FINAL PILOT REPORT

Study Title

Oral (Gavage) Dosage-Range Developmental Toxicity Study of N-EtFOSE in Rats

Sponsor's Study Number: T-6316.7

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Study Completed On

10 December 1998
(Final Pilot Report)

Performing Laboratory

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Laboratory Project ID

Argus Research Laboratories, Inc., Protocol Number: 418-011P

PROTOCOL 418-011P: ORAL (GAVAGE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF N-EtFOSE IN RATS

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

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

ABSTRACT

Fifty-six presumed pregnant Crl:CD®BR VAF/Plus® (Sprague-Dawley) rats were randomly assigned to seven dosage groups [eight per group (Groups I through VII)]. Suspensions of the N-EtFOSE were administered orally via gavage once daily to these naturally-bred female rats on days 6 through 17 of presumed gestation (DGs 6 to 17) at dosages of 0 (Vehicle), 1, 5, 10, 20, 25 and 35 mg/kg/day. The dosage volume was 5 mL/kg, adjusted daily on the basis of the individual body weights recorded immediately before administration of the test article.

Checks for viability were made twice daily. Clinical observations were recorded daily before dosage, approximately one hour after administration and then four to six hours later. These observations were also recorded once daily during the postdosage period. Body weights were recorded daily during the dosage and postdosage periods and feed consumption values were recorded on DGs 0, 4, 6, 8, 10, 12, 14, 16, 18 and 20.

All rats were sacrificed on DG 20 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.

All rats survived until scheduled sacrifice. Clinical observations during gestation considered treatment-related were limited to single rats with chromorhinorrhea, chromodacryorrhea or emaciation at the 20 and 35 mg/kg/day dosages. Clinical observations of localized alopecia and emaciation were confirmed at necropsy. No additional necropsy observations occurred.

Body weight gains and absolute and relative feed consumption values for the entire dosage period (calculated as DGs 6 to 18), the entire interval after initiation of treatment (DGs 6 to 20) and the entire gestation period (DGs 0 to 20) were reduced in the 10 mg/kg/day and higher dosage groups, compared to the control group.

Reduced fetal body weights occurred at the 25 and 35 mg/kg/day dosages, relative to the control group (-8.5% and -13.8%, respectively). No other Caesarean-sectioning or litter parameters were affected by dosages of the test article as high as 35 mg/kg/day. One litter in the 35 mg/kg/day dosage group consisted of two early resorptions and 13 fetuses with cleft palate (two also had whole body edema). These fetal findings were considered genetic in origin and not test article-related.

Based on the results of this dosage-range finding study, dosages of 0, 1, 5, 10 and 20 mg/kg/day were recommended for the full developmental toxicity study of N-EtFOSE in rats.

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 gavage to Crl:CD®BR VAF/Plus® presumed pregnant female rats.

II. Methods[1]:

The test article, N-EtFOSE [lot/batch number FM-3929 (30035, 30037, 30039)], was received on 20 May 1998, and stored at room temperature. The vehicle was 2% Tween® 80 in reverse osmosis membrane processed deionized water (R.O. deionized water). The Tween® 80 was received from J.T. Baker, Philipsburg, New Jersey, on 22 May 1998, and was stored at room temperature. The R.O. deionized water is available from a continuous source at the Testing Facility and is maintained at room temperature. The prepared vehicle was stored at room temperature. Test article formulations were prepared daily.

Fifty-six presumed pregnant Crl:CD®BR VAF/Plus® (Sprague-Dawley) rats were randomly assigned to seven dosage groups [eight per group (Groups I through VII)]. Suspensions of the test article were administered orally via gavage once daily to these naturally-bred female rats on days 6 through 17 of presumed gestation (DGs 6 to 17) at dosages of 0 (Vehicle), 1, 5, 10, 20, 25 and 35 mg/kg/day. The dosage volume was 5 mL/kg, adjusted daily on the basis of the individual body weights recorded immediately before administration of the test article.

Checks for viability were made twice daily. Clinical observations were recorded daily before dosage, approximately one hour after administration and then four to six hours later. These observations were also recorded once daily during the postdosage period. Body weights were recorded daily during the dosage and postdosage periods and feed consumption values were recorded on DGs 0, 4, 6, 8, 10, 12, 14, 16, 18 and 20.

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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.

All rats were sacrificed on DG 20 and examined for the number and distribution of corpora lutea, implantation sites live and dead fetuses and early and late resorptions. A gross necropsy of the thoracic, abdominal and pelvic viscera was performed. Fetuses were weighed and examined for gross external alterations and sex.

III. Results:

A. Mortality, Clinical and Necropsy Observations (Summary - Table 1; Individual Data - Tables 9 and 10)

A.1. Mortality

All rats survived until scheduled sacrifice.

A.2. Clinical Observations

Clinical observations during gestation considered treatment-related were limited to single rats with chromorhinorrhea, chromodacryorrhea or emaciation at the 20 and 35 mg/kg/day dosages.

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 localized alopecia on the limbs, underside, back and/or neck.

A.3. Necropsy Observations

Clinical observations of localized alopecia and emaciation were confirmed at necropsy. No additional necropsy observations occurred.

B. Maternal Body Weights and Body Weight Changes (Figure 1; Summaries - Tables 2 and 3; Individual Data - Table 11)

Maternal body weight gains in the 10 mg/kg/day and higher dosage groups were decreased, compared to the control group on gestation days (DGs) 6 to 8 and 8 to 10. Body weights were decreased for the 25 mg/kg/day and higher dosages on DGs 10 to 12, 12 to 14 and 14 to 16. Maternal body weight gains in the 1, 5, 10, 20, 25 and 35 mg/kg/day dosage groups were generally comparable to control values postdosage (DGs 18 to 20).

Reflecting these effects of the test article, weight gains for the entire dosage period (calculated as DGs 6 to 18), the entire interval after initiation of treatment (DGs 6 to 20) and the entire gestation period (DGs 0 to 20) were reduced in the 10 mg/kg/day and higher dosage groups, compared to the control group.

Maternal body weights and body weight gains for the 1 and 5 mg/kg/day dosage groups were generally comparable to control values over each interval tabulated.

C. **Maternal Absolute (g/day) and Relative (g/kg/day) Feed Consumption Values (Summaries - Tables 4 and 5; Individual Data - Table 12)**

Absolute and relative feed consumption values for the 10 mg/kg/day and higher dosage groups were decreased, compared to the control group at all tabulated intervals during the dosage period (DGs 6 to 8, 8 to 10, 10 to 12, 12 to 14, 14 to 16 and 16 to 18). Maternal feed consumption values for the 1, 5, 10, 20, 25 and 35 mg/kg/day dosage groups were generally comparable to control values postdosage (DGs 18 to 20).

Reflecting these effects of the test article, absolute and relative feed consumption values for the entire dosage period (calculated as DGs 6 to 18), the entire interval after initiation of treatment (DGs 6 to 20) and the entire gestation period (DGs 0 to 20) were reduced in the 10 mg/kg/day and higher dosage groups, compared to the control group.

Absolute and relative feed consumption values for the 1 and 5 mg/kg/day dosage groups were generally comparable to control values over each interval tabulated.

D. **Caesarean-Sectioning and Litter Observations (Summaries - Tables 6 through 8; Individual Data – Tables 13 through 15)**

Caesarean-sectioning observations were based on 8 (100%), 7 (87.5%), 8 (100%), 8 (100%), 8 (100%), 8 (100%) and 8 (100%) pregnant rats with live litters in the seven respective dosage groups.

Reduced fetal body weights occurred at the 25 and 35 mg/kg/day dosages, relative to the control group (-8.5% and -13.8%, respectively). This observation was considered an effect of the test article because it was dosage-dependent

and occurred at the dosages in which there was maternal toxicity observed (decreased body weight and feed consumption values).

No other Caesarean-sectioning or litter parameters were affected by dosages of the test article as high as 35 mg/kg/day. The litter averages for corpora lutea, implantations, litter size, live fetuses, resorptions (early and late), dams with any resorptions and percent live male fetuses were comparable among the 0 Vehicle), 1, 5, 10, 20, 25 and 35 mg/kg/day dosage groups. No dams had all resorbed conceptuses, there were no dead fetuses and all placentae appeared normal.

Totals of 109, 93, 116, 110, 118, 116 and 114 live fetuses were evaluated for external gross alterations in the seven respective dosage groups. No fetal gross external alterations were observed at dosages up to 25 mg/kg/day. One litter (10650) in the 35 mg/kg/day dosage group consisted of two early resorptions and 13 fetuses with cleft palate (two also had whole body edema). These fetal findings were considered genetic in origin and not test article-related.

IV. Conclusion:

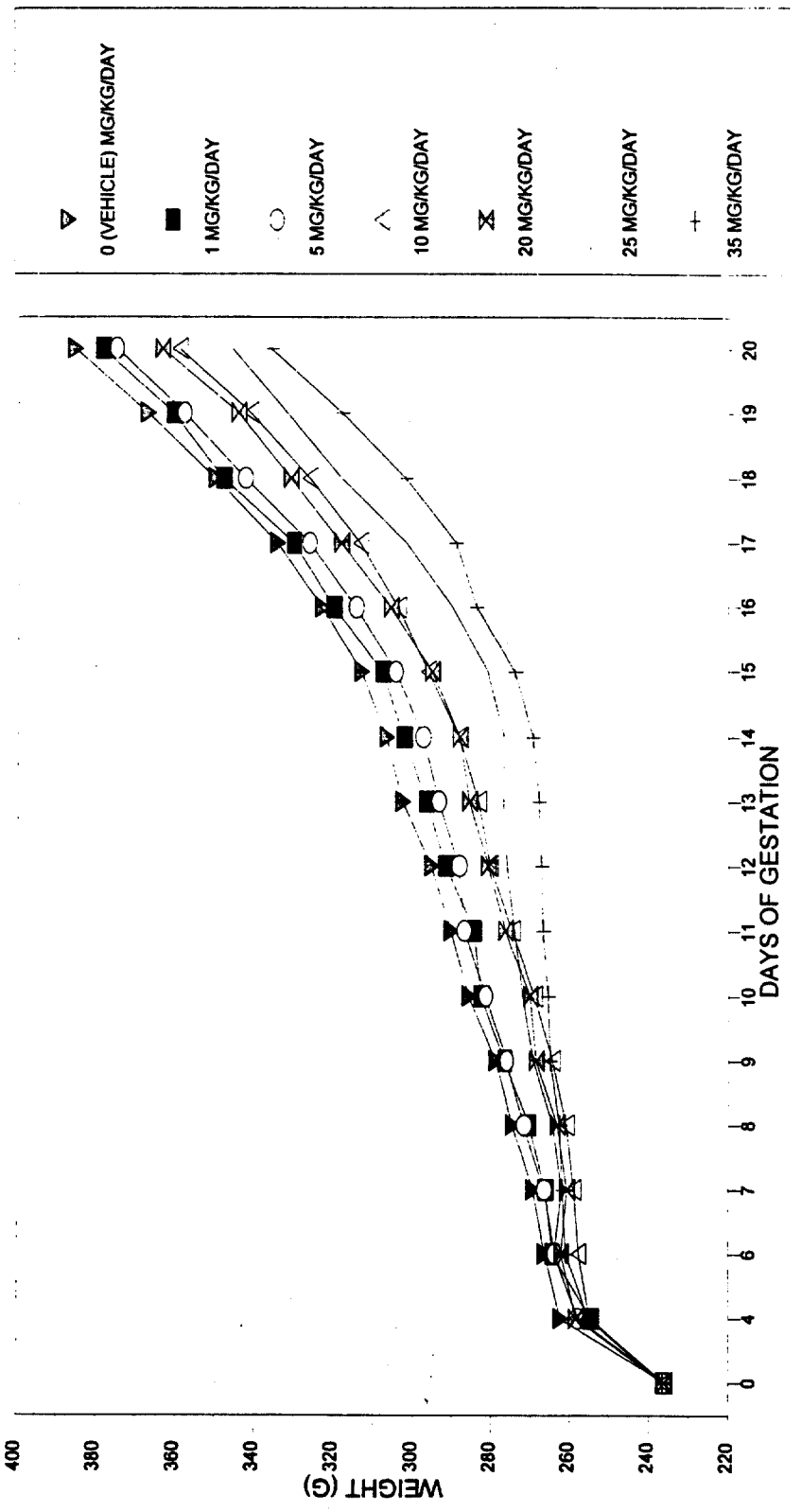
Based on the results of this study, dosages of 0 (Vehicle), 1, 5, 10 and 20 mg/kg/day of N-EtFOSE are recommended for the developmental toxicity study in rats (418-011). The 1 mg/kg/day dosage is expected to be a no-observable-effect-level (NOEL) for both maternal and embryo-fetal toxicity, and the 20 mg/kg/day dosage is expected to produce maternal toxicity (decreased maternal body weight and feed consumption values) and minimal developmental toxicity (decreased fetal body weights and possibly delayed ossification).

for _____ 10 DEC 98
Alan M. Hoberman, Ph.D., DABT Date
Director of Research

_____ 10-DEC-98
Raymond G. York, Ph.D., DABT Date
Associate Director of Research and
Study Director

MATERNAL BODY WEIGHTS

Figure 1



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

TABLE 1 (PAGE 1): CLINICAL AND NECROPSY OBSERVATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 1	III 5	IV 10
MAXIMUM POSSIBLE INCIDENCE		120/ 8	120/ 8	120/ 8	120/ 8
MORTALITY		0	0	0	0
LOCALIZED ALOPECIA:	TOTAL	0/ 0	0/ 0	15/ 2	0/ 0
	LIMBS	0/ 0	0/ 0	8/ 1	0/ 0
	UNDERSIDE	0/ 0	0/ 0	7/ 1	0/ 0
	BACK	0/ 0	0/ 0	0/ 0	0/ 0
	NECK	0/ 0	0/ 0	1/ 1	0/ 0
EMACIATION		0/ 0	0/ 0	0/ 0	0/ 0
CHROMORHINORRHEA		0/ 0	0/ 0	0/ 0	0/ 0
CHROMODACRYORRHEA		0/ 0	0/ 0	0/ 0	0/ 0

PERSISTENT ADVERSE CLINICAL OBSERVATIONS WERE CONFIRMED AT NECROPSY, NO ADDITIONAL GROSS LESIONS WERE IDENTIFIED

MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP ON DAYS 6 THROUGH 20 OF PRESUMED GESTATION.
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RATS WITH OBSERVATION.
a. Dosage occurred on days 6 through 17 of presumed gestation.

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

TABLE 1 (PAGE 2): CLINICAL AND NECROPSY OBSERVATIONS - SUMMARY

DOSAGE GROUP		V	VI	VII
DOSAGE (MG/KG/DAY)a		20	25	35
MAXIMUM POSSIBLE INCIDENCE		120/ 8	120/ 8	120/ 8
MORTALITY		0	0	0
LOCALIZED ALOPECIA:	TOTAL	0/ 0	7/ 1	20/ 2
	LIMBS	0/ 0	0/ 0	12/ 1
	UNDERSIDE	0/ 0	7/ 1	8/ 1
	BACK	0/ 0	6/ 1	8/ 1
	NECK	0/ 0	0/ 0	0/ 0
EMACIATION		0/ 0	0/ 0	4/ 1
CHROMORHINORRHEA		0/ 0	0/ 0	1/ 1
CHROMODACRYORRHEA		3/ 1	0/ 0	0/ 0

PERSISTENT ADVERSE CLINICAL OBSERVATIONS WERE CONFIRMED AT NECROPSY, NO ADDITIONAL GROSS LESIONS WERE IDENTIFIED

MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP ON DAYS 6 THROUGH 20 OF PRESUMED GESTATION.
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RATS WITH OBSERVATION.
a. Dosage occurred on days 6 through 17 of presumed gestation.

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

TABLE 2 (PAGE 1): MATERNAL BODY WEIGHTS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 1	III 5	IV 10
RATS TESTED	N	8	8	8	8
PREGNANT	N	8	7	8	8
BODY WEIGHT (G)					
DAY 0	MEAN±S.D.	235.9 ± 10.3	236.4 ± 12.6	236.4 ± 8.4	236.0 ± 8.1
DAY 4	MEAN±S.D.	262.4 ± 15.2	254.7 ± 10.3	258.0 ± 9.0	255.0 ± 11.8
DAY 6	MEAN±S.D.	266.4 ± 13.9	264.4 ± 16.3	263.9 ± 10.2	257.8 ± 12.9
DAY 7	MEAN±S.D.	269.4 ± 16.6	266.3 ± 14.9	266.5 ± 9.4	259.0 ± 14.3
DAY 8	MEAN±S.D.	274.6 ± 17.0	270.4 ± 16.6	271.8 ± 8.7	260.9 ± 18.6
DAY 9	MEAN±S.D.	278.9 ± 17.2	276.6 ± 16.2	276.1 ± 9.8	264.4 ± 16.5
DAY 10	MEAN±S.D.	285.8 ± 19.0	282.7 ± 15.5	281.4 ± 9.8	268.9 ± 17.2
DAY 11	MEAN±S.D.	290.4 ± 19.4	284.4 ± 17.9	286.9 ± 11.0	274.8 ± 18.7
DAY 12	MEAN±S.D.	295.4 ± 18.2	291.7 ± 18.6	288.4 ± 8.5	280.4 ± 18.0
DAY 13	MEAN±S.D.	302.6 ± 20.5	296.6 ± 16.5	293.4 ± 9.9	283.4 ± 20.4
DAY 14	MEAN±S.D.	306.8 ± 21.9	302.4 ± 16.5	297.5 ± 8.9	288.2 ± 19.6
DAY 15	MEAN±S.D.	313.1 ± 21.9	307.8 ± 17.8	304.4 ± 9.6	296.1 ± 21.8
DAY 16	MEAN±S.D.	323.0 ± 24.0	320.0 ± 21.6	314.5 ± 9.5	303.8 ± 20.7
DAY 17	MEAN±S.D.	334.4 ± 24.0	330.1 ± 22.8	326.1 ± 10.0	313.4 ± 22.6
DAY 18	MEAN±S.D.	350.1 ± 29.0	348.0 ± 23.6	342.5 ± 8.5	326.2 ± 22.1
DAY 19	MEAN±S.D.	367.2 ± 29.0	360.6 ± 26.6	357.8 ± 11.2	341.2 ± 25.5
DAY 20	MEAN±S.D.	385.6 ± 31.8	378.7 ± 32.3	375.0 ± 9.9	359.1 ± 27.6

DAY = DAY OF GESTATION
a. Dosage occurred on days 6 through 17 of gestation.

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

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

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		V 20	VI 25	VII 35
RATS TESTED	N	8	8	8
PREGNANT	N	8	8	8
BODY WEIGHT (G)				
DAY 0	MEAN±S.D.	236.2 ± 8.0	236.0 ± 8.5	236.5 ± 9.2
DAY 4	MEAN±S.D.	258.5 ± 8.2	257.9 ± 12.6	255.2 ± 11.3
DAY 6	MEAN±S.D.	262.1 ± 8.2	264.0 ± 14.2	261.1 ± 10.5
DAY 7	MEAN±S.D.	260.8 ± 8.1	262.0 ± 15.8	261.9 ± 9.4
DAY 8	MEAN±S.D.	263.1 ± 9.0	264.4 ± 16.5	262.6 ± 7.2
DAY 9	MEAN±S.D.	268.5 ± 12.5	269.2 ± 16.3	265.0 ± 9.3
DAY 10	MEAN±S.D.	270.1 ± 12.6	272.1 ± 15.2	265.6 ± 11.4
DAY 11	MEAN±S.D.	276.5 ± 13.7	274.1 ± 15.0	266.9 ± 10.9
DAY 12	MEAN±S.D.	280.9 ± 12.5	276.0 ± 17.8	267.2 ± 12.2
DAY 13	MEAN±S.D.	285.6 ± 15.3	277.0 ± 16.7	267.8 ± 16.9
DAY 14	MEAN±S.D.	288.1 ± 12.9	276.8 ± 18.7	269.4 ± 20.7
DAY 15	MEAN±S.D.	295.1 ± 17.1	281.0 ± 19.2	274.0 ± 25.8
DAY 16	MEAN±S.D.	305.6 ± 18.2	289.9 ± 21.6	283.8 ± 30.1
DAY 17	MEAN±S.D.	318.2 ± 18.6	301.6 ± 23.5	289.0 ± 34.6
DAY 18	MEAN±S.D.	330.9 ± 21.3	318.0 ± 22.3	302.0 ± 39.7
DAY 19	MEAN±S.D.	344.2 ± 22.5	332.0 ± 22.4	318.1 ± 41.8
DAY 20	MEAN±S.D.	363.5 ± 22.1	345.8 ± 20.4	336.1 ± 41.6

DAY = DAY OF GESTATION
a. Dosage occurred on days 6 through 17 of gestation.

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

TABLE 3 (PAGE 1): MATERNAL BODY WEIGHT CHANGES - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 1	III 5	IV 10
RATS TESTED	N	8	8	8	8
PREGNANT	N	8	7	8	8
BODY WEIGHT CHANGE (G)					
DAYS 0 - 6	MEAN±S.D.	+30.5 ± 10.3	+28.0 ± 7.2	+27.5 ± 5.8	+21.8 ± 6.4
DAYS 6 - 8	MEAN±S.D.	+8.2 ± 4.3	+6.0 ± 3.4	+7.9 ± 2.3	+3.1 ± 11.4
DAYS 8 - 10	MEAN±S.D.	+11.1 ± 2.9	+12.3 ± 1.5	+9.6 ± 3.1	+8.0 ± 5.0
DAYS 10 - 12	MEAN±S.D.	+9.6 ± 4.0	+9.0 ± 5.4	+7.0 ± 2.9	+11.5 ± 6.7
DAYS 12 - 14	MEAN±S.D.	+11.4 ± 5.0	+10.7 ± 5.8	+9.1 ± 3.1	+7.9 ± 3.2
DAYS 14 - 16	MEAN±S.D.	+16.2 ± 6.7	+17.6 ± 8.0	+17.0 ± 2.2	+15.5 ± 3.2
DAYS 16 - 18	MEAN±S.D.	+27.1 ± 7.4	+28.0 ± 4.7	+28.0 ± 4.5	+22.5 ± 4.0
DAYS 6 - 18	MEAN±S.D.	+83.8 ± 20.5	+83.6 ± 10.4	+78.6 ± 8.8	+68.5 ± 13.1
DAYS 18 - 20	MEAN±S.D.	+35.5 ± 7.0	+30.7 ± 11.4	+32.5 ± 5.1	+32.9 ± 6.8
DAYS 6 - 20	MEAN±S.D.	+119.2 ± 24.4	+114.3 ± 21.2	+111.1 ± 11.1	+101.4 ± 17.7
DAYS 0 - 20	MEAN±S.D.	+149.8 ± 33.1	+142.3 ± 26.4	+138.6 ± 12.2	+123.1 ± 20.5

DAYS = DAYS OF GESTATION
a. Dosage occurred on days 6 through 17 of gestation.

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TABLE 3 (PAGE 2): MATERNAL BODY WEIGHT CHANGES - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		V 20	VI 25	VII 35
RATS TESTED	N	8	8	8
PREGNANT	N	8	8	8
BODY WEIGHT CHANGE (G)				
DAYS 0 - 6	MEAN±S.D.	+25.9 ± 7.6	+28.0 ± 9.4	+24.6 ± 6.6
DAYS 6 - 8	MEAN±S.D.	+1.0 ± 4.8	+0.4 ± 4.5	+1.5 ± 6.7
DAYS 8 - 10	MEAN±S.D.	+7.0 ± 5.6	+7.8 ± 4.5	+3.0 ± 7.2
DAYS 10 - 12	MEAN±S.D.	+10.8 ± 3.6	+3.9 ± 7.6	+1.6 ± 10.5
DAYS 12 - 14	MEAN±S.D.	+7.2 ± 2.4	+0.8 ± 6.2	+2.1 ± 13.4
DAYS 14 - 16	MEAN±S.D.	+17.5 ± 7.9	+13.1 ± 11.3	+14.4 ± 11.1
DAYS 16 - 18	MEAN±S.D.	+25.2 ± 4.8	+28.1 ± 9.3	+18.2 ± 11.7
DAYS 6 - 18	MEAN±S.D.	+68.8 ± 15.4	+54.0 ± 13.9	+40.9 ± 42.3
DAYS 18 - 20	MEAN±S.D.	+32.6 ± 3.4	+27.8 ± 7.6	+34.1 ± 4.5
DAYS 6 - 20	MEAN±S.D.	+101.4 ± 16.1	+81.8 ± 11.9	+75.0 ± 44.6
DAYS 0 - 20	MEAN±S.D.	+127.2 ± 21.0	+109.8 ± 14.0	+99.6 ± 44.4

DAYS = DAYS OF GESTATION

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

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

TABLE 4 (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
RATS TESTED	N	8	8	8	8
PREGNANT	N	8	7	8	8
FEED CONSUMPTION (G/DAY)					
DAYS 0 - 6	MEAN±S.D.	23.6 ± 3.6	21.9 ± 2.9	23.5 ± 1.0	21.3 ± 2.4
DAYS 6 - 8	MEAN±S.D.	25.9 ± 5.4	23.5 ± 2.4	22.0 ± 4.6	19.1 ± 5.6
DAYS 8 - 10	MEAN±S.D.	25.4 ± 3.2	24.1 ± 2.5	24.2 ± 1.1	20.8 ± 2.7
DAYS 10 - 12	MEAN±S.D.	26.2 ± 3.7 [7]b	23.1 ± 2.0	24.4 ± 2.2	22.8 ± 2.0
DAYS 12 - 14	MEAN±S.D.	28.1 ± 8.2 [7]b	27.9 ± 5.2	23.5 ± 2.5	22.7 ± 3.3
DAYS 14 - 16	MEAN±S.D.	24.2 ± 2.3	25.1 ± 3.0	23.4 ± 2.5	21.1 ± 2.9
DAYS 16 - 18	MEAN±S.D.	25.9 ± 2.6	25.5 ± 4.4	25.4 ± 1.7	22.2 ± 2.6
DAYS 6 - 18	MEAN±S.D.	25.9 ± 3.4	24.8 ± 1.6	23.8 ± 1.4	21.4 ± 2.6
DAYS 18 - 20	MEAN±S.D.	26.2 ± 3.0	26.2 ± 2.0	24.8 ± 2.2	24.0 ± 3.1
DAYS 6 - 20	MEAN±S.D.	25.9 ± 3.2	25.0 ± 1.6	24.0 ± 1.3	21.8 ± 2.6
DAYS 0 - 20	MEAN±S.D.	25.2 ± 3.1	24.1 ± 1.8	23.8 ± 0.9	21.7 ± 2.3

DAYS = DAYS OF GESTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 6 through 17 of gestation.
b. Excludes values that were associated with spillage.

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TABLE 4 (PAGE 2): MATERNAL ABSOLUTE FEED CONSUMPTION VALUES (G/DAY) - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		V 20	VI 25	VII 35
RATS TESTED	N	8	8	8
PREGNANT	N	8	8	8
FEED CONSUMPTION (G/DAY)				
DAYS 0 - 6	MEAN±S.D.	24.8 ± 3.3	22.0 ± 2.7	22.6 ± 1.5
DAYS 6 - 8	MEAN±S.D.	21.2 ± 3.3	19.8 ± 3.7	21.1 ± 2.7
DAYS 8 - 10	MEAN±S.D.	22.2 ± 4.4	20.9 ± 2.4	20.1 ± 3.5
DAYS 10 - 12	MEAN±S.D.	23.1 ± 3.0	20.1 ± 2.4	18.9 ± 5.3
DAYS 12 - 14	MEAN±S.D.	23.1 ± 3.4	16.6 ± 3.3	20.1 ± 8.7
DAYS 14 - 16	MEAN±S.D.	22.6 ± 5.4	17.8 ± 5.8	18.1 ± 7.2
DAYS 16 - 18	MEAN±S.D.	23.4 ± 3.7	21.0 ± 3.3	18.6 ± 5.6
DAYS 6 - 18	MEAN±S.D.	22.6 ± 3.3	19.4 ± 2.6	19.5 ± 4.2
DAYS 18 - 20	MEAN±S.D.	23.8 ± 2.1	21.5 ± 1.6	24.2 ± 4.3
DAYS 6 - 20	MEAN±S.D.	22.8 ± 3.1	19.7 ± 2.3	20.2 ± 4.1
DAYS 0 - 20	MEAN±S.D.	23.4 ± 2.8	20.4 ± 2.1	20.9 ± 3.0

DAYS = DAYS OF GESTATION

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

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

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

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 1	III 5	IV 10
RATS TESTED	N	8	8	8	8
PREGNANT	N	8	7	8	8
FEED CONSUMPTION (G/KG/DAY)					
DAYS 0 - 6	MEAN±S.D.	92.2 ± 11.2	86.7 ± 9.8	93.1 ± 2.7	85.1 ± 7.1
DAYS 6 - 8	MEAN±S.D.	95.5 ± 16.5	88.1 ± 8.3	82.5 ± 17.8	72.9 ± 19.5
DAYS 8 - 10	MEAN±S.D.	90.7 ± 7.5	87.2 ± 7.6	87.6 ± 4.5	78.4 ± 6.2
DAYS 10 - 12	MEAN±S.D.	90.0 ± 8.8 [7]b	80.5 ± 4.2	85.6 ± 7.8	82.8 ± 3.6
DAYS 12 - 14	MEAN±S.D.	93.4 ± 26.7 [7]b	95.1 ± 23.5	80.3 ± 9.2	79.7 ± 8.5
DAYS 14 - 16	MEAN±S.D.	77.1 ± 7.2	80.8 ± 7.6	76.5 ± 8.1	71.3 ± 7.6
DAYS 16 - 18	MEAN±S.D.	77.3 ± 5.8	76.3 ± 9.6	77.7 ± 5.6	70.4 ± 4.1
DAYS 6 - 18	MEAN±S.D.	86.4 ± 9.6	84.2 ± 5.0	81.4 ± 5.7	75.5 ± 5.3
DAYS 18 - 20	MEAN±S.D.	71.4 ± 7.8	72.4 ± 3.3	69.2 ± 5.5	69.9 ± 5.9
DAYS 6 - 20	MEAN±S.D.	83.8 ± 8.9	82.1 ± 4.5	79.1 ± 5.1	74.5 ± 4.7
DAYS 0 - 20	MEAN±S.D.	83.2 ± 7.6	80.8 ± 4.5	80.4 ± 3.6	75.5 ± 3.9

DAYS = DAYS OF GESTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 6 through 17 of gestation.
b. Excludes values that were associated with spillage.

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

TABLE 6 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 1	III 5	IV 10
RATS TESTED	N	8	8	8	8
PREGNANT	N(%)	8(100.0)	7(87.5)	8(100.0)	8(100.0)
RATS PREGNANT AND CAESAREAN-SECTIONED ON DAY 20 OF GESTATION	N	8	7	8	8
CORPORA LUTEA	MEAN±S.D.	16.0 ± 2.6	15.7 ± 2.6	16.0 ± 1.8	16.0 ± 2.7
IMPLANTATIONS	MEAN±S.D.	14.0 ± 4.5	13.6 ± 3.2	15.2 ± 1.8	14.4 ± 1.7
LITTER SIZES	MEAN±S.D.	13.6 ± 4.6	13.3 ± 3.0	14.5 ± 1.7	13.8 ± 1.8
LIVE FETUSES	N	109	93	116	110
	MEAN±S.D.	13.6 ± 4.6	13.3 ± 3.0	14.5 ± 1.7	13.8 ± 1.8
DEAD FETUSES	N	0	0	0	0
RESORPTIONS	MEAN±S.D.	0.4 ± 0.7	0.3 ± 0.5	0.8 ± 1.2	0.6 ± 0.7
EARLY RESORPTIONS	N	3	2	6	4
	MEAN±S.D.	0.4 ± 0.7	0.3 ± 0.5	0.8 ± 1.2	0.5 ± 0.8
LATE RESORPTIONS	N	0	0	0	1
	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.4
DAMS WITH ANY RESORPTIONS	N(%)	2(25.0)	2(28.6)	3(37.5)	4(50.0)
DAMS WITH ALL CONCEPTUSES RESORBED	N	0	0	0	0
DAMS WITH VIABLE FETUSES	N(%)	8(100.0)	7(100.0)	8(100.0)	8(100.0)
PLACENTAE APPEARED NORMAL	N(%)	8(100.0)	7(100.0)	8(100.0)	8(100.0)

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

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

TABLE 6 (PAGE 2): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY

DOSAGE GROUP		V	VI	VII
DOSAGE (MG/KG/DAY)a		20	25	35
RATS TESTED	N	8	8	8
PREGNANT	N(%)	8(100.0)	8(100.0)	8(100.0)
RATS PREGNANT AND CAESAREAN-SECTIONED ON DAY 20 OF GESTATION	N	8	8	8
CORPORA LUTEA	MEAN±S.D.	15.5 ± 2.1	15.9 ± 2.8	16.2 ± 3.4
IMPLANTATIONS	MEAN±S.D.	15.1 ± 1.7	14.9 ± 2.8	15.1 ± 2.2
LITTER SIZES	MEAN±S.D.	14.8 ± 1.8	14.5 ± 2.6	14.2 ± 2.4
LIVE FETUSES	N	118	116	114
	MEAN±S.D.	14.8 ± 1.8	14.5 ± 2.6	14.2 ± 2.4
DEAD FETUSES	N	0	0	0
RESORPTIONS	MEAN±S.D.	0.4 ± 0.5	0.4 ± 0.7	0.9 ± 1.1
EARLY RESORPTIONS	N	3	3	7
	MEAN±S.D.	0.4 ± 0.5	0.4 ± 0.7	0.9 ± 1.1
LATE RESORPTIONS	N	0	0	0
	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
DAMS WITH ANY RESORPTIONS	N(%)	3(37.5)	2(25.0)	4(50.0)
DAMS WITH ALL CONCEPTUSES RESORBED	N	0	0	0
DAMS WITH VIABLE FETUSES	N(%)	8(100.0)	8(100.0)	8(100.0)
PLACENTAE APPEARED NORMAL	N(%)	8(100.0)	8(100.0)	8(100.0)

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

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

TABLE 7 (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	8	7	8	8
IMPLANTATIONS	MEAN±S.D.	14.0 ± 4.5	13.6 ± 3.2	15.2 ± 1.8	14.4 ± 1.7
LIVE FETUSES	N	109	93	116	110
	MEAN±S.D.	13.6 ± 4.6	13.3 ± 3.0	14.5 ± 1.7	13.8 ± 1.8
LIVE MALE FETUSES	N	49	42	59	50
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	43.1 ± 14.3	42.8 ± 22.2	50.5 ± 13.0	46.7 ± 13.8
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	3.40 ± 0.47	3.43 ± 0.22	3.28 ± 0.17	3.34 ± 0.16
MALE FETUSES	MEAN±S.D.	3.53 ± 0.47	3.56 ± 0.23	3.37 ± 0.21	3.42 ± 0.19
FEMALE FETUSES	MEAN±S.D.	3.30 ± 0.44	3.36 ± 0.21	3.18 ± 0.15	3.25 ± 0.16
% RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	2.7 ± 5.6	1.8 ± 3.0	4.6 ± 6.9	4.4 ± 5.0

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

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

TABLE 7 (PAGE 2): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		V 20	VI 25	VII 35
LITTERS WITH ONE OR MORE LIVE FETUSES	N	8	8	8
IMPLANTATIONS	MEAN±S.D.	15.1 ± 1.7	14.9 ± 2.8	15.1 ± 2.2
LIVE FETUSES	N	118	116	114
	MEAN±S.D.	14.8 ± 1.8	14.5 ± 2.6	14.2 ± 2.4
LIVE MALE FETUSES	N	66	59	58
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	55.3 ± 9.1	49.2 ± 13.8	50.4 ± 15.3
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	3.24 ± 0.15	3.11 ± 0.18	2.93 ± 0.46
MALE FETUSES	MEAN±S.D.	3.34 ± 0.17	3.21 ± 0.21	3.03 ± 0.45
FEMALE FETUSES	MEAN±S.D.	3.13 ± 0.14	3.03 ± 0.20	2.83 ± 0.44
% RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	2.6 ± 3.6	2.4 ± 4.4	5.9 ± 7.5

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

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

TABLE 8 (PAGE 1): FETAL GROSS EXTERNAL ALTERATIONS - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE (MG/KG/DAY)a		0 (VEHICLE)	1	5	10
LITTERS EVALUATED	N	8	7	8	8
FETUSES EVALUATED	N	109	93	116	110
LIVE	N	109	93	116	110
BODY: EDEMA					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
PALATE: CLEFT					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

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

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

TABLE 8 (PAGE 2): FETAL GROSS EXTERNAL ALTERATIONS - SUMMARY

DOSAGE GROUP		V	VI	VII
DOSAGE (MG/KG/DAY)a		20	25	35
LITTERS EVALUATED	N	8	8	8
FETUSES EVALUATED	N	118	116	114
LIVE	N	118	116	114
BODY: EDEMA				
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(12.5)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	2(1.8)b,c
PALATE: CLEFT				
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(12.5)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	13(11.4)b,c

a. Dosage occurred on days 6 through 17 of gestation.
b. Fetus 10650-1 had other gross external alterations.
c. Fetus 10650-10 had other gross external alterations.

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

TABLE 9 (PAGE 1): CLINICAL OBSERVATIONS - INDIVIDUAL DATA

RAT #	DESCRIPTION
DOSAGE GROUP I	0 (VEHICLE) MG/KG/DAY
10601	NO ADVERSE FINDINGS
10602	NO ADVERSE FINDINGS
10603	NO ADVERSE FINDINGS
10604	NO ADVERSE FINDINGS
10605	NO ADVERSE FINDINGS
10606	NO ADVERSE FINDINGS
10607	NO ADVERSE FINDINGS
10608	NO ADVERSE FINDINGS
DOSAGE GROUP II	1 MG/KG/DAY
10609	NO ADVERSE FINDINGS
10610	NO ADVERSE FINDINGS
10611	NO ADVERSE FINDINGS
10612	NO ADVERSE FINDINGS
10613	NO ADVERSE FINDINGS
10614	NO ADVERSE FINDINGS
10615	NO ADVERSE FINDINGS
10616	NO ADVERSE FINDINGS

DG = DAY OF PRESUMED GESTATION

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

TABLE 9 (PAGE 2): CLINICAL OBSERVATIONS - INDIVIDUAL DATA

RAT #		DESCRIPTION
DOSAGE GROUP III		5 MG/KG/DAY
10617	DG(13- 20)	LOCALIZED ALOPECIA: LIMBS a
10618		NO ADVERSE FINDINGS
10619		NO ADVERSE FINDINGS
10620		NO ADVERSE FINDINGS
10621		NO ADVERSE FINDINGS
10622		NO ADVERSE FINDINGS
10623		NO ADVERSE FINDINGS
10624	DG(14- 20)	LOCALIZED ALOPECIA: UNDERSIDE a
	DG(20)	LOCALIZED ALOPECIA: NECK a
DOSAGE GROUP IV		10 MG/KG/DAY
10625		NO ADVERSE FINDINGS
10626		NO ADVERSE FINDINGS
10627		NO ADVERSE FINDINGS
10628		NO ADVERSE FINDINGS
10629		NO ADVERSE FINDINGS
10630		NO ADVERSE FINDINGS
10631		NO ADVERSE FINDINGS
10632		NO ADVERSE FINDINGS

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

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

TABLE 9 (PAGE 3): CLINICAL OBSERVATIONS - INDIVIDUAL DATA

RAT #		DESCRIPTION	
DOSAGE GROUP V		20 MG/KG/DAY	
10633		NO ADVERSE FINDINGS	
10634		NO ADVERSE FINDINGS	
10635		NO ADVERSE FINDINGS	
10636		NO ADVERSE FINDINGS	
10637	DG(15- 17)	CHROMODACRYORRHEA	
10638		NO ADVERSE FINDINGS	
10639		NO ADVERSE FINDINGS	
10640		NO ADVERSE FINDINGS	
DOSAGE GROUP VI		25 MG/KG/DAY	
10641		NO ADVERSE FINDINGS	
10642		NO ADVERSE FINDINGS	
10643	DG(14- 20)	LOCALIZED ALOPECIA:	UNDERSIDE a
	DG(15- 20)	LOCALIZED ALOPECIA:	BACK a
10644		NO ADVERSE FINDINGS	
10645		NO ADVERSE FINDINGS	
10646		NO ADVERSE FINDINGS	
10647		NO ADVERSE FINDINGS	
10648		NO ADVERSE FINDINGS	

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

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

TABLE 9 (PAGE 4): CLINICAL OBSERVATIONS - INDIVIDUAL DATA

RAT #		DESCRIPTION
DOSAGE GROUP VII		35 MG/KG/DAY
10649		NO ADVERSE FINDINGS
10650	DG(13- 20)	LOCALIZED ALOPECIA: UNDERSIDE a
	DG(13- 20)	LOCALIZED ALOPECIA: BACK a
	DG(17- 20)	EMACIATION a
10651		NO ADVERSE FINDINGS
10652		NO ADVERSE FINDINGS
10653	DG(8- 19)	LOCALIZED ALOPECIA: LIMBS
	DG(20)	ALOPECIA NO LONGER APPARENT
10654		NO ADVERSE FINDINGS
10655		NO ADVERSE FINDINGS
10656	DG(12)	CHROMORHINORRHEA

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

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

TABLE 10 (PAGE 1): NECROPSY OBSERVATIONS - INDIVIDUAL DATA

DOSAGE GROUP (MG/KG/DAY)	RAT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
I					
0 (VEHICLE)	10601	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10602	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10603	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10604	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10605	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10606	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10607	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10608	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
II					
1	10609	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10610	DG 20	NP	12	ALL TISSUES APPEARED NORMAL.
	10611	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10612	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10613	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10614	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10615	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10616	DG 20	P	12	ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION
a. Refer to the individual clinical observations table (Table 9) for external observations confirmed at necropsy.

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

TABLE 10 (PAGE 2): NECROPSY OBSERVATIONS - INDIVIDUAL DATA

DOSAGE GROUP (MG/KG/DAY)	RAT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
III					
5	10617	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10618	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10619	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10620	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10621	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10622	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10623	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10624	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
IV					
10	10625	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10626	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10627	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10628	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10629	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10630	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10631	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10632	DG 20	P	12	ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION
a. Refer to the individual clinical observations table (Table 9) for external observations confirmed at necropsy.

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

TABLE 10 (PAGE 3): NECROPSY OBSERVATIONS - INDIVIDUAL DATA

DOSAGE GROUP (MG/KG/DAY)	RAT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
V					
20	10633	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10634	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10635	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10636	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10637	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10638	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10639	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10640	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
VI					
25	10641	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10642	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10643	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10644	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10645	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10646	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10647	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10648	DG 20	P	12	ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION
a. Refer to the individual clinical observations table (Table 9) for external observations confirmed at necropsy.

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

TABLE 10 (PAGE 4): NECROPSY OBSERVATIONS - INDIVIDUAL DATA

DOSAGE GROUP (MG/KG/DAY)	RAT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
VII					
35	10649	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10650	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10651	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10652	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10653	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10654	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10655	DG 20	P	12	ALL TISSUES APPEARED NORMAL.
	10656	DG 20	P	12	ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION
a. Refer to the individual clinical observations table (Table 9) for external observations confirmed at necropsy.

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

TABLE 11 (PAGE 1): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

RAT #	DOSAGE GROUP I	0 (VEHICLE) MG/KG/DAY											
	PREGNANCY STATUS	DAY 0	4	6	7	8	9	10	11	12	13	14	15	16
10601	P	218.	236.	244.	242.	247.	252.	257.	265.	270.	274.	274.	282.	295.
10602	P	227.	253.	263.	270.	273.	281.	287.	291.	295.	308.	311.	318.	331.
10603	P	242.	276.	286.	292.	300.	303.	314.	318.	321.	335.	341.	348.	364.
10604	P	245.	278.	280.	290.	293.	299.	306.	312.	315.	322.	325.	334.	344.
10605	P	238.	261.	260.	261.	263.	267.	270.	274.	282.	285.	289.	297.	301.
10606	P	232.	273.	275.	271.	280.	284.	294.	301.	310.	313.	321.	325.	333.
10607	P	250.	273.	269.	272.	277.	280.	285.	291.	288.	295.	301.	301.	304.
10608	P	235.	249.	254.	257.	264.	265.	273.	271.	282.	289.	292.	300.	312.

	DAY 17	18	19	20
10601 P	310.	319.	335.	361.
10602 P	338.	361.	371.	399.
10603 P	377.	400.	412.	432.
10604 P	353.	371.	390.	414.
10605 P	315.	329.	347.	362.
10606 P	348.	363.	392.	405.
10607 P	310.	315.	332.	338.
10608 P	324.	343.	359.	374.

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

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

TABLE 11 (PAGE 2): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

RAT #	DOSAGE GROUP II	1 MG/KG/DAY											
	PREGNANCY STATUS	DAY 0	4	6	7	8	9	10	11	12	13	14	15	16
10609	P	241.	267.	276.	278.	286.	289.	296.	302.	309.	313.	321.	330.	342.
10610	NP	235.	247.	250.	251.	255.	248.	256.	260.	261.	268.	259.	263.	271.
10611	P	256.	250.	285.	282.	289.	295.	301.	306.	307.	313.	314.	321.	340.
10612	P	219.	246.	251.	255.	260.	265.	272.	276.	283.	290.	292.	298.	315.
10613	P	245.	270.	280.	282.	285.	291.	296.	297.	309.	310.	321.	324.	342.
10614	P	230.	256.	258.	262.	267.	274.	281.	276.	288.	291.	290.	300.	309.
10615	P	225.	243.	241.	243.	245.	250.	259.	256.	258.	268.	279.	280.	288.
10616	P	239.	251.	260.	262.	261.	272.	274.	278.	288.	291.	300.	302.	304.

	DAY 17	18	19	20
10609 P	351.	373.	386.	412.
10610 NP	266.	270.	265.	265.
10611 P	353.	374.	389.	409.
10612 P	325.	342.	357.	383.
10613 P	354.	369.	384.	408.
10614 P	311.	328.	331.	337.
10615 P	297.	318.	325.	344.
10616 P	320.	332.	352.	358.

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

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

TABLE 11 (PAGE 3): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

RAT #		DOSAGE GROUP III			5 MG/KG/DAY								
	PREGNANCY STATUS	DAY 0	4	6	7	8	9	10	11	12	13	14	15	16
10617	P	242.	265.	270.	272.	277.	281.	286.	287.	291.	292.	295.	302.	312.
10618	P	244.	264.	273.	276.	280.	285.	291.	299.	300.	306.	310.	316.	327.
10619	P	223.	243.	249.	253.	260.	264.	274.	278.	283.	293.	294.	304.	316.
10620	P	229.	258.	265.	266.	272.	277.	280.	286.	290.	302.	300.	307.	317.
10621	P	230.	256.	251.	256.	263.	267.	270.	279.	276.	280.	289.	293.	305.
10622	P	236.	260.	268.	270.	274.	276.	280.	287.	288.	288.	294.	297.	309.
10623	P	240.	248.	258.	260.	264.	267.	272.	273.	280.	282.	287.	296.	302.
10624	P	247.	270.	277.	279.	284.	292.	298.	306.	299.	304.	311.	320.	328.

	DAY 17	18	19	20
10617 P	316.	334.	344.	371.
10618 P	339.	351.	366.	384.
10619 P	327.	341.	355.	380.
10620 P	324.	342.	352.	377.
10621 P	321.	339.	358.	373.
10622 P	328.	340.	365.	369.
10623 P	313.	334.	345.	357.
10624 P	341.	359.	377.	389.

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

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

TABLE 11 (PAGE 4): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

RAT #	DOSAGE GROUP IV				10 MG/KG/DAY								
PREGNANCY STATUS	DAY 0	4	6	7	8	9	10	11	12	13	14	15	16
10625 P	242.	268.	275.	275.	281.	285.	295.	298.	301.	309.	311.	317.	325.
10626 P	223.	234.	237.	239.	240.	243.	250.	252.	256.	259.	262.	264.	272.
10627 P	237.	258.	264.	266.	270.	273.	276.	279.	278.	285.	287.	292.	299.
10628 P	235.	254.	253.	256.	262.	265.	270.	278.	285.	289.	292.	302.	311.
10629 P	244.	270.	269.	276.	282.	286.	286.	299.	307.	308.	316.	322.	333.
10630 P	234.	254.	257.	244.	233.	246.	249.	256.	268.	260.	269.	276.	285.
10631 P	227.	244.	243.	248.	248.	252.	252.	255.	262.	264.	272.	279.	291.
10632 P	246.	258.	264.	268.	271.	265.	273.	281.	286.	293.	297.	317.	314.

	DAY 17	18	19	20
10625 P	341.	345.	365.	384.
10626 P	278.	289.	299.	312.
10627 P	311.	327.	332.	353.
10628 P	319.	330.	349.	364.
10629 P	340.	356.	377.	398.
10630 P	297.	306.	321.	342.
10631 P	294.	315.	330.	342.
10632 P	327.	342.	357.	378.

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

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

TABLE 11 (PAGE 5): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

RAT #	DOSAGE GROUP V												
	20 MG/KG/DAY												
PREGNANCY STATUS	DAY 0	4	6	7	8	9	10	11	12	13	14	15	16
10633 P	239.	259.	267.	268.	273.	277.	278.	282.	289.	295.	296.	304.	312.
10634 P	231.	260.	260.	256.	264.	269.	272.	280.	282.	290.	290.	303.	318.
10635 P	224.	244.	247.	248.	251.	251.	246.	249.	255.	255.	261.	257.	266.
10636 P	228.	260.	269.	268.	273.	283.	284.	290.	288.	299.	292.	308.	321.
10637 P	244.	259.	262.	260.	260.	266.	266.	275.	278.	281.	290.	294.	302.
10638 P	237.	250.	254.	254.	251.	255.	262.	270.	278.	281.	283.	295.	302.
10639 P	240.	266.	268.	272.	271.	285.	284.	293.	298.	304.	306.	311.	322.
10640 P	247.	270.	270.	260.	262.	262.	269.	273.	279.	280.	287.	289.	302.

	DAY 17	18	19	20
10633 P	326.	334.	351.	372.
10634 P	327.	342.	352.	376.
10635 P	277.	285.	293.	314.
10636 P	338.	356.	366.	387.
10637 P	318.	326.	340.	363.
10638 P	316.	326.	342.	358.
10639 P	331.	347.	362.	376.
10640 P	313.	331.	348.	362.

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

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

TABLE 11 (PAGE 6): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

RAT #	DOSAGE GROUP VI												25 MG/KG/DAY
PREGNANCY STATUS	DAY 0	4	6	7	8	9	10	11	12	13	14	15	16
10641 P	240.	256.	264.	256.	262.	269.	265.	274.	273.	275.	274.	286.	299.
10642 P	221.	237.	240.	236.	239.	242.	247.	247.	244.	245.	248.	261.	272.
10643 P	247.	265.	270.	268.	269.	276.	281.	288.	288.	292.	291.	298.	311.
10644 P	236.	262.	270.	267.	264.	270.	278.	277.	281.	282.	270.	263.	260.
10645 P	244.	270.	275.	275.	278.	282.	283.	285.	301.	294.	301.	303.	313.
10646 P	233.	249.	249.	247.	246.	250.	255.	258.	261.	262.	256.	254.	267.
10647 P	228.	249.	260.	261.	266.	273.	276.	274.	272.	276.	279.	284.	286.
10648 P	239.	275.	284.	286.	291.	292.	292.	290.	288.	290.	295.	299.	311.

	DAY 17	18	19	20
10641 P	304.	314.	329.	349.
10642 P	281.	297.	304.	323.
10643 P	333.	345.	360.	377.
10644 P	273.	303.	324.	340.
10645 P	325.	337.	356.	359.
10646 P	276.	285.	302.	318.
10647 P	299.	320.	329.	336.
10648 P	322.	343.	352.	364.

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

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

TABLE 11 (PAGE 7): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

RAT #		DOSAGE GROUP VII												35 MG/KG/DAY
	PREGNANCY STATUS	DAY 0	4	6	7	8	9	10	11	12	13	14	15	16
10649	P	244.	252.	258.	260.	264.	264.	267.	268.	274.	278.	281.	286.	295.
10650	P	237.	253.	266.	264.	269.	261.	268.	260.	252.	235.	223.	216.	213.
10651	P	222.	245.	251.	254.	262.	267.	268.	275.	278.	279.	285.	292.	303.
10652	P	227.	243.	248.	250.	249.	251.	256.	258.	260.	266.	269.	275.	289.
10653	P	246.	269.	276.	275.	269.	276.	274.	281.	279.	280.	277.	289.	297.
10654	P	231.	256.	261.	268.	267.	273.	274.	276.	281.	259.	289.	297.	306.
10655	P	238.	249.	254.	252.	255.	254.	242.	248.	252.	258.	266.	271.	275.
10656	P	247.	275.	275.	272.	266.	274.	276.	269.	262.	287.	265.	266.	292.

	DAY 17	18	19	20
10649 P	291.	305.	316.	332.
10650 P	207.	208.	220.	239.
10651 P	316.	334.	350.	374.
10652 P	293.	304.	316.	343.
10653 P	300.	316.	331.	350.
10654 P	313.	327.	347.	364.
10655 P	289.	302.	324.	337.
10656 P	303.	320.	341.	350.

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

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

TABLE 12 (PAGE 1): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS	DAYS 0 - 4	4 - 6	6 - 8	8 - 10	10 - 12	12 - 14	14 - 16	16 - 18	18 - 20
RAT #	DOSAGE GROUP I			0 (VEHICLE) MG/KG/DAY					
10601 P	76.	45.	40.	44.	45.	44.	47.	54.	49.
10602 P	93.	56.	49.	49.	a	a	48.	53.	54.
10603 P	97.	56.	56.	54.	56.	61.	54.	61.	54.
10604 P	115.	62.	64.	61.	60.	55.	45.	53.	61.
10605 P	87.	44.	40.	43.	44.	46.	44.	50.	52.
10606 P	103.	51.	56.	53.	57.	55.	51.	54.	56.
10607 P	89.	47.	68.	57.	60.	90.	55.	46.	53.
10608 P	72.	37.	42.	46.	45.	43.	43.	44.	40.
RAT #	DOSAGE GROUP II			1 MG/KG/DAY					
10609 P	97.	50.	49.	50.	50.	51.	50.	53.	53.
10610 NP	88.	44.	44.	39.	43.	42.	37.	49.	36.
10611 P	77.	55.	51.	52.	49.	47.	50.	59.	57.
10612 P	94.	46.	51.	54.	47.	52.	52.	57.	54.
10613 P	93.	53.	46.	49.	46.	54.	60.	62.	57.
10614 P	94.	43.	51.	50.	48.	58.	53.	44.	47.
10615 P	61.	38.	41.	40.	38.	78.	41.	42.	51.
10616 P	76.	42.	40.	43.	45.	51.	45.	40.	48.

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

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

TABLE 12 (PAGE 2): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS	DAYS 0 - 4	4 - 6	6 - 8	8 - 10	10 - 12	12 - 14	14 - 16	16 - 18	18 - 20
RAT #	DOSAGE GROUP III			5 MG/KG/DAY					
10617 P	90.	48.	45.	45.	45.	40.	45.	49.	49.
10618 P	94.	56.	22.	48.	50.	52.	51.	55.	53.
10619 P	86.	49.	49.	51.	56.	54.	53.	56.	56.
10620 P	95.	50.	50.	49.	54.	48.	46.	48.	44.
10621 P	90.	46.	44.	47.	46.	51.	48.	51.	52.
10622 P	95.	47.	47.	48.	46.	42.	36.	47.	50.
10623 P	90.	44.	45.	47.	44.	46.	48.	53.	43.
10624 P	103.	46.	50.	52.	50.	43.	47.	48.	50.
RAT #	DOSAGE GROUP IV			10 MG/KG/DAY					
10625 P	91.	50.	45.	48.	48.	46.	44.	48.	50.
10626 P	66.	33.	31.	38.	40.	35.	35.	37.	36.
10627 P	90.	56.	47.	43.	45.	40.	34.	46.	50.
10628 P	85.	42.	44.	45.	48.	50.	47.	46.	52.
10629 P	85.	45.	47.	49.	50.	55.	46.	51.	55.
10630 P	85.	46.	14.	35.	44.	40.	38.	39.	49.
10631 P	77.	40.	36.	38.	40.	47.	45.	39.	41.
10632 P	88.	43.	41.	37.	49.	50.	49.	49.	51.

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

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

TABLE 12 (PAGE 3): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS	DAYS 0 - 4	4 - 6	6 - 8	8 - 10	10 - 12	12 - 14	14 - 16	16 - 18	18 - 20
RAT #	DOSAGE GROUP V			20 MG/KG/DAY					
10633 P	88.	50.	47.	46.	47.	48.	46.	51.	48.
10634 P	89.	47.	41.	44.	46.	43.	47.	49.	44.
10635 P	78.	48.	31.	28.	33.	31.	21.	35.	41.
10636 P	105.	62.	45.	57.	44.	48.	59.	59.	53.
10637 P	87.	48.	41.	42.	50.	48.	48.	52.	51.
10638 P	140.	47.	40.	44.	51.	48.	46.	43.	44.
10639 P	95.	54.	54.	54.	52.	50.	46.	41.	51.
10640 P	103.	47.	41.	40.	47.	53.	49.	44.	49.
RAT #	DOSAGE GROUP VI			25 MG/KG/DAY					
10641 P	86.	48.	36.	40.	41.	33.	38.	37.	40.
10642 P	79.	42.	32.	34.	35.	25.	41.	41.	38.
10643 P	83.	47.	40.	45.	46.	38.	44.	53.	48.
10644 P	94.	51.	38.	45.	43.	25.	11.	40.	46.
10645 P	91.	54.	51.	45.	47.	40.	46.	39.	45.
10646 P	73.	38.	31.	35.	37.	27.	26.	32.	43.
10647 P	75.	38.	38.	45.	38.	39.	40.	48.	42.
10648 P	102.	54.	50.	46.	34.	39.	38.	46.	42.

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

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

TABLE 12 (PAGE 4): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS	DAYS 0 - 4	4 - 6	6 - 8	8 - 10	10 - 12	12 - 14	14 - 16	16 - 18	18 - 20
RAT #	DOSAGE GROUP VII			35 MG/KG/DAY					
10649 P	86.	48.	41.	41.	43.	41.	39.	38.	43.
10650 P	87.	49.	45.	39.	17.	2.	1.	13.	34.
10651 P	94.	53.	49.	48.	45.	42.	45.	51.	52.
10652 P	80.	43.	40.	38.	41.	39.	42.	44.	46.
10653 P	95.	55.	48.	43.	47.	46.	41.	35.	62.
10654 P	89.	46.	44.	46.	45.	46.	40.	36.	52.
10655 P	82.	47.	37.	25.	39.	64.	43.	43.	55.
10656 P	90.	42.	33.	42.	26.	42.	39.	38.	44.

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

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

TABLE 13 (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
RAT #	M	F																		
DOSAGE GROUP I					0 (VEHICLE) MG/KG/DAY															
10601	6	7	6	7	13	0	0	0	0	0	0	0	0	0	6	7	13	6	7	13
10602	5	10	11	4	15	0	0	0	1	0	1	0	0	0	12	4	16	12	5	17
10603	12	5	9	8	17	0	0	0	0	0	0	0	0	0	9	8	17	11	8	19
10604	5	10	3	12	15	0	0	0	0	0	0	0	0	0	3	12	15	4	12	16
10605	6	5	8	3	11	0	0	0	0	2	2	0	0	0	8	5	13	8	6	14
10606	6	9	5	10	15	0	0	0	0	0	0	0	0	0	5	10	15	5	11	16
10607	1	3	1	3	4	0	0	0	0	0	0	0	0	0	1	3	4	5	8	13
10608	8	11	10	9	19	0	0	0	0	0	0	0	0	0	10	9	19	10	10	20
DOSAGE GROUP II					1 MG/KG/DAY															
10609	11	5	7	9	16	0	0	0	0	0	0	0	0	0	7	9	16	7	11	18
10610	NOT PREGNANT																			
10611	2	13	8	7	15	0	0	0	0	1	1	0	0	0	8	8	16	9	9	18
10612	5	9	7	7	14	0	0	0	0	0	0	0	0	0	7	7	14	9	9	18
10613	9	6	9	6	15	0	0	0	0	1	1	0	0	0	9	7	16	10	7	17
10614	1	6	1	6	7	0	0	0	0	0	0	0	0	0	1	6	7	5	7	12
10615	7	6	4	9	13	0	0	0	0	0	0	0	0	0	4	9	13	5	9	14
10616	7	6	6	7	13	0	0	0	0	0	0	0	0	0	6	7	13	6	7	13

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

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

TABLE 13 (PAGE 2): 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	
RAT #	M	F	HORN		TOTAL	HORN		TOTAL	HORN		TOTAL	HORN		TOTAL	HORN		TOTAL	OVARY		TOTAL
DOSAGE GROUP III					5 MG/KG/DAY															
10617	7	6	7	6	13	0	0	0	0	1	1	0	0	0	7	7	14	7	7	14
10618	3	10	4	9	13	0	0	0	1	1	2	0	0	0	5	10	15	7	10	17
10619	7	9	10	6	16	0	0	0	0	0	0	0	0	0	10	6	16	10	7	17
10620	8	7	6	9	15	0	0	0	3	0	3	0	0	0	9	9	18	9	9	18
10621	9	6	9	6	15	0	0	0	0	0	0	0	0	0	9	6	15	10	6	16
10622	7	8	7	8	15	0	0	0	0	0	0	0	0	0	7	8	15	7	8	15
10623	7	5	4	8	12	0	0	0	0	0	0	0	0	0	4	8	12	4	9	13
10624	11	6	6	11	17	0	0	0	0	0	0	0	0	0	6	11	17	6	12	18
DOSAGE GROUP IV					10 MG/KG/DAY															
10625	5	10	11	4	15	0	0	0	1	0	1	0	0	0	12	4	16	13	8	21
10626	7	3	3	7	10	0	0	0	0	0	0	0	1	1	3	8	11	3	9	12
10627	6	7	9	4	13	0	0	0	0	1	1	0	0	0	9	5	14	9	5	14
10628	8	7	5	10	15	0	0	0	0	0	0	0	0	0	5	10	15	6	10	16
10629	6	9	8	7	15	0	0	0	0	0	0	0	0	0	8	7	15	8	7	15
10630	8	5	10	3	13	0	0	0	0	0	0	0	0	0	10	3	13	10	5	15
10631	5	10	11	4	15	0	0	0	0	0	0	0	0	0	11	4	15	12	6	18
10632	5	9	6	8	14	0	0	0	2	0	2	0	0	0	8	8	16	8	9	17

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

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

TABLE 13 (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	
RAT #	M	F	HORN		TOTAL	HORN		TOTAL	HORN		TOTAL	HORN		TOTAL	HORN		TOTAL	OVARY		TOTAL
DOSAGE GROUP V					20 MG/KG/DAY															
10633	9	5	4	10	14	0	0	0	0	0	0	0	0	0	4	10	14	4	11	15
10634	9	7	8	8	16	0	0	0	0	0	0	0	0	0	8	8	16	8	8	16
10635	5	6	7	4	11	0	0	0	0	1	1	0	0	0	7	5	12	7	5	12
10636	8	7	7	8	15	0	0	0	1	0	1	0	0	0	8	8	16	8	8	16
10637	8	7	9	6	15	0	0	0	0	0	0	0	0	0	9	6	15	9	6	15
10638	6	8	6	8	14	0	0	0	0	0	0	0	0	0	6	8	14	6	8	14
10639	9	7	8	8	16	0	0	0	0	1	1	0	0	0	8	9	17	8	9	17
10640	12	5	7	10	17	0	0	0	0	0	0	0	0	0	7	10	17	8	11	19
DOSAGE GROUP VI					25 MG/KG/DAY															
10641	4	9	7	6	13	0	0	0	0	0	0	0	0	0	7	6	13	7	6	13
10642	9	7	7	9	16	0	0	0	0	0	0	0	0	0	7	9	16	7	10	17
10643	8	7	9	6	15	0	0	0	0	0	0	0	0	0	9	6	15	9	8	17
10644	13	5	8	10	18	0	0	0	1	1	2	0	0	0	9	11	20	9	11	20
10645	7	7	6	8	14	0	0	0	0	0	0	0	0	0	6	8	14	8	8	16
10646	7	6	5	8	13	0	0	0	0	0	0	0	0	0	5	8	13	7	8	15
10647	3	7	2	8	10	0	0	0	1	0	1	0	0	0	3	8	11	3	8	11
10648	8	9	10	7	17	0	0	0	0	0	0	0	0	0	10	7	17	11	7	18

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

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

TABLE 13 (PAGE 4): 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
RAT #	M	F																		
DOSAGE GROUP VII					35 MG/KG/DAY															
10649	3	8	6	5	11	0	0	0	1	1	2	0	0	0	7	6	13	7	6	13
10650	5	8	5	8	13	0	0	0	2	1	3	0	0	0	7	9	16	8	9	17
10651	9	8	10	7	17	0	0	0	0	0	0	0	0	0	10	7	17	10	8	18
10652	8	6	7	7	14	0	0	0	0	0	0	0	0	0	7	7	14	7	8	15
10653	6	7	8	5	13	0	0	0	1	0	1	0	0	0	9	5	14	9	5	14
10654	7	10	9	8	17	0	0	0	0	1	1	0	0	0	9	9	18	9	13	22
10655	9	3	5	7	12	0	0	0	0	0	0	0	0	0	5	7	12	5	7	12
10656	11	6	9	8	17	0	0	0	0	0	0	0	0	0	9	8	17	9	10	19

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

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

TABLE 14 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - INDIVIDUAL DATA

	NUMBER OF LIVE FETUSES			AVERAGE FETAL BODY WEIGHT (G)			---- CONCEPTUSES ------		
								RESORBED	
RAT #	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL a	N	N	%
DOSAGE GROUP I			0 (VEHICLE) MG/KG/DAY						
10601	6	7	13	3.54	3.43	3.48	13	0	0.0
10602	5	10	15	3.71	3.50	3.57	16	1	6.2
10603	12	5	17	3.91	3.71	3.85	17	0	0.0
10604	5	10	15	3.68	3.44	3.52	15	0	0.0
10605	6	5	11	3.94	3.57	3.78	13	2	15.4
10606	6	9	15	3.62	3.42	3.50	15	0	0.0
10607	1	3	4	2.45	2.30	2.34	4	0	0.0
10608	8	11	19	3.38	3.06	3.20	19	0	0.0
DOSAGE GROUP II			1 MG/KG/DAY						
10609	11	5	16	3.37	3.29	3.35	16	0	0.0
10610	NOT PREGNANT								
10611	2	13	15	4.01	3.64	3.69	16	1	6.2
10612	5	9	14	3.53	3.48	3.50	14	0	0.0
10613	9	6	15	3.50	3.39	3.46	16	1	6.2
10614	1	6	7	3.31	2.96	3.01	7	0	0.0
10615	7	6	13	3.69	3.44	3.58	13	0	0.0
10616	7	6	13	3.50	3.33	3.42	13	0	0.0

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

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

TABLE 14 (PAGE 2): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - INDIVIDUAL DATA

	NUMBER OF LIVE FETUSES			AVERAGE FETAL BODY WEIGHT (G)			---- CONCEPTUSES ------ RESORBED		
RAT #	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL a	N	N	%
DOSAGE GROUP III			5 MG/KG/DAY						
10617	7	6	13	3.63	3.32	3.49	14	1	7.1
10618	3	10	13	3.40	3.19	3.24	15	2	13.3
10619	7	9	16	3.18	2.91	3.03	16	0	0.0
10620	8	7	15	3.38	3.36	3.37	18	3	16.7
10621	9	6	15	3.62	3.29	3.48	15	0	0.0
10622	7	8	15	3.02	3.07	3.05	15	0	0.0
10623	7	5	12	3.44	3.08	3.29	12	0	0.0
10624	11	6	17	3.31	3.21	3.28	17	0	0.0
DOSAGE GROUP IV			10 MG/KG/DAY						
10625	5	10	15	3.08	3.30	3.22	16	1	6.2
10626	7	3	10	3.73	3.19	3.57	11	1	9.1
10627	6	7	13	3.42	3.33	3.37	14	1	7.1
10628	8	7	15	3.47	3.38	3.43	15	0	0.0
10629	6	9	15	3.51	3.26	3.36	15	0	0.0
10630	8	5	13	3.42	3.14	3.32	13	0	0.0
10631	5	10	15	3.43	3.45	3.44	15	0	0.0
10632	5	9	14	3.27	2.92	3.05	16	2	12.5

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

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

TABLE 14 (PAGE 3): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - INDIVIDUAL DATA

	NUMBER OF LIVE FETUSES			AVERAGE FETAL BODY WEIGHT (G)			---- CONCEPTUSES ------ RESORBED		
RAT #	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL a	N	N	%
DOSAGE GROUP V			20 MG/KG/DAY						
10633	9	5	14	3.54	3.24	3.43	14	0	0.0
10634	9	7	16	3.26	3.04	3.16	16	0	0.0
10635	5	6	11	3.25	3.11	3.18	12	1	8.3
10636	8	7	15	3.54	3.37	3.46	16	1	6.2
10637	8	7	15	3.17	2.92	3.05	15	0	0.0
10638	6	8	14	3.50	3.19	3.32	14	0	0.0
10639	9	7	16	3.33	3.16	3.25	17	1	5.9
10640	12	5	17	3.12	3.01	3.09	17	0	0.0
DOSAGE GROUP VI			25 MG/KG/DAY						
10641	4	9	13	3.46	3.31	3.35	13	0	0.0
10642	9	7	16	3.12	2.89	3.02	16	0	0.0
10643	8	7	15	3.45	3.35	3.40	15	0	0.0
10644	13	5	18	2.90	2.80	2.87	20	2	10.0
10645	7	7	14	3.16	3.02	3.09	14	0	0.0
10646	7	6	13	3.05	3.02	3.03	13	0	0.0
10647	3	7	10	3.43	3.02	3.14	11	1	9.1
10648	8	9	17	3.10	2.85	2.96	17	0	0.0

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

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

TABLE 14 (PAGE 4): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - INDIVIDUAL DATA

	NUMBER OF LIVE FETUSES			AVERAGE FETAL BODY WEIGHT (G)			---- CONCEPTUSES ------		
								RESORBED	
RAT #	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL a	N	N	%
DOSAGE GROUP VII			35 MG/KG/DAY						
10649	3	8	11	2.80	2.54	2.61	13	2	15.4
10650	5	8	13	1.98	1.85	1.90	16	3	18.8
10651	9	8	17	3.24	3.16	3.20	17	0	0.0
10652	8	6	14	3.23	2.94	3.11	14	0	0.0
10653	6	7	13	3.25	3.04	3.14	14	1	7.1
10654	7	10	17	3.21	2.95	3.06	18	1	5.6
10655	9	3	12	3.30	3.07	3.24	12	0	0.0
10656	11	6	17	3.25	3.07	3.19	17	0	0.0

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

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

TABLE 15 (PAGE 1): FETAL SEX, VITAL STATUS AND BODY WEIGHT - INDIVIDUAL DATA

FETUS #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
DOSAGE GROUP I							0 (VEHICLE) MG/KG/DAY																
RAT # CLs																							
10601 6/ 7	FA	MA	FA	MA	FA	FA / FA		MA	FA	FA	MA	MA	MA										
	3.34	3.64	3.28	3.61	3.40	3.68	3.34	3.24	3.65	3.30	3.49	3.64	3.65										
10602 12/ 5	MA	FA	FA	MA	MA	FA	E	FA	FA	FA	FA	FA / FA		FA	MA	MA							
	3.37	3.38	3.55	3.31	3.69	3.19		3.57	3.58	3.29	3.59	3.71	3.52	3.63	4.00	4.18							
10603 11/ 8	FA	FA	MA	FA	MA	MA	MA	MA	MA / MA		FA	MA	MA	MA	MA	FA	MA						
	3.59	3.84	4.14	3.79	3.70	3.92	4.03	3.93	3.69	3.82	3.74	3.80	3.85	3.90	3.90	3.58	4.26						
10604 4/12	MA	FA	FA / FA		MA	FA	FA	MA	FA	FA	MA	MA	FA	FA	FA								
	3.81	3.54	3.86	2.62	3.74	3.35	3.38	3.73	3.39	3.13	3.53	3.60	3.72	3.58	3.81								
10605 8/ 6	FA	FA	FA	MA	MA	FA	FA	MA / MA		E	E	MA	MA										
	3.41	3.67	3.69	4.08	3.82	3.69	3.41	3.90	3.95			3.85	4.06										
10606 5/11	FA	FA	FA	FA	MA / MA		MA	FA	MA	FA	FA	FA	FA	MA	MA								
	3.80	3.56	3.48	3.61	3.68	3.71	3.68	3.47	3.57	3.07	3.40	3.07	3.31	3.42	3.64								
10607 5/ 8	MA / FA		FA	FA																			
	2.45	2.35	2.41	2.14																			
10608 10/10	MA	FA	FA	MA	FA	FA	FA	FA	FA	MA / MA		FA	MA	MA	MA	FA	MA	FA	FA				
	3.13	3.19	3.22	3.22	2.76	3.29	3.29	2.93	2.95	3.66	3.20	3.12	3.45	3.34	3.44	2.97	3.59	2.86	3.11				
DOSAGE GROUP II							1 MG/KG/DAY																
10609 7/11	MA	FA	MA	FA	MA	MA	MA / MA		FA	MA	MA	MA	FA	MA	FA	MA							
	3.39	3.15	3.29	3.64	3.45	3.73	3.07	3.27	3.17	3.28	3.43	3.29	3.29	3.23	3.18	3.68							
10610	NOT PREGNANT																						
10611 9/ 9	FA	FA	FA	FA	FA	MA	FA	FA / FA		FA	FA	E	FA	FA	FA	MA							
	3.84	3.60	3.39	3.82	3.56	4.06	3.59	3.93	3.47	3.50	3.46		3.82	3.68	3.70	3.96							
10612 9/ 9	MA	FA	FA	MA	MA	FA	FA / MA		FA	FA	FA	FA	MA	FA									
	3.23	3.50	3.44	3.55	3.86	3.72	3.23	3.27	3.45	3.48	3.45	3.43	3.74	3.62									
10613 10/ 7	FA	MA	FA	FA	MA	FA	MA	FA	MA / MA		MA	MA	MA	MA	FA	E							
	3.18	3.44	3.62	3.36	3.52	3.31	3.44	3.41	3.52	3.39	3.35	3.38	3.59	3.87	3.47								
10614 5/ 7	FA / FA		FA	FA	FA	MA	FA																
	2.95	2.94	2.77	3.06	3.22	3.31	2.84																
10615 5/ 9	MA	FA	FA	FA / MA		MA	FA	MA	MA	FA	FA	MA	MA										
	3.59	3.21	3.61	3.50	3.50	3.64	3.57	3.96	3.80	3.31	3.45	3.63	3.71										
10616 6/ 7	FA	MA	MA	FA	FA	MA / FA		MA	MA	MA	FA	MA	FA										
	3.33	3.56	3.66	3.41	3.06	3.39	3.39	3.70	3.36	3.33	3.49	3.54	3.30										

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

TABLE 15 (PAGE 2): 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	20	21	22	23
DOSAGE GROUP III						5 MG/KG/DAY																		
RAT #	CLs																							
10617	7/ 7	MA	MA	MA	FA	FA	MA	MA / FA		MA	MA	FA	FA	E	FA									
		3.39	3.35	3.99	3.36	3.39	3.87	3.74	3.01	3.40	3.69	3.07	3.54		3.56									
10618	7/10	MA	E	FA	FA	FA / FA		FA	FA	FA	MA	MA	FA	E	FA	FA								
		3.67		3.29	3.14	3.54	2.97	3.07	3.11	3.20	3.26	3.26	3.14		3.22	3.26								
10619	10/ 7	MA	FA	MA	FA	MA	MA	FA	FA	MA	FA / FA		MA	FA	MA	FA	FA							
		3.36	3.38	3.25	2.96	3.12	3.17	3.11	2.63	2.89	2.60	2.99	3.29	2.56	3.15	2.80	3.20							
10620	9/ 9	FA	MA	E	E	MA	FA	MA	E	FA / FA		MA	FA	MA	FA	MA	MA	MA	FA					
		3.28	4.00			3.52	3.51	3.28		3.40	3.38	3.26	3.43	3.31	3.07	2.72	3.49	3.43	3.46					
10621	10/ 6	FA	MA	MA	MA	MA	MA	FA	MA	FA / FA		FA	MA	MA	FA	MA								
		2.91	3.55	3.57	3.56	3.59	3.72	3.32	3.55	3.56	3.08	3.47	3.67	3.50	3.40	3.83								
10622	7/ 8	MA	FA	MA	MA	FA	FA	MA / FA		FA	MA	MA	MA	FA	FA	FA								
		3.25	3.20	3.10	3.18	3.07	2.85	2.54	2.95	3.10	3.04	3.32	2.72	3.38	3.16	2.86								
10623	4/ 9	FA	MA	MA	MA / FA		MA	MA	FA	FA	FA	MA	MA											
		2.96	3.28	3.40	3.34	3.24	3.81	3.41	3.02	3.13	3.04	3.40	3.46											
10624	6/12	FA	FA	MA	MA	FA	MA / MA		MA	FA	MA	MA	MA	FA	MA	MA	MA	FA						
		3.20	3.11	3.23	3.44	3.40	3.32	3.17	3.27	3.20	3.36	3.40	3.35	3.06	3.10	3.59	3.22	3.28						
DOSAGE GROUP IV						10 MG/KG/DAY																		
10625	13/ 8	MA	MA	FA	FA	MA	E	FA	FA	FA	FA	FA	MA / FA		FA	MA	FA							
		2.64	3.09	2.76	3.49	3.34		3.33	3.52	3.44	3.16	3.45	3.13	3.26	3.59	3.20	2.98							
10626	3/ 9	FA	MA	MA / FL		MA	FA	MA	MA	MA	FA	MA												
		3.71	4.02	3.74	1.68	3.78	3.42	3.57	3.76	3.51	2.44	3.72												
10627	9/ 5	FA	FA	FA	MA	MA	MA	FA	FA	FA / FA		MA	E	MA	MA									
		3.25	3.30	3.17	3.77	3.49	3.50	3.56	3.40	3.17	3.47	3.74		3.40	2.64									
10628	6/10	FA	FA	MA	MA	FA / FA		MA	FA	MA	FA	FA	MA	MA	MA	MA								
		3.24	3.66	3.59	3.63	3.30	3.05	3.41	3.48	3.28	3.43	3.50	3.52	3.44	3.24	3.65								
10629	8/ 7	FA	MA	FA	FA	FA	FA	FA	FA / MA		MA	FA	MA	FA	MA	MA								
		3.13	3.60	3.39	3.65	3.31	2.94	3.50	2.85	3.51	3.22	3.34	3.50	3.22	3.46	3.75								
10630	10/ 5	MA	FA	FA	MA	MA	MA	MA	FA	FA	FA / MA		MA	MA										
		3.08	3.10	3.26	3.52	3.33	3.40	3.33	3.08	3.26	3.00	3.51	3.62	3.61										
10631	12/ 6	MA	FA	MA	FA	FA	FA	FA	FA	MA	MA	FA / FA		FA	MA	FA								
		3.32	3.61	3.30	3.52	3.23	3.20	3.39	3.30	3.44	3.63	3.52	3.54	3.48	3.47	3.71								
10632	8/ 9	FA	FA	MA	E	MA	FA	FA	E / FA		FA	FA	MA	MA	FA	FA	MA							
		3.08	3.02	3.47		3.38	3.15	1.49		3.01	3.12	3.10	2.63	3.40	3.26	3.07	3.48							

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

TABLE 15 (PAGE 3): FETAL SEX, VITAL STATUS AND BODY WEIGHT - INDIVIDUAL DATA

FETUS #		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
DOSAGE GROUP V						20 MG/KG/DAY																		
RAT #	CLs																							
10633	4/11	MA	FA	MA	MA / FA	MA	FA	FA	MA	MA	FA	MA	MA	MA										
		3.79	3.65	3.70	3.65	2.88	3.58	3.03	3.34	3.56	3.34	3.29	3.53	3.42	3.25									
10634	8/ 8	FA	MA	FA	MA	MA	MA	MA	MA / FA		FA	FA	FA	MA	MA	MA	FA							
		2.80	3.11	3.18	3.43	3.07	3.22	3.43	3.16	2.63	3.26	3.24	3.24	3.43	3.32	3.18	2.95							
10635	7/ 5	FA	MA	FA	FA	FA	MA	FA / FA		MA	MA	MA	E											
		3.29	3.48	3.19	3.31	3.14	3.15	2.81	2.93	3.19	3.15	3.29												
10636	8/ 8	MA	FA	MA	E	FA	FA	FA	FA / FA		FA	MA	MA	MA	MA	MA	MA							
		3.35	3.26	3.64		3.50	3.45	3.35	3.57	3.00	3.46	3.53	3.59	3.61	3.71	3.48	3.44							
10637	9/ 6	FA	FA	MA	MA	MA	MA	FA	FA	FA / FA		MA	FA	MA	MA	MA								
		2.58	2.89	3.02	3.12	3.15	3.12	2.94	3.21	2.87	2.94	3.19	2.99	3.36	3.14	3.23								
10638	6/ 8	MA	FA	FA	MA	FA	FA / FA		MA	FA	MA	FA	MA	FA	MA									
		3.50	3.09	3.53	3.49	3.06	3.31	3.09	3.16	3.22	3.33	2.84	3.69	3.41	3.82									
10639	8/ 9	MA	MA	MA	FA	FA	MA	FA	MA / MA		E	MA	FA	FA	FA	MA	FA	MA						
		3.34	3.52	3.75	3.34	3.40	3.24	2.71	3.58	3.09		3.25	3.19	3.37	3.25	3.34	2.83	2.83						
10640	8/11	MA	MA	MA	MA	FA	MA	MA / MA		FA	MA	FA	FA	MA	MA	FA	MA	MA						
		3.21	3.21	3.43	3.19	3.05	3.04	2.99	3.16	3.00	3.28	2.99	3.14	3.13	3.06	2.87	2.77	3.04						
DOSAGE GROUP VI						25 MG/KG/DAY																		
10641	7/ 6	FA	FA	MA	FA	FA	FA	MA / MA		FA	FA	FA	FA	MA										
		3.49	3.42	3.69	3.47	3.14	3.22	3.21	3.53	3.11	3.30	3.24	3.38	3.40										
10642	7/10	FA	FA	MA	MA	MA	FA	MA / FA		MA	FA	MA	MA	FA	MA	FA	MA							
		3.05	2.68	3.17	3.07	3.07	3.02	3.26	2.90	3.15	2.88	3.06	3.24	2.92	3.20	2.76	2.89							
10643	9/ 8	MA	FA	FA	FA	MA	MA	MA	FA	FA / MA		FA	FA	MA	MA	MA								
		3.44	3.33	3.41	3.44	3.68	3.52	3.47	3.33	3.25	3.51	3.17	3.51	3.22	3.25	3.51								
10644	9/11	MA	MA	FA	FA	FA	E	MA	MA	MA / MA		MA	E	FA	MA	MA	MA	MA	FA	MA	MA			
		2.92	2.64	2.79	2.81	2.83		3.10	2.97	3.00	3.01	2.74		2.66	2.89	3.02	2.81	2.95	2.90	2.89	2.73			
10645	8/ 8	FA	FA	MA	MA	MA	FA / MA		FA	FA	MA	FA	MA	MA	FA									
		3.05	3.16	3.26	3.26	3.05	3.06	3.02	3.01	3.16	3.34	2.97	3.13	3.09	2.76									
10646	7/ 8	MA	FA	FA	MA	MA / MA		FA	MA	FA	FA	MA	MA	FA										
		3.07	3.04	3.16	3.02	2.97	2.95	3.02	3.13	2.77	3.15	3.12	3.07	2.98										
10647	3/ 8	FA	E	FA / MA		FA	FA	MA	FA	FA	FA	MA												
		3.25		3.18	3.37	3.18	2.66	3.61	2.84	2.92	3.12	3.32												
10648	11/ 7	MA	FA	MA	MA	FA	FA	MA	FA	FA	MA / MA		MA	MA	FA	FA	FA	FA						
		2.99	2.90	3.12	2.77	3.12	2.73	3.15	2.95	2.75	3.26	3.12	3.19	3.17	3.03	2.76	2.81	2.59						

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

TABLE 15 (PAGE 4): FETAL SEX, VITAL STATUS AND BODY WEIGHT - INDIVIDUAL DATA

FETUS #		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
DOSAGE GROUP VII						35 MG/KG/DAY																		
RAT #	CLs																							
10649	7/ 6	FA	E	FA	MA	FA	MA	MA / FA	E	FA	FA	FA	FA											
		2.36		2.61	2.85	2.44	2.80	2.75	2.35		2.61	2.30	2.57	3.08										
10650a	8/ 9	FA	FA	FA	E	E	FA	MA / E	MA	MA	FA	FA	MA	FA	FA	MA								
		2.01	1.75	2.08			2.20	2.15		2.04	2.12	1.66	1.14	1.64	2.02	1.95	1.95							
10651	10/ 8	FA	MA	FA	FA	FA	FA	MA	MA	MA	FA / MA		MA	MA	MA	FA	MA	FA						
		3.04	3.34	3.03	3.13	2.96	3.35	3.25	3.03	3.14	3.22	2.98	3.19	3.35	3.20	3.10	3.66	3.46						
10652	7/ 8	MA	MA	MA	FA	MA	MA	FA / FA	MA	FA	MA	FA	MA	FA										
		3.07	3.29	3.51	3.07	3.27	3.00	2.88	3.19	3.21	3.20	3.45	2.72	3.04	2.59									
10653	9/ 5	FA	MA	MA	FA	FA	MA	MA	FA	E / FA		FA	MA	MA	FA									
		3.04	3.20	3.09	2.71	2.90	3.46	2.93	3.22		3.27	2.94	3.29	3.55	3.17									
10654	9/13	FA	MA	FA	FA	MA	MA	FA	FA	FA / MA		FA	E	FA	MA	MA	MA	FA	FA					
		2.76	3.03	3.06	3.20	2.97	3.22	2.86	2.80	3.12	3.21	2.98		2.81	3.46	3.37	3.24	3.01	2.87					
10655	5/ 7	MA	MA	MA	FA	FA / FA		MA	MA	MA	MA	MA	MA											
		3.23	3.36	3.40	3.17	3.23	2.82	3.53	3.32	3.03	3.21	3.10	3.52											
10656	9/10	MA	FA	MA	FA	FA	MA	MA	MA	MA / MA		FA	FA	MA	FA	MA	MA	MA						
		3.37	3.30	3.12	2.85	3.22	3.35	3.33	3.52	3.13	3.22	3.11	3.36	3.45	2.56	3.21	2.84	3.25						

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).

a. Fetuses 10650-1 and 10650-10 had cleft palate and an edematous body, and fetuses 10650-2, 10650-3, 10650-6, 10650-7, 10650-9, 10650-11, 10650-12, 10650-13, 10650-14, 10650-15 and 10650-16 had cleft palate.

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 418-011P

SPONSOR'S STUDY NUMBER: T-6316.7

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

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 gavage to Crl:CD®BR VAF/Plus® presumed pregnant female rats.

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

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

Number:

Initial population acclimated: 75 virgin female rats.
Population selected for study: 56 mated female rats (8 per dosage group).

Body Weight and Age:

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

Sex:

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

Source:

Charles River Laboratories, Inc.

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

Identification:

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

ANIMAL HUSBANDRY:

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

Housing:

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

Room Air, Temperature and Humidity:

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

Light:

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

Diet:

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

Water:

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

Contaminants:

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

RANDOMIZATION AND COHABITATION:

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

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

ADMINISTRATION:

Route and Reason for Choice:

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

Method and Frequency:

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

Rationale for Dosage Selection:

Dosages 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 Rats	Dosage (mg/kg/day)	Concentration (mg/mL)	Dosage Volume (mL/kg)	Argus Batch Number
I	8	0 (Vehicle)	0	5	B-418-011P-A(Day.Month.Year)
II	8	1	0.2	5	B-418-011P-B(Day.Month.Year)
III	8	5	1	5	B-418-011P-C(Day.Month.Year)
IV	8	10	2	5	B-418-011P-D(Day.Month.Year)
V	8	20	4	5	B-418-011P-E(Day.Month.Year)
VI	8	25	5	5	B-418-011-P-F(Day.Month.Year)
VII	8	35	7	5	B-418-011-P-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:

Acclimation Period: Weekly.

Predosage Period: Day 0 of presumed gestation.

Dosage Period: Twice daily. Once approximately one hour postdosage and then four to six hours later.

Postdosage Period: Once daily.

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

Body Weights:

Acclimation Period: Weekly.

Predosage Period: Days 0 and 4 of presumed gestation.

Dosage Period: Daily.

Postdosage Period: Daily.

Feed Consumption Values (recorded and tabulated):

Predosage Period:	Days 0 and 4 of presumed gestation.
Dosage Period:	Days 6, 8, 10, 12, 14 and 16 of presumed gestation.
Postdosage Period:	Days 18 and 20 of presumed gestation.

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

Mating Performance:

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

Caesarean-Sectioning Observations:

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

Corpora Lutea.

Implantation Sites.
[Placentae 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 defined as an early resorption.)

Fetal Observations:

Fetuses will be examined for sex and for gross external alterations. Late resorptions and dead fetuses will be examined for gross external alterations to the extent possible. 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 with gross external alterations will be fixed in Bouin's solution; all other fetuses will be discarded. Representative photographs of fetal gross external alterations will be taken.

METHOD OF SACRIFICE:

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

NECROPSY:

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

Scheduled Sacrifice:

On day 20 of presumed gestation, female rats will be Caesarean-sectioned, and a gross necropsy of the thoracic, abdominal and pelvic viscera will be performed. Uteri of apparently nonpregnant rats will be stained with 10% ammonium sulfide to confirm the absence of implantation sites[5].

Rats Found Dead or Moribund:

Rats that die or are sacrificed because of moribund condition, abortion or premature delivery will be examined for the cause of death or moribund condition on the day the observation is made. The rats will be examined for gross lesions. Pregnancy status and uterine contents of female rats will be recorded. Aborted fetuses and/or delivered pups will be examined to the extent possible, using the same methods described for fetuses. Uteri of apparently nonpregnant rats will be stained with 10% ammonium sulfide to confirm the absence of implantation sites[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.
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. and Voytek, P.E. (1982). *In Vivo Reproductive and Mutagenicity Tests.* Environmental Protection Agency, Washington, D.C. National Technical Information Service, U.S. Department of Commerce, Springfield, VA 22161.

2. Christian, M.S. (1984). Reproductive toxicity and teratology evaluations of naltrexone (Proceedings of Naltrexone Symposium, New York Academy of Sciences, November 7, 1983), J. Clin. Psychiat. 45(9):7-10.

3. Lang, P.L. (1988). *Embryo and Fetal Developmental Toxicity (Teratology) Control Data in the Charles River Crl:CD®BR Rat.* Charles River Laboratories, Inc., Wilmington, MA 01887-0630. (Data base provided by Argus Research Laboratories, Inc.)

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

5. 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, Ph.D., DABT
Associate Director of Research

10-JUN-98
Date

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

10-JUN-98
Date

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

10 June 98
Date

FOR THE SPONSOR

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

11 June 1998
Date

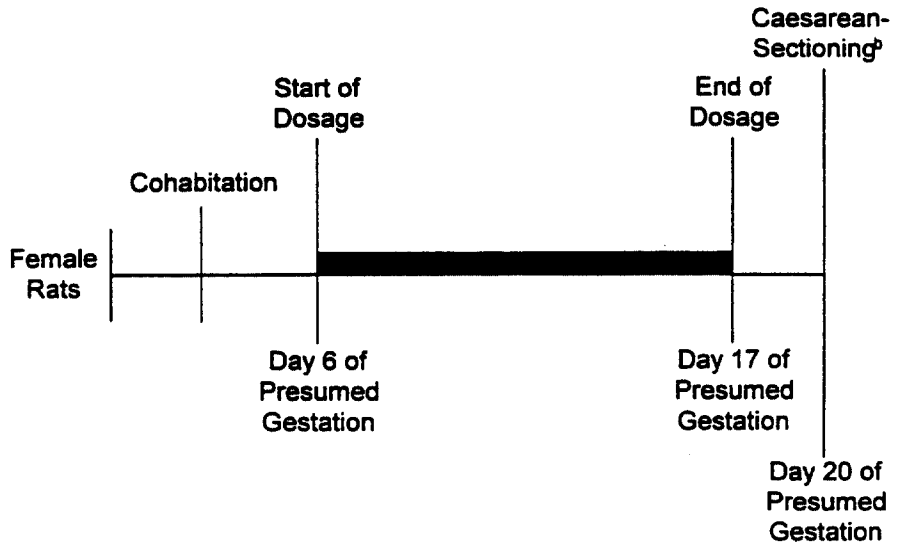
ATTACHMENT 1

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]

16 JUN 98	Arrival Date - Acclimation Begins.
22 JUN 98 PM - 27 JUN 98 AM	Cohabitation Period.
23 JUN 98 - 27 JUN 98	Day 0 of Presumed Gestation.
29 JUN 98 - 14 JUL 98	Dosage Period (Days 6 through 17 of presumed gestation).
13 JUL 98 - 17 JUL 98	Caesarean-Sectioning Period (Day 20 of presumed gestation).
24 JUL 98	Letter Report.
29 SEP 98	Summary 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 418-011P:PAGE 77

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

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

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2. PHYSICAL DATA (continued)

APPEARANCE AND ODOR:
Amber waxy solid

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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.

MSDS: FC-10 FLUORAD Brand Fluorochemical Alcohol
January 29, 1998

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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

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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

... Not Determined N/A - Not Applicable CA - Approximately

MSDS: FC-10 FLUORAD Brand Fluorochemical Alcohol
Jar.uary 29, 1998

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

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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.

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A Product Toxicity Summary Sheet is available.

MSDS: FC-10 FLUORAD Brand Fluorochemical Alcohol
January 29, 1998

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 CONTROL ARTICLE PREPARATION PROCEDURE

ATTACHMENT 3

TEST ARTICLE AND CONTROL ARTICLE PREPARATION PROCEDURE

Test Article: N-EtFOSE

Vehicle: 2% Tween® 80, in R.O. Water

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

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 CONTROL ARTICLE PREPARATION PROCEDURE

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

C. Preparation of Vehicle

1. Add the required amount of R.O. deionized water to an appropriately labeled container. Heat the water to 50°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 7-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 5-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 4-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

TEST ARTICLE AND CONTROL ARTICLE 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: George E Date: Dr/ac 10-Jun-98

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

Initials/Date : Christopher K. Rupp 7/22/95

Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, Pennsylvania 19044
T: (215) 443-8710 F: (215) 443-8587

PROTOCOL 418-011P

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

SPONSOR'S STUDY NUMBER: T-6316.7

Amendment 1 - June 18, 1998

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1. Clinical Observations and/or General Appearance (page 8 of the protocol):

Clinical observations during the dosage period will be taken twice daily, prior to dosage administration and once approximately one hour postdosage, rather than once approximately one hour postdosage and then four to six hours later.

Reason for Change:

This change was made at the request of the Sponsor to match the time frames of the other reproductive/developmental toxicity studies using the same test article.

George E. Dearlove 18-Jun-98 — Raymond G. York 18-JUN-98

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

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

Dena C Lebo 18 June 98 — Marvin T Case 22 Jun 98

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

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

APPENDIX G

HISTORICAL CONTROL DATA

SUMMARY OF REPRODUCTIVE INDICES
CD RAT

PERIOD	JUNE 1995 - JUNE 1997
NUMBER OF STUDIES	97
NUMBER OF RATS:	
TESTED	2132
PREGNANT	1967
FOUND DEAD	3
ABORTED	0
DELIVERED	0
NUMBER OF RATS PREGNANT AT CAESAREAN-SECTIONING	1957
NUMBER OF RATS WITH SINGLE CONCEPTUS LITTER:	
LIVE	5
RESORBED	0
ABORTED	0

	MEAN or %	RANGE/STUDY MEAN or %
% PREGNANT	92.8	(64.0-100)
AVERAGE # CORPORA LUTEA	17.3	(15.2-21.0)
AVERAGE # IMPLANTATIONS	15.6	(12.9-18.0)
AVERAGE LITTER SIZE		
AVERAGE # LIVE FETUSES	14.8	(11.8-17.0)
AVERAGE # DEAD FETUSES	0.1	(0-1.1)
AVERAGE # RESORPTIONS	0.8	(0-1.6)
AVERAGE # EARLY RESORPTIONS	0.7	(0-1.6)
AVERAGE # LATE RESORPTIONS	0.0	(0-0.2)

SUMMARY OF REPRODUCTIVE INDICES
CD RAT

	MEAN or %	RANGE/STUDY MEAN or %
AVERAGE % DAMS WITH ANY RESORPTIONS	48.4	(0-75.0)
AVERAGE % DAMS WITH ALL CONCEPTUSES RESORBED	0.1	(0-4.5)
AVERAGE % DAMS WITH ONE OR MORE LIVE FETUSES	99.9	(95.4-100)
AVERAGE SEX RATIO, (% MALES/LITTER)	50.2	(42.1-57.0)
AVERAGE FETAL BODY WEIGHT (G)	3.47	(3.10-3.78)
AVERAGE FOR MALES (G)	3.56	(3.17-3.90)
AVERAGE FOR FEMALES (G)	3.37	(2.98-3.66)
AVERAGE % DEAD OR RESORBED CONCEPTUSES/LITTER	5.0	(0-10.9)

SUMMARY OF MATERNAL NECROPSY OBSERVATIONS
CD RAT

PERIOD	JUNE 1995 - JUNE 1997
# STUDIES	120
# RATS TESTED	2579
# RATS PREGNANT	2387
# RATS DIED	4
# RATS ABORTED	0
# RATS DELIVERED	439
# RATS WITH 100% RESORPTION	1

EXTERNAL OBSERVATIONS	N	MEAN %	RANGE /STUDY N	%
Red substance around nose and/or mouth	1	0.04	0-1	(0-3.3)
Incisors misaligned broken and/or missing	2	0.08	0-2	(0-6.7)
Chromodacryorrhea	2	0.08	0-2	(0-6.7)
Alopecia	3	0.12	0-3	(0-10.0)
White substance present in anterior chamber of eyes	1	0.04	0-1	(0-4.2)
GROSS LESIONS				
SUBMANDIBULAR LYMPH NODES				
Dark red	1	0.04	0-1	(0-3.3)
JUGULAR VEIN				
Distended with blood	1	0.04	0-1	(0-3.3)
CHEST				
Subcutaneous fat, dark red on ventral side	1	0.04	0-1	(0-3.3)
THORACIC CAVITY				
Filled with light red fluid	1	0.04	0-1	(0-4.0)
THYMUS				
Discolored areas	2	0.08	0-2	(0-6.7)
Large	1	0.04	0-1	(0-4.0)
AXILLA				
Mass present	1	0.04	0-1	(0-4.0)

SUMMARY OF MATERNAL NECROPSY OBSERVATIONS
CD RAT

GROSS LESIONS	MEAN N	MEAN %	RANGE /STUDY N	RANGE /STUDY %
LIVER				
Adhesion between left lateral lobe and left lateral abdominal wall	1	0.04	0-1	(0-4.0)
STOMACH/INTESTINE				
Stomach, fluid-filled	1	0.04	0-1	(0-4.0)
Stomach and intestines distended with gas	1	0.04	0-1	(0-4.0)
Intestines, empty	1	0.04	0-1	(0-4.0)
Cecum contained a black substance	1	0.04	0-1	(0-4.0)
BACK				
Spine, protrusion of bone on dorsal thoracic portion	1	0.04	0-1	(0-4.0)
KIDNEY(S)				
Pelvis, slight/moderate dilation with or without fluid	17	0.66	0-2	(0-12.5)
Pelvis, marked/extreme dilation	5	0.19	0-1	(0-4.0)
Mottled	2	0.08	0-1	(0-4.0)
Large	2	0.08	0-1	(0-4.0)
Small	1	0.04	0-1	(0-4.0)
Cortex pitted	1	0.04	0-1	(0-3.4)
Left; pelvis contained yellow fluid	1	0.04	0-1	(0-4.0)
ABDOMINAL CAVITY				
Filled with light red fluid	1	0.04	0-1	(0-4.0)
SPLEEN				
Two white areas on serosal surface	1	0.04	0-1	(0-4.0)
BLADDER				
Fluid-filled	1	0.04	0-1	(0-4.0)
Wall thick, contained one calculi	1	0.04	0-1	(0-12.5)

SUMMARY OF MATERNAL NECROPSY OBSERVATIONS
CD RAT

GROSS LESIONS	N	MEAN %	RANGE N	/STUDY %
URETERS				
Distended with clear fluid	1	0.04	0-1	(0-4.0)
VAGINA/CERVIX				
Cervix distended with fluid	1	0.04	0-1	(0-4.0)
Cervix contained a thick, brown substance	1	0.04	0-1	(0-4.0)
Cervix contained a dark red, gelatinous substance	1	0.04	0-1	(0-4.0)
Cervix contained green, viscous fluid	1	0.04	0-1	(0-4.0)
Vagina contained brown, viscous fluid	1	0.04	0-1	(0-2.1)
UTERUS				
Contained red-brown fluid and one dead, brown fetus	1	0.04	0-1	(0-4.0)
Right horn, absent	2	0.08	0-1	(0-16.7)
Right horn, threadlike	1	0.04	0-1	(0-2.1)
Left horn, lumen absent on cervical end; ovarian end, distended with clear fluid	1	0.04	0-1	(0-4.0)
Right horn, clear masses, contained gelatinous substance	1	0.04	0-1	(0-4.0)
FORELIMB				
Lesion present	1	0.04	0-1	(0-3.3)

SUMMARY OF FETAL EXTERNAL ALTERATIONS
CD RAT

PERIOD JUNE 1995 - JUNE 1997

# STUDIES INCLUDED	86
# LITTERS EXAMINED	1745
# LIVE FETUSES EXAMINED	25613

ALTERATION			N	%	RANGE /STUDY N	RANGE /STUDY %
HEAD						
	Exencephaly	L	5	0.29	0-1	(0-4.5)
		F	5	0.02	0-1	(0-0.4)
	Hematoma	L	1	0.06	0-1	(0-2.2)
		F	1	0.00	0-1	(0-0.2)
	Microcephaly	L	1	0.06	0-1	(0-4.0)
		F	1	0.00	0-1	(0-0.3)
EYES						
	Eye bulges	L	14	0.80	0-2	(0-12.5)
	depressed	F	15	0.06	0-2	(0-0.9)
	Lids open	L	1	0.06	0-1	(0-4.2)
		F	1	0.00	0-1	(0-0.3)
	Microphthalmia	L	1	0.06	0-1	(0-4.0)
		F	1	0.00	0-1	(0-0.3)
EARS						
	Low set	L	3	0.17	0-1	(0-12.5)
		F	3	0.01	0-1	(0-0.9)
SNOUT						
	Short	L	2	0.11	0-1	(0-4.2)
		F	2	0.01	0-1	(0-0.3)
TONGUE						
	Absent	L	1	0.06	0-1	(0-4.0)
		F	1	0.00	0-1	(0-0.3)
PALATE						
	Cleft	L	4	0.23	0-1	(0-4.5)
		F	4	0.02	0-1	(0-0.4)

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL EXTERNAL ALTERATIONS
CD RAT

ALTERATION			N	%	RANGE /STUDY N	%
JAWS						
	Micrognathia	L	5	0.29	0-1	(0-4.5)
		F	5	0.02	0-1	(0-0.3)
	Agnathia	L	1	0.06	0-1	(0-12.5)
		F	1	0.00	0-1	(0-0.9)
BODY						
	Edema	L	2	0.11	0-1	(0-4.5)
		F	2	0.01	0-1	(0-0.4)
	Umbilical hernia	L	7	0.40	0-1	(0-16.7)
		F	7	0.03	0-1	(0-1.1)
	Gastroschisis	L	1	0.06	0-1	(0-4.0)
		F	1	0.00	0-1	(0-0.2)
	Trunk short	L	3	0.17	0-2	(0-9.1)
		F	3	0.01	0-2	(0-0.7)
	Spina bifida	L	1	0.06	0-1	(0-4.0)
		F	1	0.00	0-1	(0-0.2)
	Extra limb pro-	L	1	0.06	0-1	(0-4.5)
	truding from back	F	1	0.00	0-1	(0-0.4)
	Hematoma	L	1	0.06	0-1	(0-2.4)
		F	1	0.00	0-1	(0-0.2)
PLACENTA						
	Enlarged	L	1	0.06	0-1	(0-16.7)
		F	1	0.00	0-1	(0-1.1)
FORELIMBS						
	Two digits present	L	1	0.06	0-1	(0-4.3)
	on forepaw	F	1	0.00	0-1	(0-0.3)
HINDLIMBS						
	Rotated	L	1	0.06	0-1	(0-4.0)
		F	1	0.00	0-1	(0-0.2)
ANUS						
	No opening present	L	2	0.11	0-1	(0-4.5)
		F	2	0.01	0-1	(0-0.4)

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL EXTERNAL ALTERATIONS
CD RAT

ALTERATION		N	%	RANGE /STUDY N	%
TAIL					
Threadlike	L	5	0.29	0-1	(0-5.3)
	F	5	0.02	0-1	(0-0.4)
Agenesis	L	3	0.17	0-1	(0-4.5)
	F	3	0.01	0-1	(0-0.3)
Split	L	1	0.06	0-1	(0-4.5)
	F	1	0.00	0-1	(0-0.4)
Short	L	2	0.11	0-1	(0-4.3)
	F	2	0.01	0-1	(0-0.3)
Constricted	L	1	0.06	0-1	(0-2.4)
	F	1	0.00	0-1	(0-0.2)

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL SOFT TISSUE ALTERATIONS
CD RAT

PERIOD	JUNE 1995 - JUNE 1997
# STUDIES INCLUDED	36
# LITTERS EXAMINED	845
# FETUSES EXAMINED	6091

	ALTERATION		N	%	RANGE/STUDY N	RANGE/STUDY %
BRAIN						
	Lateral ventricles, moderate dilation	L	1	0.12	0-1	(0-3.4)
		F	1	0.02	0-1	(0-0.6)
	Lateral ventricles, marked dilation	L	1	0.12	0-1	(0-4.2)
		F	1	0.02	0-1	(0-0.6)
	Third ventricle, marked dilation	L	1	0.12	0-1	(0-4.2)
		F	1	0.02	0-1	(0-0.6)
	Lateral and third ventricles, irregularly shaped	L	1	0.12	0-1	(0-4.2)
		F	1	0.02	0-1	(0-0.6)
EYES						
	Microphthalmia	L	3	0.36	0-1	(0-4.0)
		F	3	0.05	0-1	(0-0.6)
PALATE						
	Cleft	L	2	0.24	0-1	(0-4.0)
		F	2	0.03	0-1	(0-0.6)
TONGUE						
	Small	L	1	0.12	0-1	(0-4.3)
		F	1	0.02	0-1	(0-0.6)
	Absent	L	1	0.12	0-1	(0-4.0)
		F	1	0.02	0-1	(0-0.6)
JAW						
	Micrognathia	L	1	0.12	0-1	(0-4.0)
		F	1	0.02	0-1	(0-0.6)
HEART						
	Septal defect	L	1	0.12	0-1	(0-4.0)
		F	1	0.02	0-1	(0-0.6)

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL SOFT TISSUE ALTERATIONS
CD RAT

ALTERATION			N	%	RANGE/STUDY N	RANGE/STUDY %
VESSELS						
	Innominate, absent	L	8	0.95	0-2	(0-8.0)
		F	8	0.13	0-2	(0-1.2)
	Innominate, arises on left	L	1	0.12	0-1	(0-4.0)
		F	1	0.02	0-1	(0-0.6)
	Subclavian artery, absent	L	1	0.12	0-1	(0-3.4)
		F	1	0.02	0-1	(0-0.6)
	Ductus arteriosus, absent	L	1	0.12	0-1	(0-3.4)
		F	1	0.02	0-1	(0-0.6)
	Umbilical artery, displaced	L	10	1.18	0-2	(0-8.3)
		F	11	0.18	0-2	(0-1.2)
	Situs inversus	L	1	0.12	0-1	(0-4.2)
		F	1	0.02	0-1	(0-0.6)
	Aorta, descends to right	L	1	0.12	0-1	(0-4.0)
		F	1	0.02	0-1	(0-0.6)
	Pulmonary artery, descends to right behind aorta	L	1	0.12	0-1	(0-4.0)
		F	1	0.02	0-1	(0-0.6)
LUNGS						
	Right apical, cardiac and diaphragmatic lobes appear as one	L	1	0.12	0-1	(0-4.0)
		F	1	0.02	0-1	(0-0.6)
	Intermediate lobe, absent	L	1	0.12	0-1	(0-4.0)
		F	1	0.02	0-1	(0-0.6)
BODY						
	Edema	L	1	0.12	0-1	(0-4.0)
		F	1	0.02	0-1	(0-0.6)
ABDOMINAL CAVITY						
	Situs inversus of liver, intestines, stomach, spleen, pancreas and kidneys	L	1	0.12	0-1	(0-4.0)
		F	1	0.02	0-1	(0-0.6)
KIDNEYS						
	Pelvis, slight dilation	L	1	0.12	0-1	(0-3.7)
		F	1	0.02	0-1	(0-0.6)

L: LITTER INCIDENCE
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SUMMARY OF FETAL SOFT TISSUE ALTERATIONS
CD RAT

ALTERATION		N	%	RANGE/STUDY N	%
SPLEEN					
Absent	L	1	0.12	0-1	(0-4.0)
	F	1	0.02	0-1	(0-0.5)
URETERS					
Distended	L	2	0.24	0-2	(0-8.7)
	F	3	0.05	0-3	(0-1.7)

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL SKELETAL ALTERATIONS
CD RAT

PERIOD	JUNE 1995 - JUNE 1997
# STUDIES INCLUDED	35
# LITTERS EXAMINED	820
# FETUSES EXAMINED	6318

ALTERATION		N	%	RANGE/STUDY N	RANGE/STUDY %
SKULL					
Frontal(s): incompletely or not ossified	L	2	0.24	0-1	(0-4.2)
	F	2	0.03	0-1	(0-0.6)
Parietal(s): not ossified	L	2	0.24	0-1	(0-4.2)
	F	2	0.03	0-1	(0-0.6)
Nasal(s): short	L	3	0.36	0-1	(0-4.2)
	F	3	0.05	0-1	(0-0.6)
Basisphenoid: incompletely ossified	L	1	0.12	0-1	(0-4.0)
	F	1	0.02	0-1	(0-0.5)
Sphenoid: irregularly shaped	L	1	0.12	0-1	(0-4.0)
	F	1	0.02	0-1	(0-0.5)
~~Orbit: small~~	~~L~~	~~2~~	~~0.24~~	~~0-1~~	~~(0-4.0)~~
	F	2	0.03	0-1	(0-0.6)
Maxillae and Premaxillae: short	L	3	0.36	0-1	(0-4.2)
	F	3	0.05	0-1	(0-0.6)
Skull: incompletely or not ossified	L	2	0.24	0-1	(0-4.2)
	F	3	0.05	0-2	(0-1.2)
Skull: fused	L	1	0.12	0-1	(0-4.0)
	F	1	0.02	0-1	(0-0.5)
VERTEBRAE					
Cervical: Arch, open	L	1	0.12	0-1	(0-4.0)
	F	1	0.02	0-1	(0-0.5)
: Fused	L	1	0.12	0-1	(0-4.0)
	F	1	0.02	0-1	(0-0.5)
Thoracic: Centrum, bifid	L	71	8.66	0-8	(0-29.6)
	F	77	1.22	0-9	(0-4.7)
: Centra, unilateral ossification	L	8	0.98	0-2	(0-8.0)
	F	8	0.13	0-2	(0-1.0)
: Centrum, incompletely or not ossified	L	3	0.36	0-2	(0-8.3)
	F	4	0.06	0-3	(0-1.8)

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL SKELETAL ALTERATIONS
CD RAT

ALTERATION		N	%	RANGE/STUDY N	RANGE/STUDY %
VERTEBRAE (CONT.)					
Thoracic (cont.)					
: Centra, fused	L	1	0.12	0-1	(0-4.2)
	F	1	0.02	0-1	(0-0.5)
: Arch, open	L	1	0.12	0-1	(0-4.0)
	F	1	0.02	0-1	(0-0.5)
: Arch, small	L	1	0.12	0-1	(0-3.4)
	F	1	0.02	0-1	(0-0.5)
Lumbar: Centrum, bifid	L	2	0.24	0-1	(0-3.8)
	F	2	0.03	0-1	(0-0.5)
: Centra, fused	L	1	0.12	0-1	(0-4.3)
	F	1	0.02	0-1	(0-0.6)
: Centrum, incompletely	L	2	0.24	0-2	(0-8.3)
or not ossified	F	3	0.05	0-3	(0-1.8)
: Arches, incompletely	L	15	1.83	0-3	(0-12.0)
or not ossified	F	21	0.33	0-4	(0-2.1)
: 1, present	L	1	0.12	0-1	(0-4.3)
	F	1	0.02	0-1	(0-0.6)
: Arch, open	L	1	0.12	0-1	(0-4.0)
	F	1	0.02	0-1	(0-0.5)
: Centra, unilateral	L	2	0.24	0-1	(0-4.2)
ossification	F	2	0.03	0-1	(0-0.6)
Sacral: None, present	L	1	0.12	0-1	(0-4.3)
	F	1	0.02	0-1	(0-0.6)
: Arch, open	L	1	0.12	0-1	(0-4.0)
	F	1	0.02	0-1	(0-0.5)
Caudal: None present	L	1	0.12	0-1	(0-4.3)
	F	1	0.02	0-1	(0-0.6)
: 1, present	L	1	0.12	0-1	(0-4.3)
	F	1	0.02	0-1	(0-0.6)
RIBS					
Cervical Rib(s) present	L	31	3.78	0-5	(0-20.0)
	F	32	0.51	0-5	(0-2.7)
One or more, wavy	L	44	5.36	0-7	(0-31.8)
	F	73	1.16	0-15	(0-8.3)
One or more, incompletely ossified (hypoplastic),	L	33	4.02	0-5	(0-22.7)
or not ossified	F	53	0.84	0-9	(0-5.0)

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL SKELETAL ALTERATIONS
CD RAT

ALTERATION		N	%	RANGE/STUDY N	RANGE/STUDY %
RIBS (CONT.)					
Fused	L	3	0.36	0-1	(0-4.3)
	F	3	0.05	0-1	(0-0.6)
Split	L	2	0.24	0-1	(0-4.0)
	F	2	0.03	0-1	(0-0.5)
Two segments	L	1	0.12	0-1	(0-3.7)
	F	1	0.02	0-1	(0-0.5)
MANUBRIUM					
Duplicated	L	1	0.12	0-1	(0-3.8)
	F	1	0.02	0-1	(0-0.4)
STERNEBRAE					
One or more incompletely	L	114	13.90	0-7	(0-33.3)
ossified or not ossified	F	164	2.60	0-11	(0-6.2)
Duplicated	L	1	0.12	0-1	(0-3.8)
	F	1	0.02	0-1	(0-0.4)
Fused	L	1	0.12	0-1	(0-3.7)
	F	1	0.02	0-1	(0-0.5)
Asymmetric	L	1	0.12	0-1	(0-4.2)
	F	1	0.02	0-1	(0-0.5)
PELVIS					
Pubis(es) and/or Ischium(a):	L	139	16.95	0-9	(0-39.1)
incompletely or not ossified	F	224	3.54	0-16	(0-9.0)
Pubis(es): incompletely	L	114	13.90	0-9	(0-39.1)
ossified	F	185	2.93	0-16	(0-8.9)
Pubis(es): not ossified	L	8	0.98	0-3	(0-13.6)
	F	8	0.13	0-3	(0-1.6)
Ischium(a): incompletely	L	50	6.10	0-4	(0-16.7)
or not ossified	F	70	1.11	0-9	(0-4.7)
FORELIMBS					
Metacarpals: 1, present	L	1	0.12	0-1	(0-4.3)
	F	1	0.02	0-1	(0-0.6)
: 2, present	L	1	0.12	0-1	(0-4.3)
	F	1	0.02	0-1	(0-0.6)
Foredigits: 2, present	L	1	0.12	0-1	(0-4.3)
	F	1	0.02	0-1	(0-0.6)
Forephalanges: 1, present	L	1	0.12	0-1	(0-4.3)
	F	1	0.02	0-1	(0-0.6)

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL OSSIFICATION SITES
SKELETAL AVERAGES
CD RAT
(CAESAREAN-SECTIONED DAY 20 GESTATION)

PERIOD:	JUNE 1995 - JUNE 1997
# STUDIES INCLUDED	33
# LITTERS EXAMINED	772
# FETUSES EXAMINED	5944

	FETUS/LITTER	
SKELETAL AVERAGES	MEAN	RANGE/STUDY
HYOID	0.84	(0.69-0.95)
VERTEBRAE		
CERVICAL	7.00	--
THORACIC	13.03	(12.99-13.15)
LUMBAR	5.97	(5.85-6.00)
SACRAL	3.00	(2.96-3.00)
CAUDAL	4.83	(4.35-5.21)
RIBS (pairs)	13.02	(12.99-13.08)
STERNUM		
MANUBRIUM	1.00	(0.98-1.00)
STERNAL CENTERS	3.57	(3.26-3.85)
XIPHOID	0.99	(0.94-1.00)
FOREPAWS (Calculated as average per limb)		
CARPALS	0.00	--
METACARPALS	3.49	(3.33-3.62)
DIGITS	5.00	--
PHALANGES	5.05	(4.90-5.27)
HINDPAWS (Calculated as average per limb)		
TARSALS	0.00	--
METATARSALS	3.99	(3.93-4.04)
DIGITS	5.00	--
PHALANGES	4.96	(4.77-5.13)

SUMMARY OF FETAL OSSIFICATION SITES
SKELETAL AVERAGES
CD RAT
(CAESAREAN-SECTIONED DAY 21 GESTATION)

PERIOD:	JUNE 1995 - JUNE 1997
# STUDIES INCLUDED	2
# LITTERS EXAMINED	48
# FETUSES EXAMINED	374

	FETUS/LITTER	
SKELETAL AVERAGES	MEAN	RANGE/STUDY
HYOID	0.97	(0.96-0.97)
VERTEBRAE		
CERVICAL	7.00	--
THORACIC	13.04	(13.02-13.06)
LUMBAR	5.96	(5.94-5.98)
SACRAL	3.00	--
CAUDAL	7.46	(7.23-7.67)
RIBS (pairs)	13.03	(13.01-13.05)
STERNUM		
MANUBRIUM	1.00	--
STERNAL CENTERS	3.98	(3.97-3.98)
XIPHOID	1.00	--
FOREPAWS (Calculated as average per limb)		
CARPALS	0.00	--
METACARPALS	3.98	(3.98-3.99)
DIGITS	5.00	--
PHALANGES	7.64	(7.53-7.75)
HINDPAWS (Calculated as average per limb)		
TARSALS	0.02	--
METATARSALS	4.61	(4.60-4.62)
DIGITS	5.00	--
PHALANGES	5.84	(5.78-5.89)

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

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.

17-Dec-98

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

Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
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Telephone: (215) 443-8710
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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 418-011: Oral (Gavage) Developmental Toxicity Study of N-EtFOSE in Rats
Sponsor's Study Number: T-6316.7

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 13 JUL 98.

Critical phases of this study were inspected five 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 [except for Appendix F, the Pilot Report, which was conducted in the spirit of Good Laboratory Practice (GLP)] 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 12 NOV 98 and 02 DEC 98, and for revisions requested by the Sponsor on 10 DEC 98 and 17 DEC 98.

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.

Barbara J. Patterson 17 Dec 98 Heather L. Rabuttino 17 Dec 98

Barbara J. Patterson, B.A. Date
Director of Operations
and Compliance

Heather L. Rabuttino, M.S. Date
Quality Assurance Supervisor
and Principal Auditor

TABLE 1

CRITICAL PHASES INSPECTED

Cohabitation

Date of inspection: 21 AUG 98

Date results reported to the Study Director and Management: 21 AUG 98

Test Article Preparation

Date of inspection: 02 SEP 98

Date results reported to the Study Director and Management: 28 SEP 98

Test Article Administration - Gavage

Date of inspection: 03 SEP 98

Date results reported to the Study Director and Management: 28 SEP 98

Blood Collection

Date of inspection: 10 SEP 98

Date results reported to the Study Director and Management: 10 SEP 98

Caesarean-Sectioning

Date of inspection: 10 SEP 98

Date results reported to the Study Director and Management: 28 SEP 98

TABLE 2

RAW DATA AUDIT(S)

The following study information and raw data were audited on 08 OCT 98, and 15 OCT 98 to 17 OCT 98:

Protocol.
Protocol amendments.
List of personnel and computer operator codes.
Error codes and codes for clinical sign observations.
Animal receipt, randomization, physical examination and acclimation.
In-life transaction record.
Feed consumption.
Cohabitation.
Caesarean-sectioning.
Maternal gross observations.
Fetal gross observations.
Fetal fixative assignment.
Fetal visceral examination.
Fetal skeletal examination.
Necropsy.
Tissue packing lists.
Male breeder colony records.
General comments.
Study maintenance records.
Temperature and relative humidity reports.
Feed and water analyses.
Edit requests.
Dosage volumes.
Deviations.
Data review page.
Key for test facility computer back-up record abbreviations.
Blood collection data and packing lists.

The results of this audit were reported to the Study Director and Management on 21 OCT 98.

The following study information and raw data were audited on 08 OCT 98 and 10 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 21 OCT 98.

Summary N-EtFOSE Rat Teratology

Study Numbers: 3M **T-6316.7**, Argus 418-011

Compound & Lot: N-EtFOSE (N-Ethyl-Perfluoroocyanesulfonamido Ethanol) – Lot FM3923 (30035, 30037, 30039) 98.2% pure (SMD Analytical Request 52489) Analytical Documentation filed along with final report. Note – same lot as used in two-year rat carcinogenicity study (T-6316, Covance 6329-212).

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

Report Date: 17 December 1998

Study Monitor Summary: (written by Marvin T. Case) Pregnant rat females, 25 per group, were given daily oral (intubation) of N-EtFOSE at dose levels of 0, 1, 5, 10, and 20 mg/kg/day on days 6 through 17 of gestation. The rat fetuses which had been exposed in utero during organogensis were collected at day 20 of gestation. Approximately one-half of the fetuses were examined for soft tissue (visceral) changes and other half were examined for skeletal changes.

There were no compound related clinical signs of toxicity in the dosed rat dams. A body weight effect, reduced body weight gains, occurred in the pregnant females in highest two dose levels – 10 & 20 mg/kg. This body weight effect correlated with reduced food consumption in the same two groups. The maternal toxicity at 10 & 20 mg/kg was reflected in the pups as reduced pup weights. There was no effect on other litter parameters (corpora lutea, implantations, litter size, number of live fetus, early or late resorptions, pup sex ratio) at any dose level. Increased delayed ossification sites were found in 10 & 20 mg/kg fetuses - another reflection of maternal toxicity at these dose levels.

No compound-related soft tissue or skeletal malformations were found at any dose level. Thus, the compound was not found to be teratogenic in the rat.

The maternal toxic NOEL was 5 mg/kg.

The fetal toxic NOEL was also 5 mg/kg.

Teratogenic NOEL in the rat was > 20 mg/kg.

NOTE: Dose preparation samples were collected twice during the study and these samples were sent to 3M Evironmental Analytical laboratory in Bldg 2. Likewise, samples were collected from extra females assigned as toxicokinetic satellite animals (3/group except control and high dose 5/group). These animals were killed on gestation day 18 (day after last dose) and the following samples were collected: serum and liver from pregnant dams, fetuses and placentas (pooled by litter) from uterus. These samples were frozen and sent to 3M Evironmental Analytical laboratory in Bldg 2. At time of this summary, January 1999, analysis of these samples had not been done; therefore, these analytical results were not included in the final report nor in this summary.