.03	36.96									
8619 6/ 5	MA	MA	MA	MA /	FA	FA	FA												
	33.99	32.96	28.62	27.60	32.40	30.64	33.12												
8620	NOT PREGNANT																		
8621 4/ 6	FA	FA	MA /	MA	FA	MA	FA	MA	MA										
	42.88	48.02	44.46	46.03	42.56	35.43	37.84	41.41	43.07										
8622 4/ 3	MA	FA	MA /	MA															
	44.17	45.02	46.73	44.70															
8623	NOT PREGNANT																		
8624 4/ 8	FA	FA	MA	E /	FA	MA	FA	MA	FA	FA									
	37.03	43.12	47.31		43.84	47.81	41.56	44.99	48.09	43.80									
8625 4/ 5	FA	MA	MA /	MA	MA	MA	FA												
	40.93	35.34	35.11	40.93	39.22	33.34	31.83												
8626 4/ 3	FA	MA	FA	FA /	MA	MA	MA												
	48.34	51.83	43.13	47.37	50.33	51.14	49.13												
8627 6/ 4	FA	MA	FA	FA	MA	FA /	MA	MA	FA	FA									
	36.52	43.40	39.31	37.29	39.97	38.19	34.40	44.02	34.86	38.60									
8628 5/ 6	MA	MA	MA	MA	FA /	MA	FA	MA	FA										
	45.66	43.14	42.88	39.23	45.20	45.20	39.54	43.54	41.94										

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 21 (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
DOSAGE GROUP III						1.0 MG/KG/DAY													
RABBIT # CLs																			
8629 5/ 6	FA	MA	MA	MA /	MA	FA	MA	FA	FA	FA									
	38.26	40.62	39.71	34.07	42.91	32.68	40.37	37.01	32.04	37.10									
8630 5/ 4	MA	MA	FA	FA	FA /	FA	FA	MA											
	54.05	48.56	47.43	39.21	42.17	45.38	47.48	46.03											
8631 8/ 3	FA	FA	FA	FA	FA	FA	FA /	MA	FA										
	35.24	43.84	44.36	47.44	43.31	40.76	34.09	50.67	45.15										
8632 4/ 4	MA	FA	FA	MA /	FA	FA	MA	FA											
	43.79	43.37	41.80	38.67	45.68	41.58	45.68	41.90											
8633 4/ 5	FA	MA	MA	MA /	FA	MA	MA	FA											
	51.73	52.61	49.99	49.08	44.96	43.98	37.95	43.48											
8634 6/ 5	FA	FA	MA	FA	FA /	MA	MA	FA	FA										
	46.72	38.26	41.76	40.70	37.00	46.46	48.68	38.21	42.46										
8635 6/ 5	FA	MA	FA	MA /	MA	MA	FA	MA											
	45.78	47.55	45.96	48.28	48.49	50.50	41.38	41.22											
8636 4/ 3	MA	FA	FA	MA /	FA	FA	FA												
	50.28	51.83	46.05	47.12	52.01	42.71	49.53												
8637 12/ 4	E	FA	MA	FA	FA	MA	FA	FA	FA	MA /	MA	FA	FA	MA					
		45.74	42.00	36.06	44.82	41.26	34.68	25.38	24.35	38.22	50.86	37.05	41.21	44.37					

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 21 (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
DOSAGE GROUP IV						2.5 MG/KG/DAY													
RABBIT # CLs																			
8638 2/ 5	FA	FA /	FA	MA	FA	MA	FA												
	40.28	32.90	38.25	46.95	43.41	31.64	51.17												
8639 6/ 5	FA	FA	L	FA	MA /	MA	FA	L	FA										
	23.26	24.69	5.15	18.43	29.94	26.65	26.53	16.40	12.83										
8640 1/ 6 /	MA	FA	FA	MA	FA	MA													
	44.53	33.60	38.80	34.42	38.36	37.55													
8641 4/ 6	MA	FA	FA /	MA	MA	MA	MA	MA	MA										
	39.77	42.81	46.04	39.08	33.05	37.62	36.19	38.17	48.66										
8642 6/ 4	FA	MA	FA	MA	MA /	MA	FA	MA											
	35.34	30.14	30.91	27.71	28.84	29.20	15.63	31.16											
8643 5/ 4	MA	FA	MA	MA	MA /	MA	FA												
	50.36	45.62	42.69	45.99	37.18	45.32	48.50												
8644 3/ 6	FA	FA	MA /	MA	MA	MA	MA	FA	MA										
	42.26	39.28	41.03	35.48	31.24	29.67	29.85	35.59	34.66										
8645 4/ 5	MA	MA	MA /	MA	MA	MA	FA												
	48.81	46.23	43.18	48.91	47.45	46.30	46.20												
8646 3/ 3	FA	FA	MA /	MA	MA	MA													
	41.73	40.94	47.24	48.25	43.29	38.67													
8647	ABORTED ON DAY 21 OF GESTATION																		
8648 9/14	FA	FA	FA	FA	MA	FA	FA /	FA	FA	ML	ML	MA	MA	L	L	FA	MA	FA	E
	31.21	36.66	30.62	35.19	35.13	29.89	38.65	39.35	29.65	12.63	15.99	29.30	36.20	0.57	3.81	28.46	25.93	26.72	
8649 3/ 3	FA	MA	MA /	FA	FA	FA													
	45.80	48.91	52.20	50.56	46.91	48.16													
8650 2/ 4	MA	MA /	MA	MA	FA	FA													
	40.62	34.76	47.05	34.78	36.42	41.06													

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 21 (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
DOSAGE GROUP IV						2.5 MG/KG/DAY													
RABBIT # CLs																			
8651 4/ 5	MA	FA	FA /	MA	MA	MA	MA												
	47.52	50.95	43.93	52.77	47.93	45.91	43.32												
8652	ABORTED ON DAY 26 OF GESTATION																		
8653	NOT PREGNANT																		
8654 3/ 7	FA	MA /	FA	FA	MA	MA	MA												
	51.69	50.86	50.69	50.28	50.69	43.80	44.66												
8655 6/ 4	FA /	FA	FA																
	56.63	55.06	53.82																
8656 5/ 8	MA	FA	MA	MA /	FA	MA	MA	FA	MA	FA									
	37.66	40.21	41.71	32.74	43.55	39.48	33.27	33.61	30.92	35.29									
8657 4/ 4	MA	MA	FA	MA /	FA	FA	MA	FA											
	49.99	49.18	44.11	43.64	46.72	48.48	49.62	48.81											
8658 3/ 5	FA	FA	MA /	MA	MA	MA	FA	FA											
	47.86	47.10	44.22	46.38	45.20	44.16	45.44	43.43											
8659 4/ 4	FA	MA	FA /	MA	FA	MA													
	47.92	45.38	41.33	56.20	39.65	47.95													

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 21 (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
DOSAGE GROUP V							3.75 MG/KG/DAY													
RABBIT #	CLs																			
8660		ABORTED ON DAY 20 OF GESTATION																		
8661		ABORTED ON DAY 23 OF GESTATION																		
8662	3/ 5	L	FA	MA /	L	FA	FA	ML												
		14.24	18.19	19.01	17.85	14.21	14.92	21.94												
8663		ABORTED ON DAY 26 OF GESTATION																		
8664	4/ 9	MA	FA /	FA	MA	FA	L	L	L	MA	FA									
		48.71	42.52	18.62	44.75	27.39	0.66	0.64	0.67	38.68	31.83									
8665	6/ 5	FA	FA	FA	FA	FA	MA /	FA	MA	FA	MA									
		30.36	32.81	37.90	33.12	30.14	33.64	36.87	36.62	39.80	33.57									
8666	9/ 3	MA	FA	FA	FA	FA	MA	MA	MA /	FA	FA	MA								
		48.23	42.22	44.74	42.32	45.72	40.93	38.45	41.81	47.19	41.82	45.10								
8667		ABORTED ON DAY 19 OF GESTATION																		
8668	5/ 6	MA	FA	L /	FA	L	FA	E	FA	MA										
		49.75	49.19	2.11	52.64	4.54	46.18		43.63	44.66										
8669		ABORTED ON DAY 29 OF GESTATION																		
8670	2/ 5	FA	MA /	FA	FA	L	MA													
		52.67	48.51	51.90	49.43	3.38	51.89													
8671	6/ 5	FA	FA	FA	MA	MA	FA /	MA	MA	MA										
		48.01	36.65	41.41	37.76	34.86	39.38	39.77	40.59	38.63										
8672	3/ 9	MA	MA /	MA	E	FA	MA	MA	L	FA	MA	FA								
		35.46	24.22	29.95		36.85	30.08	32.11	0.42	29.92	24.17	35.43								

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 21 (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
DOSAGE GROUP V						3.75 MG/KG/DAY													
RABBIT # CLs																			
8673 5/ 6	FA	FA	MA	MA /	MA	MA	FA	FA											
	30.95	38.53	39.90	38.87	31.37	33.22	30.59	32.22											
8674 3/ 3	FA	FA	FA /	MA	FA	MA													
	49.59	54.01	46.52	53.09	50.20	52.36													
8675 5/ 3	MA	MA	FA	FA	FA /	MA	FA	MA											
	46.05	44.30	36.36	36.46	38.11	40.70	35.83	40.51											
8676 6/ 8	MA	L	MA	MA	MA /	MA	FA	FA	FA	MA	MA	MA							
	50.42	20.57	43.22	39.04	34.96	50.88	37.16	42.56	37.34	31.27	28.67	35.07							
8677	NOT PREGNANT																		
8678 5/ 6	FA	FA	FA /	FA	FA	MA	FA	MA											
	46.40	48.47	46.74	44.42	45.12	55.24	46.76	46.02											
8679 6/ 8	FA	FA	MA	FA /	MA	MA	MA	FA	MA	MA	MA								
	49.58	51.39	46.44	45.11	46.38	44.28	41.01	42.09	38.65	40.91	36.42								
8680 4/ 4	MA	FA	FA	FA /	MA	MA	FA	FA											
	42.43	43.95	39.22	39.32	45.29	43.40	38.22	44.94											
8681 4/ 5	MA	MA	MA	FA /	MA	MA	FA	FA											
	48.74	40.64	37.25	35.10	35.94	46.95	42.29	40.92											

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 21 (PAGE 11): FETAL SEX, VITAL STATUS AND BODY WEIGHT - INDIVIDUAL DATA

PETUS #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
SATELLITE DOSAGE GROUP I						0 (VEHICLE) MG/KG/DAY													
RABBIT # CLs																			
8682 5/ 6	A	A	A	A	A /	A	A	A	A	A	A								
	4.69	4.09	4.36	4.52	4.67	4.81	4.33	4.92	5.01	4.87	4.90								
8683 3/ 5	A	A	A /	A	A	A	A	A											
	4.50	4.73	4.74	4.74	4.50	4.27	4.49	4.75											
8684 9/ 0	A	A	A	A	A	A	A	A	A /										
	4.18	5.37	3.72	4.35	3.83	5.46	4.06	3.82	4.88										
SATELLITE DOSAGE GROUP II						0.1 MG/KG/DAY													
RABBIT # CLs																			
8685 9/ 4	A	A	A	A	A	A	A	A	A /	A	A	A	A						
	5.07	4.86	5.30	5.67	5.76	6.00	5.61	5.56	5.00	5.86	5.76	5.47	5.55						
8686 6/ 5	A	A	A	A	A	A /	A	E	A	A									
	4.69	4.83	4.95	4.86	4.47	5.06	4.82		4.84	4.79									
8687 6/ 3	A	A	A	A	A	A /	A	A	A										
	4.75	4.55	4.69	4.36	4.52	4.37	4.60	4.53	4.30										
8688 5/ 5	A	A	A	A	A /	A	A	A	A	A									
	4.98	5.59	5.05	5.26	5.24	4.79	5.30	5.36	4.90	5.21									
8689 6/ 7	A	A	A	L	A /	A	A	A	A	A	A								
	5.10	4.52	4.90		4.41	5.11	4.77	4.81	4.33	4.64	5.05								
SATELLITE DOSAGE GROUP III						1.0 MG/KG/DAY													
RABBIT # CLs																			
8690 7/ 6	A	A	A	A	A	A	A /	A	A	A	A	A	A						
	5.70	5.41	3.85	5.32	5.39	5.08	5.84	4.52	4.97	5.22	5.01	5.10	5.07						
8691	ABORTED ON DAY 18 OF GESTATION																		
8692 3/ 6	A	A	A /	A	A	A	A	A											
	4.93	4.89	4.79	4.51	4.73	4.80	4.84	4.03											

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 21 (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
SATELLITE DOSAGE GROUP IV								2.5 MG/KG/DAY												
RABBIT #	CLs																			
8693		NOT PREGNANT																		
8694	3/ 7	A	A	A /	A	A	A	A	A	A	A									
		5.54	4.57	4.70	5.39	5.40	4.46	5.18	4.60	3.59	4.66									
8695	6/ 4	A	A	A	A	A /	A	A	A	A										
		5.30	5.59	5.70	6.23	4.71	5.52	5.21	5.65	5.17										
SATELLITE DOSAGE GROUP V								3.75 MG/KG/DAY												
RABBIT #	CLs																			
8696	6/ 5	A	A	A	A	A	A /	A	A	A	A									
		5.34	4.62	4.39	4.43	3.60	5.22	5.12	5.09	4.78	4.76									
8697	2/ 4	A	A /	A	A															
		5.03	5.32	5.26	5.00															
8698	5/ 3	A	A	A	A /	A	A	A												
		3.94	4.33	4.03	4.58	4.11	4.21	4.07												
8699	6/ 7	A	A	A	A	A /	A	A	A	A	A	A								
		5.30	5.62	5.10	5.11	5.17	5.29	5.53	5.38	5.34	4.29	4.67								
8700		ABORTED ON DAY 19 OF GESTATION																		

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 1): FETAL ALTERATIONS - INDIVIDUAL DATA

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

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	GROSS EXTERNAL EXAMINATION DESCRIPTION	SOFT TISSUE EXAMINATION N/N	SOFT TISSUE EXAMINATION DESCRIPTION	SKELETAL EXAMINATION N/N	SKELETAL EXAMINATION DESCRIPTION
8572	1(14.3)	0/ 7		0/ 7		1/ 7	FETUS 6 SKULL: FRONTALS, CONTAINED AN INTERFRONTAL, 0.5 mm x 1.0 mm
8573	1(14.3)	0/ 7		0/ 7		1/ 7	FETUS 1 SKULL: NASALS, CONTAINED AN INTERNASAL, 0.4 mm x 1.0 mm
8574	0(0.0)	0/ 9		0/ 9		0/ 9	
8575	1(10.0)	0/10		1/10	FETUS 10 LUNGS: INTERMEDIATE LOBE ABSENT	0/10	
8576	NOT PREGNANT						
8577	1(14.3)	0/ 7		0/ 7		1/ 7	FETUS 1 HYOID: ALA, ANGULATED, bilateral
8578	0(0.0)	0/ 7		0/ 7		0/ 7	
8579	3(42.8)	0/ 7		1/ 7	FETUS 4 EYES: CIRCUMCORNEAL HEMORRHAGE, right eye	2/ 7	FETUS 1 HYOID: ALA, ANGULATED, bilateral FETUS 2 HYOID: ALA, ANGULATED, bilateral

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 2): FETAL ALTERATIONS - INDIVIDUAL DATA

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

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	DESCRIPTION	SOFT TISSUE EXAMINATION N/N	DESCRIPTION	SKELETAL EXAMINATION N/N	DESCRIPTION
8580	NOT PREGNANT						
8581	ABORTED ON DAY 26 OF GESTATION a						
8582	1(33.3)	0/ 3		0/ 3		1/ 3	FETUS 8 THORACIC VERTEBRAE: ARCH, SMALL, left 10th; CENTRUM, UNILATERAL OSSIFICATION, left 10th RIBS: FUSED, 10th and 11th
8583	NOT PREGNANT						
8584	NOT PREGNANT						
8585	0(0.0)	0/ 8	FETUS 3 LATE RESORPTION, autolysis precluded further evaluation	0/ 8		0/ 8	

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

a. Doe 8581 aborted one late resorption and had eight late resorptions in utero on day 26 of gestation; autolysis precluded further evaluation.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 3): FETAL ALTERATIONS - INDIVIDUAL DATA

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

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	GROSS EXTERNAL EXAMINATION DESCRIPTION	SOFT TISSUE EXAMINATION N/N	SOFT TISSUE EXAMINATION DESCRIPTION	SKELETAL EXAMINATION N/N	SKELETAL EXAMINATION DESCRIPTION
8586	1(10.0)	1/10	FETUS 8 TRUNK: SHORT TAIL: ABSENT	1/10	FETUS 8 KIDNEYS: FUSED, bilateral; DISPLACED, bilateral kidneys, caudally; SMALL, bilateral ABDOMEN: SITUS INVERSUS	1/10	FETUS 8 STERNAL CENTRA: FUSED, 1st - 4th XIPHOID: FUSED, to 4th sternal centra THORACIC VERTEBRAE: 6 PRESENT a CENTRUM, NOT OSSIFIED, 5th and 6th; ARCH, NOT OSSIFIED, bilateral 5th and 6th RIBS: FUSED, left 4th and 5th, bilateral 6th, to each other; EXTRA OSSIFICATION, attached to 6th ribs LUMBAR VERTEBRAE: 0 PRESENT a SACRAL VERTEBRAE: 0 PRESENT a CAUDAL VERTEBRAE: 0 PRESENT a
8587	FOUND DEAD ON DAY 13 OF GESTATION b						
8588	0(0.0)	0/ 7		0/ 7		0/ 7	
8589	0(0.0)	0/ 9		0/ 9		0/ 9	

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

a. Excluded from ossification site group averages and statistical analyses.

b. Doe 8587 was found dead on day 13 of gestation. Eight fetuses were present in utero; viability could not be determined because of their early developmental ages. All fetuses appeared normal for developmental ages at gross external examination. Soft tissue and skeletal examinations were not performed because of the early developmental ages of the fetuses.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 4): FETAL ALTERATIONS - INDIVIDUAL DATA

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

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	DESCRIPTION	SOFT TISSUE EXAMINATION N/N	DESCRIPTION	SKELETAL EXAMINATION N/N	DESCRIPTION
8590	11(100.0)	0/11		11/11	FETUS 1 KIDNEYS: DISPLACED, left kidney, caudally FETUS 2 KIDNEYS: DISPLACED, left kidney, caudally FETUS 3 KIDNEYS: DISPLACED, left kidney, caudally FETUS 4 KIDNEYS: DISPLACED, left kidney, caudally FETUS 5 KIDNEYS: DISPLACED, left kidney, caudally FETUS 6 KIDNEYS: DISPLACED, left kidney, caudally FETUS 7 KIDNEYS: DISPLACED, left kidney, caudally FETUS 8 KIDNEYS: DISPLACED, left kidney, caudally	1/11	FETUS 8 SKULL: NASALS, CONTAINED AN INTERNASAL, 0.4 mm x 1.5 mm

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 5): FETAL ALTERATIONS - INDIVIDUAL DATA

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

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	GROSS EXTERNAL EXAMINATION DESCRIPTION	SOFT TISSUE EXAMINATION N/N	SOFT TISSUE EXAMINATION DESCRIPTION	SKELETAL EXAMINATION N/N	SKELETAL EXAMINATION DESCRIPTION
8590 (Cont.)					FETUS 9 KIDNEYS: DISPLACED, left kidney, caudally FETUS 10 KIDNEYS: DISPLACED, left kidney, caudally FETUS 11 KIDNEYS: DISPLACED, left kidney, caudally		
8591	2(22.2)	0/ 9		1/ 9	FETUS 9 LUNGS: INTERMEDIATE LOBE ABSENT	1/ 9	FETUS 1 SKULL: FRONTALS, CONTAINED AN INTERFRONTAL, 1.0 mm x 2.5 mm
8592	0(0.0)	0/13		0/13		0/13	
8593	1(11.1)	0/ 9		0/ 9		1/ 9	FETUS 1 SKULL: NASALS, MIDLINE SUTURE DISPLACED, left

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 6): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP II 0.1 MG/KG/DAY

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	GROSS EXTERNAL EXAMINATION DESCRIPTION	SOFT TISSUE EXAMINATION N/N	SOFT TISSUE EXAMINATION DESCRIPTION	SKELETAL EXAMINATION N/N	SKELETAL EXAMINATION DESCRIPTION
8594	3(60.0)	0/ 5		0/ 5		3/ 5	FETUS 4 CAUDAL VERTEBRAE: MISALIGNED, 15th FETUS 6 SKULL: FRONTALS, CONTAINED AN INTERFRONTAL, 2.0 mm x 4.5 mm FETUS 7 CAUDAL VERTEBRAE: MISALIGNED, 16th
8595	0(0.0)	0/ 5		0/ 5		0/ 5	
8596	1(14.3)	0/ 7		0/ 7		1/ 7	FETUS 1 HYOID: ALA, ANGULATED, bilateral STERNAL CENTRA: FUSED, 3rd and 4th
8597	2(22.2)	0/ 9		1/ 9	FETUS 8 EYES: CIRCUMCORNEAL HEMORRHAGE, right eye LUNGS: INTERMEDIATE LOBE ABSENT	1/ 9	FETUS 2 STERNAL CENTRA: FUSED, 3rd and 4th
8598	0(0.0)	0/ 3		0/ 3		0/ 3	

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 7): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP II 0.1 MG/KG/DAY

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	GROSS EXTERNAL EXAMINATION DESCRIPTION	SOFT TISSUE EXAMINATION N/N	SOFT TISSUE EXAMINATION DESCRIPTION	SKELETAL EXAMINATION N/N	SKELETAL EXAMINATION DESCRIPTION
8599	1(11.1)	0/ 9		1/ 9	FETUS 3 LUNGS: INTERMEDIATE LOBE ABSENT	0/ 9	
8600	3(33.3)	1/ 9	FETUS 9 LATE RESORPTION, autolysis precluded further evaluation FETUS 10 LATE RESORPTION, autolysis precluded further evaluation FETUS 11 ABDOMEN: DISTENDED	0/ 9		2/ 9	FETUS 5 SKULL: NASALS, MIDLINE SUTURE DISPLACED, right FETUS 7 STERNAL CENTRA: FUSED, 3rd and 4th

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 8): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP II 0.1 MG/KG/DAY

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	DESCRIPTION	SOFT TISSUE EXAMINATION N/N	DESCRIPTION	SKELETAL EXAMINATION N/N	DESCRIPTION
8601	2(22.2)	0/ 9		1/ 9	FETUS 8 KIDNEYS: DISPLACED, left kidney, caudally	1/ 9	FETUS 5 THORACIC VERTEBRAE: CENTRUM, UNILATERAL OSSIFICATION, right 13th
8602	0(0.0)	0/ 7		0/ 7		0/ 7	
8603	1(11.1)	0/ 9		0/ 9		1/ 9	FETUS 1 HYOID: ALA, ANGULATED, bilateral
8604	NOT PREGNANT						
8605	0(0.0)	0/10		0/10		0/10	
8606	3(33.3)	0/ 9		1/ 9	FETUS 4 LUNGS: INTERMEDIATE LOBE ABSENT	2/ 9	FETUS 6 HYOID: ALA, ANGULATED, right FETUS 8 STERNAL CENTRA: FUSED, 3rd and 4th
8607	NOT PREGNANT						
8608	0(0.0)	0/11		0/11		0/11	
8609	0(0.0)	0/ 9		0/ 9		0/ 9	
8610	0(0.0)	0/ 9		0/ 9		0/ 9	
8611	0(0.0)	0/ 9		0/ 9		0/ 9	

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 9): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP II 0.1 MG/KG/DAY

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	GROSS EXTERNAL EXAMINATION DESCRIPTION	SOFT TISSUE EXAMINATION N/N	SOFT TISSUE EXAMINATION DESCRIPTION	SKELETAL EXAMINATION N/N	SKELETAL EXAMINATION DESCRIPTION
8612	1(12.5)	0/ 8		0/ 8		1/ 8	FETUS 6 LUMBAR VERTEBRAE: HEMIVERTEBRA, right, between 6th and 7th, arch and centrum
8613	0(0.0)	0/10		0/10		0/10	
8614	3(33.3)	0/ 9		2/ 9	FETUS 3 LUNGS: INTERMEDIATE LOBE ABSENT FETUS 8 LUNGS: INTERMEDIATE LOBE ABSENT	1/ 9	FETUS 4 HYOID: ALA, ANGULATED, left; ALA, SHORT, bilateral CAUDAL VERTEBRAE: MISALIGNED, 16th
8615	2(18.2)	0/11		0/11		2/11	FETUS 4 SKULL: NASALS, CONTAINED AN INTERNASAL, 1.5 mm x 4.5 mm; NASALS, MIDLINE SUTURE DISPLACED, right FETUS 10 SKULL: NASALS, MIDLINE SUTURE DISPLACED, right

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 10): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP III 1.0 MG/KG/DAY

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	GROSS EXTERNAL EXAMINATION DESCRIPTION	SOFT TISSUE EXAMINATION N/N	SOFT TISSUE EXAMINATION DESCRIPTION	SKELETAL EXAMINATION N/N	SKELETAL EXAMINATION DESCRIPTION
8616	0(0.0)	0/ 5	FETUS 2 LATE RESORPTION, autolysis precluded further evaluation FETUS 5 LATE RESORPTION, autolysis precluded further evaluation FETUS 8 LATE RESORPTION, autolysis precluded further evaluation	0/ 5		0/ 5	
8617	1(12.5)	0/ 8		0/ 8		1/ 8	FETUS 7 SKULL: NASALS, MIDLINE SUTURE DISPLACED, right
8618	0(0.0)	0/10		0/10		0/10	
8619	0(0.0)	0/ 7		0/ 7		0/ 7	
8620	NOT PREGNANT						

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 11): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP III 1.0 MG/KG/DAY

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	DESCRIPTION	SOFT TISSUE EXAMINATION N/N	DESCRIPTION	SKELETAL EXAMINATION N/N	DESCRIPTION
8621	1(11.1)	0/ 9		0/ 9		1/ 9	FETUS 2 SKULL: FRONTALS, CONTAINED AN INTERFRONTAL, 3.0 mm x 7.5 mm
8622	0(0.0)	0/ 4		0/ 4		0/ 4	
8623	NOT PREGNANT						
8624	1(11.1)	0/ 9		0/ 9		1/ 9	FETUS 6 SKULL: NASALS, CONTAINED AN INTERNASAL, 1.5 mm x 4.0 mm
8625	1(14.3)	0/ 7		0/ 7		1/ 7	FETUS 5 THORACIC VERTEBRAE: CENTRA, FUSED, 8th to right 9th; CENTRUM, BIFID, 9th RIBS: FUSED, right 8th and 9th, bases
8626	0(0.0)	0/ 7		0/ 7		0/ 7	
8627	1(10.0)	0/10		0/10		1/10	FETUS 9 HYOID: ALA, ANGULATED, left

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 12): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP III 1.0 MG/KG/DAY

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	DESCRIPTION	SOFT TISSUE EXAMINATION N/N	DESCRIPTION	SKELETAL EXAMINATION N/N	DESCRIPTION
8628	2(22.2)	0/ 9		0/ 9		2/ 9	FETUS 6 THORACIC VERTEBRAE: CENTRA, FUSED, 12th to lumbar right 1st LUMBAR VERTEBRAE: CENTRUM, BIFID, 1st FETUS 8 THORACIC VERTEBRAE: 11 PRESENT a RIBS: 11 PRESENT, bilateral a SPLIT, right 7th, distally, left 8th, medial - distal
8629	0(0.0)	0/10		0/10		0/10	
8630	0(0.0)	0/ 8		0/ 8		0/ 8	
8631	0(0.0)	0/ 9		0/ 9		0/ 9	
8632	2(25.0)	0/ 8		1/ 8	FETUS 1 LUNGS: INTERMEDIATE LOBE ABSENT	1/ 8	FETUS 4 SKULL: NASALS, CONTAINED AN INTERNASAL, 2.0 mm x 4.0 mm
8633	0(0.0)	0/ 8		0/ 8		0/ 8	

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 13): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP III 1.0 MG/KG/DAY

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	GROSS EXTERNAL EXAMINATION DESCRIPTION	SOFT TISSUE EXAMINATION N/N	SOFT TISSUE EXAMINATION DESCRIPTION	SKELETAL EXAMINATION N/N	SKELETAL EXAMINATION DESCRIPTION
8634	9(100.0)	0/ 9		9/ 9	FETUS 1 KIDNEYS: DISPLACED, left kidney, caudally FETUS 2 KIDNEYS: DISPLACED, left kidney, caudally FETUS 3 KIDNEYS: DISPLACED, left kidney, caudally FETUS 4 KIDNEYS: DISPLACED, left kidney, caudally FETUS 5 KIDNEYS: DISPLACED, left kidney, caudally FETUS 6 KIDNEYS: DISPLACED, left kidney, caudally FETUS 7 KIDNEYS: DISPLACED, left kidney, caudally FETUS 8 KIDNEYS: DISPLACED, left kidney, caudally	0/ 9	

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 14): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP III 1.0 MG/KG/DAY

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	DESCRIPTION	SOFT TISSUE EXAMINATION N/N	DESCRIPTION	SKELETAL EXAMINATION N/N	DESCRIPTION
8634 (Cont.)					FETUS 9 KIDNEYS: DISPLACED, left kidney, caudally		
8635	8(100.0)	0/ 8		8/ 8	FETUS 1 KIDNEYS: DISPLACED, left kidney, caudally FETUS 2 KIDNEYS: DISPLACED, left kidney, caudally FETUS 3 KIDNEYS: DISPLACED, left kidney, caudally FETUS 4 KIDNEYS: DISPLACED, left kidney, caudally FETUS 5 KIDNEYS: DISPLACED, left kidney, caudally	0/ 8	

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 15): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP III 1.0 MG/KG/DAY

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	GROSS EXTERNAL EXAMINATION DESCRIPTION	SOFT TISSUE EXAMINATION N/N	SOFT TISSUE EXAMINATION DESCRIPTION	SKELETAL EXAMINATION N/N	SKELETAL EXAMINATION DESCRIPTION
8635 (Cont.)					FETUS 6 KIDNEYS: DISPLACED, left kidney, caudally FETUS 7 KIDNEYS: DISPLACED, left kidney, caudally FETUS 8 KIDNEYS: DISPLACED, left kidney, caudally		
8636	0(0.0)	0/ 7		0/ 7		0/ 7	
8637	3(23.1)	0/13		0/13		3/13	FETUS 2 STERNAL CENTRA: FUSED, 2nd - 4th FETUS 4 STERNAL CENTRA: FUSED, 3rd and 4th FETUS 14 STERNAL CENTRA: FUSED, 3rd and 4th

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 16): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP IV 2.5 MG/KG/DAY

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	GROSS EXTERNAL EXAMINATION DESCRIPTION	SOFT TISSUE EXAMINATION N/N	SOFT TISSUE EXAMINATION DESCRIPTION	SKELETAL EXAMINATION N/N	SKELETAL EXAMINATION DESCRIPTION
8638	0(0.0)	0/ 7		0/ 7		0/ 7	
8639	2(28.6)	0/ 7	FETUS 3 LATE RESORPTION, autolysis precluded further evaluation FETUS 8 LATE RESORPTION, autolysis precluded further evaluation	0/ 7		2/ 7	FETUS 4 PELVIS: PUBIS, NOT OSSIFIED, bilateral FETUS 9 PELVIS: PUBIS, NOT OSSIFIED, bilateral
8640	2(33.3)	0/ 6		0/ 6		2/ 6	FETUS 2 HYOID: ALA, ANGULATED, left FETUS 6 HYOID: ALA, ANGULATED, right
8641	0(0.0)	0/ 9		0/ 9		0/ 9	
8642	1(12.5)	0/ 8		0/ 8		1/ 8	FETUS 7 PELVIS: PUBIS, NOT OSSIFIED, bilateral

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 17): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP IV 2.5 MG/KG/DAY

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	GROSS EXTERNAL EXAMINATION DESCRIPTION	SOFT TISSUE EXAMINATION N/N	SOFT TISSUE EXAMINATION DESCRIPTION	SKELETAL EXAMINATION N/N	SKELETAL EXAMINATION DESCRIPTION
8643	1(14.3)	0/ 7		0/ 7		1/ 7	FETUS 7 SKULL: NASALS, CONTAINED AN INTERNASAL, 0.3 mm x 1.5 mm
8644	1(11.1)	1/ 9	FETUS 5 SNOUT: SHORT, tongue protrudes	0/ 9		0/ 9	
8645	3(42.8)	0/ 7		1/ 7	FETUS 6 LUNGS: INTERMEDIATE LOBE ABSENT	2/ 7	FETUS 1 SKULL: NASALS, MIDLINE SUTURE DISPLACED, left FETUS 5 SKULL: NASALS, MIDLINE SUTURE DISPLACED, left
8646	3(50.0)	0/ 6		3/ 6	FETUS 1 VESSELS: COMMON TRUNCUS ARTERIOSUS LUNGS: SMALL, all lobes; FUSED, all lobes	0/ 6	

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 18): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP IV 2.5 MG/KG/DAY

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	GROSS EXTERNAL EXAMINATION DESCRIPTION	SOFT TISSUE EXAMINATION N/N	SOFT TISSUE EXAMINATION DESCRIPTION	SKELETAL EXAMINATION N/N	SKELETAL EXAMINATION DESCRIPTION
8646 (Cont.)					FETUS 2 EYES: CIRCUMCORNEAL HEMORRHAGE, bilateral, FETUS 6 KIDNEYS: DISPLACED, left kidney, caudally		
8647	ABORTED ON DAY 21 OF GESTATION a						
8648	3(21.4)	0/14	FETUS 10 LATE RESORPTION, autolysis precluded further evaluation FETUS 11 LATE RESORPTION, autolysis precluded further evaluation	0/14		3/14	FETUS 1 STERNAL CENTRA: FUSED, 2nd and 3rd FETUS 9 STERNAL CENTRA: FUSED, 3rd and 4th

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

a. Doe 8647 aborted one live fetus and one late resorption and had eight live fetuses, 2 dead fetuses and one late resorption in utero on day 21 of gestation. Autolysis precluded further evaluation of the late resorptions. All remaining fetuses appeared normal at gross external examination for developmental ages and appeared normal at soft tissue examination. Fetuses 1, 2, 4, 5, 6, 8, 9, 10, 11 and 12 had pelvis, pubis not ossified (bilateral) at skeletal examination.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 19): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP IV 2.5 MG/KG/DAY

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	GROSS EXTERNAL EXAMINATION DESCRIPTION	SOFT TISSUE EXAMINATION N/N	SOFT TISSUE EXAMINATION DESCRIPTION	SKELETAL EXAMINATION N/N	SKELETAL EXAMINATION DESCRIPTION
8648 (Cont.)			FETUS 14 LATE RESORPTION, autolysis precluded further evaluation FETUS 15 LATE RESORPTION, autolysis precluded futher evaluation				FETUS 18 SKULL: NASALS, MIDLINE SUTURE DISPLACED, left STERNAL CENTRA: FUSED, 1st - 4th
8649	0(0.0)	0/ 6		0/ 6		0/ 6	
8650	0(0.0)	0/ 6		0/ 6		0/ 6	
8651	4(57.1)	0/ 7		4/ 7	FETUS 1 KIDNEYS: DISPLACED, left kidney, caudally FETUS 2 KIDNEYS: DISPLACED, left kidney, caudally FETUS 5 KIDNEYS: DISPLACED, left kidney, caudally	0/ 7	

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 20): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP IV	2.5 MG/KG/DAY					
RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	DESCRIPTION	SOFT TISSUE EXAMINATION N/N	DESCRIPTION	SKELETAL EXAMINATION N/N	DESCRIPTION
8651 (Cont.)					FETUS 7 KIDNEYS: DISPLACED, left kidney, caudally		
8652	ABORTED ON DAY 26 OF GESTATION a						
8653	NOT PREGNANT						
8654	0(0.0)	0/ 7		0/ 7		0/ 7	
8655	0(0.0)	0/ 3		0/ 3		0/ 3	
8656	1(10.0)	0/10		0/10		1/10	FETUS 1 SKULL: FRONTALS, CONTAINED AN INTERFRONTAL, 2.0 mm x 3.5 mm
8657	1(12.5)	0/ 8		0/ 8		1/ 8	FETUS 7 STERNAL CENTRA: FUSED, 3rd and 4th
8658	1(12.5)	0/ 8		0/ 8		1/ 8	FETUS 6 STERNAL CENTRA: FUSED, 3rd and 4th
8659	0(0.0)	0/ 6		0/ 6		0/ 6	

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

a. Doe 8652 aborted one dead fetus and had 2 live fetuses and one late resorption in utero on day 26 of gestation. All fetuses and the late resorption appeared normal at gross external examination for developmental ages. All fetuses appeared normal at soft tissue and skeletal examinations.

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TABLE 22 (PAGE 21): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP V 3.75 MG/KG/DAY

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	GROSS EXTERNAL EXAMINATION DESCRIPTION	SOFT TISSUE EXAMINATION N/N	SOFT TISSUE EXAMINATION DESCRIPTION	SKELETAL EXAMINATION N/N	SKELETAL EXAMINATION DESCRIPTION
8660	ABORTED ON DAY 20 OF GESTATION a						
8661	ABORTED ON DAY 23 OF GESTATION b						
8662	0(0.0)	0/ 4	FETUS 1 LATE RESORPTION, autolysis precluded further evaluation FETUS 4 LATE RESORPTION, autolysis precluded further evaluation FETUS 7 LATE RESORPTION, autolysis precluded further evaluation	0/ 4		0/ 4	
8663	ABORTED ON DAY 26 OF GESTATION c						

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

a. Doe 8660 aborted three dead fetuses and had seven fetuses of undetermined viability in utero on day 20 of gestation. All fetuses appeared normal for their developmental ages at gross external examination. Soft tissue and skeletal examinations were not performed because of the early developmental ages of the fetuses.

b. Doe 8661 aborted one dead fetus and had six live fetuses and two late resorptions in utero on day 23 of gestation. Autolysis precluded further evaluation of the late resorptions. Fetus 6 had edema (dorsal and ventral neck) at gross external examination. All remaining fetuses appeared normal at gross external examination for developmental age. All fetuses appeared normal at soft tissue examination. Fetuses 1, 2, 3, 5, 6, 7 and 9 had pelvis, pubis not ossified (bilateral) at skeletal examination.

c. Doe 8663 aborted nine dead fetuses and one late resorption on day 26 of gestation. Autolysis precluded further evaluation of the late resorption. All fetuses were partially cannibalized. Fetuses 1, 2, 3, 4, 5, 6, 8 and 10 appeared normal at gross external examination for developmental age and appeared normal at soft tissue examination. Fetuses 2, 3, 4, 5, 6, 8 and 10 had pelvis, pubis not ossified (bilateral) and fetus 4 had ribs, split (right 12th, medial-distal) at skeletal examination.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 22): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP V — 3.75 MG/KG/DAY

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	GROSS EXTERNAL EXAMINATION DESCRIPTION	SOFT TISSUE EXAMINATION N/N	SOFT TISSUE EXAMINATION DESCRIPTION	SKELETAL EXAMINATION N/N	SKELETAL EXAMINATION DESCRIPTION
8664	3(42.8)	0/ 7	FETUS 6 LATE RESORPTION, autolysis precluded further evaluation FETUS 7 LATE RESORPTION, autolysis precluded further evaluation FETUS 8 LATE RESORPTION, autolysis precluded further evaluation	0/ 7		3/ 7	FETUS 3 HYOID: ALA, ANGULATED, left FETUS 5 HYOID: ALA, ANGULATED, right FETUS 10 HYOID: ALA, ANGULATED, bilateral
8665	2(20.0)	1/10	FETUS 8 BODY: EDEMA, neck SNOUT: SHORT, tongue protrudes EARS: SMALL, bilateral	0/10		2/10	FETUS 7 STERNAL CENTRA: FUSED, 3rd and 4th FETUS 8 STERNAL CENTRA: FUSED, 3rd and 4th HYOID: ALA, ANGULATED, bilateral
8666	0(0.0)	0/11		0/11		0/11	

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 23): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP V 3.75 MG/KG/DAY

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	GROSS EXTERNAL EXAMINATION DESCRIPTION	SOFT TISSUE EXAMINATION N/N	SOFT TISSUE EXAMINATION DESCRIPTION	SKELETAL EXAMINATION N/N	SKELETAL EXAMINATION DESCRIPTION
8667	ABORTED ON DAY 19 OF GESTATION a						
8668	2(33.3)	0/ 6	FETUS 3 LATE RESORPTION, autolysis precluded further evaluation FETUS 5 LATE RESORPTION, autolysis precluded further evaluation	1/ 6	FETUS 2 LUNGS: INTERMEDIATE LOBE ABSENT	1/ 6	FETUS 4 HYOID: ALA, ANGULATED, left
8669	ABORTED ON DAY 29 OF GESTATION b						
8670	1(20.0)	0/ 5	FETUS 5 LATE RESORPTION, autolysis precluded further evaluation	0/ 5		1/ 5	FETUS 1 THORACIC VERTEBRAE: HEMIVERTEBRA, right 12th, arch with attached rib RIBS: SPLIT, left 10th, medial - distal
8671	2(22.2)	0/ 9		1/ 9	FETUS 5 LUNGS: INTERMEDIATE LOBE ABSENT	1/ 9	FETUS 3 SKULL: NASALS, MIDLINE SUTURE DISPLACED, right

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

a. Doe 8667 aborted two dead fetuses and had two fetuses of undetermined viability in utero on day 19 of gestation. All fetuses appeared normal for their developmental ages at gross external examination. Soft tissue and skeletal examinations were not performed because of the early developmental ages of the fetuses.

b. Doe 8669 aborted five late resorptions and had five late resorptions in utero on day 29 of gestation; autolysis precluded further evaluation.

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 24): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP V — 3.75 MG/KG/DAY

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	GROSS EXTERNAL EXAMINATION DESCRIPTION	SOFT TISSUE EXAMINATION N/N	SOFT TISSUE EXAMINATION DESCRIPTION	SKELETAL EXAMINATION N/N	SKELETAL EXAMINATION DESCRIPTION
8672	1(11.1)	0/ 9	FETUS 8 LATE RESORPTION, autolysis precluded further evaluation	1/ 9	FETUS 6 LUNGS: INTERMEDIATE LOBE ABSENT	1/ 9	FETUS 6 SKULL: NASALS, CONTAINED AN INTERNASAL, 1.5 mm x 3.0 mm STERNAL CENTRA: FUSED, 2nd and 3rd CAUDAL VERTEBRAE: MISALIGNED, 12th and 15th
8673	1(12.5)	0/ 8		1/ 8	FETUS 3 HINDLIMB: SKIN CONSTRICTED, right	0/ 8	
8674	0(0.0)	0/ 6		0/ 6		0/ 6	
8675	0(0.0)	0/ 8		0/ 8		0/ 8	
8676	0(0.0)	0/11	FETUS 2 LATE RESORPTION, autolysis precluded further evaluation	0/11		0/11	
8677	NOT PREGNANT						

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: 6316.8)

TABLE 22 (PAGE 25): FETAL ALTERATIONS - INDIVIDUAL DATA

DOSAGE GROUP V 3.75 MG/KG/DAY

RABBIT NUMBER	SPECIMENS WITH ANY ALTERATIONS N(%)	GROSS EXTERNAL EXAMINATION N/N	GROSS EXTERNAL EXAMINATION DESCRIPTION	SOFT TISSUE EXAMINATION N/N	SOFT TISSUE EXAMINATION DESCRIPTION	SKELETAL EXAMINATION N/N	SKELETAL EXAMINATION DESCRIPTION
8678	1(12.5)	0/ 8		0/ 8		1/ 8	FETUS 7 HYOID: ALA, ANGULATED, right STERNAL CENTRA: FUSED, 3rd and 4th
8679	0(0.0)	0/11		0/11		0/11	
8680	1(12.5)	0/ 8		1/ 8	FETUS 6 LUNGS: INTERMEDIATE LOBE ABSENT	0/ 8	
8681	0(0.0)	0/ 8		0/ 8		0/ 8	

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

APPENDIX C

PROTOCOL AND AMENDMENT

PRIMEDICA

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

PROTOCOL 418-010

SPONSOR'S STUDY NUMBER: 6316.8

STUDY TITLE: Oral (Stomach Tube) Developmental Toxicity Study of N-EtFOSE in Rabbits

PURPOSE: The purpose of this study is to detect adverse effects of N-EtFOSE on New Zealand White [Hra:(NZW)SPF] presumed pregnant female rabbits and development of the embryo and fetus consequent to exposure of the doe from implantation to closure of the hard palate. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process in a nonrodent species.

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

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

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 to 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:	Room temperature (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 daily 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 and a sample (5 mL) of each lot of vehicle 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:

Homogeneity and stability of prepared formulations 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 upon completion of all work with the test article.

TEST SYSTEM:

Species/Strain and Reason for Selection:

The New Zealand White [Hra:(NZW)SPF] rabbit was selected as the Test System because: 1) it is one non-rodent mammalian species accepted and widely used throughout the industry for nonclinical studies of developmental toxicity (embryo-fetal toxicity/teratogenicity); 2) this strain of rabbit 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 the species and strain.

Number and Sex:

Population evaluated:	110 timed-pregnant female rabbits (22 per dosage group).
Population selected for toxicokinetic evaluation:	19 satellite female rabbits (five at the low and high dose levels plus three at the other dose levels).

Body Weight and Age:

The individual body weights of the female rabbits will range from 2.5 kg to 5.5 kg; the rabbits will be approximately five to seven months of age at the time of study assignment. Actual body weights recorded at receipt and at study assignment will be documented in the raw data, and the weight range will be included in the final report.

Source:

Covance Research Products, Inc.
Swampbridge Road, Box 7200
Denver, Pennsylvania 17517

The rabbits will be shipped in filtered cartons by truck from Covance Research Products, Inc., Denver, Pennsylvania, to the Testing Facility.

Identification:

Rabbits are permanently identified using Monel® self-piercing ear tags (Gey Band and Tag Co., Inc., No. MSPT 20103). Female rabbits are 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 are in compliance with the *Guide for the Care and Use of Laboratory Animals*[4].

Housing:

The rabbits will be individually housed in units of six to eight stainless steel cages. No nesting materials will be supplied because the female rabbits 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. Room temperature will be maintained at 61°F (16°C) to 72°F (22°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:

Approximately 150 g of Certified Rabbit Chow® #5322 (PMI Nutrition International) will be available to each rabbit each day until the first day of dosage, at which time approximately 180 g of the same certified feed will be offered to each rabbit each day. The certified feed will be available from individual stainless steel "J-type" feeders attached to each cage.

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.

MATING AND RANDOMIZATION:

The female rabbits will be naturally bred at the Supplier by breeder male rabbits of the same source and strain before shipment to the Testing Facility. The day mating occurs will be designated day 0 of presumed gestation. The rabbits will be mated on five consecutive days and shipped to the Testing Facility after the last mating day to arrive on day 1, 2, 3, 4 or 5 of presumed gestation. Before shipment of the rabbits, the Supplier will forward breeding records and day 0 of presumed gestation body weights. A computer-generated (weight-ordered) randomization procedure will be used to assign the rabbits to dosage groups based on this information.

ADMINISTRATION:

Route and Reason for Choice:

The oral (stomach tube) 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 possible routes of human exposure.

Method and Frequency:

Female rabbits will be given the test article once daily on days 7 through 20 of presumed gestation. Dosages will be adjusted daily for body weight changes 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 418-010P).

Dosage Levels, Concentrations and Volumes:

Dosage Group	Number of Rabbits	Dosage (mg/kg/day)	Concentration (mg/mL)	Dosage Volume (mL/kg)	Argus Batch Number
I	22+3[a]	0 (Vehicle)	0	5	B-418-010-A(Day.Month.Year)
II	22+5[a]	0.1	0.02	5	B-418-010-B(Day.Month.Year)
III	22+3[a]	1.0	0.2	5	B-418-010-C(Day.Month.Year)
IV	22+3[a]	2.5	0.5	5	B-418-010-D(Day.Month.Year)
V	22+5[a]	3.75	0.75	5	B-418-010-E(Day.Month.Year)

a. Rabbits assigned to toxicokinetic evaluation.
The test article will be considered 100% pure for the purpose of dosage calculations.

TESTS, ANALYSES AND MEASUREMENTS:

Viability:

All Periods: At least twice daily.

Clinical Observations and/or General Appearance:

Predosage Period: At least once.

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:

Predosage Period: Day 0 of presumed gestation and on the day of arrival at the Testing Facility.

Dosage Period: Daily.

Postdosage Period: Daily.

Feed Consumption Values:

Predosage Period: Recorded daily after arrival at the Testing Facility (values not tabulated).

Dosage Period: Recorded daily.

Postdosage Period: Recorded daily.

Feed consumption values during the dosing period will be tabulated for the same intervals as body weight evaluations.

Caesarean-Sectioning Observations:

Rabbits will be Caesarean-sectioned on day 29 of presumed gestation. The fetuses will be removed from the uterus and placed in individual containers. The rabbits 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 identified as an early resorption.)

Fetal Observations:

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 and uterine distribution.

Gross External Alterations:

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

Soft Tissue Examination and Sex:

All fetuses will be examined internally to determine sex. Cavitated organs will be evaluated in all fetuses by dissection[5]. A single cross-section will be made between the parietal and frontal bones, and the brain will be examined *in situ*.

Skeletal Examination:

All fetuses will be examined for skeletal alterations after staining with alizarin red S[6]. 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:

Beuthanasia®-D Special (manufactured by Schering-Plough Health) will be used to sacrifice rabbits (via intravenous injection) and live fetuses (via intraperitoneal injection).

NECROPSY:

Gross lesions will be retained in neutral buffered 10% formalin for possible future evaluation (corresponding tissues will be retained from rabbits in the vehicle control group at the discretion of the Study Director). (Exception: Parovarian cysts will be discarded; these are common, spontaneous lesions in rabbits.) Unless specifically cited below, all other tissues will be discarded.

Satellite Rabbits Assigned to Toxicokinetic Sample Collection:

On day 21 of presumed gestation (the day following the last dosage), toxicokinetic samples will be collected from the rabbits assigned to the toxicokinetic evaluation. Following anesthesia of pentobarbital, blood samples (approximately 4 mL per rabbit) 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 will be taken from the right lateral lobe, frozen and retained at -70°C until shipment to the Sponsor for analysis.

Rabbits will be Caesarean-sectioned and fetuses will be examined grossly to the extent possible as described above for rabbits 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 sections, 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:

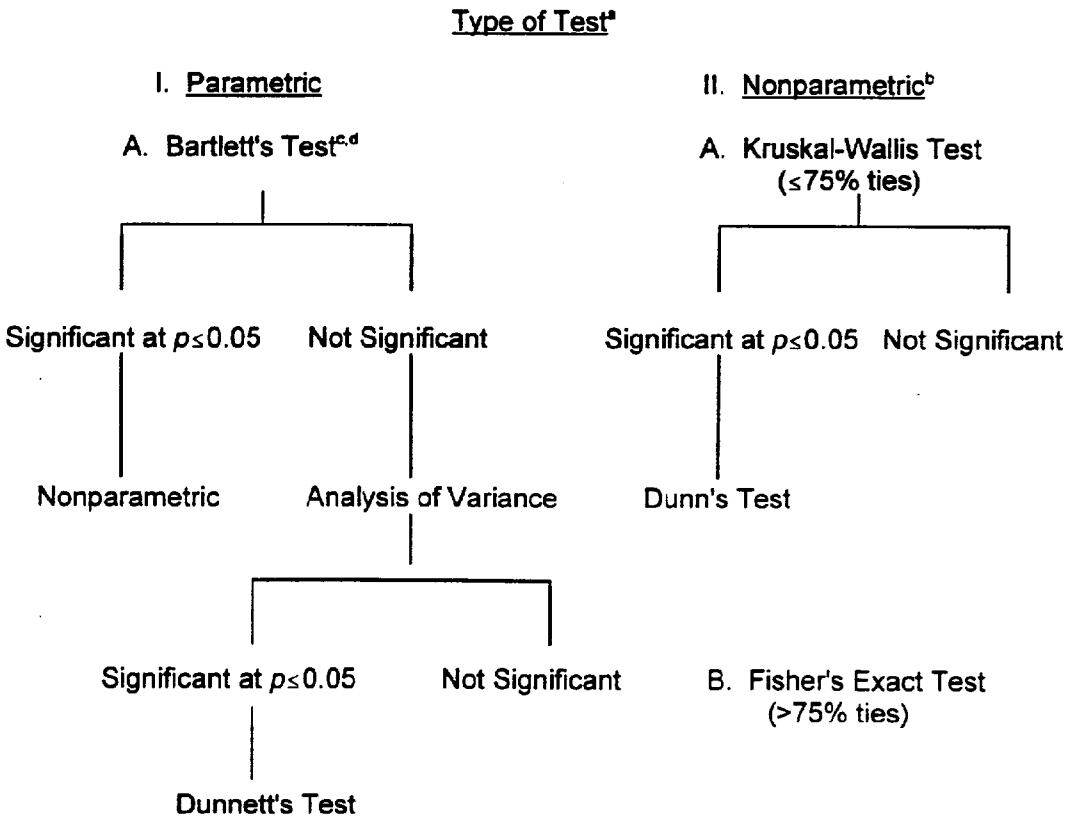
On day 29 of presumed gestation, female rabbits will be Caesarean-sectioned, and a gross necropsy of the thoracic, abdominal and pelvic viscera will be performed. Uteri of apparently nonpregnant does will be stained with 10% ammonium sulfide to confirm the absence of implantation sites[7].

Rabbits Found Dead or Moribund:

Rabbits 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. Pregnancy status and uterine contents 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 does 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.



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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.

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.
Veterinarian Examination.
Mating History.
Treatment (if prescribed by Staff Veterinarian).
General Comments.
Clinical Observations and/or General Appearance.
Blood 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., Hoberman, A.M. and Smith, T.H.F. (1982). Dosage-range study of the teratogenic potential of suspensions of trinitrofluorenone (TNF) administered orally to New Zealand White rabbits. Toxicologist 2(1):40 (#143).

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. Feussner, E.L., Lightkep, G.E., Hennesy, R.A., Hoberman, A.M. and Christian, M.S. (1992). A decade of rabbit fertility data: Study of historical control animals. Teratology 46(4):349-365.

4. Institute of Laboratory Animal Resources (1996). *Guide for the Care and Use of Laboratory Animals*. National Academy Press, Washington, D.C.

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PROTOCOL APPROVAL:

FOR THE TESTING FACILITY

George E Dearlove — 11 AUG-98

George E. Dearlove, Ph.D., DABT
Associate Director of Research — Date

Raymond G. York — 11-AUG-98

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

Dena C. Lebo — 11 Aug 98

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

FOR THE SPONSOR

Marvin T Case — 12 Aug 98

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

ATTACHMENT 1

SCHEMATIC OF STUDY DESIGN AND STUDY SCHEDULE

ATTACHMENT 1

STUDY SCHEMATIC

RABBIT DEVELOPMENTAL TOXICITY STUDY[a]

▬ Dosage Period

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

b. Fetal evaluations (external soft tissue and skeletal).

SCHEDULE[a]

28 AUG 98	Animals Arrive - Acclimation Begins.
30 AUG 98 - 16 SEP 98	Dosage Period (Days 7 through 20 of presumed gestation).
13 SEP 98 - 17 SEP 98	Toxicokinetic Sample Collection (Day 21 of presumed gestation).
21 SEP 98 - 25 SEP 98	Caesarean-Sectioning Period (Day 29 of presumed gestation).
22 DEC 98	Draft Final Report.

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

ATTACHMENT 2

MATERIAL SAFETY DATA SHEET

N-EtFOSE

MATERIAL SAFETY DATA SHEET

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

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

INGREDIENT	C.A.S. NO.	PERCENT
PERFLUOROOCTANESULFONAMIDO ALCOHOL.....	1691-99-2	80.0 - 90.0
PERFLUOROHEXANESULFONAMIDO 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

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

---

2. PHYSICAL DATA (continued)

APPEARANCE AND ODOR:
Amber waxy solid

---

3. FIRE AND EXPLOSION HAZARD DATA

FLASH POINT:..... > 148 C Setaflash
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.

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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.

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

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 H20 & 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.

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

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

INGREDIENT	VALUE	UNIT	TYPE	AUTH	SKIN*
PERFLUOROOCTANESULFONAMIDO 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

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

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.

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

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

ATTACHMENT 3

TEST ARTICLE AND VEHICLE PREPARATION PROCEDURE

Test Article: N-EtFOSE

Vehicle: 2% Tween® 80 in R.O. Deionized Water

A. Purpose: The purpose of this procedure is to provide a method for the preparation of dosage suspensions of N-EtFOSE and the vehicle for oral administration to rabbits on Argus Study 418-010.

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:
X Daily ___ 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.

TEST ARTICLE AND VEHICLE PREPARATION PROCEDURE

NOTE: The 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°C ±5°C, then add the required amount of Tween® 80 and mix until uniform (See TEST ARTICLE CALCULATIONS).

D. Test Article Suspension Preparation:

1. To prepare the 0.75 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°C ±5°C for approximately 30 minutes or until the TA/S dissolves.

2. Once the test article has dissolved; spin over night while the suspension cools. (Be sure there is a visible vortex, this will achieve the desired emulsion.)

3. To prepare the 0.5 mg/mL, Group IV suspension, remove the required amount of stock suspension (Group V) (See TEST ARTICLE CALCULATIONS), QS ad with the vehicle and mix.

4. To prepare the 0.2 mg/mL, Group III suspension, remove the required amount of stock suspension (Group IV) (See TEST ARTICLE CALCULATIONS), QS ad with the vehicle and mix.

5. To prepare the 0.02 mg/mL, Group II suspension, remove the required amount of stock suspension (Group III) (See TEST ARTICLE CALCULATIONS), QS ad with the vehicle and mix.

ATTACHMENT 3

TEST ARTICLE AND VEHICLE PREPARATION PROCEDURE

6. To prepare the 0 mg/mL, Group I suspension, add the required amount of vehicle to an appropriately sized, labeled container (See TEST ARTICLE CALCULATIONS) and mix.

Written by: Mark A. Coker

Approved by: [signature] Date: 11-AUG-98

Clarification: X No ___ Yes (See attached clarification form.)

Initials/Date : MC 10-5-98

PRIMEDICA

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

PROTOCOL 418-010

ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY
OF N-ETFOSE IN RABBITS

SPONSOR'S STUDY NUMBER: 6316.8

Amendment 1 - 22 December 1998

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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.

George E. Dearlove 22-DEC-98 — Raymond G. York 22-DEC-98

George E. Dearlove, Ph.D., DABT Date
Associate Director of Research

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

for Sally G. Lebo 22 Dec 98 — Marvin T. Case 28 Dec 98

for Dena C. Lebo, V.M.D. Date
Chairperson, Institutional Animal Care and Use Committee

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

APPENDIX D

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

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

1. On 2 September 1998 (Day 11 of presumed gestation) one rabbit in Group V (3.75 mg/kg/day dosage group, rabbit 8675) was inadvertently not dosed. This deviation does not adversely affect the outcome of the study because this represents only a small loss of data and was a single event.

   All deviations are documented in the raw data.

11-JAN-99

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

APPENDIX E

TEMPERATURE AND RELATIVE HUMIDITY REPORTS AND DEVIATIONS REPORT

ARGUS

Temperature and Relative Humidity Report
Location: Room 07

Protocol Number: 418-010

Range of Dates: 28-Aug-1998 14:00 to 21-Sep-1998 13:53

	Temperature		Relative Humidity	
Target Range:	61°F to 72°F		30% to 70%	
Species: RABBIT				
Total Number of Days:	25		25	
Total Number of Hours:	575.74		575.74	
Total Number of Data Points:	576		576	
Mean (± SD):	67.4	(± 0.4)	60.4	(± 3.0)
Maximum:	68.6		68.7	
Median:	67.4		60.5	
Minimum:	66.3		53.1	
Number of Points In Range (%):	576	(100.0)	576	(100.0)
Number of Points High (%):	0	(0.0)	0	(0.0)
Number of Points Low (%):	0	(0.0)	0	(0.0)

Report Generated: 28-Sep-1998 at 13:48

COMMENTS: _____

_____

_____

_____

REVIEWED BY: _____ **DATE:** 9-28-98

Cumulative by Location (v04.01.97)

ARGUS

Temperature and Relative Humidity Report
Location: Room 08

Protocol Number: 418-010

Range of Dates: 28-Aug-1998 14:00 to 25-Sep-1998 11:50

	Temperature		Relative Humidity	
Target Range:	61°F to 72°F		30% to 70%	
Species: RABBIT				
Total Number of Days:	29		29	
Total Number of Hours:	669.75		669.75	
Total Number of Data Points:	670		670	
Mean (± SD):	67.0	(± 0.7)	62.5	(± 3.6)
Maximum:	69.3		70.0	
Median:	66.8		63.0	
Minimum:	65.6		47.7	
Number of Points in Range (%):	670	(100.0)	669	(99.9)
Number of Points High (%):	0	(0.0)	1	(0.1)
Number of Points Low (%):	0	(0.0)	0	(0.0)

Report Generated: 28-Sep-1998 at 13:56

COMMENTS: _____

REVIEWED BY: _____ **DATE:** 9-28-98

Cumulative by Location (v04.01.97)

ARGUS

Temperature and Relative Humidity Report
Location: Room 09

Protocol Number: 418-010

Range of Dates: 28-Aug-1998 14:00 to 25-Sep-1998 11:50

	Temperature		Relative Humidity	
Target Range:	61°F to 72°F		30% to 70%	
Species: RABBIT				
Total Number of Days:	29		29	
Total Number of Hours:	669.75		669.75	
Total Number of Data Points:	670		670	
Mean (± SD):	66.7	(± 0.9)	63.7	(± 4.2)
Maximum:	69.7		73.7	
Median:	66.5		64.1	
Minimum:	64.7		44.8	
Number of Points in Range (%):	670	(100.0)	640	(95.5)
Number of Points High (%):	0	(0.0)	30	(4.5)
Number of Points Low (%):	0	(0.0)	0	(0.0)

Report Generated: 28-Sep-1998 at 13:57

COMMENTS: _____

REVIEWED BY: _____ **DATE:** 9-28-98

Cumulative by Location (v04.01.97)

ARGUS

Relative Humidity Deviations Report
Location: Room 09

Protocol Number: 418-010

Range of Dates: 28-Aug-1998 14:00 to 25-Sep-1998 11:50

Humidity Target Range: 30% to 70%
Species: Rabbit

Date	Time	R.H.	Date	Time	R.H.
29-Aug-1998	09:00	70.6 H	17-Sep-1998	23:00	70.2 H
30-Aug-1998	00:00	70.2 H	18-Sep-1998	10:00	73.1 H
30-Aug-1998	01:00	70.2 H	18-Sep-1998	11:00	70.9 H
30-Aug-1998	22:00	70.9 H	18-Sep-1998	21:00	70.1 H
31-Aug-1998	08:00	72.2 H	19-Sep-1998	21:00	70.2 H
31-Aug-1998	19:00	71.0 H	19-Sep-1998	22:00	71.3 H
02-Sep-1998	01:00	70.9 H	20-Sep-1998	10:00	70.4 H
02-Sep-1998	20:00	70.6 H	20-Sep-1998	13:00	70.4 H
04-Sep-1998	20:00	70.6 H	21-Sep-1998	10:00	72.8 H
14-Sep-1998	11:00	70.2 H	22-Sep-1998	10:00	70.4 H
14-Sep-1998	13:00	70.4 H			
15-Sep-1998	16:00	70.3 H			
15-Sep-1998	19:00	70.1 H			
15-Sep-1998	21:00	71.0 H			
16-Sep-1998	09:00	70.7 H			
16-Sep-1998	21:00	73.7 H			
17-Sep-1998	00:00	71.5 H			
17-Sep-1998	14:00	72.2 H			

H = Value out of range - High L = Value out of range - Low
R.H. = Relative Humidity (%)

Report Generated: 03-Dec-1998 at 10:02

✓ These deviations did not adversely affect the outcome or interpretation of the study.

_____ The following deviation(s) impacted on the outcome of the study as described:

Study Director: _____ Date: 03-Dec-98

Deviations by Location (v04.01.97)

APPENDIX F

PILOT REPORT

FINAL PILOT REPORT

Study Title

Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of N-EtFOSE in Rabbits

SPONSOR'S STUDY NUMBER: T-6316.8

Author

Raymond G. York, Ph.D., DABT
(Study Director)

Study Completed On

6 January 1999
(Final Pilot Report)

Performing Laboratory

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

Laboratory Project ID

Argus Research Laboratories, Inc., Protocol Number: 418-010P

PROTOCOL 418-010P ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS

SPONSOR'S STUDY NUMBER: T-6316.8

TABLE OF CONTENTS

TITLE: ORAL(STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS

ARGUS RESEARCH LABORATORIES, INC.,
PROTOCOL NUMBER: 418-010P
SPONSOR'S STUDY NUMBER: T-6316.8

ABSTRACT

The purpose of this study was to provide information for the selection of dosages to be used in the developmental toxicity (embryo-fetal toxicity and teratogenic potential) study of N-EtFOSE administered orally via stomach tube to New Zealand White [Hra:(NZW)SPF] presumed pregnant female rabbits.

Thirty-five presumed pregnant New Zealand White [Hra:(NZW)SPF] rabbits were randomly assigned to seven dosage groups, five per group. Suspensions of N-EtFOSE were administered orally once daily on days 7 through 20 of gestation (DGs 7 to 20) at dosages of 0 (Vehicle), 1, 5, 10, 25, 50 and 75 mg/kg/day. The vehicle was 2% Tween® 80 in reverse osmosis membrane processed deionized Water. The dosage volume was 5 mL/kg, adjusted daily on the basis of the individual body weights.

Checks for viability were made twice daily. Clinical observations were recorded twice daily during the dosage period (once prior to dosage administration and once approximately one hour after dosage administration) and once daily during the postdosage period. Body weights and feed consumption values were recorded daily during the dosage and postdosage periods.

All surviving rabbits were sacrificed on DG 29 of presumed gestation and examined for the number and distribution of corpora lutea, implantation sites and uterine contents. A gross necropsy of the thoracic, abdominal and pelvic viscera was performed. Fetuses were weighed and examined for gross external alterations and sex.

Severe maternal body weight loss occurred in the 10, 25, 50 and 75 mg/kg/day dosage groups; there were no surviving rabbits in these groups. Abortions occurred in 5 and 10 mg/kg/day dosage groups. Caesarean-section

observations revealed increasing late resorptions and reduced fetal body weights at 5 mg/kg/day. Increases in early resorptions were found at 1 mg/kg/day; however, there was no decrease in mean litter size.

Based on the results of this dosage-range finding study, dosages of 0, 0.1, 1.0, 2.5 and 3.75 mg/kg/day were recommended for the full developmental toxicity study of N-EtFOSE in rabbits.

I. Purpose:

The purpose of this study was to provide information for the selection of dosages to be used in the developmental toxicity (embryo-fetal toxicity and teratogenic potential) study of N- EtFOSE administered orally via stomach tube to New Zealand White [Hra:(NZW)SPF] presumed pregnant female rabbits.

II. Methods[a]:

The test article, N-EtFOSE (lot FM-3932), an off-white wax, was received on 20 May 1998, and stored at room temperature. The vehicle, 2% Tween® 80 (lot 3H05), a clear viscous liquid, was received on 22 May 1998, and stored at room temperature. The vehicle diluent, reverse osmosis membrane processed deionized water (R.O. Deionized Water) is available from a continuous source at the Testing Facility and is maintained at room temperature.

Thirty-five presumed pregnant New Zealand White [Hra:(NZW)SPF] rabbits were randomly assigned to seven dosage groups [five per group (Groups I through VII)]. Suspensions of N-EtFOSE were administered orally (stomach tube) once daily to these timed-pregnant rabbits on days 7 through 20 of gestation (DGs 7 to 20) at dosages of 0 (Vehicle), 1, 5, 10, 25, 50 and 75 mg/kg/day. The vehicle was 2% Tween® 80 in reverse osmosis membrane processed deionized Water (R.O. Deionized Water). The dosage volume was 5 mL/kg, adjusted daily on the basis of the individual body weights recorded immediately before intubation of the test article.

Checks for viability were made twice daily. Clinical observations were recorded twice daily during the dosage period (once prior to dosage administration and once approximately one hour after dosage administration) and once daily during the postdosage period. Body weights and feed consumption values were recorded daily during the dosage and postdosage periods.

All surviving rabbits were sacrificed on DG 29 of presumed gestation and examined for the number and distribution of corpora lutea, implantation sites and uterine contents. A gross necropsy of the thoracic, abdominal and pelvic viscera was performed. Fetuses were weighed and examined for gross external alterations and sex.

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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 the attached protocol and amendments. Deviations from the Protocol and Standard Operating Procedures of the Testing Facility are available in the raw data.

III. Results:

A. Mortality, Moribund Sacrifices, Abortions, Clinical and Necropsy Observations (Summaries - Tables 1 and 2; Individual Data - Tables 11, 12 and 3)

A.1. Mortality

One, two and one rabbits were found dead in the 1, 50 and 75 mg/kg/day dosage groups, respectively. The remaining rabbits in the 50 and 75 mg/kg/day dosage groups and all five rabbits in the 25 mg/kg/day dosage group were moribund sacrificed.

1 mg/kg/day Dosage Group

Doe 8206 was found dead on DG 16, within an hour following dosage administration, after 10 dosages of the test article. The rabbit had no adverse clinical signs during the dosing period. The rabbit gained weight during the dosage period, but feed consumption values were reduced on DGs 12 through 15. The uterus contained eight fetuses, which appeared normal for their developmental ages. Viability of the fetuses could not be determined because of the death of the dam. All tissues appeared normal at necropsy.

50 mg/kg/day Dosage Group

Doe 8226 was found dead on DG 14, within three hours following dosage administration, after nine dosages of the test article. The rabbit had soft or liquid feces and scant or no feces between DGs 9 and 14 and lost weight and had reduced feed consumption during the dosage period. The uterus contained six fetuses and one early resorption. Viability of the fetuses could not be determined because of the death of the dam. Necropsy revealed the stomach mucosa contained black viscous material; all other tissues appeared normal.

Doe 8229 was found dead before dosage administration on DG 12, after five dosages of the test article. The rabbit had soft or liquid feces or scant feces on DGs 9 to 12 and lost weight and had reduced feed consumption during the dosage period. The uterus contained 13 fetuses. Viability of the fetuses could not be determined because of the death of the dam. Necropsy revealed greenish-gray areas on all lobes of the liver and 30 mL of fluid in the thoracic cavity. All other tissues appeared normal for the slight degree of autolysis.

75 mg/kg/day Dosage Group

Doe 8233 was found dead before dosage administration on DG15, after nine dosages of the test article. The rabbit had soft or liquid feces or scant feces on DGs 9 to 14, decreased motor activity on DGs 13 and 14 and excess salivation on DG 14. The rabbit lost weight and had reduced feed consumption during the dosage period. The uterus contained nine fetuses and one early resorption. Viability of the fetuses could not be determined because of the death of the dam. The abdominal cavity contained approximately 18 mL of thin, brown fluid and the stomach mucosa contained a viscous, brown material. All other tissues appeared normal.

A.2. Moribund Sacrificed

All rabbits in the 25, 50 and 75 mg/kg/day dosage groups were moribund sacrificed on DG 15. Clinical observations in these rabbits included decreased motor activity, impaired righting reflex, cold to touch, emaciation, red substance in the cage pan, perioral substance, excess salivation, ungroomed coat, and abnormal feces (scant, soft or liquid, absent).

A.3. Aborted and Sacrificed

Three rabbits in the 5 mg/kg/day dosages group and all five rabbits in the 10 mg/kg/day dosages group aborted and were sacrificed.

5 mg/kg/day Dosage Group

Doe 8211 aborted on DG 26. The rabbit had scant feces, soft or liquid feces or no feces on DGs 10 through 25. There was a red substance in the cage pan on DG 26. The rabbit lost weight and had reduced feed consumption during the dosage period. There were one aborted late resorption and five late resorptions *in utero*. All tissues appeared normal at necropsy.

Doe 8212 aborted on DG 24. The rabbit had scant feces or soft or liquid feces on DGs 10 to 23. There was a red substance in the cage pan on DG 20. The rabbit lost weight and had reduced feed consumption during the dosage period. There was one aborted late resorption. There three live fetuses and eight late resorptions *in utero*. All tissues appeared normal at necropsy.

Doe 8214 aborted on DG 26. The rabbit had scant feces or no feces on DGs 17 to 25. There was a red substance in the cage pan on DG 26. The rabbit lost weight during the dosage period and had reduced feed consumption on DGs 10

to 26. There were four implantations and three aborted dead fetuses. The fourth conceptus was presumed cannibalized. All tissues appeared normal at necropsy.

10 mg/kg/day Dosage Group

Doe 8216 aborted on DG 26. The rabbit had scant feces, soft or liquid feces or no feces on DGs 10 through 25 and dark orange urine on DG 24. There was a red substance in the cage pan on DG 26. The rabbit lost weight and had reduced feed consumption during the dosage period. There were eight aborted late resorptions. The liver had pale, tan areas on all lobes, ranging in size from 1.5 cm x 1.0 cm to 4.0 cm x 1.6 cm. All other tissues appeared normal at necropsy.

Doe 8217 aborted DG 22. The rabbit had scant feces or no feces on DGs 9 to 21 and a red substance in the cage pan on DG 21. The rabbit lost weight and had reduced feed consumption during the dosage period. There were two aborted late resorptions and four early and four late resorptions *in utero*. All tissues appeared normal at necropsy.

Doe 8218 aborted on DG 24. The rabbit had scant feces, soft or liquid feces or no feces on DGs 9 to 23. The rabbit lost weight and had reduced feed consumption during the dosage period. There were eight aborted late resorptions and two late resorptions *in utero*. All tissues appeared normal at necropsy.

Doe 8219 aborted on DG 22. The rabbit had scant feces or no feces on DGs 9 through 21 and a red substance in the cage pan and dark orange urine on DG 21. The rabbit lost weight and had reduced feed consumption during the dosage period. There were eight aborted early resorptions, four aborted late resorptions and one early resorption *in utero*. Necropsy revealed that all lobes of the liver were pale. All other tissues appeared normal.

Doe 8220 aborted on DG 23. The rabbit had scant feces or soft or liquid feces on DGs 9 to 22. The rabbit lost weight and had reduced feed consumption during the dosage period. There were three aborted late resorptions and seven live fetuses *in utero*. All tissues appeared normal at necropsy.

A.4. Clinical Observations

Clinical observations considered to be test article related included scant feces, soft or liquid feces or no feces in 5, 10, 25, 50 and/or 75 mg/kg/day dosage

groups, and dark urine in the 10 mg/kg/day dosage group. Ungroomed coat, decreased motor activity, impaired righting reflex, cold to touch, lost righting reflex, emaciation, perioral substance and excess salivation occurred in rabbits that were found dead or moribund sacrificed in the 25, 50 and/or 75 mg/kg/day dosage groups. Red substance in cage pan was correlated with abortion and/or moribund condition in the 5, 10 and 75 mg/kg/day dosage groups.

All other clinical observations were considered unrelated to the test article because: 1) the incidences were not dosage-dependent; and/or 2) they occurred in only one rat. These observations included abrasion and localized alopecia on the limbs and/or back.

A.5. Necropsy

Necropsy observations from all unscheduled deaths or sacrifices have been previously described. One 5 mg/kg/day dosage group doe (7385) had pale liver lobes. The only other necropsy observations were confirmation of clinical observations of localized alopecia.

B. Maternal Body Weights and Body Weight Changes (Figure 1; Summaries - Tables 4 and 5; Individual Data - Table 13)

Severe maternal body weight losses occurred in the 10, 25, 50 and 75 mg/kg/day dosage groups; there were no surviving rabbits in these groups after DGs 26, 15, 15 and 15, respectively.

Maternal body weight losses occurred for the 5 mg/kg/day dosage group for the entire the dosage period (calculated as DGs 7 to 21), the postdosage period (DGs 21 to 29) and the entire gestation period (DGs 0 to 29).

Maternal body weights and body weight gains for the 1 mg/kg/day dosage group were generally comparable to control values during the dosage and postdosage periods (DGs 7 to 21).

C. Absolute (g/day) and Relative (g/kg/day) Feed Consumption Values (Summaries - Tables 6 and 7; Individual Data - Table 14)

Absolute and relative feed consumption values were severely reduced in the 10, 25, 50 and 75 mg/kg/day dosage groups; there were no surviving rabbits in these groups after DGs 26, 15, 15 and 15, respectively.

Absolute and relative feed consumption values for the 5 mg/kg/day dosage group were severely reduced, compared to the control group, during the dosage and postdosage periods.

Absolute and relative feed consumption values for the 1 mg/kg/day dosage group were generally comparable to control values over each interval tabulated.

D. **Caesarean-Sectioning and Litter Observations (Summaries - Tables 8 through 10; Individual Data - Tables 15 through 17)**

Caesarean-sectioning observations were based on 5, 4 and 2 pregnant rabbits with live litters in the 0 (Vehicle), 1 and 5 mg/kg/day dosage groups. There were no surviving does in the 10, 25, 50 or 75 mg/kg/day dosage groups.

An increase in early resorptions occurred in the 1 mg/kg/day dosage group, relative to the control group. This observation was considered an effect of the test article because it was outside the historical control range for the Testing Facility. An increase in late resorptions (and a concomitant decrease in litter size) and reduced fetal body weights occurred at the 5 mg/kg/day dosage, relative to the control group. These observations were also considered an effect of the test article because they were dosage-dependent and occurred at maternally toxic dosages (decreased body weight and feed consumption values).

No dams had all resorbed conceptuses and there were no dead fetuses.

Totals of 36, 34 and 13 live fetuses were evaluated for external gross alterations in the three respective dosage groups with litters. One fetus (8207-7) in the 1 mg/kg/day dosage group had a distended abdomen. One fetus (7385-1) in the 5 mg/kg/day dosage group had open eyelids and protruding tongue and another in the same litter (7385-4) had downward flexed forepaws, cleft snout, absent incisors and a large right eye. This litter also contained three late resorptions and three normal fetuses. No fetal gross external alterations were observed in the vehicle control group fetuses.

IV. Conclusion:

Based on the results of this study, dosages of 0 (Vehicle), 0.1, 1.0, 2.5 and 3.75 mg/kg/day of N-EtFOSE were recommended for the developmental toxicity study in rabbits (418-010). The 0.1 mg/kg/day dosage is expected to be a no-observable-effect-level (NOEL) for both maternal and embryo-fetal toxicity, and the 3.75 mg/kg/day dosage is expected to produce maternal toxicity (decreased maternal body weight and feed consumption values) and may produce minimal developmental toxicity (decreased fetal body weight and delayed ossification).

A. Hoberman 06 JAN 99

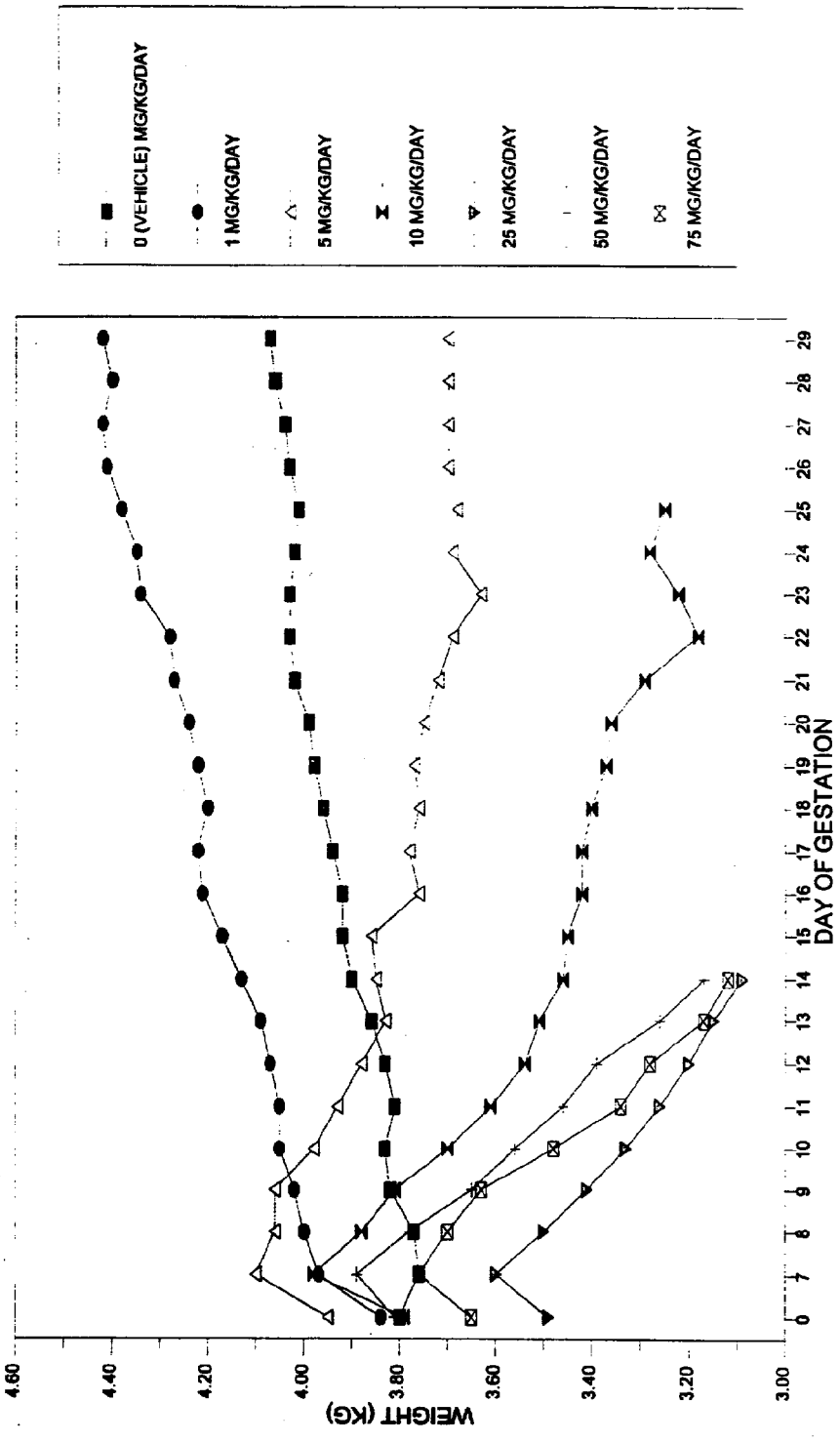
Alan M. Hoberman, Ph.D., DABT Date
Director of Research

Raymond G. York 06-JAN-99

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

MATERNAL BODY WEIGHT

FIGURE 1



PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 1 (PAGE 1): CLINICAL OBSERVATIONS - SUMMARY

DOSAGE GROUP	I	II	III	IV
DOSAGE (MG/KG/DAY)a	0 (VEHICLE)	1	5	10
MAXIMUM POSSIBLE INCIDENCE	115/ 5	102/ 5	104/ 5	87/ 5
MORTALITY	0	1	3	5
MORIBUND SACRIFICED	0	0	0	0
ABORTED AND SACRIFICED	0	0	3b	5b
FOUND DEAD	0	1b	0	0
SCANT FECES	0/ 0	0/ 0	62/ 5	59/ 5
DECREASED MOTOR ACTIVITY	0/ 0	0/ 0	0/ 0	0/ 0
UNGROOMED COAT	0/ 0	0/ 0	11/ 1	0/ 0
SOFT OR LIQUID FECES	0/ 0	0/ 0	4/ 3	7/ 3
DRIED YELLOW, BROWN OR YELLOW-BROWN PERIORAL SUBSTANCE	0/ 0	0/ 0	0/ 0	0/ 0
NO FECES	0/ 0	0/ 0	10/ 3	10/ 4
RED SUBSTANCE IN CAGE PAN	0/ 0	1/ 1	3/ 3	3/ 3
IMPAIRED RIGHTING REFLEX	0/ 0	0/ 0	0/ 0	0/ 0
COLD TO TOUCH	0/ 0	0/ 0	0/ 0	0/ 0
EMACIATION	0/ 0	0/ 0	0/ 0	0/ 0
EXCESS SALIVATION	0/ 0	0/ 0	0/ 0	0/ 0
LOST RIGHTING REFLEX	0/ 0	0/ 0	0/ 0	0/ 0
DARK URINE	0/ 0	0/ 0	0/ 0	2/ 2

MAXIMUM POSSIBLE INCIDENCE = (DAYS x RABBITS)/NUMBER OF RABBITS EXAMINED PER GROUP ON DAYS 7 THROUGH 29 OF PRESUMED GESTATION.
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RABBITS WITH OBSERVATION.
a. Dosage occurred on days 7 through 20 of presumed gestation.
b. Refer to the individual clinical observations table (Table 11) for observations for rabbits that died or aborted.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 1 (PAGE 2): CLINICAL OBSERVATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a	V 25	VI 50	VII 75
MAXIMUM POSSIBLE INCIDENCE	45/ 5	41/ 5	45/ 5
MORTALITY	5	5	5
MORIBUND SACRIFICED	5b	3b	4b
ABORTED AND SACRIFICED	0	0	0
FOUND DEAD	0	2b	1b
SCANT FECES	25/ 5	20/ 5	22/ 5
DECREASED MOTOR ACTIVITY	1/ 1	4/ 4	13/ 5
UNGROOMED COAT	5/ 2	0/ 0	15/ 4
SOFT OR LIQUID FECES	0/ 0	10/ 3	13/ 4
DRIED YELLOW, BROWN OR YELLOW-BROWN PERIORAL SUBSTANCE	0/ 0	3/ 3	5/ 2
NO FECES	2/ 1	2/ 2	4/ 2
RED SUBSTANCE IN CAGE PAN	0/ 0	0/ 0	2/ 2
IMPAIRED RIGHTING REFLEX	1/ 1	0/ 0	3/ 1
COLD TO TOUCH	0/ 0	0/ 0	1/ 1
EMACIATION	0/ 0	0/ 0	2/ 1
EXCESS SALIVATION	0/ 0	0/ 0	1/ 1
LOST RIGHTING REFLEX	0/ 0	1/ 1	0/ 0
DARK URINE	0/ 0	0/ 0	0/ 0

MAXIMUM POSSIBLE INCIDENCE = (DAYS x RABBITS)/NUMBER OF RABBITS EXAMINED PER GROUP ON DAYS 7 THROUGH 29 OF PRESUMED GESTATION.
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RABBITS WITH OBSERVATION.
a. Dosage occurred on days 7 through 20 of presumed gestation.
b. Refer to the individual clinical observations table (Table 11) for observations for rabbits that died or were moribund sacrificed.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 1 (PAGE 3): CLINICAL OBSERVATIONS - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE (MG/KG/DAY)a		0 (VEHICLE)	1	5	10
MAXIMUM POSSIBLE INCIDENCE		115/ 5	102/ 5	104/ 5	87/ 5
MORTALITY		0	1	3	5
MORIBUND SACRIFICED		0	0	0	0
ABORTED AND SACRIFICED		0	0	3b	5b
FOUND DEAD		0	1b	0	0
ABRASION c		0/ 0	0/ 0	17/ 2	0/ 0
LOCALIZED ALOPECIA:	TOTAL	1/ 1	2/ 1	0/ 0	0/ 0
	LIMBS	0/ 0	2/ 1	0/ 0	0/ 0
	BACK	1/ 1	1/ 1	0/ 0	0/ 0

MAXIMUM POSSIBLE INCIDENCE = (DAYS x RABBITS)/NUMBER OF RABBITS EXAMINED PER GROUP ON DAYS 7 THROUGH 29 OF PRESUMED GESTATION.
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RABBITS WITH OBSERVATION.

a. Dosage occurred on days 7 through 20 of presumed gestation.
b. Refer to the individual clinical observations table (Table 11) for observations for rabbits that died or aborted.
c. Located on the left forepaw or left hindpaw.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 1 (PAGE 4): CLINICAL OBSERVATIONS - SUMMARY

DOSAGE GROUP		V	VI	VII
DOSAGE (MG/KG/DAY)a		25	50	75
MAXIMUM POSSIBLE INCIDENCE		45/ 5	41/ 5	45/ 5
MORTALITY		5	5	5
MORIBUND SACRIFICED		5b	3b	4b
ABORTED AND SACRIFICED		0	0	0
FOUND DEAD		0	2b	1b
ABRASION		0/ 0	0/ 0	0/ 0
LOCALIZED ALOPECIA:	TOTAL	0/ 0	0/ 0	0/ 0
	LIMBS	0/ 0	0/ 0	0/ 0
	BACK	0/ 0	0/ 0	0/ 0

MAXIMUM POSSIBLE INCIDENCE = (DAYS x RABBITS)/NUMBER OF RABBITS EXAMINED PER GROUP ON DAYS 7 THROUGH 29 OF PRESUMED GESTATION.
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RABBITS WITH OBSERVATION.
a. Dosage occurred on days 7 through 20 of presumed gestation.
b. Refer to the individual clinical observations table (Table 11) for observations for rabbits that died or were moribund sacrificed.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 2 (PAGE 1): NECROPSY OBSERVATIONS - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE (MG/KG/DAY)a		0 (VEHICLE)	1	5	10
RABBITS EXAMINED b	N	5	5	5	5
MORTALITY	N	0	1	3	5
MORIBUND SACRIFICED	N	0	0	0	0
ABORTED	N	0	0	3c	5c
FOUND DEAD	N	0	1c	0	0
APPEARED NORMAL	N	5	5	4	3
STOMACH:					
MUCOSA, BLACK OR BROWN VISCOUS MATERIAL	N	0	0	0	0
FRIABLE	N	0	0	0	0
ABDOMINAL CAVITY:					
THIN BROWN FLUID	N	0	0	0	0
LIVER:					
ALL LOBES, GREEN-GREY AREAS	N	0	0	0	0
ALL LOBES, PALE OR PALE TAN AREAS	N	0	0	1	2
THORACIC CAVITY:					
TAN-GREY FLUID	N	0	0	0	0
LUNGS:					
ALL LOBES, TAN-GREY	N	0	0	0	0

a. Dosage occurred on days 7 through 20 of presumed gestation.
b. Refer to the individual clinical observations table (Table 11) for external observations confirmed at necropsy.
c. Refer to the individual necropsy observations table (Table 12) for observations for rabbits that died or aborted.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 2 (PAGE 2): NECROPSY OBSERVATIONS - SUMMARY

DOSAGE GROUP		V	VI	VII
DOSAGE (MG/KG/DAY)a		25	50	75
RABBITS EXAMINED b	N	5	5	5
MORTALITY	N	5	5	5
MORIBUND SACRIFICED	N	5c	3c	4c
ABORTED	N	0	0	0
FOUND DEAD	N	0	2c	1c
APPEARED NORMAL	N	5	3	3
STOMACH:				
MUCOSA, BLACK OR BROWN VISCOUS MATERIAL	N	0	1	2
FRIABLE	N	0	0	1
ABDOMINAL CAVITY:				
THIN BROWN FLUID	N	0	0	1
LIVER:				
ALL LOBES, GREEN-GREY AREAS	N	0	1	0
ALL LOBES, PALE OR PALE TAN AREAS	N	0	0	0
THORACIC CAVITY:				
TAN-GREY FLUID	N	0	1	0
LUNGS:				
ALL LOBES, TAN-GREY	N	0	1	0

a. Dosage occurred on days 7 through 20 of presumed gestation.
b. Refer to the individual clinical observations table (Table 11) for external observations confirmed at necropsy.
c. Refer to the individual necropsy observations table (Table 12) for observations for rabbits that died or were moribund sacrificed.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 3 (PAGE 1): UTERINE CONTENTS AND LITTER DATA FOR RABBITS THAT WERE FOUND DEAD, MORIBUND SACRIFICED OR ABORTED

DOSAGE GROUP / DOSAGE (MG/KG/DAY) c	RABBIT NUMBER	DAY OF DEATH	CORPORA LUTEA R	L	T	IMPLANTATIONS R	L	T	EMBRYOS/FETUSES a R	L	A	T	RESORPTIONS b R	L	A	T
I 0 (VEHICLE)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
II 1	8206	FOUND DEAD ON DAY 16 OF GESTATION	4	5	9	3	5	8	3	5	0	8d	0	0	0	0
III 5	8211	ABORTED ON DAY 26 OF GESTATION	6	4	10	3	3	6	0	0	0	0	2	3	1	6 (LR)
	8212	ABORTED ON DAY 24 OF GESTATION	6	7	13	6	6	12	1	2	0	3	4	4	1	9e (LR)
	8214	ABORTED ON DAY 26 OF GESTATION	4	4	8	2	2	4	0	0	3	3f,g	0	0	0	0
IV 10	8216	ABORTED ON DAY 26 OF GESTATION	5	7	12	4	4	8	0	0	0	0	0	0	8	8e (LR)
	8217	ABORTED ON DAY 22 OF GESTATION	5	6	11	5	5	10	0	0	0	0	4 (1LR)	4 (3LR)	2 (LR)	10e
	8218	ABORTED ON DAY 24 OF GESTATION	5	6	11	5	5	10	0	0	0	0	0	2	8	10e (LR)
	8219	ABORTED ON DAY 22 OF GESTATION	6	7	13	6	7	13	0	0	0	0	0	1	12 (4LR)	13e
	8220	ABORTED ON DAY 23 OF GESTATION	6	5	11	6	4	10	5	2	0	7	0	0	3	3 (LR)

R = RIGHT L = LEFT T = TOTAL A = ABORTED

a. Conceptuses appeared normal for developmental ages.
b. Early resorptions, unless noted otherwise.
c. Dosage occurred on days 7 through 20 of presumed gestation.
d. Unable to determine viability of conceptuses because of death of doe.
e. Autolysis precluded further evaluation.
f. One conceptus was presumed cannibalized.
g. Dead fetuses.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 3 (PAGE 2): UTERINE CONTENTS AND LITTER DATA FOR RABBITS THAT WERE FOUND DEAD, MORIBUND SACRIFICED OR ABORTED

DOSAGE GROUP DOSAGE (MG/KG/DAY)c	RABBIT NUMBER	DAY OF DEATH	CORPORA LUTEA R	L	T	IMPLANTATIONS R	L	T	EMBRYOS/FETUSES a R	L	A	T	RESORPTIONS b R	L	A	T
V																
25	7371	MORIBUND SACRIFICED ON DAY 15 OF GESTATION	3	5	8	2	5	7	2	3	0	5	0	2	0	2
	8222	MORIBUND SACRIFICED ON DAY 15 OF GESTATION	6	4	10	6	4	10	6	4	0	10	0	0	0	0
	8223	MORIBUND SACRIFICED ON DAY 15 OF GESTATION	5	5	10	4	3	7	4	3	0	7	0	0	0	0
	8224	MORIBUND SACRIFICED ON DAY 15 OF GESTATION	5	5	10	5	5	10	5	5	0	10	0	0	0	0
	8225	MORIBUND SACRIFICED ON DAY 15 OF GESTATION	5	6	11	5	6	11	5	6	0	11	0	0	0	0
VI																
50	8226	FOUND DEAD ON DAY 14 OF GESTATION	7	4	11	3	4	7	3	3	0	6d	0	1	0	1
	8227	MORIBUND SACRIFICED ON DAY 15 OF GESTATION	5	6	11	5	6	11	5	6	0	11	0	0	0	0
	8228	MORIBUND SACRIFICED ON DAY 15 OF GESTATION	2	1	3	1	1	2	1	1	0	2	0	0	0	0
	8229	FOUND DEAD ON DAY 12 OF GESTATION	7	6	13	7	6	13	7	6	0	13d	0	0	0	0
	8230	MORIBUND SACRIFICED ON DAY 15 OF GESTATION	7	5	12	3	2	5	3	2	0	5	0	0	0	0

R = RIGHT L = LEFT T = TOTAL A = ABORTED

a. Conceptuses appeared normal for developmental ages.
b. Early resorptions, unless noted otherwise.
c. Dosage occurred on days 7 through 20 of presumed gestation.
d. Unable to determine viability of conceptuses because of death of doe.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 3 (PAGE 3): UTERINE CONTENTS AND LITTER DATA FOR RABBITS THAT WERE FOUND DEAD, MORIBUND SACRIFICED OR ABORTED

DOSAGE GROUP DOSAGE (MG/KG/DAY) c	RABBIT NUMBER	DAY OF DEATH	CORPORA LUTEA R	L	T	IMPLANTATIONS R	L	T	EMBRYOS/FETUSES a R	L	A	T	RESORPTIONS b R	L	A	T
VII 75	8231	MORIBUND SACRIFICED ON DAY 15 OF GESTATION	0	4	4	0	4	4	0	0	0	0	0	4	0	4
	8232	MORIBUND SACRIFICED ON DAY 15 OF PRESUMED GESTATION	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	8233	FOUND DEAD ON DAY 15 OF GESTATION	2	9	11	1	9	10	1	8	0	9d	0	1	0	1
	8234	MORIBUND SACRIFICED ON DAY 15 OF GESTATION	4	3	7	3	3	6	3	3	0	6	0	0	0	0
	8235	MORIBUND SACRIFICED ON DAY 15 OF GESTATION	6	5	11	6	4	10	6	4	0	10	0	0	0	0

R = RIGHT L = LEFT T = TOTAL A = ABORTED
a. Conceptuses appeared normal for developmental ages.
b. Early resorptions, unless noted otherwise.
c. Dosage occurred on days 7 through 20 of presumed gestation.
d. Unable to determine viability of conceptuses because of death of doe.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 4 (PAGE 1): MATERNAL BODY WEIGHTS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 1	III 5	IV 10
RABBITS TESTED	N	5	5	5	5
PREGNANT	N	5	5	5	5
MATERNAL BODY WEIGHT (KG)					
DAY 0	MEAN±S.D.	3.80 ± 0.36	3.84 ± 0.24	3.95 ± 0.28	3.79 ± 0.28
DAY 7	MEAN±S.D.	3.76 ± 0.17	3.97 ± 0.18	4.10 ± 0.30	3.98 ± 0.29
DAY 8	MEAN±S.D.	3.77 ± 0.18	4.00 ± 0.17	4.06 ± 0.30	3.88 ± 0.28
DAY 9	MEAN±S.D.	3.82 ± 0.19	4.02 ± 0.17	4.06 ± 0.33	3.81 ± 0.25
DAY 10	MEAN±S.D.	3.83 ± 0.17	4.05 ± 0.18	3.98 ± 0.30	3.70 ± 0.25
DAY 11	MEAN±S.D.	3.81 ± 0.16	4.05 ± 0.15	3.93 ± 0.30	3.61 ± 0.21
DAY 12	MEAN±S.D.	3.83 ± 0.16	4.07 ± 0.14	3.88 ± 0.24	3.54 ± 0.23
DAY 13	MEAN±S.D.	3.86 ± 0.15	4.09 ± 0.13	3.83 ± 0.28	3.51 ± 0.20
DAY 14	MEAN±S.D.	3.90 ± 0.17	4.13 ± 0.12	3.85 ± 0.24	3.46 ± 0.21
DAY 15	MEAN±S.D.	3.92 ± 0.18	4.17 ± 0.14	3.86 ± 0.23	3.45 ± 0.22
DAY 16	MEAN±S.D.	3.92 ± 0.16	4.21 ± 0.10	3.76 ± 0.24	3.42 ± 0.19
DAY 17	MEAN±S.D.	3.94 ± 0.16	4.22 ± 0.10 [4]b	3.78 ± 0.18	3.42 ± 0.20
DAY 18	MEAN±S.D.	3.96 ± 0.17	4.20 ± 0.10 [4]b	3.76 ± 0.12	3.40 ± 0.18
DAY 19	MEAN±S.D.	3.98 ± 0.16	4.22 ± 0.10 [4]b	3.77 ± 0.16	3.37 ± 0.19
DAY 20	MEAN±S.D.	3.99 ± 0.15	4.24 ± 0.12 [4]b	3.75 ± 0.14	3.36 ± 0.19

DAY = DAY OF GESTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 20 of gestation.
b. Excludes values for a rabbit that was found dead.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 4 (PAGE 2): MATERNAL BODY WEIGHTS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 1	III 5	IV 10
RABBITS TESTED	N	5	5	5	5
PREGNANT	N	5	5	5	5
INCLUDED IN ANALYSES	N	5	4b	5	5
MATERNAL BODY WEIGHT (KG)					
DAY 21	MEAN±S.D.	4.02 ± 0.15	4.27 ± 0.13	3.72 ± 0.15	3.29 ± 0.18
DAY 22	MEAN±S.D.	4.03 ± 0.14	4.28 ± 0.11	3.69 ± 0.19	3.18 ± 0.21 [3]b
DAY 23	MEAN±S.D.	4.03 ± 0.13	4.34 ± 0.10	3.63 ± 0.20	3.22 ± 0.19 [2]b
DAY 24	MEAN±S.D.	4.02 ± 0.14	4.35 ± 0.10	3.69 ± 0.11 [4]b	3.28 ± 0.00 [1]b
DAY 25	MEAN±S.D.	4.01 ± 0.14	4.38 ± 0.10	3.68 ± 0.15 [4]b	3.25 ± 0.00 [1]b
DAY 26	MEAN±S.D.	4.03 ± 0.16	4.41 ± 0.08	3.70 ± 0.16 [2]b	b
DAY 27	MEAN±S.D.	4.04 ± 0.17	4.42 ± 0.07	3.70 ± 0.23 [2]b	
DAY 28	MEAN±S.D.	4.06 ± 0.19	4.40 ± 0.03	3.70 ± 0.29 [2]b	
DAY 29	MEAN±S.D.	4.07 ± 0.24	4.42 ± 0.05	3.70 ± 0.36 [2]b	

DAY = DAY OF GESTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 20 of gestation.
b. Excludes values for rabbits that died or aborted.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 4 (PAGE 3): MATERNAL BODY WEIGHTS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		V 25	VI 50	VII 75
RABBITS TESTED	N	5	5	5
PREGNANT	N	5	5	4
MATERNAL BODY WEIGHT (KG)				
DAY 0	MEAN±S.D.	3.49 ± 0.25	3.81 ± 0.31	3.65 ± 0.39
DAY 7	MEAN±S.D.	3.60 ± 0.18	3.89 ± 0.25	3.76 ± 0.34
DAY 8	MEAN±S.D.	3.50 ± 0.17	3.78 ± 0.27	3.70 ± 0.29
DAY 9	MEAN±S.D.	3.41 ± 0.13	3.65 ± 0.24	3.63 ± 0.32
DAY 10	MEAN±S.D.	3.33 ± 0.16	3.56 ± 0.25	3.48 ± 0.40
DAY 11	MEAN±S.D.	3.26 ± 0.16	3.46 ± 0.22	3.34 ± 0.38
DAY 12	MEAN±S.D.	3.20 ± 0.13	3.39 ± 0.23	3.28 ± 0.37
DAY 13	MEAN±S.D.	3.15 ± 0.14	3.26 ± 0.22 [4]b	3.17 ± 0.34
DAY 14	MEAN±S.D.	3.09 ± 0.14	3.17 ± 0.24 [4]b	3.12 ± 0.31
DAY 15	MEAN±S.D.	b	b	b

DAY = DAY OF GESTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 20 of gestation.
b. Excludes values for rabbits that died or were moribund sacrificed.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 5 (PAGE 1): MATERNAL BODY WEIGHT CHANGES - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 1	III 5	IV 10
RABBITS TESTED	N	5	5	5	5
PREGNANT	N	5	5	5	5
MATERNAL BODY WEIGHT CHANGE (KG)					
DAYS 0 - 7	MEAN±S.D.	-0.04 ± 0.36	+0.14 ± 0.08	+0.16 ± 0.09	+0.19 ± 0.08
DAYS 7 - 10	MEAN±S.D.	+0.07 ± 0.02	+0.08 ± 0.04	-0.13 ± 0.08	-0.28 ± 0.06
DAYS 10 - 13	MEAN±S.D.	+0.03 ± 0.03	+0.04 ± 0.08	-0.14 ± 0.05	-0.19 ± 0.12
DAYS 13 - 16	MEAN±S.D.	+0.06 ± 0.04	+0.12 ± 0.04	-0.07 ± 0.12	-0.09 ± 0.02
DAYS 16 - 19	MEAN±S.D.	+0.05 ± 0.02	+0.04 ± 0.03 [4]b	+0.01 ± 0.12	-0.04 ± 0.07
DAYS 19 - 21	MEAN±S.D.	+0.04 ± 0.02	+0.04 ± 0.04 [4]b	-0.05 ± 0.04	-0.09 ± 0.03
DAYS 21 - 25	MEAN±S.D.	-0.01 ± 0.08	+0.12 ± 0.05 [4]b	-0.09 ± 0.14 [4]b	-0.22 ± 0.00 [1]b
DAYS 25 - 29	MEAN±S.D.	+0.06 ± 0.12	+0.04 ± 0.06 [4]b	+0.00 ± 0.25 [2]b	b
DAYS 7 - 21	MEAN±S.D.	+0.26 ± 0.08	+0.34 ± 0.07 [4]b	-0.38 ± 0.21	-0.69 ± 0.20
DAYS 7 - 29	MEAN±S.D.	+0.31 ± 0.11	+0.51 ± 0.14 [4]b	-0.58 ± 0.74 [2]b	b
DAYS 0 - 29	MEAN±S.D.	+0.27 ± 0.38	+0.66 ± 0.18 [4]b	-0.36 ± 0.74 [2]b	

DAYS = DAYS OF GESTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 20 of gestation.
b. Excludes values for rabbits that died or aborted.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 5 (PAGE 2): MATERNAL BODY WEIGHT CHANGES - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		V 25	VI 50	VII 75
RABBITS TESTED	N	5	5	5
PREGNANT	N	5	5	4
MATERNAL BODY WEIGHT CHANGE (KG)				
DAYS 0 - 7	MEAN±S.D.	+0.11 ± 0.07	+0.09 ± 0.10	+0.11 ± 0.06
DAYS 7 - 10	MEAN±S.D.	-0.27 ± 0.04	-0.33 ± 0.04	-0.28 ± 0.07
DAYS 10 - 13	MEAN±S.D.	-0.18 ± 0.12	-0.27 ± 0.05 [4]b	-0.32 ± 0.07
DAYS 13 - 16	MEAN±S.D.	b	b	b

DAYS = DAYS OF GESTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 20 of gestation.
b. Excludes values for rabbits that died or were moribund sacrificed.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 6 (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
RABBITS TESTED	N	5	5	5	5
PREGNANT	N	5	5	5	5
MATERNAL FEED CONSUMPTION (G/DAY)					
DAYS 7 - 10	MEAN±S.D.	165.2 ± 20.2	167.6 ± 14.1	111.9 ± 47.8	19.5 ± 6.1
DAYS 10 - 13	MEAN±S.D.	165.9 ± 21.1	158.9 ± 17.7	21.1 ± 29.0	0.7 ± 0.2
DAYS 13 - 16	MEAN±S.D.	169.2 ± 21.6	163.6 ± 20.8 [4]b	9.1 ± 15.8	7.2 ± 9.5
DAYS 16 - 19	MEAN±S.D.	167.2 ± 17.2	155.5 ± 40.1 [4]b	2.6 ± 1.1	9.1 ± 14.5
DAYS 19 - 21	MEAN±S.D.	156.6 ± 25.4	161.4 ± 25.0 [4]b	1.9 ± 1.3	1.4 ± 1.5
DAYS 21 - 25	MEAN±S.D.	114.1 ± 58.5	164.6 ± 8.7 [4]b	25.5 ± 46.6 [4]b	1.0 ± 0.0 [1]b
DAYS 25 - 29	MEAN±S.D.	101.9 ± 47.2	123.4 ± 26.0 [4]b	79.6 ±110.1 [2]b	b
DAYS 7 - 21	MEAN±S.D.	165.4 ± 17.9	162.0 ± 21.9 [4]b	31.3 ± 17.7	8.0 ± 5.6
DAYS 7 - 29	MEAN±S.D.	144.5 ± 24.5	155.4 ± 11.8 [4]b	46.2 ± 40.6 [2]b	b

DAYS = DAYS OF GESTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 20 of gestation.
b. Excludes values for rabbits that died or aborted.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 6 (PAGE 2): MATERNAL ABSOLUTE FEED CONSUMPTION VALUES (G/DAY) - SUMMARY

DOSAGE GROUP		V	VI	VII
DOSAGE (MG/KG/DAY)a		25	50	75
RABBITS TESTED	N	5	5	5
PREGNANT	N	5	5	4
MATERNAL FEED CONSUMPTION (G/DAY)				
DAYS 7 - 10	MEAN±S.D.	12.1 ± 6.7	5.4 ± 3.4	4.5 ± 2.6
DAYS 10 - 13	MEAN±S.D.	1.4 ± 1.9	0.8 ± 0.2 [4]b	0.1 ± 0.2
DAYS 13 - 16	MEAN±S.D.	b	b	b

DAYS = DAYS OF GESTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 20 of gestation.
b. Excludes values for rabbits that died or were moribund sacrificed.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 7 (PAGE 1): MATERNAL RELATIVE FEED CONSUMPTION VALUES (G/KG/DAY) - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE (MG/KG/DAY)a		0 (VEHICLE)	1	5	10
RABBITS TESTED	N	5	5	5	5
PREGNANT	N	5	5	5	5
MATERNAL FEED CONSUMPTION (G/KG/DAY)					
DAYS 7 - 10	MEAN±S.D.	43.5 ± 4.8	41.9 ± 4.6	27.4 ± 11.4	5.1 ± 1.5
DAYS 10 - 13	MEAN±S.D.	43.2 ± 4.8	39.1 ± 4.9	5.3 ± 7.3	0.2 ± 0.1
DAYS 13 - 16	MEAN±S.D.	43.3 ± 5.1	39.6 ± 4.7 [4]b	2.4 ± 4.0	2.2 ± 3.1
DAYS 16 - 18	MEAN±S.D.	42.2 ± 4.6	36.5 ± 9.0 [4]b	0.8 ± 0.5	3.0 ± 4.4
DAYS 16 - 19	MEAN±S.D.	42.3 ± 4.3	36.9 ± 9.4 [4]b	0.7 ± 0.3	2.8 ± 4.6
DAYS 19 - 21	MEAN±S.D.	39.2 ± 6.4	38.0 ± 5.4 [4]b	0.5 ± 0.3	0.4 ± 0.5
DAYS 21 - 25	MEAN±S.D.	28.3 ± 14.2	38.0 ± 1.1 [4]b	7.0 ± 12.7 [4]b	0.3 ± 0.0 [1]b
DAYS 25 - 29	MEAN±S.D.	24.9 ± 10.4	28.0 ± 6.1 [4]b	20.6 ± 28.4 [2]b	b
DAYS 7 - 21	MEAN±S.D.	42.5 ± 4.2	39.4 ± 5.2 [4]b	8.0 ± 4.4	2.3 ± 1.8
DAYS 7 - 29	MEAN±S.D.	36.6 ± 5.5	37.0 ± 2.7 [4]b	12.0 ± 10.7 [2]b	b

DAYS = DAYS OF GESTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 20 of gestation.
b. Excludes values for rabbits that died or aborted.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 7 (PAGE 2): MATERNAL RELATIVE FEED CONSUMPTION VALUES (G/KG/DAY) - SUMMARY

DOSAGE GROUP		V	VI	VII
DOSAGE (MG/KG/DAY)a		25	50	75
RABBITS TESTED	N	5	5	5
PREGNANT	N	5	5	4
MATERNAL FEED CONSUMPTION (G/KG/DAY)				
DAYS 7 - 10	MEAN±S.D.	3.5 ± 1.9	1.5 ± 1.0	1.3 ± 0.9
DAYS 10 - 13	MEAN±S.D.	0.4 ± 0.6	0.2 ± 0.0 [4]b	0.0 ± 0.0
DAYS 13 - 16	MEAN±S.D.	b	b	b

DAYS = DAYS OF GESTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 20 of gestation.
b. Excludes values for rabbits that died or were moribund sacrificed.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 8 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE (MG/KG/DAY)a		0 (VEHICLE)	1	5	10
RABBITS TESTED	N	5	5	5	5
PREGNANT	N(%)	5(100.0)	5(100.0)	5(100.0)	5(100.0)
FOUND DEAD	N(%)	0(0.0)	1(20.0)	0(0.0)	0(0.0)
ABORTED	N(%)	0(0.0)	0(0.0)	3(60.0)	5(100.0)
MORIBUND SACRIFICED	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
RABBITS PREGNANT AND CAESAREAN-SECTIONED ON DAY 29 OF GESTATION	N	5	4	2	0
CORPORA LUTEA	MEAN±S.D.	10.8 ± 2.6	11.2 ± 1.5	11.0 ± 2.8	
IMPLANTATIONS	MEAN±S.D.	8.2 ± 3.8	10.2 ± 1.0	10.0 ± 2.8	
LITTER SIZES	MEAN±S.D.	7.0 ± 3.4	8.5 ± 3.1	6.5 ± 2.1	
LIVE FETUSES	N	35	34	13	
	MEAN±S.D.	7.0 ± 3.4	8.5 ± 3.1	6.5 ± 2.1	
DEAD FETUSES	N	0	0	0	
RESORPTIONS	MEAN±S.D.	1.2 ± 0.8	1.8 ± 2.9	3.5 ± 0.7	
EARLY RESORPTIONS	N	4	7	0	
	MEAN±S.D.	0.8 ± 0.8	1.8 ± 2.9	0.0 ± 0.0	
LATE RESORPTIONS	N	2	0	7	
	MEAN±S.D.	0.4 ± 0.5	0.0 ± 0.0	3.5 ± 0.7	
DOES WITH ANY RESORPTIONS	N(%)	4(80.0)	2(50.0)	2(100.0)	
DOES WITH ALL CONCEPTUSES RESORBED	N	0	0	0	
DOES WITH VIABLE FETUSES	N(%)	5(100.0)	4(100.0)	2(100.0)	
PLACENTAE APPEARED NORMAL	N(%)	5(100.0)	4(100.0)	2(100.0)	

a. Dosage occurred on days 7 through 20 of gestation.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 8 (PAGE 2): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY

DOSAGE GROUP		V	VI	VII
DOSAGE (MG/KG/DAY)a		25	50	75
RABBITS TESTED	N	5	5	5
PREGNANT	N(%)	5(100.0)	5(100.0)	4(80.0)
FOUND DEAD	N(%)	0(0.0)	2(40.0)	1(20.0)
ABORTED	N(%)	0(0.0)	0(0.0)	0(0.0)
MORIBUND SACRIFICED	N(%)	5(100.0)	3(60.0)	3(60.0)
RABBITS PREGNANT AND CAESAREAN-SECTIONED ON DAY 29 OF GESTATION	N	0	0	0

a. Dosage occurred on days 7 through 20 of gestation.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 9 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 1	III 5	IV 10
LITTERS WITH ONE OR MORE LIVE FETUSES	N	5	4	2	0
IMPLANTATIONS	MEAN±S.D.	8.2 ± 3.8	10.2 ± 1.0	10.0 ± 2.8	
LIVE FETUSES	N	35	34	13	
	MEAN±S.D.	7.0 ± 3.4	8.5 ± 3.1	6.5 ± 2.1	
LIVE MALE FETUSES	N	24	15	5	
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	73.1 ± 20.3	45.0 ± 4.1	38.8 ± 1.8	
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	45.66 ± 5.70	46.50 ± 6.26	23.80 ± 6.68	
MALE FETUSES	MEAN±S.D.	46.30 ± 5.33	46.75 ± 4.85	25.51 ± 3.55	
FEMALE FETUSES	MEAN±S.D.	44.74 ± 7.45 [4]b	46.44 ± 7.60	22.64 ± 8.73	
% RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	15.0 ± 10.9	17.3 ± 28.8	35.4 ± 3.0	

[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 20 of gestation.
b. Litter 8201 had no female fetuses.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 9 (PAGE 2): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - SUMMARY

DOSAGE GROUP		V	VI	VII
DOSAGE (MG/KG/DAY)a		25	50	75
LITTERS WITH ONE OR MORE LIVE FETUSES	N	0	0	0

a. Dosage occurred on days 7 through 17 of gestation.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

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

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 1	III 5	IV 10
LITTERS EVALUATED	N	5	4	2	0
FETUSES EVALUATED	N	35	34	13	0
LIVE	N	35	34	13	0
BODY: ABDOMINAL DISTENTION					
LITTER INCIDENCE	N(%)	0(0.0)	1(25.0)	0(0.0)	
FETAL INCIDENCE	N(%)	0(0.0)	1(2.9)	0(0.0)	
TONGUE: PROTRUDED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(50.0)	
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(7.7)b	
EYELIDS: OPENED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(50.0)	
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(7.7)b	
FORE AND/OR HINDLIMBS: FLEXED DOWNWARD					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(50.0)	
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(7.7)c	
INCISORS: ABSENT					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(50.0)	
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(7.7)c	
SNOUT: CLEFT					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(50.0)	
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(7.7)c	
EYES: LARGE					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(50.0)	
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(7.7)c	

a. Dosage occurred on days 7 through 20 of gestation.
b. Fetus 7385-1 had other gross external alterations.
c. Fetus 7385-4 had other gross external alterations.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 10 (PAGE 2): FETAL GROSS EXTERNAL ALTERATIONS - SUMMARY

DOSAGE GROUP		V	VI	VII
DOSAGE (MG/KG/DAY)a		25	50	75
LITTERS EVALUATED	N	0	0	0
FETUSES EVALUATED	N	0	0	0
LIVE	N	0	0	0

a. Dosage occurred on days 7 through 20 of gestation.

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TABLE 11 (PAGE 1): CLINICAL OBSERVATIONS - INDIVIDUAL DATA

RABBIT #		DESCRIPTION
DOSAGE GROUP I		0 (VEHICLE)MG/KG/DAY
8201		NO ADVERSE FINDINGS
8202	DG(29)	LOCALIZED ALOPECIA: BACK a
8203		NO ADVERSE FINDINGS
8204		NO ADVERSE FINDINGS
8205		NO ADVERSE FINDINGS
DOSAGE GROUP II		1 MG/KG/DAY
8206	DG(16)	FOUND DEAD
8207	DG(19)	RED SUBSTANCE IN CAGE PAN
8208		NO ADVERSE FINDINGS
8209	DG(28- 29)	LOCALIZED ALOPECIA: LIMBS a
	DG(29)	LOCALIZED ALOPECIA: BACK a
8210		NO ADVERSE FINDINGS

DG = DAY OF PRESUMED GESTATION
a. Observation confirmed at necropsy.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 11 (PAGE 2): CLINICAL OBSERVATIONS - INDIVIDUAL DATA

RABBIT #		DESCRIPTION
DOSAGE GROUP III		5 MG/KG/DAY
8211	DG(10- 25)	SCANT FECES
	DG(17)	NO FECES
	DG(22)	SOFT OR LIQUID FECES
	DG(26)	RED SUBSTANCE IN CAGE PAN
	DG(26)	ABORTED AND SACRIFICED
8212	DG(10- 23)	SCANT FECES
	DG(20)	RED SUBSTANCE IN CAGE PAN
	DG(20- 21)	LEFT FOREPAW: ABRASION
	DG(22)	ABRASION NO LONGER APPARENT
	DG(22)	SOFT OR LIQUID FECES
	DG(24)	ABORTED AND SACRIFICED
8213	DG(13- 25)	SCANT FECES
8214	DG(17- 19)	NO FECES
	DG(20- 25)	SCANT FECES
	DG(26)	RED SUBSTANCE IN CAGE PAN
	DG(26)	ABORTED AND SACRIFICED
7385	DG(7- 21)	LEFT HINDPAW: ABRASION (DID NOT EXCEED 0.5 CM IN DIAMETER)
	DG(22)	ABRASION NO LONGER APPARENT
	DG(10- 20)	SCANT FECES
	DG(12- 13)	SOFT OR LIQUID FECES
	DG(12- 22)	UNGROOMED COAT
	DG(21- 24)	NO FECES
	DG(26)	SCANT FECES
	DG(27)	NO FECES
	DG(28)	SCANT FECES
	DG(29)	NO FECES

DG = DAY OF PRESUMED GESTATION

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 11 (PAGE 3): CLINICAL OBSERVATIONS - INDIVIDUAL DATA

RABBIT #		DESCRIPTION
DOSAGE GROUP IV		10 MG/KG/DAY
8216	DG(10)	NO FECES
	DG(11- 15)	SCANT FECES
	DG(17- 19)	SCANT FECES
	DG(20)	NO FECES
	DG(21)	SCANT FECES
	DG(22)	NO FECES
	DG(23- 25)	SCANT FECES
	DG(24)	DARK URINE
	DG(25)	SOFT OR LIQUID FECES
	DG(26)	RED SUBSTANCE IN CAGE PAN
	DG(26)	ABORTED AND SACRIFICED
8217	DG(9- 18)	SCANT FECES
	DG(19- 20)	NO FECES
	DG(21)	RED SUBSTANCE IN CAGE PAN
	DG(21)	SCANT FECES
	DG(22)	ABORTED AND SACRIFICED
8218	DG(9- 11)	SOFT OR LIQUID FECES
	DG(10- 21)	SCANT FECES
	DG(22)	NO FECES
	DG(23)	SCANT FECES
	DG(24)	ABORTED AND SACRIFICED
8219	DG(9- 16)	SCANT FECES
	DG(17- 20)	NO FECES
	DG(21)	RED SUBSTANCE IN CAGE PAN
	DG(21)	SCANT FECES
	DG(21)	DARK URINE
	DG(22)	ABORTED AND SACRIFICED
8220	DG(9- 22)	SCANT FECES
	DG(11- 13)	SOFT OR LIQUID FECES
	DG(23)	ABORTED AND SACRIFICED

DG = DAY OF PRESUMED GESTATION

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 11 (PAGE 4): CLINICAL OBSERVATIONS - INDIVIDUAL DATA

RABBIT #		DESCRIPTION
DOSAGE GROUP V		25 MG/KG/DAY
7371	DG(9- 11)	SCANT FECES
	DG(12- 13)	NO FECES
	DG(14)	SCANT FECES
	DG(15)	MORIBUND SACRIFICED
8222	DG(9- 14)	SCANT FECES
	DG(15)	MORIBUND SACRIFICED
8223	DG(10- 14)	SCANT FECES
	DG(15)	MORIBUND SACRIFICED
8224	DG(10- 14)	SCANT FECES
	DG(11)	DECREASED MOTOR ACTIVITY
	DG(11)	IMPAIRED RIGHTING REFLEX
	DG(13- 14)	UNGROOMED COAT
	DG(15)	MORIBUND SACRIFICED
8225	DG(10- 14)	SCANT FECES
	DG(12- 14)	UNGROOMED COAT
	DG(15)	MORIBUND SACRIFICED

DG = DAY OF PRESUMED GESTATION

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 11 (PAGE 5): CLINICAL OBSERVATIONS - INDIVIDUAL DATA

RABBIT #		DESCRIPTION
DOSAGE GROUP VI		50 MG/KG/DAY
8226	DG(9- 13)	SOFT OR LIQUID FECES
	DG(10- 13)	SCANT FECES
	DG(14)	DECREASED MOTOR ACTIVITY
	DG(14)	LOST RIGHTING REFLEX
	DG(14)	NO FECES
	DG(14)	FOUND DEAD
8227	DG(10- 14)	SCANT FECES
	DG(14)	DECREASED MOTOR ACTIVITY
	DG(14)	DRIED YELLOW BROWN PERIORAL SUBSTANCE
	DG(15)	MORIBUND SACRIFICED
8228	DG(10- 14)	SCANT FECES
	DG(14)	DECREASED MOTOR ACTIVITY
	DG(14)	DRIED YELLOW PERIORAL SUBSTANCE
	DG(15)	MORIBUND SACRIFICED
8229	DG(9)	SOFT OR LIQUID FECES
	DG(10- 11)	SCANT FECES
	DG(12)	FOUND DEAD
8230	DG(10- 13)	SCANT FECES
	DG(10- 13)	SOFT OR LIQUID FECES
	DG(14)	DECREASED MOTOR ACTIVITY
	DG(14)	DRIED YELLOW PERIORAL SUBSTANCE
	DG(14)	NO FECES
	DG(15)	MORIBUND SACRIFICED

DG = DAY OF PRESUMED GESTATION

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 11 (PAGE 6): CLINICAL OBSERVATIONS - INDIVIDUAL DATA

RABBIT #		DESCRIPTION
DOSAGE GROUP VII		75 MG/KG/DAY
8231	DG(9- 14)	SCANT FECES
	DG(12- 14)	UNGROOMED COAT a
	DG(13- 14)	DECREASED MOTOR ACTIVITY
	DG(13- 14)	DRIED BROWN PERIORAL SUBSTANCE a
	DG(15)	MORIBUND SACRIFICED
8232	DG(9- 14)	SCANT FECES
	DG(13)	SOFT OR LIQUID FECES
	DG(13- 14)	DECREASED MOTOR ACTIVITY
	DG(13- 15)	DRIED YELLOW PERIORAL SUBSTANCE
	DG(13- 14)	UNGROOMED COAT
	DG(15)	RED SUBSTANCE IN CAGE PAN
	DG(15)	MORIBUND SACRIFICED
8233	DG(9- 13)	SCANT FECES
	DG(9- 13)	SOFT OR LIQUID FECES
	DG(13- 14)	DECREASED MOTOR ACTIVITY
	DG(14)	EXCESS SALIVATION
	DG(14)	NO FECES
	DG(15)	FOUND DEAD
8234	DG(9- 14)	UNGROOMED COAT
	DG(9- 14)	SOFT OR LIQUID FECES
	DG(12- 14)	SCANT FECES
	DG(13- 14)	DECREASED MOTOR ACTIVITY
	DG(15)	MORIBUND SACRIFICED
8235	DG(9)	SOFT OR LIQUID FECES
	DG(10)	IMPAIRED RIGHTING REFLEX
	DG(10- 11)	SCANT FECES
	DG(10- 14)	DECREASED MOTOR ACTIVITY
	DG(12- 15)	UNGROOMED COAT
	DG(12- 14)	NO FECES
	DG(13- 14)	IMPAIRED RIGHTING REFLEX
	DG(14)	COLD TO TOUCH
	DG(14- 15)	EMACIATION
	DG(15)	RED SUBSTANCE IN CAGE PAN
	DG(15)	MORIBUND SACRIFICED

DG = DAY OF PRESUMED GESTATION
a. Observation confirmed at necropsy.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 12 (PAGE 1): NECROPSY OBSERVATIONS - INDIVIDUAL DATA

DOSAGE GROUP DOSAGE (MG/KG/DAY)	RABBIT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
I					
0 (VEHICLE)	8201	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8202	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8203	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8204	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8205	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
II					
1	8206	DG 16	P	10	FOUND DEAD ON DAY 16 OF GESTATION (DEATH OCCURRED 13 MINUTES AFTER DOSAGE). ALL TISSUES APPEARED NORMAL.
	8207	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8208	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8209	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8210	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
III					
5	8211	DG 26	P	14	ABORTED ON DAY 26 OF GESTATION. ALL TISSUES APPEARED NORMAL.
	8212	DG 24	P	14	ABORTED ON DAY 24 OF GESTATION. ALL TISSUES APPEARED NORMAL.
	8213	DG 29	P	14	ALL TISSUES APPEARED NORMAL.
	8214	DG 26	P	14	ABORTED ON DAY 26 OF GESTATION. ALL TISSUES APPEARED NORMAL.
	7385	DG 29	P	14	LIVER: ALL LOBES, PALE. ALL OTHER TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION
a. Refer to the individual clinical observations table (Table 11) for external observations confirmed at necropsy.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 12 (PAGE 2): NECROPSY OBSERVATIONS - INDIVIDUAL DATA

DOSAGE GROUP DOSAGE (MG/KG/DAY)	RABBIT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
IV 10	8216	DG 26	P	14	ABORTED ON DAY 26 OF GESTATION. LIVER: ALL LOBES, PALE TAN AREAS (1.5 CM X 1.0 CM TO 4.0 CM X 1.6 CM). ALL OTHER TISSUES APPEARED NORMAL.
	8217	DG 22	P	14	ABORTED ON DAY 22 OF GESTATION. ALL TISSUES APPEARED NORMAL.
	8218	DG 24	P	14	ABORTED ON DAY 24 OF GESTATION. ALL TISSUES APPEARED NORMAL.
	8219	DG 22	P	14	ABORTED ON DAY 22 OF GESTATION. LIVER: ALL LOBES, PALE. ALL OTHER TISSUES APPEARED NORMAL.
	8220	DG 23	P	14	ABORTED ON DAY 23 OF GESTATION. ALL TISSUES APPEARED NORMAL.
V 25	7371	DG 15	P	9	MORIBUND SACRIFICED ON DAY 15 OF GESTATION. ALL TISSUES APPEARED NORMAL.
	8222	DG 15	P	9	MORIBUND SACRIFICED ON DAY 15 OF GESTATION. ALL TISSUES APPEARED NORMAL.
	8223	DG 15	P	9	MORIBUND SACRIFICED ON DAY 15 OF GESTATION. ALL TISSUES APPEARED NORMAL.
	8224	DG 15	P	9	MORIBUND SACRIFICED ON DAY 15 OF GESTATION. ALL TISSUES APPEARED NORMAL.
	8225	DG 15	P	9	MORIBUND SACRIFICED ON DAY 15 OF GESTATION. ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION
a. Refer to the individual clinical observations table (Table 11) for external observations confirmed at necropsy.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 12 (PAGE 3): NECROPSY OBSERVATIONS - INDIVIDUAL DATA

DOSAGE GROUP DOSAGE (MG/KG/DAY)	RABBIT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
VI 50	8226	DG 14	P	8	FOUND DEAD ON DAY 14 OF GESTATION (DEATH OCCURRED 1 HOUR AND 33 MINUTES AFTER DOSAGE). STOMACH: MUCOSA, BLACK VISCOUS MATERIAL. ALL OTHER TISSUES APPEARED NORMAL.
	8227	DG 15	P	9	MORIBUND SACRIFICED ON DAY 15 OF GESTATION. ALL TISSUES APPEARED NORMAL.
	8228	DG 15	P	9	MORIBUND SACRIFICED ON DAY 15 OF GESTATION. ALL TISSUES APPEARED NORMAL.
	8229	DG 12	P	6	FOUND DEAD ON DAY 12 OF GESTATION (DEATH OCCURRED 11 HOURS AND 53 MINUTES AFTER DOSAGE). LIVER: ALL LOBES, GREEN-GREY AREAS. THORACIC CAVITY: TAN-GREY FLUID (APPROXIMATELY 30 ML). LUNGS: ALL LOBES, TAN-GREY. ALL OTHER TISSUES APPEARED NORMAL FOR THE SLIGHT DEGREE OF AUTOLYSIS.
	8230	DG 15	P	9	MORIBUND SACRIFICED ON DAY 15 OF GESTATION. ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION
a. Refer to the individual clinical observations table (Table 11) for external observations confirmed at necropsy.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 12 (PAGE 4): NECROPSY OBSERVATIONS - INDIVIDUAL DATA

DOSAGE GROUP DOSAGE (MG/KG/DAY)	RABBIT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
VII 75	8231	DG 15	P	9	MORIBUND SACRIFICED ON DAY 15 OF GESTATION. ALL TISSUES APPEARED NORMAL.
	8232	DG 15	NP	9	MORIBUND SACRIFICED ON DAY 15 OF PRESUMED GESTATION. ALL TISSUES APPEARED NORMAL.
	8233	DG 15	P	9	FOUND DEAD ON DAY 15 OF GESTATION (DEATH OCCURRED OVERNIGHT). ABDOMINAL CAVITY: THIN BROWN FLUID (APPROXIMATELY 18 ML). STOMACH: FRIABLE; MUCOSA, VISCOUS BROWN MATERIAL. ALL OTHER TISSUES APPEARED NORMAL.
	8234	DG 15	P	9	MORIBUND SACRIFICED ON DAY 15 OF GESTATION. ALL TISSUES APPEARED NORMAL.
	8235	DG 15	P	9	MORIBUND SACRIFICED ON DAY 15 OF GESTATION. STOMACH: MUCOSA, BLACK VISCOUS MATERIAL. ALL OTHER TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION
a. Refer to the individual clinical observations table (Table 11) for external observations confirmed at necropsy.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 13 (PAGE 1): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

RABBIT #	DOSAGE GROUP I	0 (VEHICLE) MG/KG/DAY											
	PREGNANCY STATUS	DAY 0	7	8	9	10	11	12	13	14	15	16	17	18
8201	P	4.40	3.72	3.67	3.72	3.75	3.74	3.78	3.80	3.78	3.79	3.81	3.82	3.84
8202	P	3.69	3.82	3.84	3.92	3.90	3.92	3.95	3.97	4.01	4.03	4.07	4.08	4.11
8203	P	3.86	4.02	4.06	4.11	4.09	4.05	4.05	4.07	4.15	4.18	4.11	4.14	4.16
8204	P	3.53	3.58	3.60	3.64	3.67	3.68	3.70	3.72	3.75	3.76	3.76	3.77	3.78
8205	P	3.51	3.67	3.67	3.70	3.73	3.68	3.69	3.74	3.83	3.86	3.86	3.90	3.91

	DAY 19	20	21	22	23	24	25	26	27	28	29
8201	P	3.85	3.87	3.88	3.93	3.92	3.93	3.94	3.95	3.93	3.97	4.03
8202	P	4.11	4.10	4.12	4.13	4.11	4.05	3.99	4.04	4.09	4.14	4.10
8203	P	4.18	4.19	4.22	4.19	4.21	4.25	4.26	4.29	4.30	4.34	4.41
8204	P	3.80	3.82	3.86	3.86	3.89	3.90	3.89	3.87	3.87	3.83	3.73
8205	P	3.94	3.99	4.01	4.03	4.01	3.97	3.99	3.98	4.02	4.04	4.09

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 13 (PAGE 2): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

RABBIT #	DOSAGE GROUP II				1 MG/KG/DAY								
PREGNANCY STATUS	DAY 0	7	8	9	10	11	12	13	14	15	16	17	18
8206 P	4.13	4.17	4.19	4.19	4.24	4.22	4.26	4.24	4.23	4.30	4.32	a	
8207 P	3.73	3.84	3.89	3.96	3.99	4.00	4.00	4.01	4.08	4.06	4.17	4.20	4.18
8208 P	3.83	4.04	4.04	4.06	4.09	4.10	4.12	4.20	4.24	4.31	4.28	4.33	4.30
8209 P	3.98	4.08	4.10	4.14	4.15	4.12	4.10	4.10	4.16	4.18	4.23	4.26	4.26
8210 P	3.51	3.72	3.76	3.77	3.78	3.83	3.89	3.92	3.94	4.01	4.06	4.08	4.08
	DAY 19	20	21	22	23	24	25	26	27	28	29		
8206 P	FOUND DEAD ON DAY 16 OF GESTATION												
8207 P	4.17	4.13	4.16	4.17	4.26	4.26	4.32	4.36	4.38	4.38	4.36		
8208 P	4.34	4.36	4.39	4.38	4.43	4.47	4.50	4.49	4.50	4.45	4.47		
8209 P	4.28	4.32	4.37	4.36	4.42	4.41	4.42	4.46	4.45	4.41	4.46		
8210 P	4.11	4.13	4.16	4.20	4.24	4.27	4.29	4.32	4.34	4.38	4.41		

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.
a. Doe 8206 was found dead on day 16 of gestation.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 13 (PAGE 3): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

RABBIT #	DOSAGE GROUP III	5 MG/KG/DAY											
	PREGNANCY STATUS	DAY 0	7	8	9	10	11	12	13	14	15	16	17	18
8211	P	4.09	4.11	4.13	4.01	3.92	3.80	3.76	3.74	3.86	3.90	3.79	3.75	3.75
8212	P	3.61	3.72	3.64	3.61	3.56	3.51	3.54	3.43	3.44	3.49	3.38	3.49	3.56
8213	P	3.80	4.02	4.00	4.06	4.03	4.02	3.94	3.88	3.93	3.84	3.69	3.78	3.76
8214	P	3.92	4.10	4.06	4.07	3.99	3.98	3.97	3.92	3.94	3.95	3.94	3.90	3.85
7385	P	4.33	4.56	4.49	4.53	4.40	4.34	4.18	4.20	4.07	4.11	3.99	3.96	3.88

	DAY 19	20	21	22	23	24	25	26	27	28	29
8211 P	3.66	3.70	3.64	3.64	3.56	3.57	3.48	ABORTED ON DAY 26 OF GESTATION			
8212 P	3.54	3.57	3.52	3.41	3.40	ABORTED ON DAY 24 OF GESTATION					
8213 P	3.81	3.70	3.70	3.66	3.55	3.68	3.79	3.81	3.87	3.91	3.96
8214 P	3.90	3.87	3.89	3.92	3.91	3.84	3.81	ABORTED ON DAY 26 OF GESTATION			
7385 P	3.92	3.90	3.86	3.80	3.73	3.68	3.63	3.58	3.54	3.50	3.45

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 13 (PAGE 4): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

RABBIT #	DOSAGE GROUP IV				10 MG/KG/DAY								
PREGNANCY STATUS	DAY 0	7	8	9	10	11	12	13	14	15	16	17	18
8216 P	4.08	4.26	4.16	4.13	3.98	3.90	3.82	3.75	3.69	3.71	3.65	3.60	3.54
8217 P	3.75	4.02	3.93	3.82	3.71	3.65	3.60	3.64	3.55	3.58	3.53	3.58	3.55
8218 P	3.81	4.09	3.88	3.74	3.75	3.55	3.48	3.41	3.42	3.40	3.34	3.28	3.28
8219 P	3.96	4.05	4.00	3.90	3.78	3.65	3.61	3.53	3.52	3.46	3.44	3.51	3.46
8220 P	3.35	3.48	3.42	3.44	3.29	3.32	3.19	3.24	3.12	3.11	3.14	3.15	3.15

	DAY 19	20	21	22	23	24	25	26	27	28	29
8216 P	3.54	3.47	3.47	3.40	3.36	3.28	3.25	ABORTED ON DAY 26 OF GESTATION			
8217 P	3.55	3.56	3.44	ABORTED ON DAY 22 OF GESTATION							
8218 P	3.20	3.23	3.16	3.17	3.09	ABORTED ON DAY 24 OF GESTATION					
8219 P	3.44	3.45	3.32	ABORTED ON DAY 22 OF GESTATION							
8220 P	3.14	3.11	3.06	2.98	ABORTED ON DAY 23 OF GESTATION						

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 13 (PAGE 5): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

RABBIT #	DOSAGE GROUP V												
	25 MG/KG/DAY												
PREGNANCY STATUS	DAY 0	7	8	9	10	11	12	13	14	15	16	17	18
7371 P	3.14	3.34	3.26	3.28	3.11	3.06	3.10	3.14	2.98	a			
8222 P	3.63	3.70	3.56	3.46	3.42	3.30	3.23	3.18	3.15	b			
8223 P	3.79	3.82	3.72	3.60	3.53	3.49	3.41	3.38	3.30	c			
8224 P	3.52	3.61	3.50	3.38	3.28	3.24	3.14	3.04	2.99	d			
8225 P	3.39	3.55	3.47	3.31	3.31	3.19	3.11	3.03	3.02	e			
	DAY 19	20	21	22	23	24	25	26	27	28	29		
7371 P	MORIBUND SACRIFICED ON DAY 15 OF GESTATION												
8222 P	MORIBUND SACRIFICED ON DAY 15 OF GESTATION												
8223 P	MORIBUND SACRIFICED ON DAY 15 OF GESTATION												
8224 P	MORIBUND SACRIFICED ON DAY 15 OF GESTATION												
8225 P	MORIBUND SACRIFICED ON DAY 15 OF GESTATION												

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.

a. Doe 7371 was moribund sacrificed on day 15 of gestation.
b. Doe 8222 was moribund sacrificed on day 15 of gestation.
c. Doe 8223 was moribund sacrificed on day 15 of gestation.
d. Doe 8224 was moribund sacrificed on day 15 of gestation.
e. Doe 8225 was moribund sacrificed on day 15 of gestation.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 13 (PAGE 6): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

RABBIT #	DOSAGE GROUP VI				50 MG/KG/DAY								
	PREGNANCY STATUS	DAY 0	7	8	9	10	11	12	13	14	15	16	17	18
8226	P	4.21	4.17	4.07	3.90	3.84	3.70	3.61	3.52	3.43	a			
8227	P	3.76	3.89	3.70	3.63	3.51	3.40	3.36	3.26	3.18	b			
8228	P	3.83	3.84	3.83	3.63	3.57	3.45	3.35	3.27	3.23	c			
8229	P	3.89	4.05	3.95	3.80	3.72	3.64	3.60	FOUND DEAD ON DAY 12 OF GESTATION					
8230	P	3.34	3.51	3.36	3.28	3.17	3.13	3.05	2.97	2.85	d			

	DAY 19	20	21	22	23	24	25	26	27	28	29
8226	P	FOUND DEAD ON DAY 14 OF GESTATION									
8227	P	MORIBUND SACRIFICED ON DAY 15 OF GESTATION									
8228	P	MORIBUND SACRIFICED ON DAY 15 OF GESTATION									
8229	P	FOUND DEAD ON DAY 12 OF GESTATION									
8230	P	MORIBUND SACRIFICED ON DAY 15 OF GESTATION									

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.
a. Doe 8226 was found dead on day 14 of gestation
b. Doe 8227 was moribund sacrificed on day 15 of gestation.
c. Doe 8228 was moribund sacrificed on day 15 of gestation.
d. Doe 8230 was moribund sacrificed on day 15 of gestation.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 13 (PAGE 7): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

RABBIT #	DOSAGE GROUP VII												
	75 MG/KG/DAY												
PREGNANCY STATUS	DAY 0	7	8	9	10	11	12	13	14	15	16	17	18
8231 P	4.10	4.11	4.00	3.97	3.85	3.72	3.66	3.52	3.41	a			
8232 NP	3.60	3.65	3.52	3.42	3.33	3.22	3.14	3.00	2.93	b			
8233 P	3.80	3.92	3.85	3.82	3.73	3.53	3.40	3.32	3.24	c			
8234 P	3.54	3.69	3.64	3.44	3.41	3.25	3.26	3.14	3.14	d			
8235 P	3.17	3.32	3.33	3.29	2.95	2.85	2.78	2.71	2.68	e			

	DAY 19	20	21	22	23	24	25	26	27	28	29
8231 P	MORIBUND SACRIFICED ON DAY 15 OF GESTATION										
8232 NP	MORIBUND SACRIFICED ON DAY 15 OF PRESUMED GESTATION										
8233 P	FOUND DEAD ON DAY 15 OF GESTATION										
8234 P	MORIBUND SACRIFICED ON DAY 15 OF GESTATION										
8235 P	MORIBUND SACRIFICED ON DAY 15 OF GESTATION										

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.

a. Doe 8231 was moribund sacrificed on day 15 of gestation.
b. Rabbit 8232 was moribund sacrificed on day 15 of presumed gestation.
c. Doe 8233 was found dead on day 15 of gestation.
d. Doe 8234 was moribund sacrificed on day 15 of gestation.
e. Doe 8235 was moribund sacrificed on day 15 of gestation.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 14 (PAGE 1): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

RABBIT #	DOSAGE GROUP I	0 (VEHICLE) MG/KG/DAY											
	PREGNANCY STATUS DAYS	7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13	13 - 14	14 - 15	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20
8201	P	124.	135.	143.	144.	157.	128.	129.	121.	143.	127.	148.	148.	144.
8202	P	181.	181.	164.	185.	180.	185.	175.	174.	184.	154.	164.	159.	140.
8203	P	180.	182.	185.	180.	183.	181.	185.	184.	180.	180.	183.	180.	183.
8204	P	185.	173.	177.	173.	180.	184.	167.	173.	182.	167.	180.	176.	180.
8205	P	173.	150.	145.	135.	158.	135.	175.	181.	185.	181.	180.	181.	166.

	DAYS	20 - 21	21 - 22	22 - 23	23 - 24	24 - 25	25 - 26	26 - 27	27 - 28	28 - 29
8201	P	115.	148.	105.	112.	97.	82.	96.	108.	123.
8202	P	126.	105.	61.	3.	1.	37.	81.	92.	68.
8203	P	183.	184.	183.	184.	183.	182.	183.	185.	184.
8204	P	182.	173.	181.	141.	136.	113.	79.	74.	52.
8205	P	147.	119.	76.	40.	50.	73.	68.	81.	78.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAYS = DAYS OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 14 (PAGE 2): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

RABBIT #	DOSAGE GROUP II	1 MG/KG/DAY											
	PREGNANCY STATUS	DAYS 7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13	13 - 14	14 - 15	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20
8206	P	166.	156.	160.	159.	176.	132.	102.	133.	a				
8207	P	143.	171.	148.	165.	157.	114.	140.	114.	146.	74.	119.	94.	115.
8208	P	185.	185.	183.	183.	180.	181.	177.	177.	181.	181.	180.	181.	184.
8209	P	171.	163.	139.	138.	150.	131.	171.	172.	184.	169.	174.	182.	169.
8210	P	182.	181.	181.	185.	171.	162.	149.	170.	183.	156.	175.	181.	165.

	DAYS 20 - 21	21 - 22	22 - 23	23 - 24	24 - 25	25 - 26	26 - 27	27 - 28	28 - 29
8206 P	FOUND DEAD ON DAY 16 OF GESTATION								
8207 P	136.	135.	181.	154.	156.	152.	170.	135.	115.
8208 P	183.	182.	183.	174.	163.	105.	85.	79.	75.
8209 P	166.	173.	182.	159.	157.	161.	151.	137.	108.
8210 P	173.	168.	168.	149.	150.	137.	138.	121.	106.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAYS = DAYS OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).
a. Doe 8206 was found dead on day 16 of gestation.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 14 (PAGE 3): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

RABBIT #	DOSAGE GROUP III			5 MG/KG/DAY								
PREGNANCY STATUS DAYS	7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13	13 - 14	14 - 15	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20
8211 P	181.	14.	0.	2.	0.	0.	1.	0.	2.	1.	1.	2.	0.
8212 P	126.	59.	2.	1.	1.	0.	4.	0.	10.	10.	2.	1.	0.
8213 P	180.	183.	149.	96.	1.	14.	0.	1.	3.	0.	6.	1.	0.
8214 P	172.	156.	102.	113.	0.	82.	44.	46.	22.	0.	5.	3.	0.
7385 P	184.	160.	10.	1.	2.	3.	2.	0.	2.	0.	6.	1.	1.

	DAYS 20 - 21	21 - 22	22 - 23	23 - 24	24 - 25	25 - 26	26 - 27	27 - 28	28 - 29
8211 P	4.	2.	3.	2.	1.	ABORTED ON DAY 26 OF GESTATION			
8212 P	3.	2.	2.	ABORTED ON DAY 24 OF GESTATION					
8213 P	3.	17.	98.	114.	153.	149.	168.	153.	160.
8214 P	8.	4.	0.	3.	4.	ABORTED ON DAY 26 OF GESTATION			
7385 P	0.	1.	2.	3.	1.	2.	2.	1.	2.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAYS = DAYS OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 14 (PAGE 4): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

RABBIT #	DOSAGE GROUP IV	10 MG/KG/DAY											
	PREGNANCY STATUS DAYS	7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13	13 - 14	14 - 15	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20
8216	P	82.	2.	1.	2.	0.	0.	1.	1.	3.	5.	0.	1.	2.
8217	P	39.	1.	0.	1.	1.	0.	3.	0.	0.	10.	2.	1.	1.
8218	P	65.	0.	0.	1.	1.	0.	11.	3.	1.	4.	3.	0.	1.
8219	P	42.	0.	0.	1.	0.	0.	5.	7.	1.	1.	4.	0.	2.
8220	P	49.	9.	2.	2.	1.	0.	7.	29.	36.	26.	42.	37.	7.

	DAYS 20 - 21	21 - 22	22 - 23	23 - 24	24 - 25	25 - 26	26 - 27	27 - 28	28 - 29
8216 P	0.	2.	0.	1.	1.	ABORTED ON DAY 26 OF GESTATION			
8217 P	0.	ABORTED ON DAY 22 OF GESTATION							
8218 P	0.	2.	0.	ABORTED ON DAY 24 OF GESTATION					
8219 P	0.	ABORTED ON DAY 22 OF GESTATION							
8220 P	1.	1.	ABORTED AND SACRIFICED ON DAY 23 OF GESTATION						

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAYS = DAYS OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 14 (PAGE 5): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

RABBIT #	DOSAGE GROUP V			25 MG/KG/DAY					
PREGNANCY STATUS	DAYS	7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13	13 - 14	14 - 15	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20
7371 P		14.	1.	0.	11.	0.	3.	0.	1.	a				
8222 P		25.	3.	0.	2.	1.	0.	0.	1.	b				
8223 P		36.	1.	0.	1.	1.	0.	1.	0.	c				
8224 P		31.	0.	2.	0.	0.	0.	0.	0.	d				
8225 P		64.	4.	1.	1.	0.	1.	0.	0.	e				

	DAYS	20 - 21	21 - 22	22 - 23	23 - 24	24 - 25	25 - 26	26 - 27	27 - 28	28 - 29
7371 P		MORIBUND SACRIFICED ON DAY 15 OF GESTATION								
8222 P		MORIBUND SACRIFICED ON DAY 15 OF GESTATION								
8223 P		MORIBUND SACRIFICED ON DAY 15 OF GESTATION								
8224 P		MORIBUND SACRIFICED ON DAY 15 OF GESTATION								
8225 P		MORIBUND SACRIFICED ON DAY 15 OF GESTATION								

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAYS = DAYS OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Doe 7371 was moribund sacrificed on day 15 of gestation.
b. Doe 8222 was moribund sacrificed on day 15 of gestation.
c. Doe 8223 was moribund sacrificed on day 15 of gestation.
d. Doe 8224 was moribund sacrificed on day 15 of gestation.
e. Doe 8225 was moribund sacrificed on day 15 of gestation.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 14 (PAGE 6): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

RABBIT #	DOSAGE GROUP VI	50 MG/KG/DAY										
	PREGNANCY STATUS	DAYS 7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13	13 - 14	14 - 15	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20
8226	P	4.	2.	0.	2.	0.	0.	1.	FOUND DEAD ON DAY 14 OF GESTATION					
8227	P	14.	1.	0.	1.	1.	1.	2.	0.	a				
8228	P	30.	2.	0.	1.	2.	0.	0.	0.	b				
8229	P	6.	2.	1.	0.	FOUND DEAD ON DAY 12 OF GESTATION								
8230	P	5.	12.	2.	1.	1.	0.	0.	0.	c				

	DAYS 20 - 21	21 - 22	22 - 23	23 - 24	24 - 25	25 - 26	26 - 27	27 - 28	28 - 29
8226	P	FOUND DEAD ON DAY 14 OF GESTATION								
8227	P	MORIBUND SACRIFICED ON DAY 15 OF GESTATION								
8228	P	MORIBUND SACRIFICED ON DAY 15 OF GESTATION								
8229	P	FOUND DEAD ON DAY 12 OF GESTATION								
8230	P	MORIBUND SACRIFICED ON DAY 15 OF GESTATION								

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAYS = DAYS OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).
a. Doe 8227 was moribund sacrificed on day 15 of gestation.
b. Doe 8228 was moribund sacrificed on day 15 of gestation.
c. Doe 8230 was moribund sacrificed on day 15 of gestation.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 14 (PAGE 7): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

RABBIT #	DOSAGE GROUP VII	75 MG/KG/DAY								
PREGNANCY STATUS	DAYS 7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13	13 - 14	14 - 15	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20
8231 P	9.	1.	2.	0.	0.	0.	0.	0.	a				
8232 NP	2.	2.	1.	0.	0.	0.	0.	0.	b				
8233 P	2.	2.	1.	0.	0.	0.	0.	c					
8234 P	10.	2.	1.	1.	0.	0.	1.	0.	d				
8235 P	22.	2.	0.	0.	0.	0.	1.	0.	e				

	DAYS 20 - 21	21 - 22	22 - 23	23 - 24	24 - 25	25 - 26	26 - 27	27 - 28	28 - 29
8231 P	MORIBUND SACRIFICED ON DAY 15 OF GESTATION								
8232 NP	MORIBUND SACRIFICED ON DAY 15 OF PRESUMED GESTATION								
8233 P	FOUND DEAD ON DAY 15 OF GESTATION								
8234 P	MORIBUND SACRIFICED ON DAY 15 OF GESTATION								
8235 P	MORIBUND SACRIFICED ON DAY 15 OF GESTATION								

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAYS = DAYS OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Doe 8231 was moribund sacrificed on day 15 of gestation.
b. Rabbit 8232 was moribund sacrificed on day 15 of presumed gestation.
c. Doe 8233 was found dead on day 15 of gestation.
d. Doe 8234 was moribund sacrificed on day 15 of gestation.
e. Doe 8235 was moribund sacrificed on day 15 of gestation.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 15 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - INDIVIDUAL DATA

			VIABLE FETUSES			DEAD FETUSES			EARLY RESORPTIONS			LATE RESORPTIONS			IMPLANTATION SITES			CORPORA LUTEA		
	SEX		RIGHT HORN	LEFT HORN	TOTAL	RIGHT HORN	LEFT HORN	TOTAL	RIGHT HORN	LEFT HORN	TOTAL	RIGHT HORN	LEFT HORN	TOTAL	RIGHT HORN	LEFT HORN	TOTAL	RIGHT OVARY	LEFT OVARY	TOTAL
RABBIT #	M	F																		
DOSAGE GROUP I						0 (VEHICLE) MG/KG/DAY														
8201	5	0	1	4	5	0	0	0	0	0	0	0	0	0	1	4	5	5	5	10
8202	7	3	6	4	10	0	0	0	1	0	1	1	0	1	8	4	12	9	5	14
8203	2	1	1	2	3	0	0	0	1	0	1	0	0	0	2	2	4	5	4	9
8204	5	1	1	5	6	0	0	0	0	2	2	0	0	0	1	7	8	1	7	8
8205	5	6	5	6	11	0	0	0	0	0	0	1	0	1	6	6	12	7	6	13
DOSAGE GROUP II						1 MG/KG/DAY														
8206	FOUND DEAD ON DAY 16 OF GESTATION																			
8207	4	6	5	5	10	0	0	0	1	0	1	0	0	0	6	5	11	8	5	13
8208	4	5	5	4	9	0	0	0	0	0	0	0	0	0	5	4	9	5	5	10
8209	2	2	2	2	4	0	0	0	0	6	6	0	0	0	2	8	10	2	8	10
8210	5	6	6	5	11	0	0	0	0	0	0	0	0	0	6	5	11	6	6	12
DOSAGE GROUP III						5 MG/KG/DAY														
8211	ABORTED ON DAY 26 OF GESTATION																			
8212	ABORTED ON DAY 24 OF GESTATION																			
8213	3	5	4	4	8	0	0	0	0	0	0	1	3	4	5	7	12	6	7	13
8214	ABORTED ON DAY 26 OF GESTATION																			
7385	2	3	2	3	5	0	0	0	0	0	0	2	1	3	4	4	8	4	5	9
DOSAGE GROUP IV						10 MG/KG/DAY														
8216	ABORTED ON DAY 26 OF GESTATION																			
8217	ABORTED ON DAY 22 OF GESTATION																			
8218	ABORTED ON DAY 24 OF GESTATION																			
8219	ABORTED ON DAY 22 OF GESTATION																			
8220	ABORTED ON DAY 23 OF GESTATION																			

M = MALE F = FEMALE
PLACENTAE APPEARED NORMAL UNLESS NOTED OTHERWISE.

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 15 (PAGE 2): CAESAREAN-SECTIONING OBSERVATIONS - INDIVIDUAL DATA

			VIABLE FETUSES		DEAD FETUSES		EARLY RESORPTIONS		LATE RESORPTIONS		IMPLANTATION SITES		CORPORA LUTEA	
RABBIT #	SEX M	F	RIGHT LEFT HORN	TOTAL	RIGHT LEFT HORN	TOTAL	RIGHT LEFT HORN	TOTAL	RIGHT LEFT HORN	TOTAL	RIGHT LEFT HORN	TOTAL	RIGHT LEFT OVARY	TOTAL
	DOSAGE GROUP V		25 MG/KG/DAY											
7371	MORIBUND SACRIFICED ON DAY 15 OF GESTATION													
8222	MORIBUND SACRIFICED ON DAY 15 OF GESTATION													
8223	MORIBUND SACRIFICED ON DAY 15 OF GESTATION													
8224	MORIBUND SACRIFICED ON DAY 15 OF GESTATION													
8225	MORIBUND SACRIFICED ON DAY 15 OF GESTATION													
	DOSAGE GROUP VI		50 MG/KG/DAY											
8226	FOUND DEAD ON DAY 14 OF GESTATION													
8227	MORIBUND SACRIFICED ON DAY 15 OF GESTATION													
8228	MORIBUND SACRIFICED ON DAY 15 OF GESTATION													
8229	FOUND DEAD ON DAY 12 OF GESTATION													
8230	MORIBUND SACRIFICED ON DAY 15 OF GESTATION													
	DOSAGE GROUP VII		75 MG/KG/DAY											
8231	MORIBUND SACRIFICED ON DAY 15 OF GESTATION													
8232	MORIBUND SACRIFICED ON DAY 15 OF PRESUMED GESTATION													
8233	FOUND DEAD ON DAY 15 OF GESTATION													
8234	MORIBUND SACRIFICED ON DAY 15 OF GESTATION													
8235	MORIBUND SACRIFICED ON DAY 15 OF GESTATION													

M = MALE F = FEMALE
PLACENTAE APPEARED NORMAL UNLESS NOTED OTHERWISE.

PROTOCOL 418-010P: **ORAL** (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY **NUMBER:** T 6316.8)

TABLE 16 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - INDIVIDUAL DATA

	NUMBER OF LIVE FETUSES			AVERAGE FETAL BODY WEIGHT (G)			---- CONCEPTUSES ------ RESORBED		
RABBIT #	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL a	N	N	%
	DOSAGE GROUP I			0 (VEHICLE) MG/KG/DAY					
8201	5	0	5	49.35	----	49.35	5	0	0.0
8202	7	3	10	37.55	37.81	37.63	12	2	16.7
8203	2	1	3	51.50	51.48	51.50	4	1	25.0
8204	5	1	6	47.19	50.88	47.80	8	2	25.0
8205	5	6	11	45.92	38.79	42.03	12	1	8.3
	DOSAGE GROUP II			1 MG/KG/DAY					
8206	FOUND DEAD ON DAY 16 OF GESTATION								
8207	4	6	10	45.56	42.93	43.98	11	1	9.1
8208	4	5	9	44.68	45.10	44.91	9	0	0.0
8209	2	2	4	53.84	57.44	55.64	10	6	60.0
8210	5	6	11	42.93	40.28	41.49	11	0	0.0
	DOSAGE GROUP III			5 MG/KG/DAY					
8211	ABORTED ON DAY 26 OF GESTATION								
8212	ABORTED ON DAY 24 OF GESTATION								
8213	3	5	8	28.02	28.82	28.52	12	4	33.3
8214	ABORTED ON DAY 26 OF GESTATION								
7385	2	3	5	23.00	16.47	19.08	8	3	37.5
	DOSAGE GROUP IV			10 MG/KG/DAY					
8216	ABORTED ON DAY 26 OF GESTATION								
8217	ABORTED ON DAY 22 OF GESTATION								
8218	ABORTED ON DAY 24 OF GESTATION								
8219	ABORTED ON DAY 22 OF GESTATION								
8220	ABORTED ON DAY 23 OF GESTATION								

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

PROTOCOL 418 010P: **ORAL** (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-ETFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 16 (PAGE 2): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - INDIVIDUAL DATA

	NUMBER OF LIVE FETUSES			AVERAGE FETAL BODY WEIGHT (G)			---- CONCEPTUSES ------ RESORBED		
RABBIT #	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL a	N	N	%
	DOSAGE GROUP V			25 MG/KG/DAY					
7371	MORIBUND SACRIFICED ON DAY 15 OF GESTATION								
8222	MORIBUND SACRIFICED ON DAY 15 OF GESTATION								
8223	MORIBUND SACRIFICED ON DAY 15 OF GESTATION								
8224	MORIBUND SACRIFICED ON DAY 15 OF GESTATION								
8225	MORIBUND SACRIFICED ON DAY 15 OF GESTATION								
	DOSAGE GROUP VI			50 MG/KG/DAY					
8226	FOUND DEAD ON DAY 14 OF GESTATION								
8227	MORIBUND SACRIFICED ON DAY 15 OF GESTATION								
8228	MORIBUND SACRIFICED ON DAY 15 OF GESTATION								
8229	FOUND DEAD ON DAY 12 OF GESTATION								
8230	MORIBUND SACRIFICED ON DAY 15 OF GESTATION								
	DOSAGE GROUP VII			75 MG/KG/DAY					
8231	MORIBUND SACRIFICED ON DAY 15 OF GESTATION								
8232	MORIBUND SACRIFICED ON DAY 15 OF PRESUMED GESTATION								
8233	FOUND DEAD ON DAY 15 OF GESTATION								
8234	MORIBUND SACRIFICED ON DAY 15 OF GESTATION								
8235	MORIBUND SACRIFICED ON DAY 15 OF GESTATION								

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

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T 6316.8)

TABLE 17 (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
DOSAGE GROUP I		0 (VEHICLE) MG/KG/DAY																		
RABBIT #	CLs																			
8201	5/ 5	MA /	MA	MA	MA	MA														
		57.56	41.35	47.67	48.21	51.98														
8202	9/ 5	L	MA	FA	E	FA	MA	MA	FA /	MA	MA	MA	MA							
			39.86	42.07		34.09	29.66	38.33	37.27	44.39	38.89	34.11	37.61							
8203	5/ 4	E	MA /	MA	FA															
			52.60	50.41	51.48															
8204	1/ 7	MA /	FA	MA	E	MA	E	MA	MA											
		48.96	50.88	46.06		46.18		49.74	45.01											
8205	7/ 6	FA	MA	FA	FA	L	FA /	MA	MA	FA	MA	MA	FA							
		43.95	44.94	40.84	43.58		40.44	53.54	51.38	34.22	37.03	42.72	29.69							
DOSAGE GROUP II		1 MG/KG/DAY																		
8206		FOUND DEAD ON DAY 16 OF GESTATION																		
8207	8/ 5	FA	MA	E	FA	MA	MA /	MA	FA	FA	FA	FA								
		49.48	48.31		45.78	39.00	45.12	49.82	42.07	37.73	40.76	41.74								
8208	5/ 5	FA	MA	MA	MA	FA /	FA	MA	FA	FA										
		41.55	50.39	43.05	42.27	45.86	52.04	43.03	40.77	45.27										
8209	2/ 8	MA	FA /	E	E	E	E	E	E	MA	FA									
		55.77	58.25							51.91	56.63									
8210	6/ 6	MA	MA	FA	FA	FA	MA /	MA	MA	FA	FA	FA								
		45.50	41.96	34.82	37.56	41.80	41.67	42.70	42.84	44.01	41.20	42.32								
DOSAGE GROUP III		5 MG/KG/DAY																		
8211		ABORTED ON DAY 26 OF GESTATION																		
8212		ABORTED ON DAY 24 OF GESTATION																		
8213	6/ 7	FA	MA	FA	L	MA /	MA	L	FA	FA	L	FA	L							
		38.65	27.40	29.39		26.21	30.46		27.18	22.78		26.11								
8214		ABORTED ON DAY 26 OF GESTATION																		
7385	4/ 5	FA	L	L	FA /	MA	L	FA	MA											
		18.86			13.20	24.97		17.36	21.03											

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

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T 6316.8)

TABLE 17 (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
DOSAGE GROUP IV	10 MG/KG/DAY																		
RABBIT # CLs																			
8216	ABORTED ON DAY 26 OF GESTATION																		
8217	ABORTED ON DAY 22 OF GESTATION																		
8218	ABORTED ON DAY 24 OF GESTATION																		
8219	ABORTED ON DAY 22 OF GESTATION																		
8220	ABORTED ON DAY 23 OF GESTATION																		
DOSAGE GROUP V	25 MG/KG/DAY																		
7371	MORIBUND SACRIFICED ON DAY 15 OF GESTATION																		
8222	MORIBUND SACRIFICED ON DAY 15 OF GESTATION																		
8223	MORIBUND SACRIFICED ON DAY 15 OF GESTATION																		
8224	MORIBUND SACRIFICED ON DAY 15 OF GESTATION																		
8225	MORIBUND SACRIFICED ON DAY 15 OF GESTATION																		
DOSAGE GROUP VI	50 MG/KG/DAY																		
8226	FOUND DEAD ON DAY 14 OF GESTATION																		
8227	MORIBUND SACRIFICED ON DAY 15 OF GESTATION																		
8228	MORIBUND SACRIFICED ON DAY 15 OF GESTATION																		
8229	FOUND DEAD ON DAY 12 OF GESTATION																		
8230	MORIBUND SACRIFICED ON DAY 15 OF GESTATION																		

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

PROTOCOL 418-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS (SPONSOR'S STUDY NUMBER: T-6316.8)

TABLE 17 (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
DOSAGE GROUP VII	75 MG/KG/DAY																		
RABBIT # CLs																			
8231	MORIBUND SACRIFICED ON DAY 15 OF GESTATION																		
8232	MORIBUND SACRIFICED ON DAY 15 OF PRESUMED GESTATION																		
8233	FOUND DEAD ON DAY 15 OF GESTATION																		
8234	MORIBUND SACRIFICED ON DAY 15 OF GESTATION																		
8235	MORIBUND SACRIFICED ON DAY 15 OF GESTATION																		

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

ATTACHMENT 1

PROTOCOL AND AMENDMENT

Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, Pennsylvania 19044
T: (215) 443-8710 F: (215) 443-8587

PROTOCOL 418-010P

SPONSOR'S STUDY NUMBER: T-6316.8

STUDY TITLE: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of N-EtFOSE in Rabbits

PURPOSE: The purpose of this study is to provide information for the selection of dosages to be used in the developmental toxicity (embryo-fetal toxicity and teratogenic potential) study of N-EtFOSE administered orally via stomach tube to New Zealand White [Hra:(NZW)SPF] presumed pregnant female rabbits.

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: (612) 733-5180
Telefax: (612) 733-1773

ALTERNATIVE STUDY MONITOR: Andrew M. Seacat, Ph.D.
Telephone: (612) 575-3161
Telefax: (612) 733-1773

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 the spirit of the Good Laboratory Practice (GLP) regulations cited above in that the Testing Facility personnel will adhere to the Standard Operating Procedures for laboratory operations and data collection. The Testing Facility Quality Assurance Unit (QAU) will not audit the protocol, the raw data, the reports or the critical phases of the study.

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

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 to 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 (ATTACHMENT 2).

Storage:

Bulk Test Article:	Room temperature.
Vehicle Components:	Room temperature.
Prepared Vehicle:	Room temperature.
Prepared Formulations:	Frozen (-20°C).

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 daily at the Testing Facility. Vehicle 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 Sponsor will reserve a sample (1 g) of each lot of the bulk test article used during the course of this study. The Testing Facility will reserve a sample (5 mL) of each lot of the vehicle components used during the course of this 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. However, records will be maintained to document how the test article formulations were prepared.

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 New Zealand White [Hra:(NZW)SPF] rabbit was selected as the Test System because: 1) it is one non-rodent mammalian species accepted and widely used throughout the industry for nonclinical studies of developmental toxicity (embryo-fetal toxicity/teratogenicity); 2) this strain of rabbit 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 the species and strain.

Number and Sex:

Population evaluated: 35 timed-pregnant female rabbits (5 per dosage group).

Body Weight and Age:

The individual body weights of the female rabbits will range from 2.5 kg to 5.5 kg; the rabbits will be approximately five to seven months of age at the time of study assignment. Actual body weights recorded at receipt and at study assignment will be documented in the raw data.

Source:

Covance Research Products, Inc.
Swampbridge Road, Box 7200
Denver, Pennsylvania 17517

The rabbits will be shipped in filtered cartons by truck from Covance Research Products, Inc., Denver, Pennsylvania, to the Testing Facility.

Identification:

Rabbits are permanently identified using Monel® self-piercing ear tags (Gey Band and Tag Co., Inc., No. MSPT 20103). Female rabbits are 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 are in compliance with the *Guide for the Care and Use of Laboratory Animals*[4].

Housing:

The rabbits will be individually housed in units of six to eight stainless steel cages. No nesting materials will be supplied because the female rabbits 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. Room temperature will be maintained at 61°F (16°C) to 72°F (22°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:

Approximately 150 g of Certified Rabbit Chow® #5322 (PMI Nutrition International) will be available to each rabbit each day until the first day of dosage, at which time approximately 180 g of the same certified feed will be offered to each rabbit each day. The certified feed will be available from individual, stainless steel, "J-type" feeders attached to each cage.

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.

MATING AND RANDOMIZATION:

The female rabbits will be naturally bred at the Supplier by breeder male rabbits of the same source and strain before shipment to the Testing Facility. The day mating occurs will be designated day 0 of presumed gestation. The rabbits will be shipped to the Testing Facility after mating, to arrive on day 2 of presumed gestation. Before shipment of the rabbits, the Supplier will forward breeding records and day 0 of presumed gestation body weights. A computer-generated (weight-ordered) randomization procedure will be used to assign the rabbits to dosage groups based on this information.

ADMINISTRATION:

Route and Reason for Choice:

The oral (stomach tube) 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 possible routes of human exposure.

Method and Frequency:

Female rabbits will be given the test article once daily on days 7 through 20 of presumed gestation. 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 will be selected by the Sponsor on the basis of previous studies conducted with the test article.

Dosage Levels, Concentrations and Volumes:

Dosage Group	Number of Rabbits	Dosage (mg/kg/day)	Concentration (mg/mL)	Volume (mL/kg)	Argus Batch Number
I	5	0 (Vehicle)	0	5	B-418-010P-A(Day.Month.Year)
II	5	1	0.2	5	B-418-010P-B(Day.Month.Year)
III	5	5	1	5	B-418-010P-C(Day.Month.Year)
IV	5	10	2	5	B-418-010P-D(Day.Month.Year)
V	5	25	5	5	B-418-010P-E(Day.Month Year)
VI	5	50	10	5	B-418-010P-F(Day.Month.Year)
VII	5	75	15	5	B-418-010P-G(Day.Month.Year)

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

TESTS, ANALYSES AND MEASUREMENTS:

Viability:

All Periods: At least twice daily.

Clinical Observations and/or General Appearance:

Predosage Period: At least once.

Dosage Period: Twice daily. Prior to dosage administration and once approximately on 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:

Predosage Period: Day 0 of presumed gestation and on the day of arrival at the Testing Facility.

Dosage Period: Daily.

Postdosage Period: Daily.

Feed Consumption Values:

Predosage Period:	Recorded daily after arrival at the Testing Facility (values not tabulated).
Dosage Period:	Recorded daily.
Postdosage Period:	Recorded daily.

Feed consumption values during the dosage period will be tabulated for the same intervals as body weight evaluations.

Caesarean-Sectioning Observations:

Rabbits will be Caesarean-sectioned on day 29 of presumed gestation. The fetuses will be removed from the uterus and placed in individual containers. The rabbits will be examined for number and distribution of:

Corpora Lutea.

Implantation Sites.
[Placentae that appear abnormal (size, color or shape) 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 identified as an early resorption.)

Fetal Observations:

Body Weights:

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.

Gross External Alterations:

All fetuses will be examined for gross external alterations. Late resorptions and dead fetuses also will be examined for gross external alterations to the extent possible but such observations will not be included in either data summarization or statistical analyses. Fetuses with gross external alterations will be preserved in neutral buffered 10% formalin. All other fetuses will be discarded.

Representative photographs of fetal gross alterations will be taken.

Sex:

All fetuses will be examined internally to determine sex.

METHOD OF SACRIFICE:

Beuthanasia®-D Special, manufactured by Schering-Plough Animal Health, will be used to sacrifice rabbits (via intravenous injection) and live fetuses (via intraperitoneal injection).

NECROPSY:

Gross lesions will be retained in neutral buffered 10% formalin for possible future evaluation (corresponding tissues will be retained from rabbits in the vehicle control group at the discretion of the Study Director). (Exception: Parovarian cysts will be discarded; these are common, spontaneous lesions in rabbits.) Unless specifically cited below, all other tissues will be discarded.

Scheduled Sacrifice:

On day 29 of presumed gestation, female rabbits will be Caesarean-sectioned, and a gross necropsy of the thoracic, abdominal and pelvic viscera will be performed. Uteri of apparently nonpregnant does will be stained with 10% ammonium sulfide to confirm the absence of implantation sites[5].

Rabbits Found Dead or Moribund:

Rabbits 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. Pregnancy status and uterine contents 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 does will be stained with 10% ammonium sulfide to confirm the absence of implantation sites[5].

STATISTICAL EVALUATION:

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

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.
Veterinarian Examination.
Mating History.
Treatment (if prescribed by Staff Veterinarian).
General Comments.
Clinical Observations and/or General Appearance.
Body Weights.
Feed Consumption Values.
Caesarean-Sectioning and Fetal Observations.
Gross Necropsy Observations.
Organ Weights (if required).
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., 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

REPORT:

A letter report for the purpose of dosage selection for the full study will be prepared immediately following completion of the in-life phase.

A summary report will be prepared including: abstract, summaries of the methods, results and conclusion; table of contents; copy of the protocol; amendments; summary and individual tables; and reports of supporting data (if appropriate). The report will be included as an appendix to the full study report. The Sponsor will receive one copy of the draft report and two copies of the final report.

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., Hoberman, A.M. and Smith, T.H.F. (1982). Dosage-range study of the teratogenic potential of suspensions of trinitrofluorenone (TNF) administered orally to New Zealand White rabbits. Toxicologist 2(1):40 (#143).

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. Feussner, E.L., Lightkep, G.E., Hennesy, R.A., Hoberman, A.M. and Christian, M.S. (1992). A decade of rabbit fertility data: Study of historical control animals. Teratology 46(4):349-365.

4. Institute of Laboratory Animal Resources (1996). *Guide for the Care and Use of Laboratory Animals.* National Academy Press, Washington, D.C.

5. Salewski, E. (1964). Färbemethode zum makroskopischen Nachweis von Implantationsstellen am Uterus der Ratte. Arch. Pathol. Exp. Pharmakol. 247:367.

PROTOCOL APPROVAL:

FOR THE TESTING FACILITY

George E. Dearlove — 16-JUN-98

George E. Dearlove, Ph.D., DABT
Associate Director of Research

Date

Raymond G. York — 17-JUN-98

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

Date

Dena C. Lebo — 16 Jun 98

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

Date

FOR THE SPONSOR

Marvin T. Case — 19 June 1998

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

Date

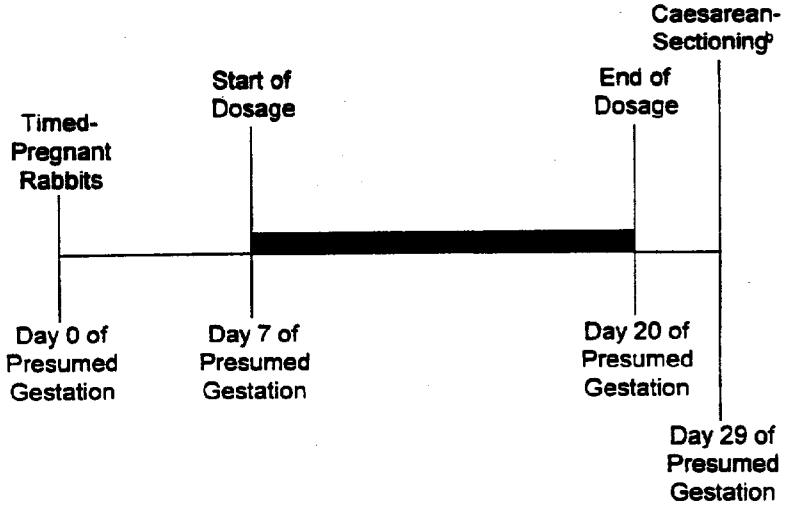
ATTACHMENT 1

SCHEMATIC OF STUDY DESIGN AND STUDY SCHEDULE

ATTACHMENT 1

STUDY SCHEMATIC

DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY[a]



■ Dosage Period.

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

b. Fetal evaluations (all fetuses - external examinations).

ATTACHMENT 1

SCHEDULE[a]

26 JUN 98	Animals Arrive - Acclimation Begins.
01 JUL 98 - 14 JUL 98	Dosage Period (Days 7 through 20 of presumed gestation).
23 JUL 98	Caesarean-Sectioning Period (Day 29 of presumed gestation).
30 JUL 98	Letter Report.
06 OCT 98	Summary Report.

---

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

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)

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

INGREDIENT	C.A.S. NO.	PERCENT
PERFLUOROOCTANESULFONAMIDO ALCOHOL.....	1691-99-2	80.0 - 90.0
PERFLUOROHEXANESULFONAMIDO 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

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

---

2. PHYSICAL DATA (continued)

APPEARANCE AND ODOR:
Amber waxy solid

---

3. FIRE AND EXPLOSION HAZARD DATA

FLASH POINT:..... > 148 C Setaflash
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.

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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.

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

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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

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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.

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

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

INGREDIENT	VALUE	UNIT	TYPE	AUTH	SKIN*
PERFLUOROOCTANESULFONAMIDO 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

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

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.

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

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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

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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 AND VEHICLE PREPARATION PROCEDURE

ATTACHMENT 3

TEST ARTICLE AND VEHICLE 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 vehicle for oral administration to rabbits on Argus Study 418-010P.

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:
_X_ Daily ___ 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 solutions 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.

ATTACHMENT 3

TEST ARTICLE AND VEHICLE PREPARATION PROCEDURE

NOTE: **The 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°C, ±5°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 15-mg/mL, Group VII 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°C, ±5°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 10-mg/mL, Group VI suspension, remove the required amount of stock suspension (Group VII) (See TEST ARTICLE CALCULATIONS), add the required amount of vehicle and mix.

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

5. To prepare the 2-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.

ATTACHMENT 3

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TEST ARTICLE AND VEHICLE PREPARATION PROCEDURE

6. To prepare the 1-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.

7. 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: _____

Approved by: _____ Date: 12-JUN-98

Clarification: X No ___ Yes (See attached clarification form.)

Initials/Date : _____

Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, Pennsylvania 19044
T: (215) 443-8710 F: (215) 443-8587

PROTOCOL 418-010P

ORAL (STOMACH TUBE)DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS

SPONSOR'S STUDY NUMBER: T-6316.8

Amendment 1 - June 25, 1998

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1. Clinical Observations and/or General Appearance (page 8 of the protocol):

The postdosage observation will be made approximately one hour postdosage.

Reason for Change:

This change corrects a typographical error.

25 JUN 98 — George E. Dearlove, Ph.D., DABT, Associate Director of Research, Date — FOR

25 JUN 98 — Raymond G. York, Ph.D., DABT, Associate Director of Research and Study Director, Date

25 Jun 98 — Dena C. Lebo, V.M.D., Member, Institutional Animal Care and Use Committee, Date

1 Jul 98 — Marvin T. Case, D.V.M., Ph.D., Study Monitor, Date

APPENDIX G

HISTORICAL CONTROL DATA

SUMMARY OF REPRODUCTIVE INDICES
NZW RABBIT

PERIOD: JANUARY 1996 - JANUARY 1998

NUMBER OF STUDIES: 66

NUMBER OF RABBITS:

TESTED	901
PREGNANT	861
FOUND DEAD	6*
ABORTED	22
DELIVERED PREMATURELY	4

NUMBER OF RABBITS PREGNANT AT CAESAREAN-SECTIONING ON DAY 29 OF GESTATION: 825

NUMBER OF RABBITS WITH SINGLE CONCEPTUS LITTER:

LIVE	1
RESORBED	1
ABORTED	2

	MEAN or %	RANGE/STUDY MEAN or %
% PREGNANT	96.0	(75.0-100)
AVERAGE # CORPORA LUTEA	9.7	(7.8-11.7)
AVERAGE # IMPLANTATIONS	8.9	(3.8-10.6)
AVERAGE LITTER SIZE		
AVERAGE # LIVE FETUSES	8.4	(3.2-10.4)
AVERAGE # DEAD FETUSES	0.0	(0-0.1)
AVERAGE # RESORPTIONS	0.4	(0-3.2)
AVERAGE # EARLY RESORPTIONS	0.3	(0-2.8)
AVERAGE # LATE RESORPTIONS	0.1	(0-1.2)

* Three were moribund sacrifices, one was attributed to an intubation accident

SUMMARY OF REPRODUCTIVE INDICES
NZW RABBIT

	MEAN or %	RANGE/STUDY MEAN or %
AVERAGE % DOES WITH ANY RESORPTIONS	26.8	(0-100)
AVERAGE % DOES WITH ALL CONCEPTUSES RESORBED	0.6	(0-20.0)
AVERAGE % DOES WITH ONE OR MORE LIVE FETUSES	99.4	(80.0-100)
AVERAGE SEX RATIO, (% MALES/LITTER)	51.2	(31.4-61.0)
AVERAGE FETAL BODY WEIGHT (G)	43.74	(31.85-55.74)
AVERAGE FOR MALES (G)	44.26	(29.55-56.97)
AVERAGE FOR FEMALES (G)	43.08	(32.25-53.76)
AVERAGE % DEAD OR RESORBED CONCEPTUSES/LITTER	4.4	(0-18.8)

SUMMARY OF MATERNAL NECROPSY OBSERVATIONS
NZW RABBITS

PERIOD	JANUARY 1996 - JANUARY 1998	
TOTAL # STUDIES	67	
TOTAL # DOES	921	
# PREGNANT	876	% OF PREGNANT
# DIED	6*	0.6
# ABORTED	22	2.4
# DELIVERED PREMATURELY	4	0.4
# DOES WITH 100% RESORPTIONS	5	0.5

EXTERNAL OBSERVATIONS	N	%	RANGE / STUDY N	%
Fecal material in perianal region	1	0.11	0-1	(0-5.0)
Localized alopecia	2	0.22	0-1	(0-5.0)
Left ear, torn	1	0.11	0-1	(0-5.0)
GROSS LESIONS				
THYMUS				
Small	1	0.11	0-1	(0-5.0)
LUNGS				
Discolored	6	0.65	0-4	(0-20.0)
Tear in right diaphragmatic lobe	1	0.11	0-1	(0-4.0)
Multiple lesions	1	0.11	0-1	(0-4.2)
THORACIC CAVITY				
Contained red fluid	1	0.11	0-1	(0-4.0)
LIVER				
Pale and/or discolored	7	0.76	0-4	(0-16.0)
Accentuated lobular pattern on lobe(s)	1	0.11	0-1	(0-5.0)
BACK				
Break present in lumbar region of spine	1	0.11	0-1	(0-5.0)

* Three were moribund sacrifices, one was attributed to an intubation accident

SUMMARY OF MATERNAL NECROPSY OBSERVATIONS
NZW RABBITS

GROSS LESIONS	N	%	RANGE / STUDY N	%
BACK (CONT.)				
Dorsal muscles, three hemorrhagic areas in lumbar region	1	0.11	0-1	(0-12.5)
STOMACH				
Trichobezoar	2	0.22	0-1	(0-4.3)
Mucosa, eroded in areas	1	0.11	0-1	(0-4.2)
SPLEEN				
Small	3	0.32	0-1	(0-20.0)
Large	1	0.11	0-1	(0-4.0)
KIDNEY(S)				
Small	1	0.11	0-1	(0-20.0)
Right, displaced caudally	1	0.11	0-1	(0-5.0)
ADRENAL GLAND				
Right, absent	1	0.11	0-1	(0-5.0)
UTERUS				
Right horn contained dark brown fluid	1	0.11	0-1	(0-16.7)
Horns contained a viscous, green-brown substance	1	0.11	0-1	(0-4.0)
Vascularization	1	0.11	0-1	(0-4.3)
Placentae surrounded by a thick, yellow substance	1	0.11	0-1	(0-5.0)
OVARIES				
Parovarian cyst(s)	30	3.26	0-5	(0-25.0)

SUMMARY OF FETAL GROSS EXTERNAL ALTERATIONS
NZW RABBITS

PERIOD	JANUARY 1996 - JANUARY 1998
# OF STUDIES	65
# LITTERS EXAMINED	816
# LIVE FETUSES EXAMINED (DAY 29)	6929

	ALTERATION				RANGE / STUDY	
			N	%	N	%
SKIN						
	Absent area	L	1	0.12	0-1	(0-5.3)
		F	1	0.01	0-1	(0-0.6)
HEAD						
	Meningocele	L	2	0.24	0-1	(0-16.7)
		F	3	0.04	0-2	(0-3.7)
	Cyclops	L	1	0.12	0-1	(0-5.9)
		F	1	0.01	0-1	(0-0.7)
	Upper jaw in two segments	L	1	0.12	0-1	(0-5.9)
		F	1	0.01	0-1	(0-0.7)
	Nares absent	L	1	0.12	0-1	(0-5.3)
		F	1	0.01	0-1	(0-0.6)
	Fleshy protrusion	L	1	0.12	0-1	(0-5.3)
		F	1	0.01	0-1	(0-0.6)
EYES						
	Bulge depressed	L	3	0.37	0-1	(0-5.3)
		F	3	0.04	0-1	(0-0.6)
	Eyelids open	L	1	0.12	0-1	(0-5.9)
		F	1	0.01	0-1	(0-0.7)
SNOUT						
	Short	L	2	0.24	0-1	(0-5.9)
		F	2	0.03	0-1	(0-0.7)
TONGUE						
	Protrudes	L	1	0.12	0-1	(0-5.3)
		F	1	0.01	0-1	(0-0.6)
BODY						
	Umbilical Hernia	L	9	1.10	0-2	(0-50.0)
		F	10	0.14	0-3	(0-12.0)
	Edema	L	1	0.12	0-1	(0-5.3)
		F	1	0.01	0-1	(0-0.6)

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL GROSS EXTERNAL ALTERATIONS
NZW RABBITS

ALTERATION		N	%	RANGE / STUDY N	%
BODY (CONT.)					
Skin discolored	L	1	0.12	0-1	(0-5.3)
purple	F	3	0.04	0-3	(0-1.9)
Spina bifida	L	2	0.24	0-1	(0-20.0)
	F	2	0.03	0-1	(0-1.9)
Hemorrhagic area(s)	L	2	0.24	0-1	(0-5.0)
	F	2	0.03	0-1	(0-0.6)
Meningocele	L	2	0.24	0-1	(0-16.7)
	F	2	0.03	0-1	(0-2.0)
Hematoma	L	1	0.12	0-1	(0-5.9)
	F	1	0.01	0-1	(0-0.8)
Dark red areas	L	1	0.12	0-1	(0-5.6)
	F	1	0.01	0-1	(0-0.6)
FORELIMBS AND/OR HINDLIMBS					
Paw(s): Flexed/	L	2	0.24	0-1	(0-5.6)
Rotated	F	2	0.03	0-1	(0-0.6)
Paw: Short digits	L	1	0.12	0-1	(0-5.6)
	F	1	0.01	0-1	(0-0.7)
Limb(s): Rotated	L	2	0.24	0-1	(0-16.7)
	F	2	0.03	0-1	(0-1.9)
Limb(s): Absent	L	1	0.12	0-1	(0-5.3)
	F	1	0.01	0-1	(0-0.6)
TAIL					
Short	L	7	0.86	0-1	(0-20.0)
	F	10	0.14	0-4	(0-2.3)

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL SOFT TISSUE ALTERATIONS
NZW RABBITS

PERIOD	JANUARY 1996 - JANUARY 1998
# STUDIES	38
# LITTERS EXAMINED	674
# FETUSES EXAMINED	5739

ALTERATION		N	%	RANGE/STUDY N	RANGE/STUDY %
BRAIN					
Dilated lateral ventricles	L	2	0.30	0-1	(0-5.0)
(Moderate) (Grade 2)	F	2	0.03	0-1	(0-0.6)
EYE(S)					
Circumcorneal hemorrhage	L	20	2.97	0-2	(0-16.7)
	F	21	0.36	0-3	(0-1.9)
Microphthalmia	L	1	0.15	0-1	(0-5.0)
	F	1	0.02	0-1	(0-0.6)
HEART					
Large	L	1	0.15	0-1	(0-5.9)
	F	1	0.02	0-1	(0-0.6)
Three ventricles	L	1	0.15	0-1	(0-5.9)
	F	1	0.02	0-1	(0-0.6)
VESSELS					
Persistent truncus	L	1	0.15	0-1	(0-5.0)
arteriosis	F	1	0.02	0-1	(0-0.6)
Innominate, absent	L	1	0.15	0-1	(0-5.3)
	F	1	0.02	0-1	(0-0.7)
Two pulmonary arteries	L	1	0.15	0-1	(0-5.9)
	F	1	0.02	0-1	(0-0.6)
LUNGS					
One or more lobes, partial	L	69	10.24	0-5	(0-27.8)
or complete agenesis	F	90	1.57	0-9	(0-5.0)
Right apical and cardiac	L	1	0.15	0-1	(0-5.3)
lobes fused	F	1	0.02	0-1	(0-0.6)
DIAPHRAGM					
Hernia	L	1	0.15	0-1	(0-5.0)
	F	1	0.02	0-1	(0-0.6)

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL SOFT TISSUE ALTERATIONS
NZW RABBITS

ALTERATION		N	%	RANGE/STUDY N	%
KIDNEY(S)					
Absent	L	1	0.15	0-1	(0-5.6)
	F	1	0.02	0-1	(0-0.6)
Displaced caudally	L	1	0.15	0-1	(0-4.3)
	F	1	0.02	0-1	(0-0.5)
SPLEEN					
Pale	L	1	0.15	0-1	(0-7.1)
	F	1	0.02	0-1	(0-0.9)
GONADS					
Right testis displaced caudally	L	1	0.15	0-1	(0-5.9)
	F	1	0.02	0-1	(0-0.6)

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL SKELETAL ALTERATIONS
NZW RABBITS

PERIOD	JANUARY 1996 - JANUARY 1998
# STUDIES	37
# LITTERS EXAMINED	668
# FETUSES EXAMINED	5684

ALTERATIONS				RANGE / STUDY		# OF STUDIES WITH
SKULL		N	%	N	%	ALTERATION
Summarization of all irregular ossification of skull	L	185	27.69	0-11	(0-66.7)	35
	F	237	4.17	0-17	(0-9.8)	
Anterior Fontanelle						
: Irregularly shaped	L	1	0.15	0-1	(0-5.3)	1
	F	1	0.02	0-1	(0-0.5)	
Posterior Fontanelle						
: Enlarged (Slight) (Grade 1)	L	1	0.15	0-1	(0-5.3)	1
	F	1	0.02	0-1	(0-0.6)	
Frontals						
: Irregular suture	L	18	2.69	0-3	(0-16.7)	13
	F	20	0.35	0-3	(0-1.8)	
: Interfrontals present	L	17	2.54	0-3	(0-15.0)	13
	F	17	0.30	0-3	(0-1.7)	
: Fused	L	5	0.75	0-2	(0-10.5)	4
	F	5	0.09	0-2	(0-1.1)	
: Two segments	L	1	0.15	0-1	(0-5.9)	1
	F	1	0.02	0-1	(0-0.7)	
: Suture large	L	1	0.15	0-1	(0-5.0)	1
	F	1	0.02	0-1	(0-0.6)	
: Small	L	1	0.15	0-1	(0-5.3)	1
	F	1	0.02	0-1	(0-0.6)	
Parietal(s)						
: Contain holes	L	3	0.45	0-1	(0-5.6)	3
	F	3	0.05	0-1	(0-0.6)	
: Fused and small	L	1	0.15	0-1	(0-5.3)	1
	F	1	0.02	0-1	(0-0.6)	
: Interparietals irregularly shaped	L	1	0.15	0-1	(0-5.3)	1
	F	1	0.02	0-1	(0-0.5)	
: Interparietals incompletely ossified	L	1	0.15	0-1	(0-16.7)	1
	F	1	0.02	0-1	(0-1.9)	

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL SKELETAL ALTERATIONS
NZW RABBITS

ALTERATIONS				RANGE / STUDY		# OF STUDIES WITH
SKULL (CONT.)		N	%	N	%	ALTERATION
Nasals						
: Irregular suture	L	4	0.60	0-2	(0-10.0)	3
	F	4	0.07	0-2	(0-1.2)	
: Internasals	L	26	3.89	0-3	(0-15.8)	18
	F	29	0.51	0-4	(0-2.3)	
: Intranasals	L	16	2.40	0-2	(0-16.7)	13
	F	16	0.28	0-2	(0-1.9)	
: Displaced suture	L	116	17.36	0-8	(0-40.0)	34
	F	129	2.27	0-9	(0-5.2)	
: Fused	L	10	1.50	0-2	(0-10.0)	9
	F	11	0.19	0-2	(0-1.3)	
: Small	L	1	0.15	0-1	(0-5.0)	1
	F	1	0.02	0-1	(0-0.6)	
Nasal/Frontal sutures:	L	12	1.80	0-2	(0-11.1)	9
irregular and/or misaligned	F	13	0.23	0-3	(0-1.9)	
Premaxillae: fused	L	1	0.15	0-1	(0-5.9)	1
	F	1	0.02	0-1	(0-0.7)	
Premaxillae: not ossified	L	1	0.15	0-1	(0-5.0)	1
	F	1	0.02	0-1	(0-0.6)	
Maxillae: fused	L	1	0.15	0-1	(0-5.3)	1
	F	1	0.02	0-1	(0-0.6)	
Supraoccipitals: irregularly	L	1	0.15	0-1	(0-5.3)	1
shaped	F	1	0.02	0-1	(0-0.5)	
Eye socket: small	L	2	0.30	0-1	(0-5.0)	2
	F	2	0.04	0-1	(0-0.6)	
Skull: extra ossification	L	1	0.15	0-1	(0-5.6)	1
	F	1	0.02	0-1	(0-0.6)	
HYOID						
A1a(e), angulated	L	108	16.17	0-8	(0-40.0)	34
	F	137	2.41	0-18	(0-9.9)	
Small	L	1	0.15	0-1	(0-5.3)	1
	F	4	0.07	0-4	(0-2.4)	
Irregularly shaped	L	1	0.15	0-1	(0-5.3)	1
	F	1	0.02	0-1	(0-0.6)	

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL SKELETAL ALTERATIONS
NZW RABBITS

ALTERATIONS		N	%	RANGE / STUDY N	RANGE / STUDY %	# OF STUDIES WITH ALTERATION
VERTEBRAE						
Cervical						
: Centrum, unilateral ossification	L	2	0.30	0-1	(0-5.6)	2
	F	2	0.04	0-1	(0-0.7)	
: Arches and/or Centra, fused	L	3	0.45	0-1	(0-5.6)	3
	F	3	0.05	0-1	(0-0.7)	
: Hemivertebra	L	3	0.45	0-1	(0-5.9)	3
	F	3	0.05	0-1	(0-0.6)	
: Centrum, asymmetric	L	1	0.15	0-1	(0-5.6)	1
	F	1	0.02	0-1	(0-0.7)	
: Centra, bifid	L	1	0.15	0-1	(0-5.3)	1
	F	1	0.02	0-1	(0-0.6)	
Thoracic						
: Hemivertebra	L	10	1.50	0-1	(0-5.9)	10
	F	11	0.19	0-2	(0-1.1)	
: Arches and/or Centra, fused	L	5	0.75	0-2	(0-10.5)	4
	F	6	0.10	0-2	(0-1.2)	
: Centrum, unilateral ossification	L	5	0.75	0-1	(0-5.3)	5
	F	5	0.09	0-1	(0-0.6)	
: Centra, one or more asymmetric	L	1	0.15	0-1	(0-5.6)	1
	F	1	0.02	0-1	(0-0.6)	
: Centrum, bifid	L	4	0.60	0-2	(0-10.5)	3
	F	4	0.07	0-2	(0-1.2)	
: Centra, not ossified	L	1	0.15	0-1	(0-4.5)	1
	F	1	0.02	0-1	(0-0.6)	
: Arch, absent	L	1	0.15	0-1	(0-5.6)	1
	F	1	0.02	0-1	(0-0.6)	
: Arch, small	L	3	0.45	0-1	(0-5.9)	3
	F	3	0.05	0-1	(0-0.6)	
Lumbar						
: Hemivertebra	L	2	0.30	0-1	(0-5.9)	2
	F	2	0.04	0-1	(0-0.8)	
: Centrum, unilateral ossification	L	1	0.15	0-1	(0-5.0)	1
	F	1	0.02	0-1	(0-0.6)	
: Arch, small	L	2	0.30	0-1	(0-5.0)	2
	F	2	0.04	0-1	(0-0.6)	
: Centrum, not ossified	L	1	0.15	0-1	(0-5.0)	1
	F	1	0.02	0-1	(0-0.6)	

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL SKELETAL ALTERATIONS
NZW RABBITS

ALTERATIONS		N	%	RANGE / STUDY N	RANGE / STUDY %	# OF STUDIES WITH ALTERATION
VERTEBRAE (CONT.)						
Sacral						
: Arches open	L	1	0.15	0-1	(0-5.3)	1
	F	1	0.02	0-1	(0-0.5)	
Caudal						
: One or more misaligned	L	30	4.49	0-3	(0-16.7)	24
	F	31	0.54	0-3	(0-2.0)	
: Fused	L	8	1.20	0-1	(0-5.6)	8
	F	10	0.18	0-3	(0-1.6)	
: 11 present	L	1	0.15	0-1	(0-4.3)	1
	F	1	0.02	0-1	(0-0.5)	
: 12 present	L	1	0.15	0-1	(0-4.3)	1
	F	2	0.04	0-2	(0-1.0)	
: 13 to 14 present	L	3	0.45	0-1	(0-5.6)	3
	F	3	0.05	0-1	(0-0.6)	
: 15 present	L	1	0.15	0-1	(0-4.3)	1
	F	1	0.02	0-1	(0-0.5)	
: Irregularly shaped	L	1	0.15	0-1	(0-5.0)	1
	F	1	0.02	0-1	(0-0.6)	
VERTEBRAE/RIB						
Interrelated Vertebral / Rib malformations	L	3	0.45	0-3	(0-15.8)	1
	F	3	0.05	0-3	(0-1.6)	
RIBS						
Cervical Rib present	L	2	0.30	0-1	(0-5.6)	2
	F	2	0.04	0-1	(0-0.6)	
Two or more, fused	L	6	0.90	0-2	(0-10.5)	5
	F	6	0.10	0-2	(0-1.2)	
Bases proximate	L	10	1.50	0-2	(0-9.1)	9
	F	10	0.18	0-2	(0-1.1)	
One or more, split	L	8	1.20	0-1	(0-5.6)	8
	F	8	0.14	0-1	(0-0.6)	
One or more, thickened areas	L	27	4.04	0-3	(0-16.7)	19
	F	29	0.51	0-3	(0-2.2)	
Flat	L	2	0.30	0-1	(0-5.6)	2
	F	2	0.04	0-1	(0-0.6)	

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL SKELETAL ALTERATIONS
NZW RABBITS

ALTERATIONS		N	%	RANGE / STUDY N	RANGE / STUDY %	# OF STUDIES WITH ALTERATION
RIBS (CONT.)						
Extra rib	L	1	0.15	0-1	(0-4.3)	1
	F	1	0.02	0-1	(0-0.5)	
Small	L	2	0.30	0-1	(0-5.9)	2
	F	2	0.04	0-1	(0-0.6)	
Broad	L	1	0.15	0-1	(0-5.9)	1
	F	1	0.02	0-1	(0-0.8)	
Bent	L	1	0.15	0-1	(0-4.5)	1
	F	1	0.02	0-1	(0-0.6)	
MANUBRIUM						
Duplicated	L	1	0.15	0-1	(0-5.9)	1
	F	1	0.02	0-1	(0-0.7)	
Fused	L	3	0.45	0-2	(0-10.5)	2
	F	3	0.05	0-2	(0-1.1)	
STERNEBRAE						
Two or more, fused	L	64	9.58	0-5	(0-27.8)	31
	F	78	1.37	0-7	(0-3.9)	
One or more, asymmetric	L	6	0.90	0-2	(0-10.5)	5
	F	6	0.10	0-2	(0-1.2)	
One or more, incompletely	L	11	1.65	0-2	(0-10.5)	9
or not ossified	F	11	0.19	0-2	(0-1.2)	
Duplicated	L	1	0.15	0-1	(0-5.9)	1
	F	1	0.02	0-1	(0-0.7)	
PELVIS						
Pubis(es): incompletely	L	4	0.60	0-1	(0-5.9)	4
or not ossified	F	5	0.09	0-2	(0-1.1)	
SCAPULAE						
Ala(e): irregularly	L	4	0.60	0-2	(0-10.5)	3
shaped	F	4	0.07	0-2	(0-1.2)	
Ala(e): wavy	L	1	0.15	0-1	(0-5.3)	1
	F	1	0.02	0-1	(0-0.6)	

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL SKELETAL ALTERATIONS
NZW RABBITS

ALTERATIONS		N	%	RANGE / STUDY N	RANGE / STUDY %	# OF STUDIES WITH ALTERATION
SCAPULAE (CONT.)						
Misaligned	L	5	0.75	0-2	(0-10.5)	4
	F	5	0.09	0-2	(0-1.2)	
Bent	L	1	0.15	0-1	(0-5.0)	1
	F	1	0.02	0-1	(0-0.6)	
FORELIMB(S)						
1 Phalanx present	L	1	0.15	0-1	(0-5.6)	1
	F	1	0.02	0-1	(0-0.7)	
0 Phalanges present	L	1	0.15	0-1	(0-5.6)	1
	F	1	0.02	0-1	(0-0.7)	
Humerus, Radius, Ulna, Carpals, Metacarpals, Fore-digits and Forephalanges absent	L	1	0.15	0-1	(0-5.3)	1
	F	1	0.02	0-1	(0-0.6)	

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL OSSIFICATION SITES
NZW RABBITS

PERIOD	JANUARY 1996 - JANUARY 1998
# STUDIES	37
# LITTERS EXAMINED	667
# FETUSES EXAMINED	5682

	FETUS / LITTER	
SKELETAL AVERAGES	MEAN	RANGE/STUDY
HYOID	1.00	(0.98-1.00)
VERTEBRAE		
CERVICAL	7.00	–
THORACIC	12.58	(12.44-12.72)
LUMBAR	6.41	(6.27-6.57)
SACRAL	3.00	–
CAUDAL	16.96	(16.75-17.13)
RIBS (Pairs)	12.51	(12.36-12.67)
STERNUM		
MANUBRIUM	1.00	–
STERNAL CENTERS	3.92	(3.83-3.99)
XIPHOID	0.98	(0.92-1.00)
FOREPAWS (Calculated as average per limb)		
CARPALS	0.00	–
METACARPALS	4.99	(4.96-5.00)
DIGITS	5.00	–
PHALANGES	13.91	(13.80-13.99)
HINDPAWS (Calculated as average per limb)		
TARSALS	2.00	(1.98-2.00)
METATARSALS	4.00	–
DIGITS	4.00	–
PHALANGES	12.00	(11.97-12.00)

APPENDIX H

STATEMENT OF THE STUDY DIRECTOR

PRIMEDICA

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

PROTOCOL 418-010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RABBITS
SPONSOR'S STUDY NUMBER: 6316-8

STATEMENT OF THE STUDY DIRECTOR

This final report accurately reflects the raw data obtained during the performance of the study. No significant deviations from the U.S. Food and Drug Administration (FDA) Good Laboratory Practice Regulations; Final Rule[a], the Japanese Ministry of Health and Welfare (MHW) *Good Laboratory Practice Standard for Safety Studies on Drugs*[b] and the European Economic Community (EEC) *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*[c] occurred that affected the quality or integrity of the study.

11-JAN 99

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

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a. U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58.
b. Japanese Ministry of Health and Welfare (1988). *Good Laboratory Practice Standard for Safety Studies on Drugs*, MHW Ordinance Number 21, March 26, 1997.
c. 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.

APPENDIX I

QUALITY ASSURANCE UNIT FINAL REPORT STATEMENT

PRIMEDICA

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905 Sheehy Drive, Building A
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QUALITY ASSURANCE UNIT FINAL REPORT STATEMENT

Study Director: Raymond G. York, Ph.D., DABT

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

Protocol 418-010: Oral (Stomach Tube) Developmental Toxicity Study of N-EtFOSE in Rabbits
Sponsor's Study Number: 6316.8

The draft protocol for this study was audited for adherence to U.S. Food and Drug Administration (FDA) Good Laboratory Practice Regulations, Japanese Ministry of Health and Welfare (MHW); Good Laboratory Practice Standard for Safety Studies on Drugs, and 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 on 10 AUG 98.

Critical phases of this study were inspected four times; study information and raw data were audited twice (see tables 1 and 2 for dates and phases/data).

The draft final report and the raw data for this study were compared and audited for accuracy, for adherence to protocol requirements, and for adherence to U.S. Food and Drug Administration (FDA) Good Laboratory Practice Regulations, Japanese Ministry of Health and Welfare (MHW); Good Laboratory Practice Standard for Safety Studies on Drugs, and 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 between 14 DEC 98 and 23 DEC 98, for revisions requested by the Sponsor 07 JAN 99, and for finalization on 11 JAN 99.

This study was conducted according to U.S. Food and Drug Administration (FDA) Good Laboratory Practice Regulations, Japanese Ministry of Health and Welfare (MHW); Good Laboratory Practice Standard for Safety Studies on Drugs, and 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.

11 Jan 99

Barbara J. Patterson, B.A. Date
Director of Operations
and Compliance

11 JAN 99

Heather L. Rabuttino, M.S. Date
Quality Assurance Supervisor
and Principal Auditor

TABLE 1

CRITICAL PHASES INSPECTED

Test Article Preparation

Date of inspection: 31 AUG 98

Date results reported to the Study Director and Management: 31 AUG 98

Test Article Administration - Gavage

Date of inspection: 01 SEP 98

Date results reported to the Study Director and Management: 02 SEP 98

Blood Collection

Date of inspection: 17 SEP 98

Date results reported to the Study Director and Management: 18 SEP 98

Caesarean-Sectioning

Date of inspection: 21 SEP 98

Date results reported to the Study Director and Management: 24 SEP 98

TABLE 2

RAW DATA AUDIT(S)

The following study information and raw data were audited on 11 OCT 98, 13 OCT 98 to 17 OCT 98:

Protocol.
List of personnel and computer operator codes.
Error codes and codes for clinical sign observations.
Animal receipt, randomization, and acclimation.
Veterinary examination.
In-life transaction record.
Feed consumption.
Caesarean-sectioning.
Maternal gross observations.
Fetal gross observations.
Fetal fixative assignment.
Fetal visceral examination.
Fetal skeletal examination.
Tissue packing lists.
General comments.
Study maintenance records.
Temperature and relative humidity reports.
Feed and water analyses.
Edit requests.
Dosage volumes.
Data review page.
Blood collection data and packing lists.
Liver weights.
Deviations.

The results of this audit were reported to the Study Director and Management on 19 OCT 98.

The following study information and raw data were audited on 27 OCT 98:

Vehicle receipt, preparation and use.
Test article receipt, preparation and use.
Test article packing lists.

The results of this audit were reported to the Study Director and Management on 29 OCT 98.