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FINAL REPORT

PROTOCOL 418-009

COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND
PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-EtFOSE
IN RATS.

SPONSOR'S STUDY NUMBER: 6316.5

FINAL REPORT DATE: 30 JUNE 1999

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TITLE: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-EtFOSE IN RATS.

ARGUS RESEARCH LABORATORIES, INC.
PROTOCOL NUMBER: 418-009
SPONSOR'S STUDY NUMBER: 6316.5

I. SUMMARY AND CONCLUSION

A. Methods^a

Text Figure 1 provides a schematic of the study design.

A.1. Fo Generation Rats/F1 Generation Litters

One hundred seventy-five male and female Crl:CD®BR VAF/Plus® (Sprague-Dawley) rats were assigned to five dosage groups (Groups I through V), 35 rats per sex per dosage group. The rats were administered the test article, N-EtFOSE^b, or the vehicle, 2.0% Tween® 80, orally (via gavage). The male rats were dosed once daily beginning 28 days before cohabitation and continuing through the day before sacrifice. The female rats were dosed once daily beginning 28 days before cohabitation and continuing through DG^c 9 (rats assigned to Caesarean-sectioning), DG 24 (rats assigned to natural delivery that did not deliver a litter), or DL^d 20 (rats that delivered a litter). The dosage volume was 5 mL/kg.

All Fo generation rats were observed for viability at least twice daily during the study and for effects of the test article twice daily during the dosage period before and approximately one hour postdosage) and on the day sacrificed. Body weights and feed consumption values for male rats were recorded weekly during the dosage period and at sacrifice. Body weights for the female rats were recorded weekly to cohabitation, daily during the gestation period, on DLs 1, 4, 7, 10 and 14 (rats assigned to natural delivery) and at sacrifice. Feed consumption values were recorded weekly to cohabitation, daily during the gestation period and on DLs 1, 4, 7, 10 and 14 (rats assigned to natural delivery).

-
- a. Detailed descriptions of all procedures used in the conduct of this study are provided in the appropriate sections of this report and in APPENDIX F (PROTOCOL AND AMENDMENTS).
 - b. N-EtFOSE is a metabolite of PFOS, the test article administered in Argus Research Laboratories, Inc., Protocol 418-008.
 - c. DG is used as an abbreviation for day of (presumed) gestation).
 - d. DL is used as an abbreviation for day of lactation or day postpartum.

The first ten female rats per dosage group with a confirmed date of mating were assigned to Cesarean-sectioning on DG 10. The remaining female rats were permitted to naturally deliver litters. These rats were evaluated for clinical observations during parturition, duration of gestation, litter size and pup viability at birth. Maternal behavior of the dams was evaluated daily when the pups were examined during the 21-day postpartum period.

Each litter was evaluated for viability at least twice each day during the 21-day postpartum period. Pups in each litter were counted once daily. Physical signs in the pups were recorded once daily for 21 days postpartum. Pup body weights and observed nursing behavior were recorded on DLs 1 (birth), 4, 7, 14 and 21. Surface righting reflex, pinna unfolding, eye opening, acoustic startle response and air righting reflex were monitored during the 21-day postpartum period until all pups in the litter reached the criterion for the specific test. Pupil constriction was evaluated once on DL 21. On DL 4, a table of random units was used to cull litters to four male and four female pups, where possible. On DL 21, a table of random units was used to select 25 male and 25 female pups in Groups I, II and III for continued evaluation.

Fo generation male rats were sacrificed after completion of the cohabitation period and necropsied; gross lesions were retained. The testes, epididymides, prostate and seminal vesicles (with and without fluid) were excised, individually weighed and retained.

Fo generation female rats assigned to Cesarean-sectioning were sacrificed on DG 10 and necropsied; pregnancy status was confirmed. Ovaries and gross lesions were retained. The rats were examined for the number and distribution of corpora lutea in each ovary and implantation sites, and viable and nonviable embryos. Embryos were discarded after examination.

Fo generation female rats assigned to natural delivery were sacrificed on DL 21 and necropsied. Ovaries and gross lesions were retained. The number and distribution of implantation sites were recorded.

At scheduled sacrifice after completion of the cohabitation period (males rats that sired litters of dams allowed to naturally deliver a litter) and on DL 21 (female rats allowed to naturally deliver a litter) blood samples (approximately 4 mL per rat) were collected from the inferior vena cava from five rats per sex per dosage group and shipped to the Sponsor for pharmacokinetic analysis. The liver was excised, weighed, and a sample section (lateral lobe) was frozen and shipped to the Sponsor for analysis.

Pups not selected for continued evaluation on DL 4 were sacrificed and necropsied. The stomach contents (milk curd) were collected from all culled pups from five of the largest litters from Groups I, II and III, frozen and shipped to the Sponsor for analysis.

Pups not selected for continued evaluation were sacrificed on DL 21.

The livers of the pups from the litters of the five dams in Groups I through IV selected for pharmacokinetic sample collection were excised, pooled per litter, frozen and shipped to the Sponsor for analysis. Dams in the 15 mg/kg/day dosage group (Group V) did not have surviving pups on DL 21.

A.2. F1 Generation Rats/F2 Generation Litters

Only the 0 (Vehicle), 1 and 5 mg/kg/day dosage groups were continued into the second generation because of severe pup mortality during lactation. There were 150 male and female F1 generation rats in the three dosage groups (Groups I through III), 25 rats per sex per dosage group.

F1 generation male and female rats were given appropriate dosages of the test article orally (gavage) beginning on DL 22 and continuing through the day before sacrifice.

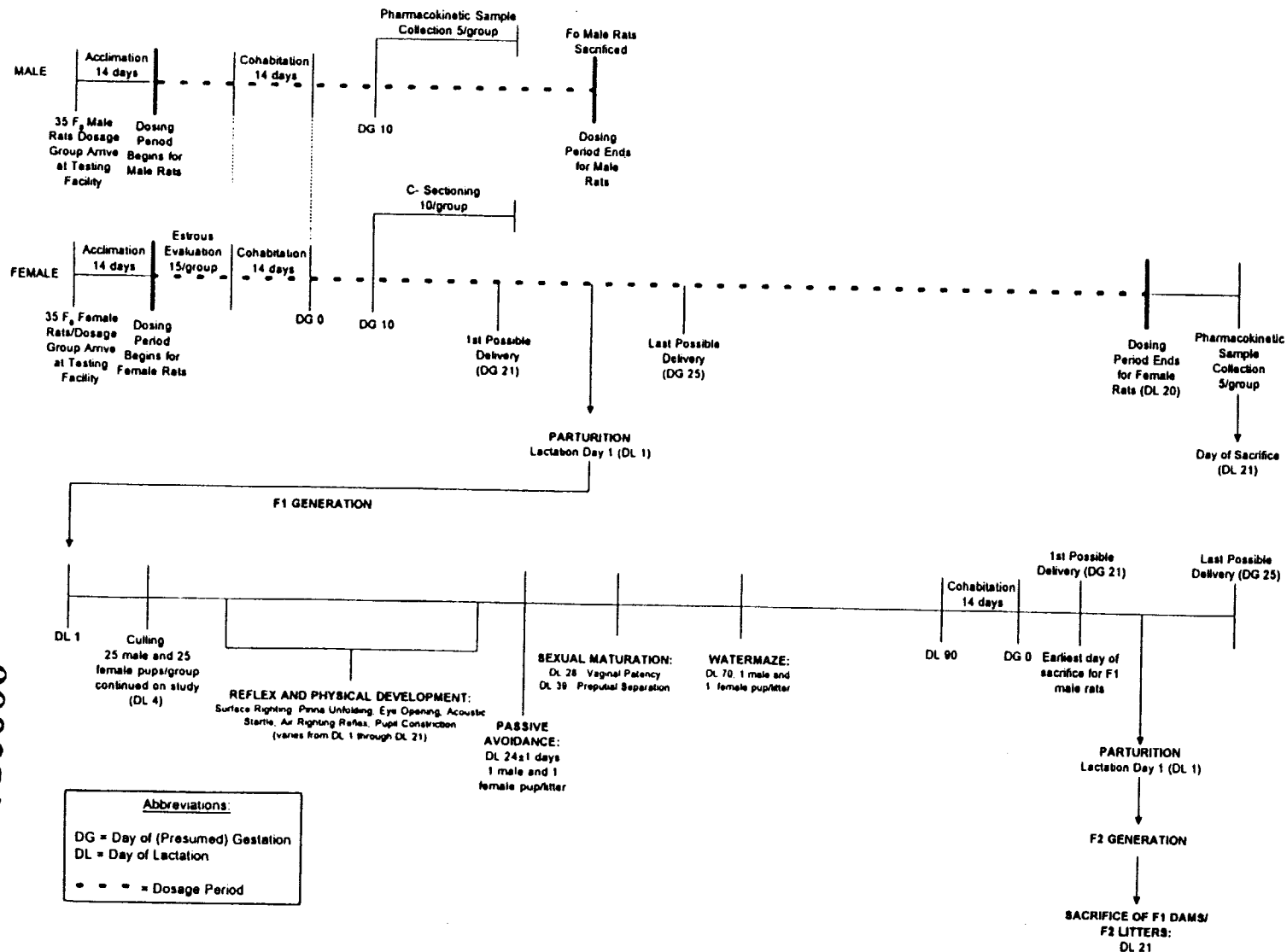
Beginning at 24 days of age, one male rat and one female rat from each litter in each dosage group were tested in a passive avoidance paradigm. Female rats were evaluated for the age of vaginal patency beginning on DL 28. Male rats were evaluated for the age of preputial separation beginning on DL 34. On postpartum day 70, one male rat and one female rat from each litter were evaluated in a water-filled M-maze. On approximately DL 90, the rats within each dosage group were assigned to cohabitation.

F1 generation male rats were sacrificed after completion of the cohabitation period and necropsied, as previously described for the Fo generation male rats. All F1 generation female rats were permitted to naturally deliver litters. All dams that delivered litters were sacrificed on DL 21 as previously described for Fo generation female rats.

On DL 21, all F2 generation pups were sacrificed and examined for gross lesions.

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Protocol 418-009: Combined Oral (Gavage) Fertility, Developmental and Perinatal/Postnatal Reproduction Toxicity Study of N-EtFOSE in Rats



Text Figure 1

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B. Results**B.1. Fo Generation Male Rats**

No Fo generation male rats died during this study. The only clinical observation attributable to the test article was impaired righting reflex in the 15 mg/kg/day dosage group rats.

Groups administered 5 mg/kg/day and higher dosages of the test article had reduced body weight gains for the entire dosage period. The 10 and 15 mg/kg/day dosage groups had significantly reduced absolute feed consumption values for the entire treatment period.

Dosages of the test article as high as 15 mg/kg/day did not affect any mating and fertility parameters evaluated.

Necropsy observations considered related to the test article included a significantly increased number of male rats in the 15 mg/kg/day dosage group with small seminal vesicles and one 15 mg/kg/day dosage group male rat with a small prostate.

The 5, 10 and 15 mg/kg/day dosage groups had significantly reduced terminal body weights. The absolute weights of the left epididymis, seminal vesicles with fluid, and prostate were significantly reduced in the 15 mg/kg/day dosage group. The ratios of the weight of the left and right testes to terminal body weights were significantly increased in the 5 (left only), 10 and 15 mg/kg/day dosage groups.

B.2. Fo Generation Female Rats/F1 Generation Litters

No Fo generation female rats died during this study as a result of treatment with N-EtFOSE.

Observations of localized alopecia were significantly increased in the 5, 10 and 15 mg/kg/day dosage groups during the gestation and lactation periods.

Groups administered 5 mg/kg/day and higher dosages of the test article had significantly reduced body weight gains for the entire prehabitation period (DSs^a 1 to 29). Gestation body weight gains were significantly reduced in the 10 and 15 mg/kg/day dosage groups on DGs 0 to 7 and in the 15 mg/kg/day dosage group on DGs 18 to 20. As a result, body weight gains were significantly reduced in the 15 mg/kg/day dosage group for the entire gestation period (DGs 0 to 20). Absolute body weights were significantly reduced in the 5 mg/kg/day dosage group on DGs 0 through 17, and in the 10 and 15 mg/kg/day dosage groups on all days of the gestation period. The 10 and 15 mg/kg/day dosage groups had significantly reduced body weights on DL 1. Lactation body weights continued to be significantly reduced in the 10 mg/kg/day dosage group on

a. DS is used as an abbreviation for day of study.

DLs 4, 7, 10 and 14. Body weight loss occurred in the 10 and 15 mg/kg/day dosage groups on DLs 1 to 4. The 15 mg/kg/day dosage group was precluded from further evaluation because all pups died before DL 5. A significant increase in body weight gain on DLs 14 to 21 in the 10 mg/kg/day dosage group was possibly associated with reduced litter size and reduced milk demand and production.

Absolute and relative feed consumption values were significantly reduced in the 10 and 15 mg/kg/day dosage groups for the entire prehabitation period. The 10 and 15 mg/kg/day dosage groups continued to have significantly reduced absolute and relative feed consumption values early in the gestation period. Absolute feed consumption values were also significantly reduced in the 5 mg/kg/day dosage group on DGs 0 to 7. Absolute feed consumption values continued to be significantly reduced in the 10 mg/kg/day dosage group on DGs 10 to 12 and 12 to 15, and in the 15 mg/kg/day dosage group throughout the remainder of the gestation period (DGs 10 to 12, 12 to 15, 15 to 18 and 18 to 20). Absolute and relative feed consumption values were significantly reduced for the entire gestation period (DGs 0 to 20) in the 5 (absolute only), 10 and 15 mg/kg/day dosage groups.

Absolute and relative feed consumption values were significantly reduced in the 5 (absolute only) and 10 mg/kg/day dosage groups for the entire lactation period. Significant reductions in absolute and relative feed consumption values occurred on DLs 7 to 10 in the 5 mg/kg/day dosage group, and for all tabulated intervals in the 10 mg/kg/day dosage group. Absolute and relative feed consumption values were reduced in the one litter was available for evaluation in the 15 mg/kg/day dosage group on DLs 1 to 4. The 15 mg/kg/day dosage group was precluded from further evaluation because all pups died before DL 5.

Dosages of the test article as high as 15 mg/kg/day did not affect estrous cycling in the 15 rats per dosage group that were evaluated.

All necropsy observations were considered unrelated to treatment with the test article.

Statistically significant reductions in the averages for implantations and viable embryos occurred in the 15 mg/kg/day dosage group at Caesarean-sectioning on DG 10. There were no biologically important or statistically significant differences in the litter averages for corpora lutea or nonviable embryos at Caesarean-sectioning on DG 10.

The duration of gestation was significantly reduced in the 5, 10 and 15 mg/kg/day dosage groups, an observation associated with preimplantation loss in the 15 mg/kg/day dosage group (the average number of implantation sites per dam was significantly reduced, resulting in a significantly reduced litter size).

Pup viability was significantly affected by the 10 and 15 mg/kg/day dosages of the test article. Reflecting these effects, the viability and lactation indices were significantly reduced in the 10 and 15 mg/kg/day dosage groups.

A dosage-dependent pattern of reduced pup body weights was evident in each group administered the test article. The 1 mg/kg/day dosage group tended to have reduced pup body weights on DL 4 (pre-and postculling). The 5, 10 and 15 mg/kg/day dosage groups had significantly reduced pup body weights on all weighing days (no pups survived after DL 4 in the 15 mg/kg/day dosage group).

Clinical and necropsy observations associated with reduced pup viability and potential reduction in maternal care occurred in the 5, 10 and 15 mg/kg/day dosage groups. Clinical observations included 1, 7 and 3 litters with pups that were not nursing in the 5, 10 and 15 mg/kg/day dosage groups, respectively; the incidence was significant in the 10 mg/kg/day dosage group. The number of litters with cold to touch pups was also significantly increased in the 10 mg/kg/day dosage group. Necropsy observations in pups that were found dead included significant increases in the number of pups with no milk in stomach in the 10 and 15 mg/kg/day dosage group litters.

Reversible delays in reflex and physical development that are highly correlated with body weight occurred in the 5 and 10 mg/kg/day dosage groups. Surface righting was delayed in the 5, 10 and 15 mg/kg/day dosage groups. The time of development for pinna unfolding was delayed in the 5, 10 and 15 mg/kg/day dosage groups. Eye opening was delayed in the 5 and 10 mg/kg/day dosage groups (no 15 mg/kg/day dosage group pups were evaluated for this parameter). The time of development of the acoustic startle reflex was delayed in the 5 and 10 mg/kg/day dosage groups (no 15 mg/kg/day dosage group pups survived to be tested for this reflex). The ability to air right was delayed in the 5 and 10 mg/kg/day dosage groups (no 15 mg/kg/day dosage group pups survived to be tested for this reflex).

B.3. F1 Generation Male Rats

No deaths occurred in the F1 generation male rats. All clinical observations were considered unrelated to the test article.

The 1 and 5 mg/kg/day dosage groups weighed less than the control group on day 1 postweaning (significant in the 5 mg/kg/day dosage group) and body weight gains were reduced in these groups throughout the postweaning period. Weight gains in the 1 and 5 mg/kg/day dosage groups were significantly reduced for the prehabitation period and for day 1 postweaning to termination (significant at 5 mg/kg/day only). Absolute body weights were significantly reduced in the 5 mg/kg/day dosage group throughout the postweaning dosage period.

Absolute and relative feed consumption values in the F1 generation male rats were significantly reduced in the 5 mg/kg/day dosage group on days 8 to 15

postweaning. The absolute feed consumption value was significantly reduced in this dosage group on days 1 to 8 postweaning. Relative feed consumption values were also significantly reduced on days 15 to 22, 22 to 29, 29 to 36 and 36 to 43 in the 5 mg/kg/day dosage group.

The average day of preputial separation was significantly delayed for the F1 generation male rats in the 5 mg/kg/day dosage group value, but the increase was approximately one day and not considered toxicologically important.

There were no biologically important differences in the values for learning, short-term retention, long-term retention or response inhibition in the F1 generation male rats, as evaluated by performance in a passive avoidance or watermaze performance paradigm.

Dosages of the test article as high as 5 mg/kg/day did not affect any mating and fertility parameters evaluated in the F1 generation male rats.

All necropsy observations in the F1 generation male rats were considered unrelated to the test article. Terminal body weights were significantly reduced in the 5 mg/kg/day dosage group. The ratios of the left and right testis weights to the terminal body weight in the 5 mg/kg/day dosage group were significantly increased. No statistically significant differences occurred in the absolute weights of the epididymides, testes, seminal vesicles (with and without fluid) and prostate, and the ratios of the epididymides, seminal vesicles (with and without fluid) and prostate weights to the terminal body weight of the F1 generation male rats.

B.4. F1 Generation Female Rats/F2 Generation Litters

All F1 generation female rats survived until scheduled sacrifice. All clinical observations during the prehabitation, gestation and lactation periods were considered unrelated to the test article.

The 1 and 5 mg/kg/day dosage groups weighed less than the control group on day 1 postweaning (the reduction was significant in the 5 mg/kg/day dosage group) and body weight gains were generally reduced in these groups throughout the prehabitation period. Body weight gains were significantly reduced in both test article-treated groups for the entire prehabitation period [day 1 postweaning to prehabitation and day 1 to 57 postweaning (significant at 5 mg/kg/day only)]. Absolute body weights in the 5 mg/kg/day dosage group were significantly reduced throughout the prehabitation dosage period.

Maternal body weight gains during the gestation period were significantly reduced in the 1 and 5 mg/kg/day dosage groups on days 0 to 7 of gestation. Body weight gains in the 5 mg/kg/day dosage group were significantly increased on DGs 14 to 17. Absolute body weights were significantly reduced on DGs 0 through 18 in the 1 and 5 mg/kg/day dosage groups. Maternal body weights

remained significantly reduced in the 5 mg/kg/day dosage group on DLs 1, 4, 7, 10, 14 and 21 and in the 1 mg/kg/day dosage group on DLs 1, 7 and 14.

Feed consumption values were significantly reduced for the entire precohabitation period (days 1 to 57 postweaning) in both groups administered the test article. Relative feed consumption values in the 5 mg/kg/day dosage group were significantly increased on days 8 to 15, 15 to 22 and 22 to 29 postweaning. Absolute feed consumption values in the 1 and 5 mg/kg/day dosage groups were significantly reduced during the first week of the gestation period. Absolute feed consumption values for the 5 mg/kg/day dosage group were also significantly reduced on DGs 7 to 10. The relative feed consumption value on DGs 14 to 17 was significantly reduced in the 5 mg/kg/day dosage group. The absolute maternal feed consumption value was significantly reduced for the entire lactation in the 5 mg/kg/day dosage group. The relative feed consumption value was significantly reduced on DLs 4 to 7 and 7 to 10 in the 5 mg/kg/day dosage group, as compared to the control group values.

Dosages of the test article as high as 5 mg/kg/day did not affect the average day of vaginal patency in the F1 generation female rats. There were no biologically important differences in the values for learning, long-term retention or response inhibition in the F1 generation female rats, as evaluated by performance in a passive avoidance or watermaze performance paradigm.

Dosages of the test article as high as 5 mg/kg/day did affect any mating and fertility parameters evaluated in the F1 generation female rats.

All necropsy observations in the F1 generation female rats were considered unrelated to the test article.

As occurred in the previous generation, there was a tendency for reduced pup viability in the 5 mg/kg/day dosage group. The number of dams with stillborn pups was significantly increased, and the number of pup deaths was significantly increased in this dosage group. As also occurred in the previous generation, pup body weights were significantly reduced in the 5 mg/day dosage group on days 1, 4 (pre and postculling), 7, 14 and 21.

No clinical or necropsy observations in the F2 generation were attributable to dosages of the test article as high as 5 mg/kg/day.

C. Conclusion

On the basis of these data, the Fo generation maternal and paternal no-observable-effect-level (NOEL) of N-EtFOSE is 1 mg/kg/day (5 mg/kg/day and higher dosages caused reductions in body weight gain, the 10 and 15 mg/kg/day dosages also caused reduced feed consumption values).

The Fo generation reproductive NOEL is greater than 15 mg/kg/day; no effects on mating, fertility or estrous cycling occurred. The NOEL for viability and growth in the F1 generation offspring is 1 mg/kg/day (the 5 mg/kg/day dosage caused reductions in pup body weight gains, the 10 and 15 mg/kg/day dosages caused preimplantation loss and reductions in litter size, pup viability, growth and survival).

The F1 generation maternal and paternal NOEL of N-EtFOSE is less than 1 mg/kg/day (the 1 and 5 mg/kg/day dosages caused reductions in body weight gain and feed consumption).

The F1 generation reproductive NOEL is a dosage of 5 mg/kg/day; no effects on mating or fertility occurred. The NOEL for viability and growth in the F2 generation offspring is 1 mg/kg/day (the 5 mg/kg/day dosage caused stillbirths and reductions in litter size, pup viability, growth and survival).

for George E. Christian 30-JUN-99
 George E. Christian, Ph.D., Fellow, ATS Date
 Executive Director of Research

for George E. Christian 30-JUN-99
 Alan M. Hoberman, Ph.D., DABT Date
 Director of Research

Raymond G. York 30-JUN-99
 Raymond G. York, Ph.D., DABT Date
 Associate Director of Research and Study Director

II. DESCRIPTION OF TEST PROCEDURES

A. Conduct of Study:

A.1. Sponsor:

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

A.2. Testing Facility:

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

A.3. Study Number:

418-009

A.4. Sponsor's Study Number:

6316.5

A.5. Purpose of the Study:

The purpose of this study was to test for toxic effects/disturbances resulting from N-EtFOSE treatment of CrI:CD®BR VAF/Plus® male and female rats before cohabitation and continuing through mating, gestation and lactation. This study was designed to evaluate ICH Harmonised Tripartite Guideline stages A through F of the reproductive process and should detect effects on the estrous cycle, tubal transport, implantation, gestation, parturition, lactation and maternal behavior in female rats, on the development of the offspring of the treated male and female rats, and permit detection of functional effects (e.g., effects on libido or epididymal sperm maturation) that may not be detected by histological examinations of male rat reproductive organs. Because manifestations of effects induced during this period may be delayed in the offspring, observations were continued through production of F2 litters.

A.6. Study Design:

A modification of the requirements of the U.S. Food and Drug Administration (FDA)⁽¹⁾ was used as the basis for study design.

A.7. Regulatory Compliance:

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

A.8. Ownership of the Study:

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

A.9. Study Monitor:

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

A.10. Alternate Study Monitor:

Andrew M. Seacat, Ph.D.

A.11. Study Director:

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

A.12. Technical Performance:

John F. Barnett, B.S. (Director of Laboratory Operations)

Aaron J. Weilerstein, B.S. (Research Assistant)

Karen D. Klein, B.S. (Laboratory Scheduler)

A.13. Report Preparation:

Raymond G. York, Ph.D., DABT

Jo Ann Frazee, M.S. (Study Coordinator)

Erin Hagan, B.A. (Data Management Specialist)

Karen G. Parker, A.A. (Report Administrator)

A.14. Report Review:

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

A.15. Date Protocol Signed:

28 May 1998

A.16. Dates of Technical Performance:**A.16.a. Fo Generation Male Rats:**

Rat Arrival Date	02 JUN 98
Dosage Period (28 days before cohabitation, and continuing through a 14-day cohabitation period and until day before sacrifice)	08 JUN 98 - 29 JUL 98
Scheduled Sacrifice	30 JUL 98

A.16.b. Fo Generation Female Rats:

Rat Arrival Date	02 JUN 98
Dosage Period - Female Rats Assigned to Caesarean-Sectioning (28 days before cohabitation and continuing through DG ^a 9)	08 JUN 98 - 29 JUL 98
Dosage Period - Female Rats Assigned to Natural Delivery [28 days before cohabitation and continuing through DG 24 (rats that did not deliver a litter) or DL ^b 20 (rats that delivered a litter)]	08 JUN 98 - 30 AUG 98
Dosage Period Estrous Cycle Evaluation	23 JUN 98 - 06 JUL 98
Cohabitation Period	
Male 1	06 JUL 98 PM - 13 JUL 98 AM
Male 2	13 JUL 98 PM - 20 JUL 98 AM
DG 10 Caesarean-Sectioning	17 JUL 98 - 21 AUG 98
Natural Delivery Period (DL 1)	28 JUL 98 - 11 AUG 98
DG 25 Sacrifice (rats that did not deliver a litter)	01 AUG 98 - 03 AUG 98
DL 21 Sacrifice (dams and pups not selected for continued study)	17 AUG 98 - 31 AUG 98

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- a. DG is used as an abbreviation for day of (presumed) gestation.
 b. DL is used as an abbreviation for day of lactation or day postpartum.

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A.16.c. F1 Generation Rats:

Dosage Period (Male Rats)	18 AUG 98 - 17 NOV 98
Dosage Period (Female Rats)	18 AUG 98 - 28 DEC 98
Passive Avoidance Testing	20 AUG 98 - 11 SEP 98
Watermaze Testing	07 OCT 98 - 26 OCT 98
Cohabitation Period	
Male 1	02 NOV 98 PM - 09 NOV 98 AM
Male 2	09 NOV 98 PM - 16 NOV 98 AM
Male Rats Sacrificed	18 NOV 98
Natural Delivery Period	24 NOV 98 - 09 DEC 98
DL 21 Sacrifice	14 DEC 98 - 29 DEC 98

A.17. Records Maintained:

The original report, raw data and reserve samples of the bulk test article and vehicle components are retained in the archives of Argus Research Laboratories, Inc. Any preserved tissues are retained in the archives of the Testing Facility for one year after the mailing of the draft final report, after which time the Sponsor will decide their final disposition. All unused prepared formulations were discarded at the Testing Facility. Unused bulk test article was returned to the Study Monitor.

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

N-EtFOSE - a waxy solid

B.2. Lot Number:

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

B.3. Date Received and Storage Conditions:

The test article was received on 20 May 1998, and stored at room temperature. Prepared suspensions were stored frozen (-20°C).

B.4. Special Handling Instructions:

Standard safety precautions (use of protective clothing, gloves, dust-mist respirator and safety goggles) were taken when handling the bulk test article and prepared suspensions.

B.5. Analysis of Purity:

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

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

2.0% Tween® 80 in reverse osmosis membrane processed deionized water (R.O. deionized water)

C.2. Lot Number:

M03H05

C.3. Dates Received and Storage Conditions:

Shipments of Tween® 80 were received from J.T. Baker, Phillipsburg, New Jersey, on 22 May, 1 July and 8 July 1998, and 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.

C.4. Special Handling Instructions:

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

C.5. Analysis of Purity:

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

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D. Test Article Preparation:

Suspensions of N-EtFOSE were prepared daily at concentrations of 0, 0.2, 1, 2 and 3 mg/mL. The test article was considered 100% pure for the purpose of dosage calculations.

D.1 Sample Information:

Sample Type	Size	Date Retained	Storage/Shipping Conditions	Shipped To	Date Shipped
Homogeneity	5 mL ^a	08 JUN 98	Frozen (-20°C)	Sponsor	09 JUN 98
Concentration	5 mL ^b	08 JUN 98 ^c 15 JUL 98 ^c 22 DEC 98 ^d 27 DEC 98 ^e 28 DEC 98 ^f	Frozen (-20°C)	Sponsor	09 JUN 98 15 JUL 98 04 JAN 99 04 JAN 99 04 JAN 99
Vehicle Component Reserve Tween® 80 R.O. Deionized Water	5 mL 5 mL	10 JUN 98 10 JUN 98	Room temperature	Testing Facility Archives	20 JUL 98 20 JUL 98

- A syringe was used to withdraw samples from the top, middle and bottom of the highest concentration on the first day prepared. Each sample was divided into two aliquots (2 mL and 3 mL, respectively). One aliquot (2 mL) was shipped for analysis. The other aliquot (3 mL) was retained at the Testing Facility as a backup.
- A syringe was used to withdraw samples during the first and sixth weeks of dosage administration for the Fo generation and during the first and last weeks of dosage administration for the F1 generation. Each sample was divided into two aliquots (2 mL and 3 mL, respectively). One aliquot (2 mL) was shipped for analysis. The other aliquot (3 mL) was retained at the Testing Facility as a backup.
- 0, 0.2 and 1 mg/mL concentrations.
- 0 mg/mL concentration.
- 0.2 mg/mL concentration.
- 1 mg/mL concentration.

D.2. Analytical Results:

Information on the stability of the bulk test article is on file with the Sponsor. Stability data for prepared formulations bracketing the range of concentrations and conditions of this study are on file with the Sponsor. Results of the concentration and homogeneity analyses were not available at the time of the writing of this report.

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

Rat

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E.2. Strain:

Crl:CD®BR VAF/Plus® (Sprague-Dawley)

E.3. Supplier (Source):

Charles River Laboratories, Inc., Raleigh, North Carolina

E.4. Sex:

Male and female

E.5. Rationale for Test System:

The Crl:CD®BR VAF/Plus® (Sprague-Dawley) rat was selected as the Test System because: 1) this strain of rat has been demonstrated to be sensitive to reproductive and developmental toxins and has been widely used throughout industry for reproductive and developmental toxicity evaluations; 2) historical data and experience exist at the Testing Facility⁽⁵⁻⁷⁾; and 3) the test article is pharmacologically active in the species and strain.

E.6. Test System Data:

	<u>Male Rats</u>		<u>Female Rats</u>
	<u>Shipment 1</u>	<u>Shipment 2</u>	
Number of Rats	100	95	205
Approximate Dates of Birth	28 MAR 98	06 APR 98	30 MAR 98
Approximate Age at Arrival	67 days	58 days	65 days
Weight (g) on the Day after Arrival	223 - 331		179 - 229
Weight (g) at Study Assignment	223 - 336		193 - 216

E.7. Method of Randomization:**E.7.a. Fo Generation Rats:**

Upon arrival, Fo generation rats were assigned to individual housing on the basis of computer-generated random units. After acclimation, male and female rats were selected for study on the basis of physical appearance and body weights recorded during acclimation. Separate shipments of male rats were randomized as one group to ensure an equivalent distribution of body weights. Rats were assigned to five dosage groups (Groups I through V), 35 rats per sex per dosage group, using a computer-generated (weight-ordered) randomization procedure.

The first ten female rats per dosage group with a confirmed date of mating were assigned to Caesarean-sectioning on DG 10. The remaining female rats were permitted to naturally deliver litters.

A table of random units was used to select five male rats per dosage group from among those that successfully mated a female rat assigned to natural delivery for scheduled sacrifice after completion of the cohabitation period. The same method was used to select five female rats per group from among those that delivered a litter for scheduled for sacrifice on DL 21.

E.7.b. F1 Generation Pups:

On DL 4, a table of random units was used to select pups to be culled, and litters were reduced to eight pups each. Whenever possible, the same number of male and female pups per litter were continued on study.

At weaning of the F1 generation pups on DL 21, a table of random units was used to select 25 male and 25 female pups in each of Groups I, II and III, resulting in a total of 150 F1 generation rats (75 per sex) chosen for continued postnatal evaluation. At least one male pup and one female pup per litter, when possible, was selected. Group IV was not continued on the study due to severe pup toxicity (mortality) during lactation. This decision was made in consultation with the study veterinarian and the Sponsor. There were no surviving pups in Group V after DL 5.

E.8. System of Identification:

E.8.a. Fo Generation Rats:

Male and female rats were assigned temporary numbers at receipt and given unique permanent identification numbers when assigned to the study before administration of the first dosage of the test article. Rats were permanently identified using Monel® self-piercing ear tags (Gey Band and Tag Co., Inc., No. MSPT 20101).

E.8.b. F1/F2 Generation Pups and Rats:

Pups were not individually identified during lactation; all parameters were evaluated in terms of the litter. At weaning, each F1 generation rat selected for continued observation was identified with a Monel® self-piercing ear tag.

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

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

F.2. Study Rooms:

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

F.3. Housing:

All cage sizes and housing conditions were in compliance with the *Guide for the Care and Use of Laboratory Animals*⁽⁸⁾.

F.3.a. Fo Generation Rats/F1 Generation Litters:

Fo generation rats were individually housed in stainless steel wire-bottomed cages except during the cohabitation and postpartum periods. During cohabitation, each pair of rats was housed in the male rat's cage. Beginning no later than DG 20, Fo generation female rats assigned to natural delivery were individually housed in nesting boxes. Each dam and delivered litter were housed in a common nesting box during the postpartum period.

F.3.b. F1 Generation Rats/F2 Generation Litters:

After weaning, the F1 generation rats were individually housed before cohabitation, housed in pairs (one male rat per female rat) during cohabitation, and individually housed after cohabitation. The same type of caging was used as described for the Fo generation rats. Beginning no later than DG 20, F1 generation female rats were individually housed in nesting boxes. Each dam and delivered litter were housed in a common nesting box during the postpartum period.

F.4. Lighting:

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

F.5. Sanitization:

Cage pan liners were changed approximately three times each week. Cages were changed approximately every other week. Bedding was changed as often as necessary to keep the rats dry and clean.

F.6. Feed:

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

F.7. Feed Analysis:

Analyses were routinely performed by the feed supplier. No contaminants at levels exceeding the maximum concentration for certified feed or deviations from expected nutritional requirements were detected by these analyses. Copies of the results of the feed analyses are available in the raw data.

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

F.8. Water:

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

F.9. Water Analysis:

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

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

F.10. Nesting Material:

Bed-o'cobs® was used as nesting material (The Andersons Industrial Products Group, Maumee, Ohio).

F.11. Bedding Analysis:

Neither the Sponsor nor the Study Director was aware of any potential contaminants likely to be present in the bedding that would interfere with the results of this study. Analyses for possible contamination are conducted annually. Copies of the results of the bedding analyses are available in the raw data.

G. Methods:**G.1. Dosage Administration:**

Dosage Group	Dosage (mg/kg/day)	Concentration (mg/mL)	Dosage Volume (mL/kg)	Number of Fo Generation Rats Per Sex	Number of F1 Generation Rats Per Sex
I	0 (Vehicle)	0	5	35	25
II	1	0.2	5	35	25
III	5	1	5	35	25
IV	10	2	5	35	a
V	15	3	5	35	b

- a. Group IV F1 generation pups were sacrificed at weaning on DL 21 because of severe pup mortality during lactation.
- b. There were no surviving Group V F1 generation pups after DL 5.

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

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- a. See APPENDIX G (DEVIATIONS FROM THE PROTOCOL AND STANDARD OPERATING PROCEDURES OF THE TESTING FACILITY), items 1 and 2.

G.2. Assigned Rat Numbers:

Dosage Group	Assigned Fo Generation Rat Numbers		Assigned F1 Generation Rat Numbers	
	Male	Female	Male	Female
I	9001 - 9935	10076 - 10110	12076 - 12100	12202 - 12225
II	9936 - 9970	10111 - 10124, 16400 ^a , 10126 - 10145	12101 - 12125	12226 - 12260
III	9971 - 10005	10146 - 10180	12126 - 12150	12251 - 12275
IV	10006 - 10040	10181 - 10215	b	b
V	10041 - 10075	10216 - 10250	c	c

- Female rat 10125 escaped and was missing overnight; this rat was excluded and replaced with female rat 16400 on day 1 of study, at the request of the Study Director.
- Group IV F1 generation pups were sacrificed at weaning on DL 21 because of severe pup mortality during lactation.
- There were no surviving Group V F1 generation pups after DL 5.

G.3. Rationale for Dosage Selection:

Dosages were selected by the Sponsor on the basis of previous studies conducted with the test article.

G.4. Route of Administration:

Oral (gavage)

G.5. Rationale for Route of Administration:

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

G.6. Frequency of Administration:**G.6.a. Fo Generation Rats:**

The Fo generation male rats were given appropriate dosages of the test article or vehicle once daily^a beginning 28 days before cohabitation (which continued for a maximum of 14 days) and continuing through the day before sacrifice after the completion of the cohabitation period. All male rats received a total of 52 consecutive daily dosages.

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- See APPENDIX G, item 3.

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The Fo generation female rats were given the appropriate dosages of the test article or vehicle once daily beginning 28 days before cohabitation (which continued for a maximum of 14 days) and continuing through DG 9 (rats assigned to Caesarean-sectioning), DG 24 (rats assigned to natural delivery that did not deliver a litter), or DL 20 (rats that delivered a litter). The dosage volume (5 mL/kg) was adjusted daily on the basis of the most recently recorded body weight and given at approximately the same time each day.

Dams in the process of delivering pups were not dosed until completion of parturition, in order to preclude possible disruption of maternal behavior and/or cannibalization of the pups. Consequently, some dams were not administered one daily dosage during the delivery period. No dam missed more than one daily dosage.

G.6.b. F1 Generation Rats:

F1 generation male and female rats were given appropriate dosages of the test article^a or vehicle once daily beginning on day 1 postweaning (DL 21) and continuing through the day before sacrifice. F2 generation pups were not directly given the test article, but may have been possibly exposed to the test article during the maternal gestation (*in utero* exposure) or via maternal milk during the lactation period.

G.7. Length of Study:

Approximately seven months

G.8. Method of Study Performance:

G.8.a. Fo Generation Rats:

All Fo generation rats were observed for viability at least twice daily during all periods of the study. Rats were also observed for general appearance at least once during the acclimation period, and examined for clinical observations of effects of the test article, abortions, premature deliveries and deaths prior to and approximately one hour after dosage and on the day sacrificed.

Body weights for Fo generation male rats were recorded at least once during the acclimation period, weekly during the dosage period and at sacrifice. Feed consumption values for male rats were recorded weekly during the dosage period.

a. See APPENDIX G, items 4 and 5.

Body weights for Fo generation female rats were recorded at least once during the acclimation period, weekly to cohabitation, daily during the gestation period, on DLs 1, 4, 7, 10 and 14 (rats assigned to natural delivery) and at sacrifice. Feed consumption values were recorded weekly to cohabitation, daily during the gestation period and on DLs 1, 4, 7, 10 and 14 (rats assigned to natural delivery). Feed consumption values were not recorded after DL 14, when it was expected that the pups would begin to consume maternal feed.

A table of random units was used to select 15 female rats per dosage group for evaluation of estrous cycling by examination of vaginal cytology for 14 days before the start of the cohabitation period and continuing until mating.

Within each dosage group, consecutive order was used to assign rats to cohabitation, one male rat per female rat. The cohabitation period consisted of a maximum of 14 days. During cohabitation, all female rats were evaluated daily until spermatozoa were observed in a smear of the vaginal contents and/or a copulatory plug was observed *in situ* (DG 0) and were assigned to individual housing. Female rats not mated within the first seven days of cohabitation were assigned alternate male rats that had mated (within the same dosage group) and remained in cohabitation for a maximum of seven additional days.

Rats allowed to naturally deliver litters were evaluated for clinical observations during parturition, duration of gestation (DG 0 to the day the first pup was observed), litter size (all pups delivered) and pup viability at birth. Pups that either appeared stillborn or that died before initial examination of the litters for viability were examined for vital status at birth. The lungs were removed and immersed in water. Pups with lungs that sank were considered stillborn; pups with lungs that floated were considered liveborn and to have died shortly after birth. Each litter was subsequently examined daily for pup viability. Maternal behavior of the dams was evaluated daily when the pups were examined during the 21-day postpartum period. Maternal behavior was recorded on DLs 1, 4, 7, 14 and 21. Variations from expected maternal behavior were recorded, if present, on all other days of the postpartum period.

Fertility parameters were assessed for all dams assigned to natural delivery. These parameters included a fertility index (percentage of matings that resulted in pregnancies), gestation index (percentage of pregnancies that resulted in the birth of live litters), number of offspring per litter (live and dead pups), number of implantation sites, general condition of the dam and litter during the postpartum period, viability indices (percentage of pups born that survived 4 and 7 days), and lactation index (percentage of pups born that survived 21 days).

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G.8.b. F1/F2 Generation Pups – Prewaning Observations:

Day 1 of lactation (postpartum) was defined as the day of birth and was also the first day in which all pups in a litter were individually weighed (pup body weights were recorded after all pups in a litter were delivered and groomed by the dam).

Vital status at birth was determined for pups that either appeared stillborn or that died before initial examination of the litter for viability. Pups that either appeared stillborn or that died before initial examination of the litter for viability were examined for vital status at birth, as previously described.

Each litter was evaluated for viability at least twice each day during the 21-day postpartum period. Pups in each litter were counted once daily. Physical signs (including variations from expected nursing behavior and gross external physical anomalies) in the pups were recorded once daily for 21 days postpartum. Dead pups observed at these times were removed from the nesting box. When not precluded by autolysis or cannibalization by the dam, any pup found dead was necropsied and examined for the cause of death. Pup body weights were recorded on DLs 1 (birth), 4, 7, 14 and 21.

Reflex and physical development parameters in the F1 generation pups only were monitored during the 21-day postpartum period. Surface righting reflex [ability to right in 5 seconds (from DL 1)], pinna unfolding (from DL 2), eye opening (from DL 12), acoustic startle response (from DL 13) and air righting reflex (from DL 14) were monitored daily until all pups (100%) in the litter reached the criterion for the specific test. Pupil constriction was evaluated once on DL 21; the number of pups per litter with this reflex present was recorded.

G.8.c. F1 Generation Rats - Postweaning Observations:

"Postweaning day" observations were recorded beginning on DL 22. All F1 generation rats were observed for viability at least twice daily during all periods of the study. Rats were also observed for clinical observations of effects of the test article, abortions and premature deliveries prior to and approximately one hour after dosage and at sacrifice. Body weights of F1 generation male rats were recorded weekly during the dosage period and at sacrifice. Body weights for F1 generation female rats were recorded weekly to cohabitation, daily during the gestation period, on DLs 1, 4, 7, and 14 postpartum (rats assigned to natural delivery) and at sacrifice. Feed consumption values were recorded weekly except during cohabitation and on DGs 0, 7, 10, 14 and 20 and DLs 1, 4, 7, 10 and 14 (female rats only).

Beginning at 23 to 25 days of age, one male rat and one female rat from each litter, where possible, were evaluated in a passive avoidance test for learning,

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short-term retention and long-term retention. Each rat was tested on two days separated by a one-week interval, and the criterion for learning was the same for both days of testing. The passive avoidance apparatus consisted of a two-compartment chamber with hinged Plexiglas® lids. One compartment was fitted with a bright light and Plexiglas® floor. The other compartment was fitted with a grid floor to which a brief (1 second) pulse of mild electric current (1 mA) could be delivered. The two compartments were separated by a sliding door.

During each trial, the rat was placed into the "bright" compartment, the sliding door was opened and the light was turned on. The rat was allowed to explore the apparatus until it entered the "dark" compartment. The sliding door was then immediately closed, the light was turned off and the brief pulse of current was delivered to the grid floor. The rat was then removed from the apparatus and placed into a holding cage for 30 seconds before the start of the next trial. Trials were repeated until the rat remained in the "bright" compartment for 60 seconds on two consecutive trials (the criterion for learning) or until 15 trials were completed. The latency to enter the dark compartment or the maximum 60-second interval was recorded for each trial.

Dosage groups were compared for the following dependent measures: the number of trials to the criterion in the first session (overall learning performance); the latency (in seconds) to enter the "dark" compartment from the "bright" compartment on trial 1 in the first test session (activity level and exploratory tendency in a novel environment); the latency (in seconds) to enter the "dark" compartment from the "bright" compartment on trial 2 in the first test session (short-term retention); the number of trials to the criterion in the second test session (long-term retention); and the latency (in seconds) to enter the "dark" compartment from the "bright" compartment on trial 1 in the second session (long-term retention).

Beginning at approximately 70 days postpartum, one male rat and one female rat from each litter were evaluated in a water-filled M-maze for overt coordination, swimming ability, learning and memory. Each rat was tested in a watertight 16-gauge stainless steel modified M-maze. The maze was filled with water to a depth of approximately nine inches, and the water was monitored for temperature (range of $21^{\circ}\text{C} \pm 1^{\circ}\text{C}$). On each test trial, the rat was placed into the starting position (base of the M-maze stem farthest from the two arms) and required to swim to one of the two goals of the M-maze, in order to be removed from the water. On the first trial, the rat was required to enter both arms of the maze before being removed from the water. The initial arm chosen on trial 1 was designated the incorrect goal during the remaining trials. Rats that failed to make a correct goal choice within 60 seconds in any given trial were guided to the correct goal and were then removed from the water. A 15-second intertrial interval separated each trial. Each rat was required to reach a criterion of five

consecutive errorless trials to terminate the test session. The maximum number of trials in any test session was 15. Latency (measured in seconds) to choose the correct goal or the maximum 60-second interval was recorded for each trial, as is the number of errors (incorrect turns in the maze) during each trial.

Each rat was tested twice. The test sessions were separated by a one-week interval, and the correct goal and the criterion were the same for both test sessions. Dosage groups were compared for the following dependent measures: the number of trials to criterion on the first day of testing (overall learning); the average number of errors (incorrect turns in the maze) for each trial on the first day of testing (overall learning); the latency (in seconds) to reach the correct goal on trial 2 of the first day of testing (short-term retention); the number of trials to criterion on the second day of testing (long-term retention); the average number of errors for each trial on the second day of testing (long-term retention); and the latency (in seconds) to reach the correct goal on trial 1 of day 2 of testing (long-term retention).

Female rats were evaluated for the age of vaginal patency beginning on day 28 postpartum^a. Male rats were evaluated for the age of preputial separation beginning on day 39 postpartum.

On DLs 84 to 97, the F1 generation rats within each dosage group were assigned to cohabitation, one male rat per female rat, based on computer-generated random units, with the exclusion of sibling matings. The cohabitation period consisted of a maximum of 14 days. Female rats with spermatozoa observed in a smear of the vaginal contents and/or a copulatory plug observed *in situ* were considered to be at DG 0 and assigned to individual housing. Female rats that did not mate within the first seven days of cohabitation were assigned alternate male rats from the same dosage group that had mated. Female rats were allowed to naturally deliver and maintain litters through a 21-day postpartum period.

These rats were evaluated for clinical observations during parturition, duration of gestation (DG 0 to the day the first pup was observed), litter size (all pups delivered) and pup viability at birth. Pups that either appeared stillborn or that died before initial examination of the litters for viability were examined for vital status at birth. The lungs were removed and immersed in water. Pups with lungs that sank were considered stillborn; pups with lungs that floated were considered liveborn and to have died shortly after birth. Each litter was subsequently examined daily for pup viability. Maternal behavior of the dams was evaluated daily when the pups were examined during the 21-day postpartum period. Maternal behavior was recorded on DLs 1, 4, 7, 14 and 21.

a. See APPENDIX G, item 6.

Variations from expected maternal behavior were recorded, if present, on all other days of the postpartum period.

Fertility parameters were assessed for all dams assigned to natural delivery. These parameters included a fertility index (percentage of matings that resulted in pregnancies), gestation index (percentage of pregnancies that resulted in the birth of live litters), number of offspring per litter (live and dead pups), number of implantation sites, general condition of the dam and litter during the postpartum period, viability indices (percentage of pups born that survived 4 and 7 days), and lactation index (percentage of pups born that survived 21 days).

G.9. Gross Necropsy²:

G.9.a. Fo Generation Male and Female Rats Assigned to Pharmacokinetic Sample Collection:

At scheduled sacrifice after completion of the cohabitation period (male rats that sired litters of dams allowed to naturally deliver a litter) and on DL 21 (female rats allowed to naturally deliver a litter) blood samples (approximately 4 mL per rat) were collected from five rats per sex per dosage group from the inferior vena cava into serum separator tubes and centrifuged. The resulting serum was immediately frozen on dry ice and maintained frozen (-70°C) until shipment to the Sponsor for analysis. The liver was excised, weighed, and a sample section (lateral lobe) was frozen and retained at -70°C until shipment to the Sponsor for analysis.

The livers of the pups from the litters of the five dams in Groups I to IV selected for pharmacokinetic sample collection were excised, pooled per litter, frozen and retained at -70°C until shipment to the Sponsor for analysis. The dams in the 15 mg/kg/day dosage group (Group V) did not have surviving pups on DL 21.

G.9.b. Fo and F1 Generation Male Rats:

Male rats were sacrificed by carbon dioxide asphyxiation after completion of the cohabitation period, and a gross necropsy of the thoracic, abdominal and pelvic viscera was performed. Gross lesions were retained in neutral buffered 10% formalin for possible future evaluation. Representative photographs of gross lesions are available in the raw data. The following organs were excised, individually weighed and retained for possible histologic evaluation: testes,

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- a. A table of random units was used to select one control group Fo and F1 generation rat of each sex from which all tissues examined at necropsy were retained, in order to provide control tissues for any possible histopathological evaluations of gross lesions.

epididymides, prostate and seminal vesicles (with and without fluid). The testes were fixed in Bouin's solution for 48 to 96 hours and then retained in neutral buffered 10% formalin. The remaining organs were retained in neutral buffered 10% formalin.

G.9.c. Fo Generation Female Rats Assigned to Cesarean-Sectioning:

Female rats assigned to Cesarean-sectioning were sacrificed by carbon dioxide asphyxiation on DG 10, and a gross necropsy of the thoracic, abdominal and pelvic viscera was performed. Uteri of apparently nonpregnant rats were stained with 10% ammonium sulfide to confirm the absence of implantation sites⁽⁹⁾. All ovaries and gross lesions were retained in neutral buffered 10% formalin for possible future evaluation. Representative photographs of gross lesions are available in the raw data. The rats were examined for placentae that appeared abnormal (size, color or shape) and the number of corpora lutea in each ovary, implantation sites and viable and nonviable embryos. A viable embryo is oval or crescent shaped, pink and enclosed in an amniotic sac filled with clear fluid. A nonviable embryo is amorphous, small, pale pink to tan or deep red to black, soft and enclosed in an amniotic sac filled with clear, cloudy or opaque fluid. Embryos were discarded after examination.

G.9.d. Fo Generation Female Rats Assigned Natural Delivery and F1 Generation Female Rats:

After completion of the 21-day postpartum period, all dams that delivered litters were sacrificed, and gross necropsy of the thoracic, abdominal and pelvic viscera was performed. The number and distribution of implantation sites was recorded. Female rats assigned to natural delivery that did not deliver a litter were sacrificed on DG 25 and examined for gross lesions. To confirm the pregnancy status, uteri from rats that appeared nonpregnant were stained with 10% ammonium sulfide⁽⁹⁾. Dams with no surviving pups were sacrificed after the last pup was found dead, missing or presumed cannibalized. A gross necropsy of the thoracic, abdominal and pelvic viscera was performed. All ovaries were retained in neutral buffered 10% formalin for possible future evaluation.

The Fo generation female rat in the 5 mg/kg/day dosage group selected for natural delivery that died was examined for the cause of death on the day the observation was made. The rat was examined for gross lesions. Pregnancy status and uterine contents were recorded. Delivered pups were examined to the extent possible. Ovaries were retained in neutral buffered 10% formalin.

G.9.e. F1/F2 Generation Pups:

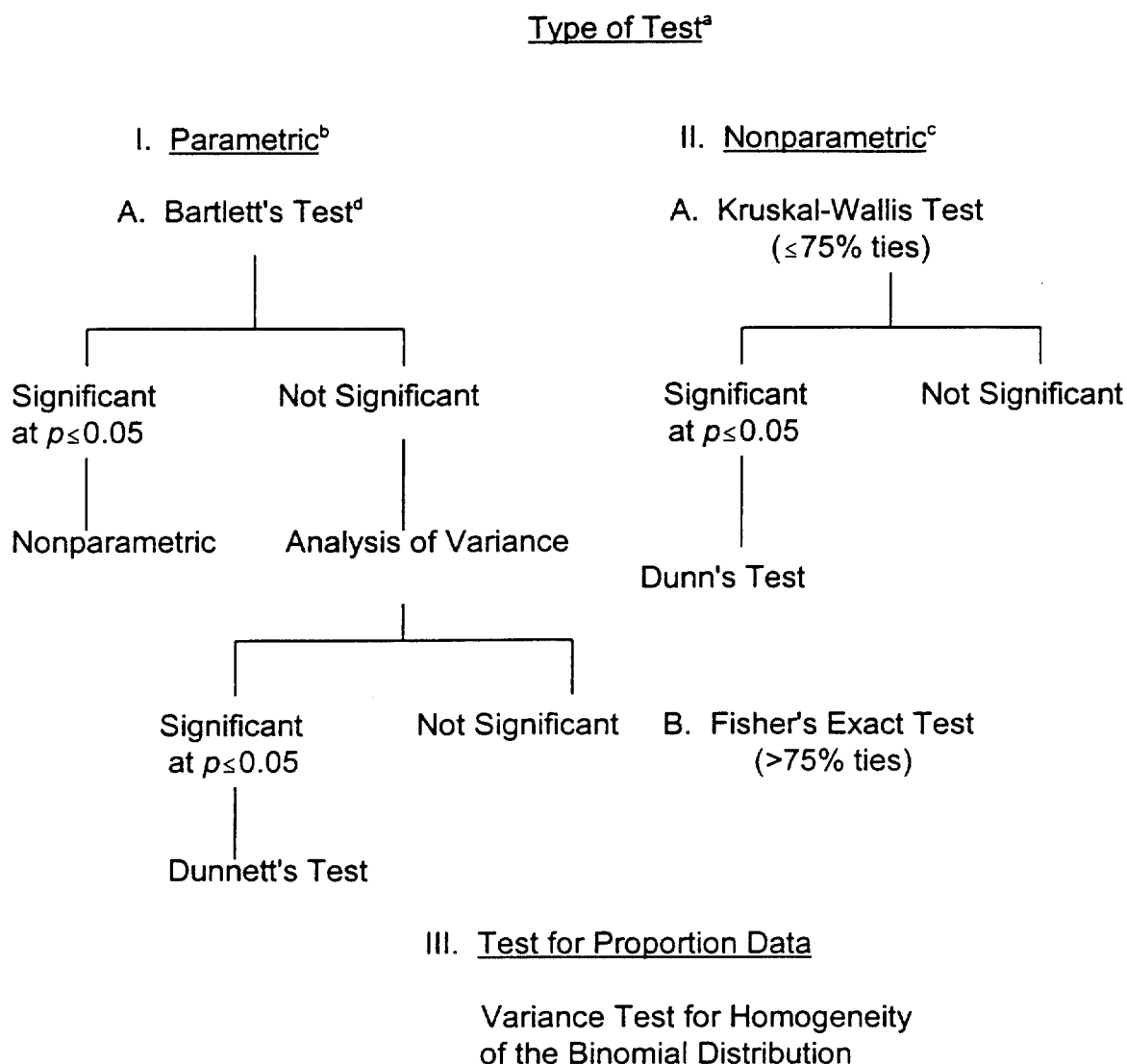
Pups that died before examination of the litter for pup viability were evaluated for vital status at birth, as described previously. Pups found dead were examined for gross lesions and for the cause of death. Pups with gross lesions found on DLs 1 to 4 were preserved in Bouin's solution. Gross lesions of pups found on DLs 5 to 21 were preserved in neutral buffered 10% formalin. Representative photographs of pup gross lesions are available in the raw data.

Pups not selected for continued evaluation on DL 4 were sacrificed by carbon dioxide asphyxiation and examined for gross lesions; pups with gross lesions were preserved in Bouin's solution. Necropsy included a single cross-section of the head at the level of the frontal-parietal suture and examination of the cross-sectioned brain for apparent hydrocephaly. The stomach contents (milk curd) were collected from culled pups from Groups I, II and III. Samples were collected from all pups from five of the largest litters in these three dosage groups. Individual pup samples were combined by litter into polypropylene tubes and frozen at -20°C. After completion of sample collection, samples were shipped (frozen on dry ice) to the Sponsor for analysis.

On DL 21, F1 generation pups not continued on study and all F2 generation pups were sacrificed and examined for gross lesions; gross lesions were preserved in neutral buffered 10% formalin. The 10 mg/kg/day F1 generation (Group IV) litters were sacrificed on DL 21 because of the severe pup toxicity during lactation (mortality and reduced body weights and delayed development). Necropsy procedures were the same as those used for pups culled on DL 4.

G.10. Statistical Analyses:

The following schematic represents the statistical analyses of the data:



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

Proportion data were analyzed using the Variance Test for Homogeneity of the Binomial Distribution⁽¹⁰⁾.

Continuous data (e.g., body weights, body weight changes, feed consumption data and organ weights) were analyzed using Bartlett's Test of Homogeneity of Variances⁽¹¹⁾ and the Analysis of Variance⁽¹²⁾, when appropriate [i.e., Bartlett's Test was not significant ($p > 0.05$)]. If the Analysis of Variance was significant ($p \leq 0.05$), Dunnett's Test⁽¹³⁾ was used to identify the statistical significance of the individual groups. If the Analysis of Variance was not appropriate [i.e., Bartlett's Test was significant ($p \leq 0.05$)], the Kruskal-Wallis Test⁽¹⁴⁾ was used ($\leq 75\%$ ties). In cases where the Kruskal-Wallis Test was statistically significant ($p \leq 0.05$), Dunn's Method of Multiple Comparisons⁽¹⁵⁾ was used to identify the statistical significance of the individual groups. If there were greater than 75% ties, Fisher's Exact Test⁽¹⁶⁾ was used.

Data obtained at Cesarean-sectioning, natural delivery, preweaning reflex/physical developmental data involving discrete data (e.g., number of corpora lutea, number of pups per litter trials to a criterion), were evaluated by the Kruskal-Wallis Test⁽¹⁴⁾, as described above.

One F1 generation dam (12228) in the 1 mg/kg/day dosage group had a litter consisting of only two pups. Because such occurrences can abnormally skew the distribution of the data⁽¹⁷⁾, statistical analyses of gestation body weights, feed consumption values and natural delivery and litter data were made without the values for this dam and litter.

III. **RESULTS - Fo GENERATION MALE RATS**

A. **Mortality and Clinical Observations (Summary - Table B1; Individual Data - Table B10)**

No Fo generation male rats died during this study.

The only clinical observation attributable to the test article was impaired righting reflex. This observation occurred in significant numbers ($p \leq 0.01$) of 15 mg/kg/day dosage group rats, as compared with the control group values. All other adverse clinical observations were considered unrelated to the test article because the incidences were not dosage-dependent. These observations included localized alopecia on the limbs, dental problems (missing, broken or misaligned incisors), chromodacryorrhea, red peripenial substance and chromorhinorrhea.

B. **Body Weights and Body Weight Changes (Figure 1; Summaries - Tables B2 and B3; Individual Data - Table B11)**

Groups administered 5 mg/kg/day and higher dosages of the test article had reduced body weight gains. The values were significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) in the 5 mg/kg/day dosage group on DSs 15 to 22, 22 to 29 and 29 to 36; in the 10 mg/kg/day dosage group on DSs 8 to 15, 15 to 22, 22 to 29, 29 to 36, 36 to 43 and 50 to 53; and at all tabulated intervals in the 15 mg/kg/day dosage group. Reflecting these effects of the test article, body weight gains were significantly reduced ($p \leq 0.01$) for the entire dosage period (DSs 1 to 53) in groups administered 5 mg/kg/day and higher of the test article. Absolute body weights were significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) in the 5 mg/kg/day dosage group on DSs 29, 36, 43, 50 and 53, and in the 10 and 15 mg/kg/day dosage groups on DSs 15, 22, 29, 36, 43, 50 and 53.

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

C. **Absolute (g/day) and Relative (g/kg/day) Feed Consumption Values (Summaries - Tables B4 and B5; Individual Data - Table B12)**

Absolute (g/day) feed consumption values were significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) in the 10 and 15 mg/kg/day dosage groups after the first week of treatment (DSs 8 to 15, 15 to 22, 22 to 29, 43 to 50 and 50 to 53). Reflecting these effects of the test article, the 10 and 15 mg/kg/day dosage groups had significantly reduced ($p \leq 0.01$) absolute feed consumption values for the entire treatment period (DSs 1 to 53).

Absolute and relative (g/kg/day) feed consumption values were significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) in the 15 mg/kg/day dosage group on DSs 15 to 22, 22 to 29, 43 to 50 and 50 to 53, as compared with the control group values.

Feed consumption values were unaffected by the 5 mg/kg/day dosage of the test article.

D. Mating and Fertility (Summary - Table B6; Individual Data - Table B13)

Dosages of the test article as high as 15 mg/kg/day did not affect any mating and fertility parameters evaluated in the male rats. Values for the fertility and pregnancy indices (number of pregnancies per number of rats in cohabitation and rats that mated, respectively), the number of days to inseminate, the number of rats that mated and the number of rats with confirmed mating dates during the first week of cohabitation were comparable among the five dosage groups.

E. Necropsy Observations (Summary - Table B7; Individual Data - Table B14)

A significantly increased ($p \leq 0.01$) number of male rats in the 15 mg/kg/day dosage group had small seminal vesicles. One of these rats mated but did not impregnate a female rat; the other two rats impregnated female rats. One 15 mg/kg/day dosage group male rat (10051) had a small prostate; this male rat was cohabited with and impregnated two female rats. Both of these gross lesions were considered related to the test article because: 1) the incidences were dosage-dependent; and 2) the absolute weights of the seminal vesicles with fluid and prostate were significantly reduced ($p \leq 0.01$) in the 15 mg/kg/day dosage group (see section III.F).

All other necropsy observations were considered unrelated to the test article because: 1) the observation occurred in a control group rat; or 2) the observation was considered a congenital malformation. One control group rat had a missing portion of a hindpaw digit. One 5 mg/kg/day dosage group male rat did not have a right testis and epididymis; this rat did not mate.

F. Terminal Body Weights and Organ Weights and Ratios (%) of Organ Weight to Terminal Body Weight (Summaries - Tables B8 and B9; Individual Data - Table B15)

The 5, 10 and 15 mg/kg/day dosage groups had significantly reduced ($p \leq 0.01$) terminal body weights. The absolute weights of the left epididymis, seminal vesicles with fluid, and prostate were significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) in the 15 mg/kg/day dosage group. The absolute weights of the seminal vesicles

without fluid and the right epididymis were also reduced in the 15 mg/kg/day dosage group, however not significantly ($p>0.05$). Testes weights were unaffected by dosages of the test article as high as 15 mg/kg/day.

The ratios of the weight of the left and right testes to terminal body weights were significantly increased ($p\leq 0.05$ or $p\leq 0.01$) in the 5 (left only), 10 and 15 mg/kg/day dosage groups, as compared to the control group values. These observations were associated with the significantly reduced ($p\leq 0.01$) terminal body weights in these dosage groups. The ratios of the weights of the epididymides, seminal vesicles and prostate were generally comparable among the five dosage groups.

IV. RESULTS - Fo GENERATION FEMALE RATS/F1 GENERATION LITTERS

A. Mortality and Clinical Observations (Summaries - Table C1 and C15; Individual Data - Tables C22 and C30)

A.1. Mortality

No deaths were caused by dosages of EtFOSE as high as 15 mg/kg/day. One dam (10170) in the 5 mg/kg/day dosage group died during delivery on gestation day (DG) 22. The event was considered unrelated to the test article because the incidence was not dosage-dependent. No other adverse clinical observations occurred in this dam, and its body weight and feed consumption values were unremarkable throughout the gestation period. Necropsy of the dam revealed external observations of red and wet perioral and perivaginal substance presumed to be evidence of bleeding during parturition. There were 15 implantation sites; eight normal pups were delivered and six dead fetuses were *in utero*. One conceptus was presumed cannibalized, because pup tissues were found in the stomach of the dam. All other dams survived to scheduled sacrifice.

A.2. Clinical Observations

Relatively low incidences of localized alopecia occurred during the precohabitation, gestation and lactation periods only in groups treated with EtFOSE. These incidences of localized alopecia (total of all areas and limbs) were significant ($p \leq 0.05$ or $p \leq 0.01$) in the 5, 10 and 15 mg/kg/day dosage groups during the gestation and lactation periods.

All other clinical observations during the precohabitation, gestation and lactation periods were considered unrelated to the test article because: 1) the incidences were not dosage-dependent; and/or 2) the observation occurred in only one rat. These observations included dehydration, cold to touch, portion of tail black or missing, chromodacryorrhea, dental problems and chromorhinorrhea.

B. Body Weights (Figure 2; Summaries - Tables C2 through C7; Individual Data - Tables C23 through C25)

B.1. Precohabitation

Groups administered 5 mg/kg/day and higher dosages of the test article had significantly reduced ($p \leq 0.01$) body weight gains for the entire precohabitation period (DSs 1 to 29). During this period, values were significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) in the 5 mg/kg/day dosage group on DSs 8 to 16 and 23 to

29; and in the 10 and 15 mg/kg/day dosage groups on DSs 1 to 8, 8 to 16, 16 to 23 and 23 to 29, as compared with the control group values.

Body weights were significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) in the 5 mg/kg/day dosage group on DSs 16 and 29, and in the 10 and 15 mg/kg/day dosage groups on DSs 16, 23 and 29, as compared with the control group values.

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

B.2. Gestation

Gestation body weight gains tended to be reduced in the 1 and 5 mg/kg/day dosage groups and were significantly reduced ($p \leq 0.01$) in the 10 and 15 mg/kg/day dosage groups on DGs 0 to 7. Weight gains generally continued to be reduced in these groups until DGs 10 to 12 (1 and 5 mg/kg/day dosage groups) or 12 to 15 (10 and 15 mg/kg/day dosage groups). Body weight gains were again significantly reduced ($p \leq 0.01$) in the 15 mg/kg/day dosage group on DGs 18 to 20. Reflecting these effects of the test article, body weight gains tended to be reduced in the 5 and 10 mg/kg/day dosage groups and were significantly reduced ($p \leq 0.01$) in the 15 mg/kg/day dosage group for the entire gestation period (DGs 0 to 20).

Body weights continued to be significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) in the 5 mg/kg/day dosage group on DGs 0 through 17, and in the 10 and 15 mg/kg/day dosage groups on all days of the gestation period (DGs 0 through 20).

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

B.3. Lactation

The 10 and 15 mg/kg/day dosage groups had significantly reduced ($p \leq 0.01$) body weights on DL 1. Lactation body weights continued to be significantly reduced ($p \leq 0.01$) in the 10 mg/kg/day dosage group on DLs 4, 7, 10 and 14.

Body weight loss occurred in the 10 and 15 mg/kg/day dosage groups on DLs 1 to 4. The 15 mg/kg/day dosage group was precluded from further evaluation because all pups died before DL 5. A significant increase ($p \leq 0.05$) in body weight gain on DLs 14 to 21 in the 10 mg/kg/day dosage group was possibly associated with reduced litter size, milk demand and production.

Body weights and body weight gains during lactation were unaffected by the 1 and 5 mg/kg/day dosage of the test article.

C. Absolute (g/day) and Relative (g/kg/day) Feed Consumption Values (Summaries - Tables C8 through C13; Individual Data - Tables C26 through C28)

C.1. Precohabitation

Absolute (g/day) and relative (g/kg/day) feed consumption values were significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) during the precohabitation period in the 10 and 15 mg/kg/day dosage groups on DSs 8 to 16, 16 to 23 and 23 to 29. Reflecting these effects of the test article, absolute and relative feed consumption values were significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) in the 10 and 15 mg/kg/day dosage group for the entire precohabitation period (DSs 1 to 29).

Feed consumption values during the precohabitation period were unaffected by the 5 mg/kg/day dosage of the test article.

C.2. Gestation

The 10 and 15 mg/kg/day dosage groups continued to have significantly reduced ($p \leq 0.01$) absolute and relative feed consumption values early in the gestation period (DGs 0 to 7 and 7 to 10). Absolute feed consumption values were also significantly reduced ($p \leq 0.05$) in the 5 mg/kg/day dosage group on DGs 0 to 7. Absolute feed consumption values continued to be significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) in the 10 mg/kg/day dosage group on DGs 10 to 12 and 12 to 15, and in the 15 mg/kg/day dosage group throughout the remainder of the gestation period (DGs 10 to 12, 12 to 15, 15 to 18 and 18 to 20). As a result of these changes, absolute and relative feed consumption values were significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) for the entire gestation period (DGs 0 to 20) in the 5 (absolute only), 10 and 15 mg/kg/day dosage groups.

Feed consumption values during gestation were unaffected by the 1 mg/kg/day dosage of the test article.

C.3. Lactation

Absolute and relative feed consumption values were significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) in the 5 (absolute only) and 10 mg/kg/day dosage groups for the entire lactation period (DLs 1 to 14). Significant reductions ($p \leq 0.05$ or $p \leq 0.01$) in absolute and relative feed consumption values occurred on DLs 7 to 10 in the 5 mg/kg/day dosage group, and for all tabulated intervals in the 10 mg/kg/day dosage group. Absolute and relative feed consumption values were reduced in the 15 mg/kg/day dosage group on DLs 1 to 4, however the reductions were not statistically significant because only one litter was available for evaluation in this dosage group. The 15 mg/kg/day dosage group was precluded from further evaluation because all pups died before DL 5.

Feed consumption values during lactation were unaffected by the 1 mg/kg/day dosage of the test article.

D. Estrous Cycling, Mating and Fertility (Summary - Table C14; Individual Data - Table C29)

Dosages of the test article as high as 15 mg/kg/day did not affect estrous cycling (number of estrus stages per 14 days) in the 15 rats per dosage group that were evaluated. A total of 34 or 35 female rats mated in each dosage group. The number of days in cohabitation, the number of rats that mated, the fertility and pregnancy indices (number of pregnancies per number of rats that mated and rats in cohabitation, respectively), and the number of rats with confirmed mating dates during the first and second week of cohabitation were comparable in the five dosage groups. Pregnancy occurred in 35, 33, 32, 32 and 34 female rats in Groups I through V, respectively.

E. Necropsy Observations (Summary - Table C15; Individual Data - Table C30)

All necropsy observations were considered unrelated to treatment with the test article. One, one and two rats in the 1, 10 and 15 mg/kg/day dosage groups, respectively, had moderate or marked dilation of the pelvis of one or both kidneys, observations that are common in this species and strain. Red and wet perioral and perivaginal substance occurred in the 5 mg/kg/day dosage group rat that died during delivery and was previously discussed. One rat in the 5 mg/kg/day dosage group had localized alopecia at necropsy.

F. Caesarean-Sectioning and Litter Observations (Summary - Table C16; Individual Data - Tables C31 through C33)

Caesarean-sectioning observations on DG 10 were based on 10 pregnant dams in each of the five dosage groups.

Statistically significant reductions ($p \leq 0.01$) in the averages for implantations and viable embryos occurred in the 15 mg/kg/day dosage group, as compared to the control group.

There were no biologically important or other statistically significant differences in the litter averages for corpora lutea or nonviable embryos. There were no dams with all nonviable embryos.

G. Natural Delivery and Litter Observations (Summaries - Table C17 and C18; Individual Data – Tables C34 through C37)

There were 25 presumed pregnant rats assigned to natural delivery in each of the five dosage groups and 22 to 25 pregnant dams in each dosage group. One pregnant dam in the 5 mg/kg/day dosage group died during delivery on DG 22, as previously described. One dam in the 10 mg/kg/day dosage group was not observed to have delivered a litter but had one implantation site *in utero* at necropsy on DG 25, an event that may indicate resorption of the litter, as such generally occurs for litters of one conceptus. All other pregnant rats delivered a litter.

The duration of gestation was significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) in the 5, 10 and 15 mg/kg/day dosage groups, an observation associated with preimplantation loss in the 15 mg/kg/day dosage group [the average number of implantation sites per dam was significantly reduced ($p \leq 0.01$), resulting in a significantly reduced ($p \leq 0.01$) litter size] and an effect of the test article.

Pup viability was significantly affected ($p \leq 0.05$ or $p \leq 0.01$) by the 10 and 15 mg/kg/day dosages of the test article, as described in the following information. The 10 mg/kg/day dosage group had a significantly increased ($p \leq 0.01$) number of dams with stillborn pups and the numbers of pups that died or were presumed cannibalized were significantly increased ($p \leq 0.01$) on DLs, 1, 2 to 4, 5 to 7 and 8 to 14. The 15 mg/kg/day dosage group had postimplantation loss evident as reduced pup viability at birth [the gestation index (number of dams with liveborn pups per pregnant rats) was significantly reduced ($p \leq 0.01$), four** dams in this dosage group had no liveborn pups, the number of dams with stillborn pups was significantly increased ($p \leq 0.01$), the litter average and number of stillborn pups was significantly increased ($p \leq 0.01$) and the litter average and number of liveborn pups was significantly reduced ($p \leq 0.01$)], as well as peripartum deaths [significant ($p \leq 0.01$) numbers of dead and presumed cannibalized pups on DLs 1, 2 to 4 and 5 to 7 (all liveborn pups died by DL 5) and significant ($p \leq 0.01$) numbers of dams had all pups dead or presumed cannibalized on DLs 1 to 4]. Reflecting these effects, the viability and lactation indices were significantly reduced ($p \leq 0.01$) in the 10 and 15 mg/kg/day dosage groups, as also were the averages for surviving pups ($p \leq 0.01$) in the 10 mg/kg/day dosage group on DLs 4 (pre- and postculling) and 7, and in the 15 mg/kg/day dosage group on DLs 1 and 4 (preculling). The live litter size at weighing was significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) on DL 1 in the 10 and 15 mg/kg/day dosage groups and on DLs 1, 4 (postculling), 7, 14 and 21 in the 10 mg/kg/day dosage group.

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

A dosage-dependent pattern of reduced pup body weights was evident in each group administered the test article. The 1 mg/kg/day dosage group tended to have reduced pup body weights on DL 4 (pre-and postculling). The 5, 10 and 15 mg/kg/day dosage groups had significantly reduced ($p \leq 0.01$) pup body weights on all weighing days (no pups survived after DL 4 in the 15 mg/kg/day dosage group).

The percentage of male pups was comparable across all five dosage groups.

H. Pup Clinical and Necropsy Observations (Summaries – Tables C19 and C21; Individual Data – Tables C38 and C45)

Adverse clinical and necropsy observations associated with reduced pup viability and potential reduction in maternal care occurred in the 5, 10 and 15 mg/kg/day dosage groups. Adverse clinical observations included 1, 7 and 3 litters with pups that were not nursing in the 5, 10 and 15 mg/kg/day dosage groups, respectively; the incidence was significant ($p \leq 0.01$) in the 10 mg/kg/day dosage group. The number of litters with cold to touch pups was also significantly increased ($p \leq 0.01$) in the 10 mg/kg/day dosage group. Two litters in the 10 mg/kg/day dosage group had pups that were not nesting and one 10 mg/kg/day dosage group litter had dehydrated pups. The placentae and umbilical cords were not removed from pups in one 5 mg/kg/day dosage group litter.

Necropsy observations in pups that were found dead included increases in the number of pups with no milk in the stomach in the 5, 10 and 15 mg/kg/day dosage group litters; the incidence was significant ($p \leq 0.01$) in the 10 and 15 mg/kg/day dosage groups.

All other clinical and necropsy observations in the F1 generation pups were considered unrelated to the test article because: 1) the incidences were not dosage-dependent; or 2) the observation occurred in only one or two pups. Clinical observations included a black area on the right hindpaw, swollen left hindlimb, mass(es) in mouth, lesion on the neck and portion of tail missing or black. Necropsy revealed one 15 mg/kg/day dosage group stillborn pup with a short jaw and one 5 mg/kg/day pup with moderate dilation of the pelvis of the right kidney at necropsy on DL 21.

I. Reflex and Physical Development (Summary – Table C20; Individual Data – Tables C39 through C44)

Reversible delays in reflex and physical development that are highly correlated with body weight^(1,18) occurred in the 5 and 10 mg/kg/day dosage groups, as described below.

I.1. Surface Righting

Surface righting was delayed in the 5, 10 and 15 mg/kg/day dosage groups, as described below. The percentage of pups that could surface right was significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) in the 5 mg/kg/day dosage group on DLs 2, 3, 6, 9 and 10, in the 10 mg/kg/day dosage group on DLs 2 through 18, and in the 15 mg/kg/day dosage group on DL 1. After DL 1, no pups in the 15 mg/kg/day dosage group surface righted; all pups were dead after DL 4. The average day that at least 50% of the pups in a dosage group had the ability to surface right was significantly increased ($p \leq 0.01$) in the 10 mg/kg/day dosage group. All surviving pups ultimately attained the ability to surface right.

The ability to surface right was unaffected by the 1 mg/kg/day dosage of the test article.

I.2. Pinna Unfolding

Pinna unfolding was delayed in the 1, 5, 10 and 15 mg/kg/day dosage groups. The effect was transient (evident only on one day) in the 1 mg/kg/day dosage group, and considered of no toxicological importance [the percentage of pups per litter with pinna unfolding was significantly reduced ($p \leq 0.05$) on DL 3 only]. The percentage of pups with an unfolded pinna was significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) on DLs 3 and 4 in the 5 mg/kg/day dosage group, on DLs 3, 4, 5 and 6 in the 10 mg/kg/day dosage group and on DLs 3 and 4 in the 15 mg/kg/day dosage group. No pups in the 15 mg/kg/day dosage group had an unfolded pinna on DLs 2, 3 or 4; all pups in this group were dead after DL 4. The average day that at least 50% of the pups in a dosage group had an unfolded pinna was significantly increased ($p \leq 0.01$) in the 5 and 10 mg/kg/day dosage groups. All surviving pups ultimately had unfolded pinnae.

I.3. Eye Opening

Eye opening was delayed in the 5 and 10 mg/kg/day dosage groups (no 15 mg/kg/day dosage group pups were evaluated for this parameter). The percentage of pups with at least one open eye was significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) in the 5 and 10 mg/kg/day dosage groups on DLs 14, 15 and 16. The day that at least 50% of the pups had at least one open eye was increased in the 5 and 10 mg/kg/day dosage groups; the value was significant ($p \leq 0.01$) in the 5 mg/kg/day dosage group. All pups had open eyelids by DL 21, when pupil constriction was tested.

The time to eye opening was unaffected by the 1 mg/kg/day dosage of the test article.

I.4. Acoustic Startle

The time of development of the acoustic startle reflex was delayed in the 1, 5 and 10 mg/kg/day dosage groups; no 15 mg/kg/day dosage group pups survived to be tested for this reflex. The effect was transient (evident only on two days) in the 1 mg/kg/day dosage group, and considered of no toxicological importance [the percentage of pups per litter with this reflex was significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) on DLs 14 and 15]. The percentage of pups in the 10 and 15 mg/kg/day dosage groups with this reflex was significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) on DLs 13, 14 and 15. The day that at least 50% of the pups had the acoustic startle reflex was significantly increased ($p \leq 0.01$) in the 5 and 10 mg/kg/day dosage groups.

I.5. Air Righting

The ability to air right was delayed in the 5 and 10 mg/kg/day dosage groups; no 15 mg/kg/day dosage group pups survived to be tested for this reflex. The percentage of pups that air righted was significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) in the 5 mg/kg/day dosage group on DLs 14 through 18 and in the 10 mg/kg/day dosage group on DLs 14 through 20. The day that at least 50% of the pups could air right was significantly increased ($p \leq 0.05$ or $p \leq 0.01$) in the 5 and 10 mg/kg/day dosage groups.

The ability to air right was unaffected by the 1 mg/kg/day dosage of the test article.

I.6. Pupil Constriction

All live pups in the 0 (Vehicle), 1, 5 and 10 mg/kg/day dosage groups had the pupil constriction response present on DL 21.

V. RESULTS– F1 GENERATION MALE AND FEMALE RATS

A. F1 Generation Male Rats

A.1. Mortality and Clinical Observations (Summary - Table D1; Individual Data - Table D13)

All F1 generation male rats survived until scheduled sacrifice.

All adverse clinical observations were considered unrelated to the test article because 1) the incidences were not dosage-dependent; and/or 2) the observation occurred in only one or two rats. These observations included dental problems (missing, broken and/or misaligned incisors), chromodacryorrhea, chromorhinorrhea and swollen and purple ears. Observations of emaciation, dehydration, brown perinasal discharge, labored breathing, brown or red perioral substance, excess salivation, gasping and rales occurred in one rat (12123) in the 1 mg/kg/day dosage group on days 70 to 85 postweaning and were considered related to a possible intubation injury on day 70 postweaning. This rat lost 101 g from days 71 to 78 postweaning but regained 88 g by day 85 postweaning.

A.2. Body Weights and Body Weight Changes (Figure 3; Summaries - Tables D2 and D3; Individual Data - Table D14)

The 1 and 5 mg/kg/day dosage groups weighed less than the control group on day 1 postweaning [the reduction was significant ($p \leq 0.01$) in the 5 mg/kg/day dosage group] and body weight gains were reduced in these groups throughout the postweaning period. Body weight gains were significantly reduced ($p \leq 0.01$ and $p \leq 0.05$) in the 1 and 5 mg/kg/day dosage groups on days 22 to 29 and 43 to 50 postweaning, and additionally in the 5 mg/kg/day dosage group on days 1 to 8, 8 to 15 and 15 to 22 postweaning. Reflecting this pattern of weight gain, weight gains in the 1 and 5 mg/kg/day dosage groups were significantly reduced ($p \leq 0.05$ and $p \leq 0.01$) for the prehabitation period (day 1 postweaning to prehabitation) and for day 1 postweaning to termination (significant at 5 mg/kg/day only). Absolute body weights were significantly reduced ($p \leq 0.05$) in the 1 mg/kg/day dosage group on days 36, 50 and 57 postweaning and significantly reduced ($p \leq 0.01$) in the 5 mg/kg/day dosage group throughout the postweaning dosage period.

A.3. Absolute (g/day) and Relative (g/kg/day) Feed Consumption Values (Summaries - Tables D4 and D5; Individual Data - Table D15)

Absolute (g/day) and relative (g/kg/day) feed consumption values in the F1 generation male rats were significantly reduced ($p \leq 0.01$) in the 5 mg/kg/day dosage group on days 1 to 8 and 8 to 15 postweaning. Relative feed

consumption values were also significantly reduced ($p \leq 0.01$) on days 15 to 22, 22 to 29, 29 to 36, 36 to 43 and 1 to 57 in the 5 mg/kg/day dosage group.

Feed consumption values were unaffected by the 1 mg/kg/day dosage of the test article.

A.4. Sexual Maturation (Summary - Table D6; Individual Data - Table D16)

The average day of preputial separation was unaffected by the 1 mg/kg/day dosage of the test article. The average day of preputial separation was significantly delayed ($p \leq 0.01$) for the F1 generation male rats in the 5 mg/kg/day dosage group, as compared to the control group value, but the increase was approximately one day and not considered toxicologically important.

A.5. Passive Avoidance Performance (Summary - Table D7; Individual Data - Table D17)

There were no biologically important differences in the values for learning, short-term retention, long-term retention or response inhibition in the F1 generation male rats, as evaluated by performance in a passive avoidance paradigm. No statistically significant differences occurred in the number of trials to criterion, trial latencies or numbers of rats that failed to learn.

A.6. Watermaze Performance (Summary - Table D8; Individual Data - Table D18)

No biologically important dosage-dependent differences occurred in watermaze performance of the F1 generation male rats regarding learning, short-term retention, long-term retention or response inhibition. No statistically significant differences occurred in the number of trials to criterion, trial latencies or numbers of rats that failed to learn.

A.7. Mating and Fertility (Summary - Table D9; Individual Data - Table D19)

Dosages of the test article as high as 5 mg/kg/day did not affect any mating and fertility parameters evaluated. Values for the fertility and pregnancy indices (number of pregnancies per number of rats that mated and rats in cohabitation, respectively), the number of days to inseminate, the number of rats that mated and the number of rats with confirmed mating dates during the first week of cohabitation were comparable among the three dosage groups. Of the male rats assigned to cohabitation, 80.0%, 88.0% and 92.0% impregnated the cohort female rat.

A.8. Necropsy Observations (Summary - Table D10; Individual Data - Table D20)

All necropsy observations in the F1 generation male rats were considered unrelated to the test article because: 1) the incidences were not dosage-dependent; and/or 2) the observation occurred in only one rat in a group.

These observations included one control rat (12080) with small and flaccid left testis and epididymis and one 1 mg/kg/day dosage group male rat (12123) with a small left epididymis. Control group rat 12080 sired a litter. Rat 12123 in the 1 mg/kg/day dosage group did not mate, however this rat had clinical observations that suggested an intubation injury occurred two days before cohabitation, as previously described.

A.9. Terminal Body Weights and Organ Weights and Ratios (%) of Organ Weight to Terminal Body Weight (Summaries - Tables D11 and D12; Individual Data - Table D21)

Terminal body weights were significantly reduced ($p \leq 0.01$) in the 5 mg/kg/day dosage group, as compared to the control group value.

The ratios of the left and right testis weights to the terminal body weight in the 5 mg/kg/day dosage group were significantly increased ($p \leq 0.01$), as compared to the control group values. This significant increase in the relative testis weights reflects the significant reduction in terminal body weights for this dosage group.

The absolute weights of the epididymides, testes, seminal vesicles (with and without fluid) and prostate, and the ratios of the epididymides, seminal vesicles (with and without fluid) and prostate weights to the terminal body weight of the F1 generation male rats were comparable among the three dosage groups.

The mean absolute weight of the left testis in the 1 mg/kg/day dosage group was significantly reduced ($p \leq 0.01$), as compared to the control group value. This significant reduction was not considered an effect of the test article because: 1) the value was not dosage-dependent; and 2) a similar reduction did not occur for the weight of the right testis.

B. F1 Generation Female Rats

B.1. Mortality and Clinical Observations (Summary - Table E1; Individual Data - Table E23)

All F1 generation female rats survived until scheduled sacrifice.

All clinical observations during the prehabitation, gestation and lactation periods were considered unrelated to the test article because: 1) the incidences were not dosage-dependent; and/or 2) the observation occurred in only one to two rats. These clinical observations included portion of tail missing, dental problems (misaligned, missing and/or broken incisors), chromodacryorrhea, swollen and purple ears, localized alopecia on the back, head and/or limbs, ptosis, urine-stained abdominal fur and scab or lesion on the head.

In contrast to the slightly increased incidences of localized alopecia in the EtFOSE treated Fo generation female rats, the total incidence of localized alopecia was significantly reduced ($p \leq 0.01$) during the gestation period in the 1 and 5 mg/kg/day dosage groups, as compared to the control group. This significant reduction was not considered treatment-related because: 1) it was not dosage-dependent; and 2) the incidence of an adverse clinical observation is expected to increase, not decrease, in a toxicology study.

B.2. Maternal Body Weights and Body Weight Changes (Figure 4: Summaries - Tables E2 through E7; Individual Data - Tables E24 through E26)

B.2.a. Prehabitation

The 1 and 5 mg/kg/day dosage groups weighed less than the control group on day 1 postweaning [the reduction was significant ($p \leq 0.01$) in the 5 mg/kg/day dosage group] and body weight gains were generally reduced in these groups throughout the prehabitation period. Body weight gains were reduced in the 1 mg/kg/day dosage group to 86% to 95% of the control group values on days 22 to 29, 36 to 43 and 43 to 50 postweaning and body weight gains were significantly reduced ($p \leq 0.01$) in the 5 mg/kg/day dosage group on days 1 to 8 and 8 to 15 postweaning. Reflecting these effects of the test article, body weight gains were significantly reduced ($p \leq 0.05$ and $p \leq 0.01$) in both test article-treated groups for the entire prehabitation period [day 1 postweaning to prehabitation and days 1 to 57 postweaning (significant at 5 mg/kg/day only)].

Absolute body weights were slightly reduced (97% to 98% of the control group value) in the 1 mg/kg/day dosage group throughout the prehabitation period and were significantly reduced ($p \leq 0.05$) on the first day of the cohabitation period. Absolute body weights in the 5 mg/kg/day dosage group were significantly reduced ($p \leq 0.01$) throughout the prehabitation dosage period.

B.2.b. Gestation

Maternal body weight gains during the gestation period were significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) in the 1 and 5 mg/kg/day dosage groups on days 0 to 7 of gestation (DGs 0 to 7), as compared to the control group values. Body

weight gains in the 5 mg/kg/day dosage group were significantly increased ($p \leq 0.01$) on DGs 14 to 17.

Body weights were significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) on DGs 0 through 18 in the 1 and 5 mg/kg/day dosage groups and in the 5 mg/kg/day dosage group only on DGs 19 and 20.

B.2.c. Lactation

Maternal body weights remained significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) in the 5 mg/kg/day dosage group on DLs 1, 4, 7, 10, 14 and 21 and in the 1 mg/kg/day dosage group on DLs 1 and 7.

Maternal body weight gains during the lactation period were significantly reduced ($p \leq 0.05$) in the 1 and 5 mg/kg/day dosage groups on DLs 1 to 21.

B.3. Maternal Absolute (g/day) and Relative (g/kg/day) Feed Consumption Values (Summaries - Tables E8 through E13; Individual Data - Tables E27 through E29)

B.3.a. Precohabitation

The 1 mg/kg/day dosage of the test article was associated with a significant reduction ($p \leq 0.05$) in absolute (g/day) feed consumption values on days 43 to 50 and 50 to 57 of the precohabitation period. Absolute feed consumption values for the 5 mg/kg/day dosage group were significantly reduced ($p \leq 0.01$) on days 1 to 8, 36 to 43, 43 to 50 and 50 to 57 postweaning, as compared to the control group values. Reflecting these effects of the test article, feed consumption values were significantly reduced ($p \leq 0.05$ and $p \leq 0.01$, respectively) for the entire precohabitation period (days 1 to 57 postweaning) in both groups administered the test article.

Relative (g/kg/day) feed consumption values in the 5 mg/kg/day dosage group were significantly increased ($p \leq 0.05$ or $p \leq 0.01$) on days 8 to 15, 15 to 22 and 22 to 29 postweaning, compared to the control group.

B.3.b. Gestation

Absolute feed consumption values in the 1 and 5 mg/kg/day dosage groups were significantly reduced ($p \leq 0.05$) during the first week of the gestation period (DGs 0 to 7), as compared to the control group. Absolute feed consumption values for the 5 mg/kg/day dosage group were also significantly reduced ($p \leq 0.01$) on DGs 7 to 10, as compared to the control group.

The relative feed consumption value on DGs 14 to 17 was significantly reduced ($p \leq 0.05$) in the 5 mg/kg/day dosage group, as compared to the control group value.

B.3.c. Lactation

The absolute maternal feed consumption value was significantly reduced ($p \leq 0.05$ to $p \leq 0.01$) for the entire lactation period (DLs 1 to 14) and at all tabulated intervals during the lactation period in the 5 mg/kg/day dosage group.

The relative feed consumption value was significantly reduced ($p \leq 0.01$) on DLs 4 to 7 and 7 to 10 in the 5 mg/kg/day dosage group, as compared to the control group values.

Absolute and relative feed consumption values during the lactation period were unaffected by the 1 mg/kg/day dosage of the test article.

B.4. Sexual Maturation (Summary - Table E14; Individual Data - Table E30)

The average day of vaginal patency was unaffected by the 1 and 5 mg/kg/day dosages of the test article. The average day of vaginal patency was significantly delayed ($p \leq 0.01$) for the F1 generation female rats in the 1 mg/kg/day dosage group, as compared to the control group value, but the delay was not dosage-dependent and not considered toxicologically important.

B.5. Passive Avoidance Performance (Summary - Table E15; Individual Data - Table E31)

There were no biologically important differences in the values for learning, long-term retention or response inhibition in the F1 generation female rats, as evaluated by performance in a passive avoidance paradigm. No statistically significant differences occurred in the number of trials to criterion or numbers of rats that failed to learn.

The latency of the second trial in the first testing session was significantly increased ($p \leq 0.05$) in the 5 mg/kg/day dosage group, as compared to the control group. This observation was not considered an effect of the test article because a decrease in short-term memory, rather than an increase, would be expected as an indication of toxicity.

B.6. Watermaze Performance (Summary - Table E16; Individual Data - Table E32)

No biologically important dosage-dependent differences occurred in watermaze performance of the F1 generation female rats regarding learning, short-term retention, long-term retention or response inhibition. No statistically significant differences occurred in the number of trials to criterion, trial latencies or numbers of rats that failed to learn.

B.7. Mating and Fertility (Summary - Table E17; Individual Data - Table E33)

Dosages of the test article as high as 5 mg/kg/day did not affect any mating and fertility parameters evaluated. Values for the number of days in cohabitation, the number of rats that mated, the fertility and pregnancy indices (number of pregnancies per number of rats that mated and rats in cohabitation, respectively), and the number of rats with confirmed mating dates during the first and second week of cohabitation were comparable among the three dosage groups.

B.8. Necropsy Observations (Summary - Table E18; Individual Data - Table E34)

The only necropsy observation was moderate dilation of the pelvis of the right kidney in one 1 mg/kg/day dosage group female rat (12239). This observation was considered unrelated to the test article because it was a single occurrence of an observation that commonly occurs in this strain.

B.9. Natural Delivery and Litter Observations (Summaries - Tables E19 and E20; Individual Data - Tables E35 through E38)

Pregnancy occurred in 23 (92.0%), 25 (100.0%) and 24 (96.0%) of the 25 female rats in each dosage group assigned to cohabitation in the 0 (Vehicle), 1 and 5 mg/kg/day dosage groups, respectively. All pregnant dams delivered litters. The gestation index (the percentage of pregnant rats with live offspring) was comparable across the three dosage groups.

As occurred in the previous generation, there was a tendency for reduced pup viability in the 5 mg/kg/day dosage group. The number of dams with stillborn pups was significantly increased ($p \leq 0.01$) in this dosage group. The number of pups found dead or presumed cannibalized was significantly increased ($p \leq 0.01$) on DLs 1, 2 to 4 and 8 to 14 and one 5 mg/kg/day dosage group dam (12255) had all pups die by DL 4. As a result, the viability and lactation indices and the average number of surviving pups per litter on days 4 (preculling), 14 and 21 postpartum were significantly reduced ($p \leq 0.05$) in this dosage group.

As also occurred in the previous generation, pup body weights were significantly reduced ($p \leq 0.01$) in the 5 mg/kg/day dosage group on days 1, 4 (pre and postculling), 7, 14 and 21, as compared to the control group values. There was not effect on pup viability or pup body weights in the 1 mg/kg/day dosage group.

Administration of the test article at dosages as high as 5 mg/kg/day did not adversely affect any other parameter evaluated at natural delivery or during the 21-day lactation period (averages for implantations and live litter sizes and pup sex ratios). The duration of gestation was significantly reduced ($p \leq 0.05$) in the 5 mg/kg/day dosage group. This slight reduction was considered unrelated to the test article because the magnitude of the change was small [0.3 day, or 99% of the 0 (Vehicle) and 1 mg/kg/day dosage group values].

B.10. Pup Clinical and Necropsy Observations (Summaries - Tables E21 and E22; Individual Data - Tables E39 and E40)

All clinical and necropsy observations were unrelated to dosages of the test article as high as 5 mg/kg/day because: 1) the incidences were not dosage-dependent; and 2) the observation occurred in only one or two litters. These clinical observations included one pup in the 1 mg/kg/day dosage group and three pups in the 5 mg/kg/day dosage group that were not nursing; nine littermates in the 5 mg/kg/day dosage group that were cold to the touch; one control group pup with exophthalmos and a traumatized cornea; and one control group pup with a portion of the tail black.

No milk in the stomach occurred in 2 (100%), 2 (50.0%) and 13 (52.0%) of the pups that were found dead in the three respective dosage groups. The only necropsy observation at scheduled sacrifice was an absent left eye in one control group pup.

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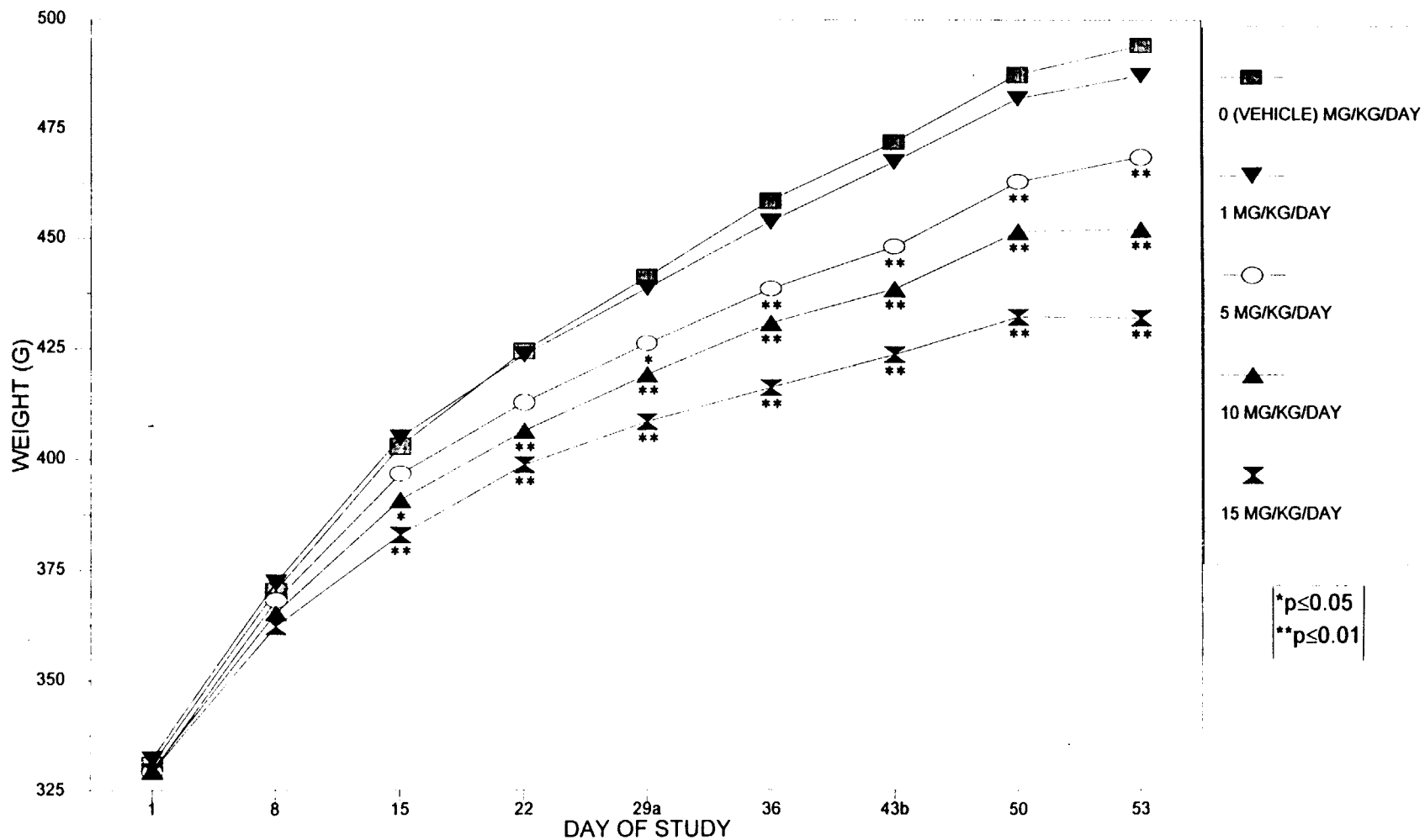
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APPENDIX A
REPORT FIGURES

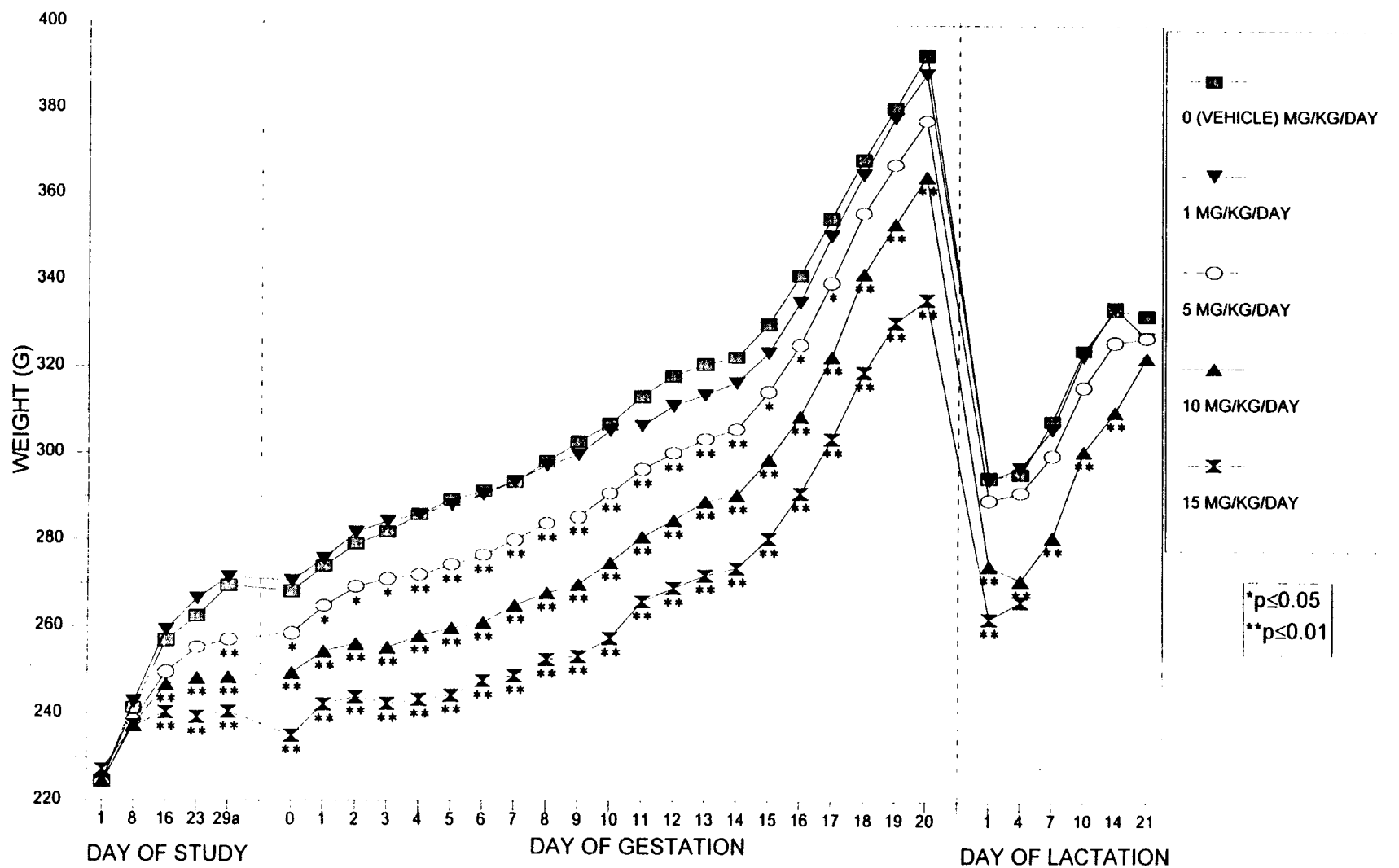
BODY WEIGHTS Fo GENERATION MALE RATS

Figure 1



a. Last value recorded before cohabitation.
b. First value recorded after cohabitation.

BODY WEIGHTS
Fo GENERATION FEMALE RATS
Figure 2

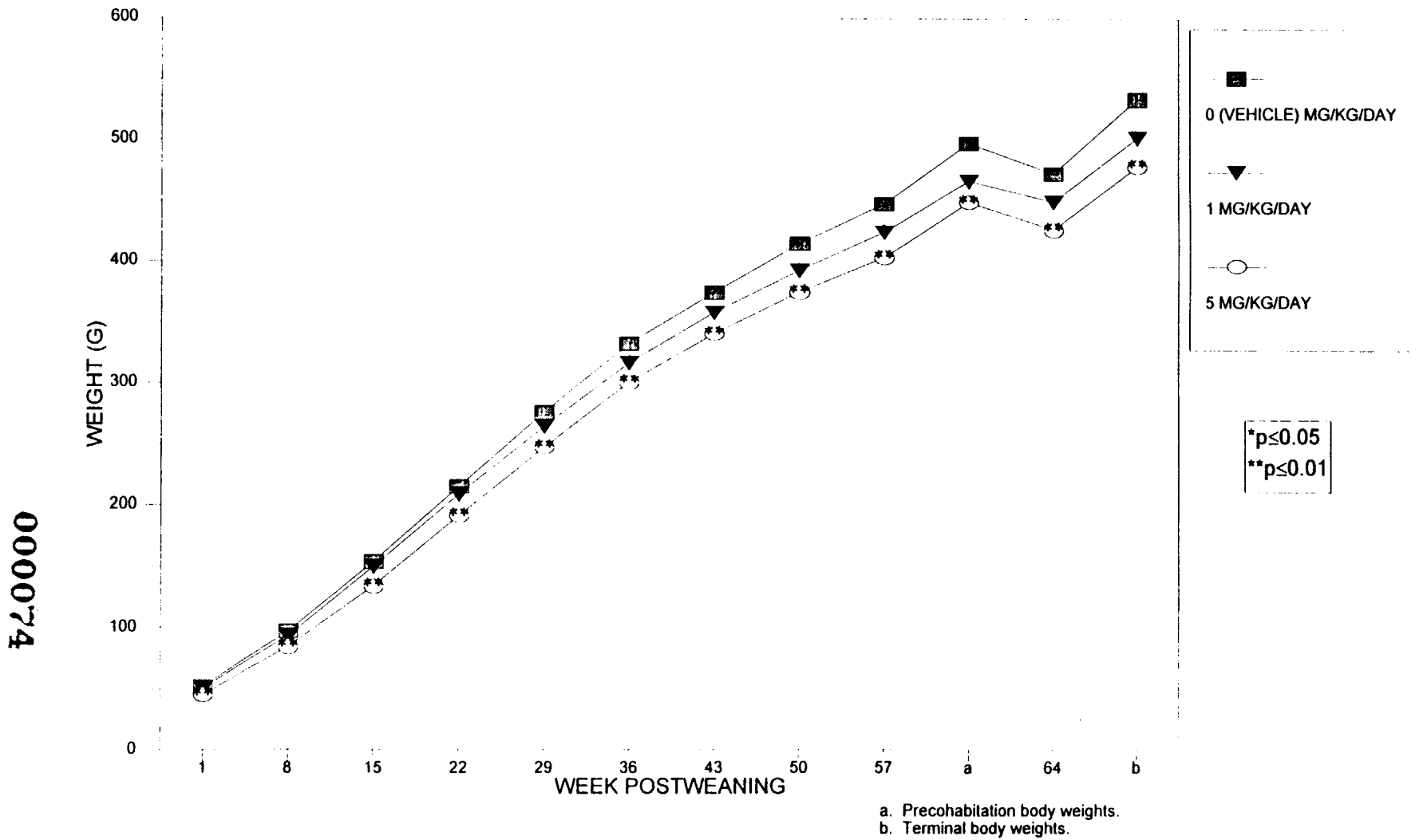


a. Last value recorded before cohabitation.

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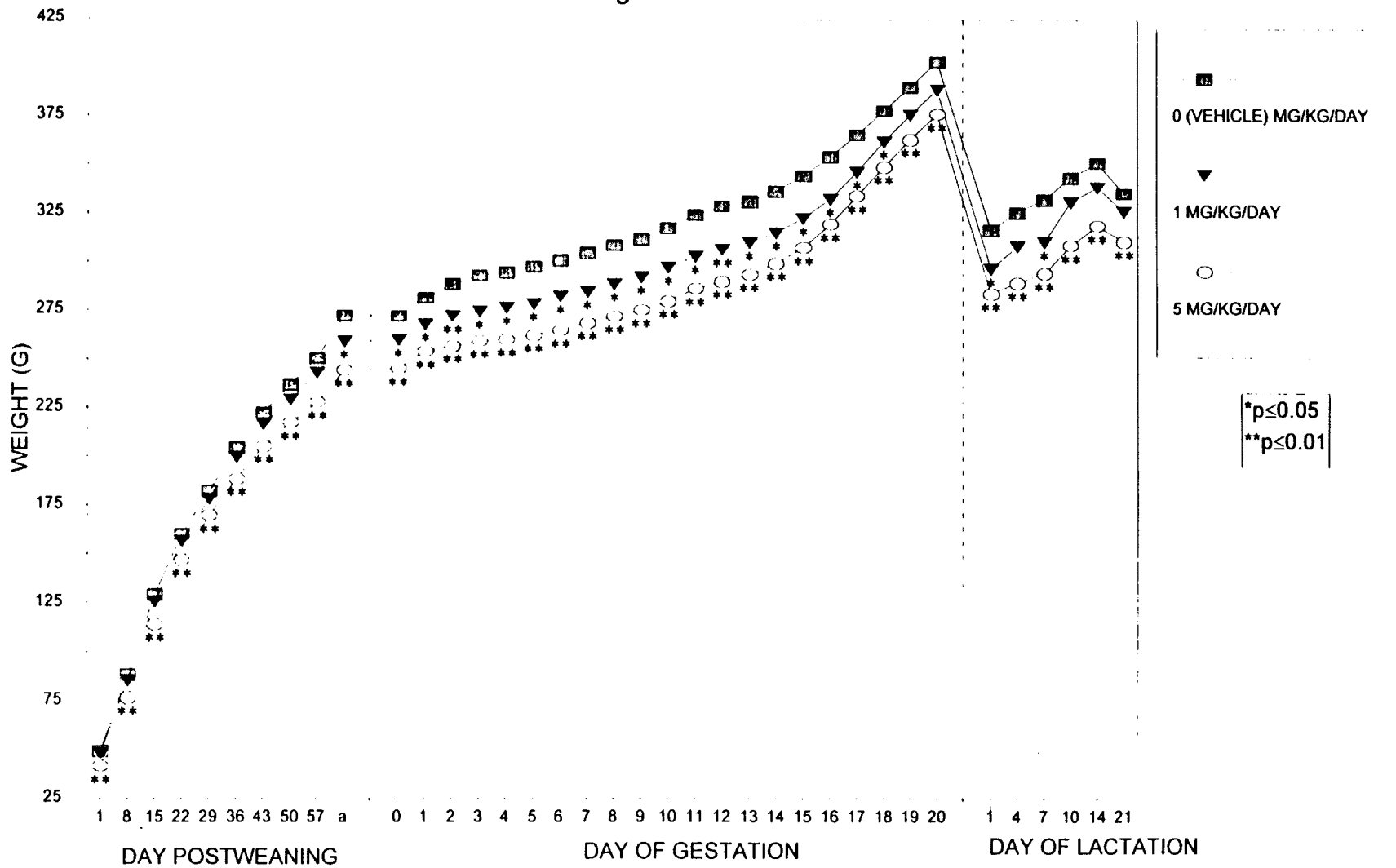
BODY WEIGHTS F1 GENERATION MALE RATS

Figure 3



BODY WEIGHTS F1 GENERATION FEMALE RATS

Figure 4



a. Precohabitation body weight.

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APPENDIX B
REPORT TABLES - F₀ GENERATION MALE RATS

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE B1 (PAGE 1): CLINICAL OBSERVATIONS - SUMMARY - P₀ GENERATION MALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)	I 0 (VEHICLE)		II 1		III 5		IV 10		V 15	
MAXIMUM POSSIBLE INCIDENCE	1855/	35	1855/	35	1855/	35	1855/	35	1855/	35
MORTALITY	0		0		0		0		0	
IMPAIRED RIGHTING REFLEX	0/	0	0/	0	0/	0	0/	0	7/	6**
LOCALIZED ALOPECIA: LIMBS	95/	3	0/	0	39/	1	42/	1	9/	1
INCISORS: TOTAL	74/	3	21/	1	21/	1	77/	2	7/	1
MISALIGNED	74/	3	21/	1	21/	1	77/	2	4/	1
MISSING/BROKEN	14/	1	11/	1	0/	0	42/	2	7/	1
CHROMODACRYORRHEA	33/	3	0/	0	0/	0	24/	2	0/	0
RED PERIPENIAL SUBSTANCE	0/	0	0/	0	1/	1	0/	0	0/	0
CHROMORHINORRHEA	0/	0	1/	1	0/	0	0/	0	0/	0

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

MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP.

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

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

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE B2 (PAGE 1): BODY WEIGHTS - SUMMARY - F0 GENERATION MALE RATS

DOSAGE GROUP		I	II	III	IV	V
DOSAGE (MG/KG/DAY)		0 (VEHICLE)	1	5	10	15
RATS TESTED	N	35	35	35	35	35
BODY WEIGHT (G)						
DAY 1	MEAN±S.D	330.8 ± 17.3	332.1 ± 18.6	329.1 ± 19.5	329.5 ± 16.0	329.2 ± 18.2
DAY 8	MEAN±S.D	370.2 ± 19.8	372.0 ± 18.4	367.9 ± 22.0	365.1 ± 14.6	362.0 ± 18.0
DAY 15	MEAN±S.D	402.8 ± 23.5	404.7 ± 20.4	396.5 ± 27.3	390.7 ± 18.3*	382.8 ± 19.3**
DAY 22	MEAN±S.D	424.4 ± 28.5	423.6 ± 23.4	412.8 ± 30.3	406.3 ± 22.3**	398.7 ± 21.3**
DAY 29a	MEAN±S.D	441.1 ± 31.0	438.6 ± 27.0	426.0 ± 32.5*	418.9 ± 24.9**	408.2 ± 22.9**
DAY 36	MEAN±S.D	458.5 ± 35.0	453.6 ± 27.8	438.4 ± 31.6**	430.6 ± 26.9**	415.9 ± 26.1**
DAY 43b	MEAN±S.D	471.9 ± 36.4	467.3 ± 29.5	447.9 ± 36.5**	438.3 ± 28.3**	423.4 ± 28.1**
DAY 50	MEAN±S.D	487.5 ± 39.8	481.9 ± 31.8	462.8 ± 37.5**	451.5 ± 29.3**	432.0 ± 30.5**
DAY 53	MEAN±S.D	494.2 ± 41.4	487.2 ± 34.1	468.4 ± 37.5**	452.0 ± 31.4**	431.8 ± 29.6**

DAY = DAY OF STUDY

a. Last value recorded before cohabitation.

b. First value recorded after cohabitation.

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

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

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE B3 (PAGE 1): BODY WEIGHT CHANGES - SUMMARY - F₀ GENERATION MALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
RATS TESTED	N	35	35	35	35	35
BODY WEIGHT CHANGE (G)						
DAYS 1 - 8	MEAN±S.D.	+39.5 ± 10.0	+40.0 ± 8.6	+38.8 ± 9.4	+35.6 ± 9.7	+32.8 ± 11.1**
DAYS 8 - 15	MEAN±S.D.	+32.5 ± 9.5	+32.7 ± 9.4	+28.5 ± 10.1	+25.6 ± 12.1**	+20.7 ± 8.2**
DAYS 15 - 22	MEAN±S.D.	+21.7 ± 8.1	+18.9 ± 7.5	+16.3 ± 8.5*	+15.6 ± 8.3**	+15.9 ± 5.1**
DAYS 22 - 29a	MEAN±S.D.	+16.7 ± 7.0	+14.9 ± 7.1	+13.2 ± 5.1*	+12.6 ± 6.2*	+9.5 ± 5.9**
DAYS 29a- 36	MEAN±S.D.	+17.4 ± 7.9	+15.0 ± 6.2	+12.3 ± 7.0**	+11.7 ± 7.0**	+7.7 ± 6.8**
DAYS 36 - 43b	MEAN±S.D.	+13.4 ± 9.0	+13.7 ± 5.0	+9.6 ± 9.5	+7.7 ± 6.8**	+7.5 ± 5.4**
DAYS 43b- 50	MEAN±S.D.	+15.6 ± 6.3	+14.6 ± 6.4	+14.9 ± 7.6	+13.2 ± 6.4	+8.6 ± 6.2**
DAYS 50 - 53	MEAN±S.D.	+6.7 ± 5.8	+5.3 ± 4.3	+5.5 ± 4.4	+0.5 ± 4.2**	-0.2 ± 5.1**
DAYS 1 - 53	MEAN±S.D.	+163.4 ± 39.5	+155.1 ± 35.0	+139.2 ± 30.8**	+122.5 ± 34.4**	+102.5 ± 30.2**

DAYS = DAYS OF STUDY

a. Last value recorded before cohabitation.

b. First value recorded after cohabitation.

* Significantly different from the vehicle control group value (p≤0.05).

** Significantly different from the vehicle control group value (p≤0.01).

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE B4 (PAGE 1): ABSOLUTE FEED CONSUMPTION VALUES (G/DAY) - SUMMARY - F₀ GENERATION MALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
RATS TESTED	N	35	35	35	35	35
FEED CONSUMPTION (G/DAY)						
DAYS 1 - 8	MEAN±S.D.	26.9 ± 2.8 [34]a	27.1 ± 2.2 [34]a	27.2 ± 2.4	26.4 ± 1.9	26.2 ± 2.3
DAYS 8 - 15	MEAN±S.D.	27.2 ± 2.6 [34]a	27.2 ± 2.2	26.9 ± 2.6	25.8 ± 2.1*	25.6 ± 2.3*
DAYS 15 - 22	MEAN±S.D.	27.2 ± 2.7 [33]a	27.1 ± 2.6	26.6 ± 2.5	25.9 ± 2.3*	24.5 ± 2.1**
DAYS 22 - 29b	MEAN±S.D.	27.8 ± 2.8	27.5 ± 2.4	27.0 ± 2.5	25.7 ± 2.2** [34]a	24.7 ± 2.1**
DAYS 43c- 50	MEAN±S.D.	27.2 ± 2.9 [33]a	27.4 ± 2.4 [34]a	26.4 ± 2.1 [33]a	24.7 ± 1.8**	23.2 ± 2.4**
DAYS 50 - 53	MEAN±S.D.	28.1 ± 3.1 [34]a	28.1 ± 3.2 [34]a	27.2 ± 2.3 [34]a	25.4 ± 2.2**	23.7 ± 2.4**
DAYS 1 - 53	MEAN±S.D.	27.3 ± 2.4 [34]a	27.4 ± 2.2 [34]a	26.8 ± 2.1 [34]a	25.7 ± 1.8**	24.8 ± 2.0**

DAYS = DAYS OF STUDY

[] = NUMBER OF VALUES AVERAGED

a. Excludes values that were associated with spillage or wet feed.

b. Last value recorded before cohabitation.

c. First value recorded after cohabitation.

* Significantly different from the vehicle control group value (p≤0.05).

** Significantly different from the vehicle control group value (p≤0.01).

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE B5 (PAGE 1): RELATIVE FEED CONSUMPTION VALUES (G/KG/DAY) - SUMMARY - F0 GENERATION MALE RATS

DOSAGE GROUP		I	II	III	IV	V
DOSAGE (MG/KG/DAY)		0 (VEHICLE)	1	5	10	15
RATS TESTED	N	35	35	35	35	35
FEED CONSUMPTION (G/KG/DAY)						
DAYS 1 - 8	MEAN±S.D.	76.8 ± 7.5 [34]a	77.2 ± 5.8 [34]a	78.2 ± 5.9	76.0 ± 5.5	75.8 ± 7.0
DAYS 8 - 15	MEAN±S.D.	70.4 ± 5.0 [34]a	70.0 ± 4.4	70.4 ± 5.2	68.4 ± 4.6	68.8 ± 5.3
DAYS 15 - 22	MEAN±S.D.	65.8 ± 4.8 [33]a	65.3 ± 4.4	65.7 ± 4.4	64.9 ± 4.1	62.7 ± 4.4**
DAYS 22 - 29b	MEAN±S.D.	64.2 ± 4.0	63.8 ± 3.7	64.3 ± 4.8	62.5 ± 3.3 [34]a	61.2 ± 4.3**
DAYS 43c- 50	MEAN±S.D.	56.6 ± 3.2 [33]a	57.6 ± 3.0 [34]a	57.9 ± 4.4 [33]a	55.5 ± 3.3	54.2 ± 4.5*
DAYS 50 - 53	MEAN±S.D.	57.3 ± 3.7 [34]a	57.9 ± 4.0 [34]a	58.4 ± 3.0 [34]a	56.3 ± 3.4	55.0 ± 4.4*
DAYS 1 - 53	MEAN±S.D.	63.8 ± 3.2 [34]a	64.1 ± 3.1 [34]a	64.8 ± 3.5 [34]a	63.2 ± 2.7	62.5 ± 3.9

DAYS = DAYS OF STUDY

[] = NUMBER OF VALUES AVERAGED

a. Excludes values that were associated with spillage or wet feed.

b. Last value recorded before cohabitation.

c. First value recorded after cohabitation.

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

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

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE B6 (PAGE 1): MATING AND FERTILITY - SUMMARY - P₀ GENERATION MALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
RATS IN COHABITATION	N	35	35	35	35	35
INCLUDED IN ANALYSES	N	35	35	34b	35	35
DAYS IN COHABITATION a	MEAN±S.D	1.9 ± 1.1	2.1 ± 1.4	2.5 ± 1.5 [34]	2.1 ± 1.5	2.1 ± 1.2
RATS THAT MATED c	N(%)	35(100.0)	34(97.1)	33(97.0)	33(94.3)	34(97.1)
FERTILITY INDEX d,e	N/N (%)	35/35 (100.0)	33/34 (97.0)	31/33 (93.9)	30/33 (90.9)	33/34 (97.0)
RATS WITH CONFIRMED MATING DATES f	N	35	34	33	33	34
RATS MATING g DAYS 1-7	N(%)	35(100.0)	34(100.0)	33(100.0)	33(100.0)	34(100.0)
RATS PREGNANT/RATS IN COHABITATION f	N/N (%)	35/35 (100.0)	33/35 (94.3)	31/34 (91.2)	30/35 (85.7)	33/35 (94.3)

- a. Restricted to rats with a confirmed mating date on days 1 to 7 of cohabitation and rats that did not mate.
b. Excludes values for rat 9985, which did not have a right testis or right epididymis.
c. Includes only one mating for each male rat.
d. Number of pregnancies/number of rats that mated.
e. Includes only one pregnancy for each rat that impregnated more than one female rat.
f. Includes only one confirmed mating for each male rat.
g. Restricted to rats with a confirmed mating date on days 1 to 7 of cohabitation.

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-ElFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE B7 (PAGE 1): NECROPSY OBSERVATIONS - SUMMARY - Fo GENERATION MALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
RATS EXAMINED a	N	35	35	35	35	35
MORTALITY	N	0	0	0	0	0
APPEARED NORMAL	N	34	35	34	35	31
SEMINAL VESICLES: SMALL	N	0	0	0	0	3**
PROSTATE: SMALL	N	0	0	0	0	1
TESTES: RIGHT, ABSENT	N	0	0	1	0	0
EPIDIDYMIDES: RIGHT, ABSENT	N	0	0	1	0	0
HINDLIMB: LEFT, DISTAL PORTION OF DIGIT MISSING	N	1	0	0	0	0

a. Refer to the individual clinical observations table (Table B10) for external observations confirmed at necropsy.

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

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE B8 (PAGE 1): TERMINAL BODY WEIGHTS AND ORGAN WEIGHTS - SUMMARY - F0 GENERATION MALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
RATS TESTED		N	35	35	35	35
TERMINAL BODY WEIGHT	MEAN±S.D.	494.2 ± 41.4	487.2 ± 34.1	468.4 ± 37.5**	452.0 ± 31.4**	431.8 ± 29.6**
EPIDIDYMIS LEFT	MEAN±S.D.	0.66 ± 0.09	0.67 ± 0.07	0.64 ± 0.08	0.63 ± 0.07	0.61 ± 0.07*
TESTIS LEFT	MEAN±S.D.	1.72 ± 0.15	1.73 ± 0.12	1.74 ± 0.18	1.71 ± 0.12	1.74 ± 0.14
SEMINAL VESICLES WITH FLUID	MEAN±S.D.	1.80 ± 0.30	1.83 ± 0.36 [32]a	1.77 ± 0.44	1.65 ± 0.32	1.50 ± 0.39** [33]a
SEMINAL VESICLES WITHOUT FLUID	MEAN±S.D.	0.91 ± 0.19	0.96 ± 0.22	0.96 ± 0.29	0.88 ± 0.19	0.86 ± 0.24
EPIDIDYMIS RIGHT	MEAN±S.D.	0.67 ± 0.10	0.68 ± 0.06	0.65 ± 0.08 [34]b	0.65 ± 0.07	0.63 ± 0.07
TESTIS RIGHT	MEAN±S.D.	1.73 ± 0.17	1.72 ± 0.13	1.71 ± 0.14 [34]b	1.71 ± 0.12	1.73 ± 0.16
PROSTATE	MEAN±S.D.	1.13 ± 0.23	1.08 ± 0.24	1.02 ± 0.22	1.03 ± 0.25	0.86 ± 0.27**

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

[] = NUMBER OF VALUES AVERAGED

a. Excludes values for rats that had abnormal organs (weight affected) or organs damaged (weight affected).

b. Excludes values for rat 9985, which did not have a right testis or right epididymis.

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

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

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE B9 (PAGE 1): RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - SUMMARY - F₀ GENERATION MALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
RATS TESTED		N	35	35	35	35
TERMINAL BODY WEIGHT	MEAN±S.D.	494.2 ± 41.4	487.2 ± 34.1	468.4 ± 37.5**	452.0 ± 31.4**	431.8 ± 29.6**
EPIDIDYMIS LEFT	MEAN±S.D.	0.133 ± 0.021	0.138 ± 0.017	0.138 ± 0.019	0.140 ± 0.017	0.142 ± 0.018
TESTIS LEFT	MEAN±S.D.	0.350 ± 0.039	0.357 ± 0.032	0.373 ± 0.040*	0.381 ± 0.034**	0.404 ± 0.039**
SEMINAL VESICLES WITH FLUID	MEAN±S.D.	0.363 ± 0.055	0.376 ± 0.072 [32]a	0.378 ± 0.095	0.364 ± 0.071	0.348 ± 0.093 [33]a
SEMINAL VESICLES WITHOUT FLUID	MEAN±S.D.	0.184 ± 0.036	0.197 ± 0.045	0.205 ± 0.063	0.195 ± 0.042	0.200 ± 0.058
EPIDIDYMIS RIGHT	MEAN±S.D.	0.134 ± 0.025	0.141 ± 0.017	0.139 ± 0.016 [34]b	0.142 ± 0.016	0.146 ± 0.017
TESTIS RIGHT	MEAN±S.D.	0.352 ± 0.042	0.355 ± 0.030	0.365 ± 0.033 [34]b	0.380 ± 0.035**	0.402 ± 0.042**
PROSTATE	MEAN±S.D.	0.230 ± 0.048	0.222 ± 0.049	0.219 ± 0.048	0.228 ± 0.058	0.199 ± 0.064

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

[] = NUMBER OF VALUES AVERAGED

a. Excludes values for rats that had abnormal organs (weight affected) or organs damaged (weight affected).

b. Excludes values for rat 9985, which did not have a right testis or right epididymis.

* Significantly different from the vehicle control group value (p≤0.05).

** Significantly different from the vehicle control group value (p≤0.01).

REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) x 100.

APPENDIX C
REPORT TABLES - F₀ GENERATION FEMALE RATS

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C1 (PAGE 1): CLINICAL OBSERVATIONS - SUMMARY - P0 GENERATION FEMALE RATS

DOSAGE GROUP	I		II		III		IV		V	
DOSAGE (MG/KG/DAY)	0 (VEHICLE)		1		5		10		15	
<u>PRECOHABITATION (DAY 1 OF STUDY TO THE DAY OF COHABITATION):</u>										
MAXIMUM POSSIBLE INCIDENCE	1015/ 35		1015/ 35		1015/ 35		1015/ 35		1015/ 35	
FOUND DEAD	0		0		0		0		0	
LOCALIZED ALOPECIA: TOTAL	0/ 0		16/ 2		38/ 3		31/ 3		35/ 3	
UNDERSIDE	0/ 0		0/ 0		4/ 1		4/ 1		20/ 2	
NECK	0/ 0		0/ 0		16/ 1		0/ 0		15/ 1	
LIMBS	0/ 0		16/ 2		18/ 1		27/ 2		0/ 0	
PORTION OF TAIL MISSING	0/ 0		0/ 0		0/ 0		0/ 0		14/ 1	
DEHYDRATION	0/ 0		0/ 0		0/ 0		0/ 0		12/ 1	
PORTION OF TAIL BLACK	0/ 0		0/ 0		0/ 0		0/ 0		4/ 1	
COLD TO TOUCH	0/ 0		0/ 0		0/ 0		0/ 0		3/ 1	
CHROMODACRYORRHEA	5/ 1		3/ 1		0/ 0		0/ 0		0/ 0	
INCISORS: MISALIGNED	6/ 1		0/ 0		0/ 0		0/ 0		0/ 0	

STATISTICAL ANALYSES OF CLINICAL OBSERVATION DATA WERE RESTRICTED TO THE NUMBER OF RATS WITH OBSERVATIONS.
 MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP.
 N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RATS WITH OBSERVATION.

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-ElFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C1 (PAGE 2): CLINICAL OBSERVATIONS - SUMMARY - F₀ GENERATION FEMALE RATS

DOSAGE GROUP	I		II		III		IV		V		
DOSAGE (MG/KG/DAY)	0 (VEHICLE)		1		5		10		15		
<u>PRESUMED GESTATION: a</u>											
MAXIMUM POSSIBLE INCIDENCE	684/ 35		660/ 34		657/ 34		686/ 35		678/ 35		
FOUND DEAD	0		0		1b		0		0		
LOCALIZED ALOPECIA: TOTAL	0/ 0		32/ 2		69/ 6**		117/ 8**		75/ 4*		
UNDERSIDE	0/ 0		0/ 0		39/ 3		77/ 4		65/ 3		
BACK	0/ 0		0/ 0		0/ 0		0/ 0		10/ 1		
LIMBS	0/ 0		32/ 2		30/ 3**		40/ 5**		0/ 0		
PORTION OF TAIL MISSING	0/ 0		0/ 0		0/ 0		0/ 0		21/ 1		
DEHYDRATION	0/ 0		0/ 0		0/ 0		0/ 0		7/ 1		
CHROMODACRYORRHEA	1/ 1		0/ 0		0/ 0		4/ 1		0/ 0		
INCISORS: MISALIGNED	22/ 1		0/ 0		0/ 0		0/ 0		0/ 0		

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

MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP.

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

a. Restricted to rats with a confirmed mating date.

b. Dam 10170 was found dead on day 22 of gestation.

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

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

000088

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C1 (PAGE 3): CLINICAL OBSERVATIONS - SUMMARY - F0 GENERATION FEMALE RATS

DOSAGE GROUP	I		II		III		IV		V		
DOSAGE (MG/KG/DAY)	0 (VEHICLE)		1		5		10		15		
LACTATION:											
MAXIMUM POSSIBLE INCIDENCE	506/ 25		504/ 24		462/ 22		223/ 21		38/ 24		
FOUND DEAD	0		0		0		0		0		
LOCALIZED ALOPECIA: TOTAL	0/ 0		25/ 2		128/ 8**		26/ 4**		4/ 3		
NECK	0/ 0		0/ 0		21/ 1		0/ 0		0/ 0		
LIMBS	0/ 0		25/ 2		65/ 5**		4/ 2		0/ 0		
UNDERSIDE	0/ 0		0/ 0		21/ 1		22/ 2		2/ 2		
BACK	0/ 0		0/ 0		21/ 1		0/ 0		2/ 1		
PORTION OF TAIL MISSING	0/ 0		0/ 0		0/ 0		0/ 0		1/ 1		
INCISORS: TOTAL	21/ 1		0/ 0		0/ 0		0/ 0		0/ 0		
MISALIGNED	21/ 1		0/ 0		0/ 0		0/ 0		0/ 0		
MISSING/BROKEN	12/ 1		0/ 0		0/ 0		0/ 0		0/ 0		
CHROMODACRYORRHEA	2/ 1		0/ 0		0/ 0		0/ 0		0/ 0		
CHROMORHINORRHEA	1/ 1		0/ 0		0/ 0		0/ 0		0/ 0		

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

MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP.

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

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

000089

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C2 (PAGE 1): BODY WEIGHTS - PRECOHABITATION - SUMMARY - P₀ GENERATION FEMALE RATS

DOSAGE GROUP		I	II	III	IV	V
DOSAGE (MG/KG/DAY)		0 (VEHICLE)	1	5	10	15
RATS TESTED	N	35	35	35	35	35
BODY WEIGHT (G)						
DAY 1	MEAN±S.D	224.5 ± 9.0	224.4 ± 7.2	224.0 ± 6.6	224.4 ± 7.9	227.2 ± 7.9
DAY 8	MEAN±S.D	241.2 ± 10.5	242.7 ± 8.9	238.3 ± 9.2	237.4 ± 11.2	237.2 ± 10.4
DAY 16	MEAN±S.D	256.8 ± 13.8	259.2 ± 10.8	249.5 ± 12.5*	246.6 ± 15.8**	240.2 ± 14.3**
DAY 23	MEAN±S.D	262.3 ± 14.8	266.4 ± 13.5	255.0 ± 15.1	248.0 ± 15.5**	239.2 ± 13.7**
DAY 29a	MEAN±S.D	269.4 ± 16.0	271.4 ± 13.8	256.9 ± 15.4**	248.3 ± 15.2**	240.4 ± 13.4**

DAY = DAY OF STUDY

a. Last value recorded before cohabitation.

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

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

0000090

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C3 (PAGE 1): BODY WEIGHT CHANGES - PRECOHABITATION - SUMMARY - P₀ GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
RATS TESTED	N	35	35	35	35	35
BODY WEIGHT CHANGE (G)						
DAYS 1 - 8	MEAN±S.D.	+16.7 ± 6.6	+18.2 ± 5.7	+14.3 ± 4.7	+13.0 ± 6.3*	+10.0 ± 5.7**
DAYS 8 - 16	MEAN±S.D.	+15.6 ± 5.2	+16.5 ± 6.4	+11.2 ± 6.1*	+9.2 ± 8.3**	+2.9 ± 6.7**
DAYS 16 - 23	MEAN±S.D.	+5.4 ± 4.9	+7.2 ± 6.3	+5.5 ± 5.7	+1.4 ± 5.3**	-1.0 ± 5.0**
DAYS 23 - 29a	MEAN±S.D.	+7.1 ± 5.9	+4.9 ± 4.4	+1.8 ± 5.5**	+0.3 ± 5.2**	+1.2 ± 6.7**
DAYS 1 - 29a	MEAN±S.D.	+44.8 ± 11.8	+46.9 ± 12.6	+32.9 ± 11.7**	+23.9 ± 11.8**	+13.1 ± 9.5**

DAYS = DAYS OF STUDY

a. Last value recorded before cohabitation.

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

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

0000091

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C4 (PAGE 1): MATERNAL BODY WEIGHTS - GESTATION - SUMMARY - F0 GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
RATS TESTED	N	35	35	35	35	35
PREGNANT	N	35	34	33	32	34
INCLUDED IN ANALYSES	N	35	33a	32a	31b	34
MATERNAL BODY WEIGHT (G)						
DAY 0	MEAN±S.D.	268.2 ± 17.8	270.5 ± 13.2	258.5 ± 15.8*	249.4 ± 16.6**	235.0 ± 14.8**
DAY 1	MEAN±S.D.	273.9 ± 17.8	275.7 ± 13.4	264.7 ± 15.3*	254.2 ± 17.0**	242.1 ± 14.2**
DAY 2	MEAN±S.D.	279.1 ± 18.6	281.7 ± 12.2	269.1 ± 16.4*	256.0 ± 17.5**	243.8 ± 14.5**
DAY 3	MEAN±S.D.	281.8 ± 17.5	284.3 ± 14.6	271.0 ± 16.8*	255.1 ± 17.0**	242.3 ± 15.1**
DAY 4	MEAN±S.D.	285.9 ± 18.9	285.9 ± 15.3	271.8 ± 17.5**	257.8 ± 16.0**	243.2 ± 15.2**
DAY 5	MEAN±S.D.	289.3 ± 18.6	288.1 ± 15.7	274.2 ± 16.6**	259.6 ± 14.8**	244.2 ± 13.8**
DAY 6	MEAN±S.D.	291.2 ± 19.0	290.5 ± 14.9	276.5 ± 17.1**	261.0 ± 14.8**	247.6 ± 14.0**
DAY 7	MEAN±S.D.	293.4 ± 19.5	293.7 ± 13.5	280.1 ± 17.4**	264.9 ± 16.9**	248.8 ± 17.4**
DAY 8	MEAN±S.D.	298.2 ± 19.7	297.2 ± 14.6	283.8 ± 17.4**	267.8 ± 16.5**	252.4 ± 17.3**
DAY 9	MEAN±S.D.	302.7 ± 20.5	299.8 ± 15.7	285.4 ± 17.5**	269.8 ± 14.6**	253.2 ± 17.7**
DAY 10	MEAN±S.D.	307.0 ± 20.6	305.4 ± 15.8	290.8 ± 19.9**	274.9 ± 16.0**	257.4 ± 17.5**
DAY 11	MEAN±S.D.	313.4 ± 22.1 [25]c	306.5 ± 13.7 [23]c	296.4 ± 19.4** [22]c	280.8 ± 17.2** [21]c	265.9 ± 17.1** [24]c

DAY = DAY OF GESTATION

[] = NUMBER OF VALUES AVERAGED

a. Excludes values for rats that did not have a confirmed mating date.

b. Excludes values for dam 10207; delivery was not observed (only one implantation site was present and one conceptus was presumed cannibalized).

c. Excludes values for rats that were assigned to Cesarean-sectioning on day 10 of gestation.

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

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

000092

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C4 (PAGE 2): MATERNAL BODY WEIGHTS - GESTATION - SUMMARY - F0 GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
RATS TESTED	N	35	35	35	35	35
PREGNANT	N	35	34	33	32	34
INCLUDED IN ANALYSES	N	25a	23a,b	22a,b	21a,c	24a
MATERNAL BODY WEIGHT (G)						
DAY 12	MEAN±S.D.	318.1 ± 21.1	311.1 ± 14.0	300.1 ± 19.8**	284.7 ± 18.3**	269.0 ± 17.4**
DAY 13	MEAN±S.D.	320.8 ± 21.4	313.7 ± 15.4	303.4 ± 20.4**	289.0 ± 19.0**	271.8 ± 18.0**
DAY 14	MEAN±S.D.	322.4 ± 21.4	316.5 ± 15.2	305.6 ± 19.5**	290.4 ± 18.5**	273.5 ± 18.3**
DAY 15	MEAN±S.D.	330.2 ± 22.8	323.5 ± 14.4	314.4 ± 20.2*	298.7 ± 19.2**	280.4 ± 20.3**
DAY 16	MEAN±S.D.	341.3 ± 24.0	335.2 ± 15.2	325.4 ± 20.2*	308.8 ± 18.3**	290.9 ± 20.4**
DAY 17	MEAN±S.D.	354.7 ± 26.0	350.5 ± 15.2	339.8 ± 21.2*	322.6 ± 20.0**	303.5 ± 19.0**
DAY 18	MEAN±S.D.	368.5 ± 25.1	364.9 ± 16.4	355.8 ± 22.2	341.8 ± 21.3**	319.0 ± 20.7**
DAY 19	MEAN±S.D.	380.7 ± 26.2	378.3 ± 16.8	367.2 ± 24.4	353.4 ± 24.0**	330.7 ± 21.4**
DAY 20	MEAN±S.D.	393.2 ± 25.6	388.6 ± 20.6	377.6 ± 27.6	364.6 ± 25.8**	335.9 ± 22.4**

DAY = DAY OF GESTATION

a. Excludes values for rats that were assigned to Caesarean-sectioning on day 10 of gestation.
b. Excludes values for rats that did not have a confirmed mating date.

c. Excludes values for dam 10207; delivery was not observed (only one implantation site was present and one conceptus was presumed cannibalized).

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

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

000093

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C5 (PAGE 1): MATERNAL BODY WEIGHT CHANGES - GESTATION - SUMMARY - Fo GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
RATS TESTED	N	35	35	35	35	35
PREGNANT	N	35	34	33	32	34
INCLUDED IN ANALYSES	N	35	33a	32a	31b	34
MATERNAL BODY WEIGHT CHANGE (G)						
DAYS 0 - 7	MEAN±S.D.	+25.1 ± 8.4	+23.2 ± 7.8	+21.5 ± 6.6	+15.5 ± 9.2**	+13.7 ± 11.4**
DAYS 7 - 10	MEAN±S.D.	+13.6 ± 7.2	+11.8 ± 6.3	+10.7 ± 7.3	+10.0 ± 6.8	+8.6 ± 7.5
DAYS 10 - 12	MEAN±S.D.	+10.2 ± 5.2	+10.4 ± 4.1	+10.0 ± 5.8	+9.3 ± 4.6	+7.6 ± 5.5
DAYS 12 - 15	MEAN±S.D.	[25]c +12.1 ± 7.4	[23]c +12.4 ± 4.8	[22]c +14.3 ± 6.3	[21]c +14.0 ± 4.6	[24]c +11.4 ± 7.1
DAYS 15 - 18	MEAN±S.D.	[25]c +38.3 ± 10.0	[23]c +41.4 ± 6.7	[22]c +41.4 ± 7.3	[21]c +43.1 ± 6.7	[24]c +38.5 ± 9.7
DAYS 18 - 20	MEAN±S.D.	[25]c +24.6 ± 7.3	[23]c +23.6 ± 8.5	[22]c +21.8 ± 9.6	[21]c +22.8 ± 7.7	[24]c +17.0 ± 8.5**
DAYS 0 - 20	MEAN±S.D.	[25]c +121.6 ± 17.2	[23]c +120.1 ± 14.8	[22]c +117.9 ± 20.4	[21]c +112.7 ± 17.8	[24]c +97.0 ± 18.2**

DAYS = DAYS OF GESTATION

[] = NUMBER OF VALUES AVERAGED

- a. Excludes values for rats that did not have a confirmed mating date.
b. Excludes values for dam 10207; delivery was not observed (only one implantation site was present and one conceptus was presumed cannibalized).
c. Excludes values for rats that were assigned to Cesarean-sectioning on day 10 of gestation.
** Significantly different from the vehicle control group value ($p \leq 0.01$).

000094

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C6 (PAGE 1): MATERNAL BODY WEIGHTS - LACTATION - SUMMARY - F₀ GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
RATS ASSIGNED TO NATURAL DELIVERY	N	25	25	25	25	25
PREGNANT	N	25	24	23	22	24
DELIVERED LITTERS	N	25	24	22a	21b	24
MATERNAL BODY WEIGHT (G)						
DAY 1	MEAN±S.D.	294.7 ± 25.7	294.1 ± 19.8	289.5 ± 19.6	274.3 ± 18.4**	262.0 ± 15.1**
DAY 4	MEAN±S.D.	295.5 ± 18.7	297.0 ± 17.3	291.1 ± 17.7	270.9 ± 14.9**	266.0 ± 0.0
DAY 7	MEAN±S.D.	307.8 ± 15.8 [24]c	305.9 ± 13.8	299.9 ± 15.9	281.0 ± 17.9** [10]c	[1]c
DAY 10	MEAN±S.D.	324.2 ± 19.7 [24]c	323.0 ± 13.9	315.8 ± 17.6	300.8 ± 14.6** [10]c	
DAY 14	MEAN±S.D.	333.6 ± 18.7 [24]c	334.2 ± 13.4	326.2 ± 18.6	310.1 ± 14.9** [9]c	
DAY 21	MEAN±S.D.	332.4 ± 23.1 [24]c	327.3 ± 14.9	327.2 ± 18.0	322.6 ± 11.6 [9]c	

DAY = DAY OF LACTATION

[] = NUMBER OF VALUES AVERAGED

a. Excludes values for dam 10170, which was found dead on day 22 of gestation.

b. Excludes values for dam 10207; delivery was not observed (only one implantation site was present and one conceptus was presumed cannibalized).

c. Excludes values for dams that had no surviving pups.

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

000095

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C7 (PAGE 1): MATERNAL BODY WEIGHT CHANGES - LACTATION - SUMMARY - FO GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
RATS ASSIGNED TO NATURAL DELIVERY		N	25	25	25	25
PREGNANT		N	25	24	22	24
DELIVERED LITTERS		N	25	24	22a	24
MATERNAL BODY WEIGHT CHANGE (G)						
DAYS 1 - 4	MEAN±S.D.	-1.4 ± 11.2 [24]c	+2.8 ± 12.5	+1.6 ± 10.6	-6.5 ± 10.2 [10]c	-10.0 ± 0.0 [1]c
DAYS 4 - 7	MEAN±S.D.	+12.2 ± 8.3 [24]c	+9.0 ± 8.8	+8.8 ± 6.8	+10.1 ± 8.2 [10]c	
DAYS 7 - 10	MEAN±S.D.	+16.4 ± 8.4 [24]c	+17.1 ± 7.6	+16.0 ± 7.3	+17.3 ± 10.4 [9]c	
DAYS 10 - 14	MEAN±S.D.	+9.4 ± 7.7 [24]c	+11.2 ± 9.6	+10.4 ± 11.2	+9.3 ± 12.6 [9]c	
DAYS 14 - 21	MEAN±S.D.	-1.2 ± 12.6 [24]c	-6.9 ± 13.0	+1.0 ± 13.4	+12.4 ± 9.3* [9]c	
DAYS 1 - 21	MEAN±S.D.	+35.4 ± 18.6 [24]c	+33.2 ± 17.3	+37.7 ± 14.7	+45.2 ± 6.3 [9]c	

DAYS = DAYS OF LACTATION

[] = NUMBER OF VALUES AVERAGED

- a. Excludes values for dam 10170, which was found dead on day 22 of gestation.
- b. Excludes values for dam 10207; delivery was not observed (only one implantation site was present and one conceptus was presumed cannibalized).
- c. Excludes values for dams that had no surviving pups.
- * Significantly different from the vehicle control group value ($p \leq 0.05$).

000096

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C8 (PAGE 1): ABSOLUTE FEED CONSUMPTION VALUES (G/DAY) - PRECOHABITATION - SUMMARY - F₀ GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
RATS TESTED	N	35	35	35	35	35
FEED CONSUMPTION (G)						
DAYS 1 - 8	MEAN±S.D.	20.0 ± 3.0	20.8 ± 2.5 [34]a	20.2 ± 1.8	19.2 ± 2.4 [34]a	19.7 ± 2.5
DAYS 8 - 16	MEAN±S.D.	19.7 ± 1.8 [33]a	20.2 ± 2.1 [34]a	19.5 ± 2.3 [34]a	18.0 ± 2.2** [33]a	17.3 ± 2.4**
DAYS 16 - 23	MEAN±S.D.	19.7 ± 1.6 [34]a	20.2 ± 1.8	18.9 ± 1.7 [33]a	17.0 ± 2.1** [34]a	16.1 ± 2.1**
DAYS 23 - 29b	MEAN±S.D.	20.3 ± 3.4 [34]a	20.1 ± 1.6	19.5 ± 3.2 [34]a	17.5 ± 2.4**	16.2 ± 3.5**
DAYS 1 - 29b	MEAN±S.D.	20.0 ± 1.8 [34]a	20.3 ± 1.6	19.4 ± 1.7 [34]a	18.1 ± 2.0**	17.4 ± 2.1**

DAYS = DAYS OF STUDY

[] = NUMBER OF VALUES AVERAGED

a. Excludes values that were associated with spillage.

b. Last value recorded before cohabitation.

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

000097

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C9 (PAGE 1): RELATIVE FEED CONSUMPTION VALUES (G/KG/DAY) - PRECOHABITATION - SUMMARY - Fo GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
RATS TESTED	N	35	35	35	35	35
FEED CONSUMPTION (G/KG/DAY)						
DAYS 1 - 8	MEAN±S.D.	85.9 ± 13.2	89.2 ± 10.3 [34]a	87.6 ± 7.4	82.8 ± 8.3 [34]a	84.9 ± 9.7
DAYS 8 - 16	MEAN±S.D.	79.0 ± 5.4 [33]a	80.4 ± 7.7 [34]a	80.0 ± 8.7 [34]a	74.1 ± 6.7* [33]a	72.5 ± 8.1**
DAYS 16 - 23	MEAN±S.D.	75.9 ± 5.6 [34]a	76.7 ± 5.2	75.1 ± 5.2 [33]a	68.5 ± 5.8** [34]a	67.2 ± 7.2**
DAYS 23 - 29b	MEAN±S.D.	76.2 ± 12.2 [34]a	74.6 ± 4.2	76.3 ± 12.0 [34]a	70.7 ± 9.8*	67.6 ± 13.5**
DAYS 1 - 29b	MEAN±S.D.	79.4 ± 6.8 [34]a	80.4 ± 5.0	79.5 ± 5.5 [34]a	75.1 ± 7.6*	73.4 ± 7.2**

DAYS = DAYS OF STUDY

[] = NUMBER OF VALUES AVERAGED

a. Excludes values that were associated with spillage.

b. Last value recorded before cohabitation.

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

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

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C10 (PAGE 1): MATERNAL ABSOLUTE FEED CONSUMPTION VALUES (G/DAY) - GESTATION - SUMMARY - Fo GENERATION FEMALE RATS

DOSAGE GROUP		I	II	III	IV	V
DOSAGE (MG/KG/DAY)		0 (VEHICLE)	1	5	10	15
RATS TESTED	N	35	35	35	35	35
PREGNANT	N	35	34	33	32	34
INCLUDED IN ANALYSES	N	35	33a	32a	31b	34
MATERNAL FEED CONSUMPTION (G/DAY)						
DAYS 0 - 7	MEAN±S.D.	23.1 ± 2.2	22.5 ± 3.3	21.0 ± 2.0**	18.4 ± 2.0**	17.0 ± 2.4**
DAYS 7 - 10	MEAN±S.D.	24.0 ± 2.7	[32]c	22.6 ± 2.9	19.9 ± 2.2**	17.6 ± 3.5**
DAYS 10 - 12	MEAN±S.D.	24.5 ± 3.0	23.3 ± 3.3	22.6 ± 2.7	20.8 ± 3.4**	19.3 ± 3.1**
DAYS 12 - 15	MEAN±S.D.	[25]d	[23]d	[22]d	[21]d	[24]d
DAYS 15 - 18	MEAN±S.D.	23.5 ± 2.4	23.0 ± 2.3	23.4 ± 2.9	21.4 ± 2.4*	19.6 ± 3.1**
DAYS 18 - 20	MEAN±S.D.	[25]d	[23]d	[21]c,d	[21]d	[24]d
DAYS 0 - 20	MEAN±S.D.	26.3 ± 2.8	25.9 ± 2.4	25.9 ± 3.3	24.6 ± 3.1	23.1 ± 3.3**
	MEAN±S.D.	[25]d	[22]c,d	[22]d	[21]d	[24]d
	MEAN±S.D.	22.4 ± 3.2	22.7 ± 4.3	22.7 ± 3.0	21.8 ± 3.5	19.2 ± 3.0**
	MEAN±S.D.	[25]d	[23]d	[22]d	[21]d	[24]d
	MEAN±S.D.	24.0 ± 1.8	23.0 ± 1.8	22.7 ± 1.7*	20.7 ± 1.8**	19.3 ± 1.9**
	MEAN±S.D.	[25]d	[23]d	[22]d	[21]d	[24]d

DAYS = DAYS OF GESTATION

[] = NUMBER OF VALUES AVERAGED

a. Excludes values for rats that did not have a confirmed mating date.

b. Excludes values for dam 10207; delivery was not observed (only one implantation site was present and one conceptus was presumed cannibalized).

c. Excludes values that were associated with spillage.

d. Excludes values for rats that were assigned to Caesarean-sectioning on day 10 of gestation.

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

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

000099

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C11 (PAGE 1): MATERNAL RELATIVE FEED CONSUMPTION VALUES (G/KG/DAY) - GESTATION - SUMMARY - Fo GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
RATS TESTED	N	35	35	35	35	35
PREGNANT	N	35	34	33	32	34
INCLUDED IN ANALYSES	N	35	33a	32a	31b	34
MATERNAL FEED CONSUMPTION (G/KG/DAY)						
DAYS 0 - 7	MEAN±S.D.	81.6 ± 7.0	79.1 ± 9.9 [32]c	77.4 ± 6.2	71.6 ± 6.8**	69.7 ± 8.4**
DAYS 7 - 10	MEAN±S.D.	79.8 ± 7.0	77.1 ± 8.9	79.4 ± 10.0	73.8 ± 6.9**	69.2 ± 10.9**
DAYS 10 - 12	MEAN±S.D.	78.5 ± 9.2 [25]d	76.0 ± 10.4 [23]d	76.8 ± 9.0 [22]d	73.9 ± 10.4 [21]d	72.6 ± 8.9 [24]d
DAYS 12 - 15	MEAN±S.D.	72.8 ± 5.5 [25]d	72.6 ± 6.8 [23]d	76.4 ± 8.3 [21]c,d	73.7 ± 7.4 [21]d	71.4 ± 7.2 [24]d
DAYS 15 - 18	MEAN±S.D.	75.5 ± 7.1 [25]d	75.8 ± 8.4 [22]c,d	77.7 ± 9.9 [22]d	77.4 ± 8.3 [21]d	77.3 ± 8.9 [24]d
DAYS 18 - 20	MEAN±S.D.	59.0 ± 9.6 [25]d	60.1 ± 11.0 [23]d	61.9 ± 7.3 [22]d	61.7 ± 8.9 [21]d	58.5 ± 9.2 [24]d
DAYS 0 - 20	MEAN±S.D.	75.9 ± 4.8 [25]d	74.2 ± 5.6 [23]d	75.5 ± 4.8 [22]d	72.0 ± 4.0* [21]d	71.0 ± 4.4** [24]d

DAYS = DAYS OF GESTATION

[] = NUMBER OF VALUES AVERAGED

- a. Excludes values for rats that did not have a confirmed mating date.
- b. Excludes values for dam 10207; delivery was not observed (only one implantation site was present and one conceptus was presumed cannibalized).
- c. Excludes values that were associated with spillage.
- d. Excludes values for rats that were assigned to Cesarean-sectioning on day 10 of gestation.
- * Significantly different from the vehicle control group value ($p \leq 0.05$).
- ** Significantly different from the vehicle control group value ($p \leq 0.01$).

000100

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C12 (PAGE 1): MATERNAL ABSOLUTE FEED CONSUMPTION VALUES (G/DAY) - LACTATION - SUMMARY - Fo GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
RATS ASSIGNED TO NATURAL DELIVERY		N	25	25	25	25
PREGNANT		N	25	24	22	24
DELIVERED LITTERS		N	25	24	22a	24
MATERNAL FEED CONSUMPTION (G/DAY)						
DAYS 1 - 4	MEAN±S.D.	23.0 ± 5.4 [23]c,d	27.5 ± 10.3 [20]d	24.2 ± 5.6	16.4 ± 4.1*	12.3 ± 0.0
DAYS 4 - 7	MEAN±S.D.	38.7 ± 4.9 [24]c	41.4 ± 11.0 [22]d	35.6 ± 4.6	25.9 ± 5.8** [10]c	[1]c c
DAYS 7 - 10	MEAN±S.D.	48.3 ± 4.0 [24]c	48.9 ± 6.6 [22]d	43.6 ± 6.4* [21]d	33.6 ± 7.5** [9]c	
DAYS 10 - 14	MEAN±S.D.	57.1 ± 4.7 [24]c	58.9 ± 5.3	54.0 ± 6.5	40.6 ± 9.7** [8]c,d	
DAYS 1 - 14	MEAN±S.D.	43.2 ± 3.4 [24]c	46.8 ± 7.4	40.4 ± 4.8*	30.2 ± 5.9** [8]c,d	

DAYS = DAYS OF LACTATION

[] = NUMBER OF VALUES AVERAGED

a. Excludes values for dam 10170, which was found dead on day 22 of gestation.

b. Excludes values for dam 10207; delivery was not observed (only one implantation site was present and one conceptus was presumed cannibalized).

c. Excludes values for dams that had no surviving pups.

d. Excludes values that were associated with spillage or wet feed.

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

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

000101

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-ElFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C13 (PAGE 1): MATERNAL RELATIVE FEED CONSUMPTION VALUES (G/KG/DAY) - LACTATION - SUMMARY - Fo GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
RATS ASSIGNED TO NATURAL DELIVERY		N	25	25	25	25
PREGNANT		N	25	24	22	24
DELIVERED LITTERS		N	25	24	22a	24
MATERNAL FEED CONSUMPTION (G/KG/DAY)						
DAYS 1 - 4	MEAN±S.D.	78.5 ± 20.9 [23]c,d	94.1 ± 39.5 [20]d	83.5 ± 18.7	59.7 ± 14.8 [10]c	45.4 ± 0.0 [1]c
DAYS 4 - 7	MEAN±S.D.	128.9 ± 19.8 [24]c	137.4 ± 37.1 [22]d	120.6 ± 15.8	93.4 ± 18.1** [10]c	c
DAYS 7 - 10	MEAN±S.D.	153.1 ± 12.2 [24]c	155.4 ± 22.9 [22]d	141.4 ± 17.5* [21]d	115.4 ± 25.9** [9]c	
DAYS 10 - 14	MEAN±S.D.	173.8 ± 14.8 [24]c	179.4 ± 15.2	167.8 ± 15.1	132.4 ± 30.5** [8]c,d	
DAYS 1 - 14	MEAN±S.D.	139.0 ± 13.1 [24]c	151.1 ± 25.8	132.8 ± 13.3	104.0 ± 19.7** [8]c,d	

DAYS = DAYS OF LACTATION

[] = NUMBER OF VALUES AVERAGED

- Excludes values for dam 10170, which was found dead on day 22 of gestation.
 - Excludes values for dam 10207; delivery was not observed (only one implantation site was present and one conceptus was presumed cannibalized).
 - Excludes values for dams that had no surviving pups.
 - Excludes values that were associated with spillage or wet feed.
- * Significantly different from the vehicle control group value ($p \leq 0.05$).
- ** Significantly different from the vehicle control group value ($p \leq 0.01$).

000102

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C14 (PAGE 1): ESTROUS CYCLING, MATING AND FERTILITY - SUMMARY - F0 GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
RATS EVALUATED		N	15	15	15	15
ESTRUS STAGES/ 14 DAYS	MEAN±S.D.	3.2 ± 0.8	3.1 ± 0.6	2.9 ± 0.8	2.9 ± 0.8	2.9 ± 1.0
RATS WITH 6 OR MORE CONSECUTIVE DAYS OF DIESTRUS	N	0	1	2	0	3
RATS WITH 6 OR MORE CONSECUTIVE DAYS OF ESTRUS	N	0	0	1	0	0

000103

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C14 (PAGE 2): ESTROUS CYCLING, MATING AND FERTILITY - SUMMARY - F₀ GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
<u>MATING OBSERVATIONS</u>						
RATS IN COHABITATION	N	35	35	35	35	35
DAYS IN COHABITATION a	MEAN±S.D.	1.9 ± 1.1	2.0 ± 1.1 [34]	2.7 ± 2.4 [34]	2.3 ± 2.4	2.3 ± 1.9
RATS THAT MATED	N(%)	35(100.0)	34(97.1)	34(97.1)	35(100.0)	35(100.0)
FERTILITY INDEX b	N/N (%)	35/35 (100.0)	33/34 (97.0)	32/34 (94.1)	32/35 (91.4)	34/35 (97.1)
RATS WITH CONFIRMED MATING DATES	N	35	34	34	35	35
MATED BY FIRST MALE c DAYS 1-7	N(%)	35(100.0)	34(100.0)	33(97.0)	33(94.3)	34(97.1)
MATED BY SECOND MALE c DAYS 8-14	N(%)	0(0.0)	0(0.0)	1(2.9)	2(5.7)	1(2.8)
RATS PREGNANT/RATS IN COHABITATION	N/N (%)	35/35 (100.0)	33/35 (94.3)	32/35 (91.4)	32/35 (91.4)	34/35 (97.1)

[] = NUMBER OF VALUES AVERAGED

- a. Restricted to rats with a confirmed mating date and rats that did not mate.
b. Number of pregnancies/number of rats that mated.
c. Restricted to rats with a confirmed mating date.

000104

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C15 (PAGE 1): NECROPSY OBSERVATIONS - SUMMARY - Fo GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
RATS EXAMINED a	N	35	35	35	35	35
FOUND DEAD	N	0	0	1b	0	0
APPEARED NORMAL	N	35	34	33	34	33
KIDNEYS:						
BILATERAL OR RIGHT, PELVIS, MODERATE TO MARKED DILATION	N	0	1	0	1	2
EXTERNAL OBSERVATIONS:						
RED AND WET PERIORAL AND PERIVAGINAL SUBSTANCE	N	0	0	1b	0	0
LOCALIZED ALOPECIA, LIMBS	N	0	0	1	0	0

- a. Refer to the individual clinical observations table (Table 21) for external observations confirmed at necropsy.
b. Dam 10170 was found dead on day 22 of gestation.

000105

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C16 (PAGE 1): CAESAREAN-SECTIONING AND LITTER OBSERVATIONS - SUMMARY - F0 GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
RATS TESTED	N	35	35	34	35	35
PREGNANT	N(%)	35(100.0)	34(97.1)	32(94.1)	32(91.4)	34(97.1)
RATS PREGNANT AND CAESAREAN-SECTIONED ON DAY 10 OF GESTATION	N	10	10	10	10	10
CORPORA LUTEA	MEAN±S.D.	17.0 ± 1.5	18.4 ± 2.4	17.7 ± 1.3	16.9 ± 1.6	15.3 ± 3.1
IMPLANTATIONS	MEAN±S.D.	15.6 ± 1.3	15.7 ± 2.7	15.3 ± 2.2	14.3 ± 1.2	11.1 ± 2.0**
VIABLE EMBRYOS	N	156	157	152	143	110
	MEAN±S.D.	15.6 ± 1.3	15.7 ± 2.7	15.2 ± 2.2	14.3 ± 1.2	11.0 ± 1.9**
NONVIABLE EMBRYOS	N	0	0	1	0	1
	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.3	0.0 ± 0.0	0.1 ± 0.3
DAMS WITH ANY NONVIABLE EMBRYOS	N(%)	0(0.0)	0(0.0)	1(10.0)	0(0.0)	1(10.0)
DAMS WITH ALL NONVIABLE EMBRYOS	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
DAMS WITH VIABLE EMBRYOS	N(%)	10(100.0)	10(100.0)	10(100.0)	10(100.0)	10(100.0)
% NONVIABLE EMBRYOS/LITTER	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.0	0.6 ± 2.0	0.0 ± 0.0	0.8 ± 2.4

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

000106

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-ElFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C17 (PAGE 1): NATURAL DELIVERY OBSERVATIONS - SUMMARY - Fo GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
RATS ASSIGNED TO NATURAL DELIVERY	N	25	25	25	25	25
PREGNANT	N(%)	25 (100.0)	24 (96.0)	23 (92.0)	22 (88.0)	24 (96.0)
DELIVERED LITTERS	N(%)	25 (100.0)	24 (100.0)	22 (95.6)	21 (95.4)	24 (100.0)
DURATION OF GESTATION a	MEAN±S.D.	23.0 ± 0.4	22.8 ± 0.5 [23]	22.5 ± 0.5** [21]	22.5 ± 0.5**	22.6 ± 0.5*
IMPLANTATION SITES PER DELIVERED LITTER	N MEAN±S.D.	385 15.4 ± 3.1	366 15.2 ± 1.9	331 15.0 ± 2.2	294 14.0 ± 2.4	324 13.5 ± 9.4**
DAMS WITH STILLBORN PUPS	N(%)	3 (12.0)	2 (8.3)	5 (22.7)	9 (42.8)*	18 (75.0)**
DAMS WITH NO LIVEBORN PUPS	N	0	0	0	0	4**
GESTATION INDEX	% N/N	100.0 25/ 25	100.0 24/ 24	100.0 22/ 22	95.4 21/ 22	83.3** 20/ 24
DAMS WITH ALL PUPS DYING DAYS 1-4 POSTPARTUM	N(%)	1 (4.0)	0 (0.0)	0 (0.0)	11 (52.4)	19 (95.0)**
DAMS WITH ALL PUPS DYING DAYS 5-21 POSTPARTUM	N(%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	1 (5.0)

[] = NUMBER OF VALUES AVERAGED

GESTATION INDEX = (NUMBER OF DAMS WITH LIVEBORN PUPS/NUMBER OF PREGNANT RATS) X 100.

a. Calculated as the time (in days) elapsed between confirmed mating (arbitrarily defined as 0 hour) and the time (in days) the first pup was delivered.

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

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

000107

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-ElFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C18 (PAGE 1): LITTER OBSERVATIONS (NATURALLY DELIVERED PUPS) - SUMMARY - F1 GENERATION LITTERS

MATERNAL DOSAGE GROUP		I		II		III		IV		V	
MATERNAL DOSAGE (MG/KG/DAY)		0 (VEHICLE)		1		5		10		15	
DELIVERED LITTERS WITH ONE OR MORE LIVEBORN PUPS		N		25		24		22		21	
PUPS DELIVERED (TOTAL)		N		355		339		307		268	
		MEAN±S.D.		14.2 ± 3.2		14.1 ± 1.9		14.0 ± 3.1		12.8 ± 2.7	
LIVEBORN		MEAN±S.D.		14.0 ± 3.2		14.0 ± 1.8		13.7 ± 3.2		11.0 ± 3.2**	
		N(%)		350(98.6)		335(98.8)		302(98.4)		248(92.5)	
STILLBORN		MEAN±S.D.		0.2 ± 0.6		0.1 ± 0.3		0.2 ± 0.4		0.6 ± 1.0	
		N(%)		5(1.4)		2(0.6)		5(1.6)		13(4.8)	
UNKNOWN VITAL STATUS		N		0		2		0		7	
PUPS FOUND DEAD OR PRESUMED CANNIBALIZED		N		0		2		0		7	
DAY 1	N/N(%)	3/350(0.8)		0/335(0.0)		4/302(1.3)		79/248(31.8)**		113/161(70.2)**	
DAYS 2- 4	N/N(%)	22/347(6.3)		3/335(0.9)		20/298(6.7)		94/169(55.6)**		46/ 48(95.8)**	
DAYS 5- 7	N/N(%)	0/190(0.0)		0/192(0.0)		2/175(1.1)		2/ 60(3.3)**		2/ 2(100.0)**	
DAYS 8-14	N/N(%)	2/190(1.0)		1/192(0.5)		2/173(1.2)		4/ 58(6.9)**		0/ 0(0.0)	
DAYS 15-21	N/N(%)	0/188(0.0)		0/191(0.0)		0/171(0.0)		0/ 54(0.0)		0/ 0(0.0)	
VIABILITY INDEX a		%		92.8		99.1		92.0		30.2**	
		N/N		325/350		332/335		278/302		75/248	
LACTATION INDEX b		%		98.9		99.5		97.7		90.0**	
		N/N		188/190		191/192		171/175		54/ 60	
DAY(S) = DAY(S) POSTPARTUM										0.0**	
a. Number of live pups on day 4 postpartum(preculling)/number of liveborn pups on day 1 postpartum.										2	
b. Number of live pups on day 21 postpartum/number of live pups on day 4 postpartum(postculling).											

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

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-ELFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C18 (PAGE 2): LITTER OBSERVATIONS (NATURALLY DELIVERED PUPS) - SUMMARY - F1 GENERATION LITTERS

MATERNAL DOSAGE GROUP MATERNAL DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
DELIVERED LITTERS WITH ONE OR MORE LIVEBORN PUPS	N	25	24	22	21	20
SURVIVING PUPS/LITTER ^a						
DAY 1 ^b	MEAN±S.D.	14.0 ± 3.2	14.0 ± 1.8	13.7 ± 3.2	11.8 ± 3.3	8.0 ± 4.3**
DAY 4 PRECULLING	MEAN±S.D.	13.0 ± 4.0	13.8 ± 1.9	12.6 ± 2.6	3.6 ± 4.7**	0.1 ± 0.4**
DAY 4 POSTCULLING	MEAN±S.D.	7.6 ± 1.6	8.0 ± 0.0	8.0 ± 0.2	2.8 ± 3.4**	0.1 ± 0.4
DAY 7	MEAN±S.D.	7.6 ± 1.6	8.0 ± 0.0	7.9 ± 0.4	2.8 ± 3.3**	0.0 ± 0.0
DAY 14	MEAN±S.D.	7.5 ± 1.6	8.0 ± 0.2	7.8 ± 0.7	2.6 ± 3.3	0.0 ± 0.0
DAY 21	MEAN±S.D.	7.5 ± 1.6	8.0 ± 0.2	7.8 ± 0.7	2.6 ± 3.3	0.0 ± 0.0
PERCENT MALE PUPS PER NUMBER OF PUPS SEXED						
DAY 1 ^b	MEAN±S.D.	53.4 ± 15.1	56.0 ± 16.0	53.0 ± 15.2	51.8 ± 19.6	53.6 ± 24.6
DAY 4 PRECULLING	MEAN±S.D.	53.8 ± 16.4	56.0 ± 16.0	53.4 ± 15.6	62.1 ± 24.3	[19]c
DAY 4 POSTCULLING	MEAN±S.D.	53.0 ± 9.3	51.0 ± 8.2	50.4 ± 8.6	59.2 ± 24.1	[1]c
DAY 7	MEAN±S.D.	53.0 ± 9.3	51.0 ± 8.2	51.0 ± 8.8	60.4 ± 22.5	[1]c
DAY 14	MEAN±S.D.	52.4 ± 9.7	50.8 ± 7.9	52.1 ± 10.7	64.4 ± 19.9	c
DAY 21	MEAN±S.D.	52.4 ± 9.7	50.8 ± 7.9	52.1 ± 10.7	64.4 ± 19.9	[9]c

[] = NUMBER OF VALUES AVERAGED

DAY = DAY POSTPARTUM

a. Average number of live pups per litter, including litters with no surviving pups.

b. Includes pups born alive, found dead day 1 postpartum.

c. Excludes values for dams that had no surviving pups.

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

000109

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-ElFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C18 (PAGE 3): LITTER OBSERVATIONS (NATURALLY DELIVERED PUPS) - SUMMARY - F1 GENERATION LITTERS

MATERNAL DOSAGE GROUP MATERNAL DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
DELIVERED LITTERS WITH ONE OR MORE LIVEBORN PUPS	N	25	24	22	21	20
LIVE LITTER SIZE AT WEIGHING						
DAY 1	MEAN±S.D.	13.9 ± 3.1	14.0 ± 1.8	13.5 ± 3.2	9.4 ± 4.2**	5.4 ± 3.5**
DAY 4 PRECULLING	MEAN±S.D.	13.5 ± 3.1	13.8 ± 1.9	12.6 ± 2.6	{ 19}a	{ 10}a
DAY 4 POSTCULLING	MEAN±S.D.	7.9 ± 0.4	8.0 ± 0.0	8.0 ± 0.2	7.5 ± 4.0	2.0 ± 0.0
DAY 7	MEAN±S.D.	{ 24}a			{ 10}a	{ 1}a
DAY 14	MEAN±S.D.	7.9 ± 0.4	8.0 ± 0.0	7.9 ± 0.4	6.0 ± 2.0**	2.0 ± 0.0
DAY 21	MEAN±S.D.	{ 24}a			{ 10}a	{ 1}a
		7.8 ± 0.5	8.0 ± 0.2	7.8 ± 0.7	5.8 ± 2.2**	a
		{ 24}a			{ 10}a	
		7.8 ± 0.5	8.0 ± 0.2	7.8 ± 0.7	6.0 ± 2.2*	
		{ 24}a			{ 9}a	
					6.0 ± 2.2*	
					{ 9}a	
PUP WEIGHT/LITTER (GRAMS)						
DAY 1	MEAN±S.D.	6.3 ± 0.7	6.2 ± 0.5	5.7 ± 0.6**	5.5 ± 0.8**	5.3 ± 0.5**
DAY 4 PRECULLING	MEAN±S.D.	8.2 ± 1.1	7.9 ± 0.9	7.2 ± 1.1**	{ 17}a	{ 9}a
DAY 4 POSTCULLING	MEAN±S.D.	{ 24}a			6.5 ± 1.1**	5.0 ± 0.0**
DAY 7	MEAN±S.D.	8.4 ± 1.0	8.0 ± 0.9	7.4 ± 1.1**	{ 10}a	{ 1}a
DAY 14	MEAN±S.D.	{ 24}a			6.7 ± 1.1**	5.0 ± 0.0**
DAY 21	MEAN±S.D.	13.3 ± 1.4	13.1 ± 1.7	11.5 ± 2.1**	{ 10}a	{ 1}a
		{ 24}a			9.0 ± 1.7**	a
		29.3 ± 2.4	28.6 ± 3.0	25.9 ± 3.4**	{ 10}a	
		{ 24}a			20.7 ± 3.3**	
		47.4 ± 4.4	47.0 ± 4.3	41.8 ± 5.0**	{ 9}a	
		{ 24}a			35.6 ± 4.7	
					{ 9}a	

{ } = NUMBER OF VALUES AVERAGED

DAY = DAY POSTPARTUM

a. Excludes values for dams that had no surviving pups.

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

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

000110

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C19 (PAGE 1): CLINICAL OBSERVATIONS FROM BIRTH TO DAY 21 POSTPARTUM - SUMMARY - F1 GENERATION PUPS

MATERNAL DOSAGE GROUP	I	II	III	IV	V
MATERNAL DOSAGE (MG/KG/DAY)	0 (VEHICLE)	1	5	10	15
LITTERS EXAMINED (N)	25	24	23	21	24
TRANSIENT CLINICAL OBSERVATIONS: a					
	TOTAL FREQUENCY (DAYS x PUPS)/LITTERS WITH OBSERVATIONS				
NOT NURSING	N/N 0/ 0	0/ 0	1/ 1	35/ 7**	5/ 3
COLD TO TOUCH	N/N 0/ 0	0/ 0	0/ 0	17/ 3**	0/ 0
NOT NESTING	N/N 0/ 0	0/ 0	0/ 0	8/ 2	0/ 0
DEHYDRATION	N/N 0/ 0	0/ 0	0/ 0	7/ 1	0/ 0
SPARSE COAT	N/N 0/ 0	0/ 0	0/ 0	1/ 1	0/ 0
RIGHT HINDPAW, BLACK AREA	N/N 0/ 0	0/ 0	0/ 0	1/ 1	0/ 0
LEFT HINDLIMB, SWOLLEN	N/N 0/ 0	0/ 0	15/ 1	0/ 0	0/ 0
PLACENTAS AND UMBILICAL CORDS NOT REMOVED	N/N 0/ 0	0/ 0	10/ 1	0/ 0	0/ 0
MOUTH, MASS(ES)	N/N 13/ 2	0/ 0	5/ 1	0/ 0	0/ 0
NECK, LESION	N/N 0/ 0	20/ 1	0/ 0	0/ 0	0/ 0
PERSISTENT CLINICAL OBSERVATIONS: a					
	TOTAL FREQUENCY (DAYS x PUPS)/LITTERS WITH OBSERVATIONS				
PORTION OF TAIL MISSING	N/N 0/ 0	0/ 0	0/ 0	10/ 1	0/ 0
PORTION OF TAIL BLACK	N/N 0/ 0	0/ 0	12/ 2	0/ 0	0/ 0

STATISTICAL ANALYSES WERE RESTRICTED TO THE NUMBER OF LITTERS WITH OBSERVATIONS.

N/N = TOTAL FREQUENCY (DAYS x PUPS)/LITTERS WITH OBSERVATIONS

a. Tabulation restricted to adverse observations; all other pups appeared normal.

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

000111

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C20 (PAGE 1): REFLEX AND PHYSICAL DEVELOPMENT - SUMMARY - F1 GENERATION LITTERS

MATERNAL DOSAGE GROUP		I		II		III		IV		V	
MATERNAL DOSAGE (MG/KG/DAY)		0 (VEHICLE)		1		5		10		15	
SURFACE RIGHTING a		N		25		24		22		21	
INCLUDED IN ANALYSES		N		25		24		22		17b	
DAY		MEAN+S.D.		23.4 ± 21.5		25.4 ± 20.3		22.2 ± 18.1		11.4 ± 13.6	
DAY 1											
DAY 2		MEAN+S.D.		20.0 ± 17.1		17.6 ± 18.3		7.0 ± 7.6**		3.2 ± 6.6**	
DAY 3				[24]b						[14]b	
DAY 4		MEAN+S.D.		23.3 ± 16.0		19.3 ± 13.7		10.6 ± 16.9**		7.0 ± 11.1**	
DAY 5				[24]b						[12]b	
DAY 6		MEAN+S.D.		19.9 ± 15.1		29.8 ± 20.6		15.2 ± 19.1		4.2 ± 7.3*	
DAY 7				[24]b						[10]b	
DAY 8		MEAN+S.D.		51.4 ± 26.5		56.8 ± 33.4		36.0 ± 26.6		6.7 ± 9.2**	
DAY 9				[24]b						[10]b	
DAY 10		MEAN+S.D.		69.3 ± 23.3		72.9 ± 28.0		39.8 ± 21.3**		15.2 ± 22.8**	
DAY 11				[24]b						[10]b	
DAY 12		MEAN+S.D.		71.2 ± 26.2		85.9 ± 20.0		58.9 ± 29.0		19.1 ± 20.1**	
DAY 13				[24]b						[10]b	
DAY 14		MEAN+S.D.		87.9 ± 21.2		91.7 ± 14.1		72.5 ± 29.6		21.5 ± 23.1**	
DAY 15				[24]b						[10]b	
DAY 16		MEAN+S.D.		96.4 ± 8.6		94.3 ± 11.0		78.4 ± 25.4*		47.0 ± 36.6**	
DAY 17				[24]b						[10]b	
DAY 18		MEAN+S.D.		98.4 ± 5.6		96.4 ± 11.3		89.0 ± 16.0*		58.8 ± 37.1**	
DAY 19				[24]b						[9]b	
DAY 20		MEAN+S.D.		99.5 ± 2.6		99.5 ± 2.6		96.0 ± 11.2		58.7 ± 34.6**	
DAY 21				[24]b						[9]b	
DAY 22		MEAN+S.D.		99.5 ± 2.6		100.0 ± 0.0		97.7 ± 8.3		76.3 ± 21.8**	
DAY 23				[24]b						[9]b	
DAY 24		MEAN+S.D.		100.0 ± 0.0		100.0 ± 0.0		98.9 ± 5.3		67.0 ± 40.0**	
DAY 25				[24]b						[9]b	
DAY 26		MEAN+S.D.		100.0 ± 0.0		100.0 ± 0.0		99.4 ± 2.7		70.9 ± 27.3**	
DAY 27				[24]b						[9]b	
DAY 28		MEAN+S.D.		100.0 ± 0.0		100.0 ± 0.0		98.9 ± 5.3		75.3 ± 35.6**	
DAY 29				[24]b						[9]b	

DAY = DAY POSTPARTUM

[] = NUMBER OF VALUES AVERAGED

a. The average percentage of pups meeting the criterion for the developmental landmark tested on each day postpartum.
b. Excludes values for dams that had no surviving pups.

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

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

000112

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-ElFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C20 (PAGE 2): REFLEX AND PHYSICAL DEVELOPMENT - SUMMARY - F1 GENERATION LITTERS

MATERNAL DOSAGE GROUP		I		II		III		IV		V	
MATERNAL DOSAGE (MG/KG/DAY)		0 (VEHICLE)		1		5		10		15	
SURFACE RIGHTING a	N	25		24		22		21		24	
INCLUDED IN ANALYSES	N	24b		24		22		9b		0b	
DAY 16	MEAN±S.D.	100.0 ±	0.0	100.0 ±	0.0	100.0 ±	0.0	91.1 ±	17.6**		
DAY 17	MEAN±S.D.	100.0 ±	0.0	100.0 ±	0.0	100.0 ±	0.0	93.3 ±	14.1**		
DAY 18	MEAN±S.D.	100.0 ±	0.0	100.0 ±	0.0	100.0 ±	0.0	95.6 ±	8.8**		
DAY 19	MEAN±S.D.	100.0 ±	0.0	100.0 ±	0.0	100.0 ±	0.0	100.0 ±	0.0		
	MEAN%±S.D.c	4.9 ±	1.8	4.9 ±	1.8	5.4 ±	2.3	9.1 ±	2.9**		

DAY = DAY POSTPARTUM

[] = NUMBER OF VALUES AVERAGED

- a. The average percentage of pups meeting the criterion for the developmental landmark tested on each day postpartum.
b. Excludes values for dams that had no surviving pups.
c. The average day postpartum that at least 50% of the pups had the developmental measure present.
** Significantly different from the vehicle control group value ($p \leq 0.01$).

000113

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C20 (PAGE 3): REFLEX AND PHYSICAL DEVELOPMENT - SUMMARY - F1 GENERATION LITTERS

MATERNAL DOSAGE GROUP		I		II		III		IV		V	
MATERNAL DOSAGE (MG/KG/DAY)		0 (VEHICLE)		1		5		10		15	
PINNA UNFOLDING a	N	25		24		22		21		24	
INCLUDED IN ANALYSES	N	24b		24		22		14b		2b	
DAY 2	MEAN±S.D.	12.7 ± 27.6		5.6 ± 20.6		0.9 ± 4.3		0.0 ± 0.0		0.0 ± 0.0	
DAY 3	MEAN±S.D.	71.2 ± 32.4		47.8 ± 38.2*		15.2 ± 34.1**		4.2 ± 14.4**		0.0 ± 0.0**	
DAY 4	MEAN±S.D.	99.1 ± 3.0		91.5 ± 26.9		46.7 ± 43.0**		[12]b		0.0 ± 0.0**	
DAY 5	MEAN±S.D.	100.0 ± 0.0		100.0 ± 0.0		92.6 ± 22.4		26.6 ± 39.6**		0.0 ± 0.0**	
DAY 6	MEAN±S.D.	100.0 ± 0.0		100.0 ± 0.0		95.4 ± 21.3		[10]b		[1]b	
DAY 7	MEAN±S.D.	100.0 ± 0.0		100.0 ± 0.0		100.0 ± 0.0		76.0 ± 36.6**		b	
DAY 8	MEAN±S.D.	100.0 ± 0.0		100.0 ± 0.0		100.0 ± 0.0		[10]b			
DAY 9	MEAN±S.D.	100.0 ± 0.0		100.0 ± 0.0		100.0 ± 0.0		82.5 ± 37.4*			
	MEAN±S.D.c	3.1 ± 0.6		3.5 ± 0.7		4.5 ± 0.9**		97.5 ± 7.9			
								[10]b			
								96.7 ± 10.5			
								100.0 ± 0.0			
								[10]b			
								5.0 ± 1.0**			

DAY = DAY POSTPARTUM

[] = NUMBER OF VALUES AVERAGED

- a. The average percentage of pups meeting the criterion for the developmental landmark tested on each day postpartum.
b. Excludes values for dams that had no surviving pups.
c. The average day postpartum that at least 50% of the pups had the developmental measure present.
* Significantly different from the vehicle control group value ($p \leq 0.05$).
** Significantly different from the vehicle control group value ($p \leq 0.01$).

000114

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-ElFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C20 (PAGE 4): REFLEX AND PHYSICAL DEVELOPMENT - SUMMARY - F1 GENERATION LITTERS

MATERNAL DOSAGE GROUP		I		II		III		IV		V	
MATERNAL DOSAGE (MG/KG/DAY)		0 (VEHICLE)		1		5		10		15	
EYE OPENING a	N	25		24		22		21		24	
INCLUDED IN ANALYSES	N	24b		24		22		9b		0b	
DAY 12	MEAN±S.D.	4.4 ± 11.7		3.6 ± 13.0		1.1 ± 3.7		0.0 ± 0.0			
DAY 13	MEAN±S.D.	23.0 ± 31.2		16.1 ± 29.1		9.6 ± 20.0		6.3 ± 13.8			
DAY 14	MEAN±S.D.	57.7 ± 34.7		50.8 ± 31.4		24.4 ± 37.3**		24.5 ± 33.5*			
DAY 15	MEAN±S.D.	94.8 ± 12.2		90.6 ± 18.2		58.2 ± 38.0**		56.9 ± 37.6**			
DAY 16	MEAN±S.D.	100.0 ± 0.0		99.5 ± 2.6		86.7 ± 27.4*		85.6 ± 29.6*			
DAY 17	MEAN±S.D.	100.0 ± 0.0		100.0 ± 0.0		98.2 ± 8.5		100.0 ± 0.0			
DAY 18	MEAN±S.D.	100.0 ± 0.0		100.0 ± 0.0		99.1 ± 4.3		100.0 ± 0.0			
DAY 19	MEAN±S.D.	100.0 ± 0.0		100.0 ± 0.0		100.0 ± 0.0		100.0 ± 0.0			
	MEAN±S.D.c	14.2 ± 0.8		14.3 ± 0.9		15.2 ± 1.0**		15.1 ± 0.9			

DAY = DAY POSTPARTUM

[] = NUMBER OF VALUES AVERAGED

a. The average percentage of pups meeting the criterion for the developmental landmark tested on each day postpartum.

b. Excludes values for dams that had no surviving pups.

c. The average day postpartum that at least 50% of the pups had the developmental measure present.

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

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

000115

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C20 (PAGE 5): REFLEX AND PHYSICAL DEVELOPMENT - SUMMARY - F1 GENERATION LITTERS

MATERNAL DOSAGE GROUP		I		II		III		IV		V	
MATERNAL DOSAGE (MG/KG/DAY)		0 (VEHICLE)		1		5		10		15	
ACOUSTIC STARTLE a		N	25	24	24	22	21	21	21	24	24
INCLUDED IN ANALYSES		N	24b	24	24	22	21	9b	9b	24	0b
DAY 13	MEAN±S.D.		58.6 ± 24.4	49.0 ± 27.6	21.6 ± 31.6**	13.9 ± 19.2**					
DAY 14	MEAN±S.D.		79.0 ± 23.5	62.9 ± 24.0*	38.2 ± 32.5**	26.8 ± 25.6**					
DAY 15	MEAN±S.D.		96.4 ± 8.6	81.5 ± 19.8**	80.3 ± 27.1*	50.2 ± 35.5**					
DAY 16	MEAN±S.D.		92.7 ± 20.5	89.6 ± 18.7	90.1 ± 19.3	76.4 ± 28.1					
DAY 17	MEAN±S.D.		95.3 ± 13.2	96.9 ± 11.2	94.3 ± 15.3	92.2 ± 11.8					
DAY 18	MEAN±S.D.		93.8 ± 17.3	99.0 ± 5.1	96.0 ± 11.2	90.6 ± 20.7					
DAY 19	MEAN±S.D.		96.4 ± 11.3	97.9 ± 10.2	94.9 ± 16.7	95.6 ± 13.3					
DAY 20	MEAN±S.D.		97.9 ± 7.0	98.4 ± 7.6	97.2 ± 13.3	100.0 ± 0.0					
DAY 21	MEAN±S.D.		96.4 ± 13.5	99.0 ± 5.1	98.9 ± 5.3	100.0 ± 0.0					
	MEAN±S.D.c		13.2 ± 0.5	13.6 ± 0.8	14.6 ± 1.0**	14.9 ± 1.2**					

DAY = DAY POSTPARTUM

[] = NUMBER OF VALUES AVERAGED

a. The average percentage of pups meeting the criterion for the developmental landmark tested on each day postpartum.

b. Excludes values for dams that had no surviving pups.

c. The average day postpartum that at least 50% of the pups had the developmental measure present.

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

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

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C20 (PAGE 6): REFLEX AND PHYSICAL DEVELOPMENT - SUMMARY - F1 GENERATION LITTERS

MATERNAL DOSAGE GROUP		I		II		III		IV		V	
MATERNAL DOSAGE (MG/KG/DAY)		0 (VEHICLE)		1		5		10		15	
AIR RIGHTING a	N	25		24		22		21		24	
INCLUDED IN ANALYSES	N	24b		24		22		9b		0b	
DAY 14	MEAN±S.D.	56.2 ± 23.5		43.2 ± 24.2		41.0 ± 23.9*		18.0 ± 15.2**			
DAY 15	MEAN±S.D.	74.2 ± 27.1		69.8 ± 26.0		47.8 ± 26.4**		33.8 ± 34.5**			
DAY 16	MEAN±S.D.	88.7 ± 18.9		89.1 ± 14.4		60.6 ± 25.9**		49.8 ± 34.9*			
DAY 17	MEAN±S.D.	100.0 ± 0.0		95.8 ± 10.8		80.1 ± 19.5**		66.5 ± 31.3**			
DAY 18	MEAN±S.D.	100.0 ± 0.0		100.0 ± 0.0		92.5 ± 12.6*		75.7 ± 20.7**			
DAY 19	MEAN±S.D.	100.0 ± 0.0		100.0 ± 0.0		97.7 ± 8.3		83.8 ± 33.4**			
DAY 20	MEAN±S.D.	100.0 ± 0.0		100.0 ± 0.0		98.9 ± 5.3		90.9 ± 14.8**			
DAY 21	MEAN±S.D.	100.0 ± 0.0		100.0 ± 0.0		100.0 ± 0.0		100.0 ± 0.0			
	MEAN±S.D.c	14.3 ± 0.6		14.5 ± 0.6		15.1 ± 1.2*		16.0 ± 1.5**			

DAY = DAY POSTPARTUM

[] = NUMBER OF VALUES AVERAGED

- a. The average percentage of pups meeting the criterion for the developmental landmark tested on each day postpartum.
b. Excludes values for dams that had no surviving pups.
c. The average day postpartum that at least 50% of the pups had the developmental measure present.
* Significantly different from the vehicle control group value ($p \leq 0.05$).
** Significantly different from the vehicle control group value ($p \leq 0.01$).

000117

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C20 (PAGE 7): REFLEX AND PHYSICAL DEVELOPMENT - SUMMARY - F1 GENERATION LITTERS

MATERNAL DOSAGE GROUP		I		II		III		IV		V	
MATERNAL DOSAGE (MG/KG/DAY)		0 (VEHICLE)		1		5		10		15	
PUPIL CONSTRICTION a	N	25		24		22		21		24	
INCLUDED IN ANALYSES	N	24b		24		22		9b		0b	
DAY 21	MEAN±S.D.	100.0 ± 0.0		100.0 ± 0.0		100.0 ± 0.0		100.0 ± 0.0			
	MEAN%±S.D.c	21.0 ± 0.0		21.0 ± 0.0		21.0 ± 0.0		21.0 ± 0.0			

DAY = DAY POSTPARTUM

- a. The average percentage of pups meeting the criterion for the developmental landmark tested on each day postpartum.
- b. Excludes values for dams that had no surviving pups.
- c. The average day postpartum that at least 50% of the pups had the developmental measure present.

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE C21 (PAGE 1): NECROPSY OBSERVATIONS - SUMMARY - F1 GENERATION PUPS

MATERNAL DOSAGE GROUP MATERNAL DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5	IV 10	V 15
LITTERS EXAMINED (N)		25	24	23	21	24
TOTAL PUPS STILLBORN						
OR FOUND DEAD a	N	10	5	22	140	194
STILLBORN	N	5	2	5	11	78
FOUND DEAD	N	5	3	17	129	116
NO MILK IN STOMACH b	N(%)	1 (20.0)	1 (33.3)	4 (23.5)	120 (93.0)**	108 (93.1)**
LOWER JAW, SHORT	N(%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
PUPS SACRIFICED AND NECROPSIED ON DAYS 4 OR 21 POSTPARTUM a						
LITTERS EVALUATED	N	24	24	22	9	0c
PUPS EVALUATED	N	273	281	224	69	0
APPEARED NORMAL						
LITTER INCIDENCE	N(%)	24 (100.0)	24 (100.0)	21 (95.4)	9 (100.0)	
PUP INCIDENCE	N(%)	273 (100.0)	281 (100.0)	223 (99.6)	69 (100.0)	
KIDNEYS: RIGHT, PELVIS, MODERATE DILATION						
LITTER INCIDENCE	N(%)	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)	
PUP INCIDENCE	N(%)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	

- a. Complete necropsies were not performed on pups in which autolysis or cannibalization precluded evaluation.
b. Analysis restricted to pups found dead and necropsied.
c. Excludes values for dams that had no surviving pups.
** Significantly different from the vehicle control group value ($p \leq 0.01$).

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APPENDIX D
REPORT TABLES - F1 GENERATION MALE RATS

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE D1 (PAGE 1): CLINICAL OBSERVATIONS - SUMMARY - F1 GENERATION MALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)	I 0 (VEHICLE)	II 1	III 5
MAXIMUM POSSIBLE INCIDENCE	2261/ 25	2258/ 25	2241/ 25
MORTALITY	0	0	0
INCISORS: TOTAL	68/ 3	13/ 1	32/ 2
MISALIGNED	57/ 2	13/ 1	32/ 2
MISSING/BROKEN	11/ 1	0/ 0	0/ 0
CHROMODACRYORRHEA	0/ 0	3/ 1	7/ 2
CHROMORHINORRHEA	0/ 0	0/ 0	2/ 1
EMACIATION	0/ 0	12/ 1	0/ 0
DEHYDRATION	0/ 0	6/ 1	0/ 0
BROWN PERINASAL DISCHARGE	0/ 0	4/ 1	0/ 0
LABORED BREATHING	0/ 0	4/ 1	0/ 0
BROWN OR RED PERIORAL SUBSTANCE	0/ 0	3/ 1	0/ 0
EXCESS SALIVATION	0/ 0	3/ 1	0/ 0
GASPING	0/ 0	2/ 1	0/ 0
RALES	0/ 0	1/ 1	0/ 0
EARS: SWOLLEN AND PURPLE	16/ 1	0/ 0	0/ 0

STATISTICAL ANALYSES OF CLINICAL OBSERVATION DATA WERE RESTRICTED TO THE NUMBER OF RATS WITH OBSERVATIONS.
MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP.
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RATS WITH OBSERVATION.

000121

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE D2 (PAGE 1): BODY WEIGHTS - SUMMARY - F1 GENERATION MALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
RATS TESTED	N	25	25	25
BODY WEIGHT (G)				
DAY 1	MEAN±S.D.	52.0 ± 6.0	50.6 ± 5.6	45.4 ± 5.6**
DAY 8	MEAN±S.D.	97.0 ± 10.5	93.2 ± 8.9	84.5 ± 9.4**
DAY 15	MEAN±S.D.	153.4 ± 16.0	149.2 ± 13.4	133.5 ± 14.0**
DAY 22	MEAN±S.D.	214.7 ± 20.4	208.4 ± 16.3	190.8 ± 17.4**
DAY 29	MEAN±S.D.	275.5 ± 26.4	264.0 ± 19.9	246.7 ± 22.6**
DAY 36	MEAN±S.D.	331.5 ± 31.9	316.0 ± 22.8*	299.9 ± 26.0**
DAY 43	MEAN±S.D.	374.0 ± 37.6	357.4 ± 27.1	339.9 ± 27.3**
DAY 50	MEAN±S.D.	414.6 ± 40.9	392.5 ± 29.3*	374.5 ± 29.5**
DAY 57	MEAN±S.D.	447.2 ± 45.8	424.1 ± 31.3*	403.3 ± 31.5**
DAY 64	MEAN±S.D.	472.3 ± 48.1	448.9 ± 32.8	426.2 ± 29.9**
PRECOHABITATION a	MEAN±S.D.	497.1 ± 60.6	466.1 ± 41.4	448.6 ± 33.1**
TERMINAL BODY WEIGHTS b	MEAN±S.D.	533.7 ± 65.2	502.0 ± 42.4	478.1 ± 40.9**

DAY = DAY POSTWEANING

a. Precohabitation body weights were recorded on the day cohabitation was begun for the F1 generation rats; at that time these rats were 84 to 98 days of age.

b. Terminal body weights were recorded when the rats were 100 to 114 days of age.

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

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

000122

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE D3 (PAGE 1): BODY WEIGHT CHANGES - SUMMARY - F1 GENERATION MALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
RATS TESTED		N	25	25
BODY WEIGHT CHANGE (G)				
DAYS 1 - 8	MEAN±S.D.	+44.9 ± 5.1	+42.6 ± 4.5	+39.1 ± 4.8**
DAYS 8 - 15	MEAN±S.D.	+56.4 ± 6.5	+56.0 ± 5.4	+49.0 ± 6.3**
DAYS 15 - 22	MEAN±S.D.	+61.3 ± 5.7	+59.2 ± 5.3	+57.3 ± 4.9**
DAYS 22 - 29	MEAN±S.D.	+60.8 ± 8.0	+55.6 ± 5.2**	+55.9 ± 6.2*
DAYS 29 - 36	MEAN±S.D.	+56.0 ± 7.2	+52.0 ± 6.0	+53.2 ± 6.2
DAYS 36 - 43	MEAN±S.D.	+42.5 ± 8.5	+41.4 ± 6.6	+40.0 ± 6.6
DAYS 43 - 50	MEAN±S.D.	+40.6 ± 8.6	+35.1 ± 5.1*	+34.6 ± 5.6*
DAYS 50 - 57	MEAN±S.D.	+32.6 ± 8.5	+31.6 ± 5.2	+28.8 ± 4.9
DAY 1 - PRECOHABITATION a	MEAN±S.D.	+445.1 ± 56.9	+415.6 ± 39.2*	+403.2 ± 31.2**
DAY 1 - TERMINATION b	MEAN±S.D.	+481.6 ± 61.6	+451.4 ± 39.3	+432.7 ± 38.2**

ALL WEIGHT VALUES IN GRAMS (G).

a. Precohabitation body weights were recorded on the day cohabitation was begun for the F1 generation rats; at that time these rats were 84 to 98 days of age.

b. Terminal body weights were recorded when the rats were 100 to 114 days of age.

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

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

000123

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE D4 (PAGE 1): ABSOLUTE FEED CONSUMPTION VALUES (G/DAY) - SUMMARY - F1 GENERATION MALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
RATS TESTED	N	25	25	25
FEED CONSUMPTION (G/DAY)				
DAYS 1 - 8	MEAN±S.D.	13.2 ± 1.4	12.8 ± 1.2	11.7 ± 1.5**
DAYS 8 - 15	MEAN±S.D.	19.4 ± 1.6	18.8 ± 1.6	17.6 ± 1.5**
DAYS 15 - 22	MEAN±S.D.	22.6 ± 3.6	22.1 ± 3.2	21.9 ± 2.1
DAYS 22 - 29	MEAN±S.D.	26.8 ± 2.7	25.6 ± 2.1	25.3 ± 2.1
DAYS 29 - 36	MEAN±S.D.	29.1 ± 3.1	27.8 ± 2.3	27.3 ± 2.4
DAYS 36 - 43	MEAN±S.D.	30.9 ± 3.3	30.0 ± 2.7	[24]a 29.4 ± 2.5
DAYS 43 - 50	MEAN±S.D.	31.1 ± 3.8	29.6 ± 3.0	28.9 ± 2.0
DAYS 50 - 57b	MEAN±S.D.	31.4 ± 3.5 [21]a	29.6 ± 2.2 [22]a	[24]a 29.3 ± 2.2
DAYS 1 - 57b	MEAN±S.D.	25.2 ± 2.4 [21]a	24.4 ± 2.0 [22]a	[24]a 23.9 ± 1.6

DAYS = DAYS POSTWEANING

[] = NUMBER OF VALUES AVERAGED

a. Excludes values that were associated with spillage.

b. Because feed consumption was recorded at weekly intervals, based on each rat's day postweaning, days 50-57 postweaning was the last interval in which a feed consumption value was recorded for the youngest rats in this group.

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

000124

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE D5 (PAGE 1): RELATIVE FEED CONSUMPTION VALUES (G/KG/DAY) - SUMMARY - F1 GENERATION MALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
RATS TESTED		N	25	25
FEED CONSUMPTION (G/KG/DAY)				
DAYS 1 - 8	MEAN±S.D.	177.2 ± 8.6	178.1 ± 13.7	180.4 ± 17.0
DAYS 8 - 15	MEAN±S.D.	155.6 ± 7.9	155.3 ± 9.1	162.7 ± 12.7*
DAYS 15 - 22	MEAN±S.D.	122.9 ± 15.8	123.7 ± 15.8	135.6 ± 12.6**
DAYS 22 - 29	MEAN±S.D.	109.4 ± 4.2	108.3 ± 4.8	116.1 ± 6.9**
DAYS 29 - 36	MEAN±S.D.	95.7 ± 3.4	95.9 ± 4.8	99.8 ± 6.4**
DAYS 36 - 43	MEAN±S.D.	87.6 ± 4.4	89.2 ± 6.3	[24]a
DAYS 43 - 50	MEAN±S.D.	78.8 ± 4.8	78.9 ± 7.0	92.2 ± 5.9**
DAYS 50 - 57b	MEAN±S.D.	74.0 ± 7.0	72.0 ± 2.8	81.3 ± 3.7
DAYS 1 - 57b	MEAN±S.D.	[21]a	[22]a	[24]a
		97.6 ± 3.4	97.0 ± 4.5	75.7 ± 4.8
		[21]a	[22]a	[24]a
				101.8 ± 4.4**
				[24]a

DAYS = DAYS POSTWEANING

[] = NUMBER OF VALUES AVERAGED

a. Excludes values that were associated with spillage.

b. Because feed consumption was recorded at weekly intervals, based on each rat's day postweaning, days 50-57 postweaning was the last interval in which a feed consumption value was recorded for the youngest rats in this group.

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

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

000125

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE D6 (PAGE 1): SEXUAL MATURATION - SUMMARY - F1 GENERATION MALE RATS

DOSAGE GROUP		I	II	III
DOSAGE (MG/KG/DAY)		0 (VEHICLE)	1	5
RATS TESTED	N	30	30	30
PREPUTIAL SEPARATION a	MEAN±S.D.	45.7 ± 1.6	45.2 ± 1.8	47.3 ± 1.7**

a. Average day postpartum that the prepuce was observed to be separated.

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

000126

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE D7 (PAGE 1): PASSIVE AVOIDANCE PERFORMANCE - SUMMARY - F1 GENERATION MALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
SESSION 1a	N	24	24	22
TRIALS TO CRITERION	MEAN±S.D.	5.3 ± 2.4	5.9 ± 2.9	4.4 ± 1.0
LATENCY TRIAL 1b	MEAN±S.D.	5.9 ± 3.7	6.7 ± 3.4	6.8 ± 3.6
LATENCY TRIAL 2b	MEAN±S.D.	27.6 ± 22.5	22.7 ± 16.7	34.8 ± 21.9
FAILED TO LEARN c	N(%)	0(0.0)	1(4.2)	0(0.0)
SESSION 2a	N	24	23	22
TRIALS TO CRITERION	MEAN±S.D.	3.5 ± 2.6	3.2 ± 1.9	3.2 ± 1.2
LATENCY TRIAL 1b	MEAN±S.D.	37.8 ± 22.8	34.6 ± 24.0	38.7 ± 24.0

- a. Sessions 1 (Learning Phase) and 2 (Retention Phase) of testing were separated by a one-week interval.
b. The latency was recorded in seconds.
c. Number of rats that did not meet the criterion in Session 1 (Learning Phase); Session 2 (Retention Phase) values for these rats were excluded from group averages and statistical analyses.

000127

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE D8 (PAGE 1): WATERMAZE PERFORMANCE - SUMMARY - F1 GENERATION MALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
SESSION 1a	N	24	24	22
TRIALS TO CRITERION	MEAN±S.D.	8.9 ± 2.6	8.5 ± 2.1	9.6 ± 3.0
ERRORS PER TRIAL	MEAN±S.D.	0.36 ± 0.19	0.38 ± 0.18	0.39 ± 0.19
LATENCY TRIAL 2b	MEAN±S.D.	11.7 ± 12.0	15.4 ± 12.0	9.8 ± 4.7
FAILED TO LEARN c	N(%)	1(4.2)	0(0.0)	2(9.1)
SESSION 2a	N	23	24	20
TRIALS TO CRITERION	MEAN±S.D.	5.5 ± 0.9	6.0 ± 2.0	5.6 ± 1.6
ERRORS PER TRIAL	MEAN±S.D.	0.06 ± 0.10	0.07 ± 0.13	0.06 ± 0.10
LATENCY TRIAL 1b	MEAN±S.D.	8.4 ± 6.5	8.4 ± 5.0	7.4 ± 3.3

- a. Session 1 (Learning Phase) and Session 2 (Retention Phase) of testing were separated by a one-week interval.
b. The latency was recorded in seconds.
c. Number of rats that did not meet the criterion in Session 1 (Learning Phase); session 2 (Retention Phase) values for these rats were excluded from group averages and statistical analyses.

000128

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE D9 (PAGE 1): MATING AND FERTILITY - SUMMARY - F1 GENERATION MALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
RATS IN COHABITATION	N	25	25	25
DAYS IN COHABITATION a	MEAN±S.D.	4.0 ± 1.8	3.3 ± 2.0	3.0 ± 1.5
RATS THAT MATED b	N(%)	21 (84.0)	22 (88.0)	24 (96.0)
FERTILITY INDEX c,d	N/N (%)	20/21 (95.2)	22/25 (88.0)	23/25 (92.0)
RATS WITH CONFIRMED MATING DATES e	N	21	22	24
RATS MATING f DAYS 1-7	N(%)	21 (100.0)	22 (100.0)	24 (100.0)
RATS PREGNANT/RATS IN COHABITATION e	N/N (%)	20/25 (80.0)	22/25 (88.0)	23/25 (92.0)

- a. Restricted to rats with a confirmed mating date on days 1 to 7 of cohabitation and rats that did not mate.
b. Includes only one mating for each male rat.
c. Number of pregnancies/number of rats that mated.
d. Includes only one pregnancy for each rat that impregnated more than one female rat.
e. Includes only one confirmed mating for each male rat.
f. Restricted to rats with a confirmed mating date on days 1 to 7 of cohabitation.

000129

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE D10 (PAGE 1): NECROPSY OBSERVATIONS - SUMMARY - F1 GENERATION MALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
RATS EXAMINED a	N	25	25	25
MORTALITY	N	0	0	0
APPEARED NORMAL	N	24	24	25
TESTES:				
LEFT, SMALL AND FLACCID	N	1	0	0
EPIDIDYMIDES:				
LEFT, SMALL AND FLACCID	N	1	0	0
SMALL	N	0	1	0

a. Refer to the individual clinical observations table (Table D13) for external observations confirmed at necropsy.

000130

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE D11 (PAGE 1): TERMINAL BODY WEIGHTS AND ORGAN WEIGHTS - SUMMARY - F1 GENERATION MALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
RATS TESTED	N	25	25	25
TERMINAL BODY WEIGHTS	MEAN±S.D.	533.7 ± 65.2	502.0 ± 42.4	478.1 ± 40.9**
EPIDIDYMIS LEFT	MEAN±S.D.	0.70 ± 0.08 [24]a	0.67 ± 0.08 [24]a	0.67 ± 0.09
TESTIS LEFT	MEAN±S.D.	1.86 ± 0.12 [24]a	1.74 ± 0.14**	1.82 ± 0.13
SEMINAL VESICLES WITH FLUID	MEAN±S.D.	1.68 ± 0.28	1.62 ± 0.31	1.53 ± 0.37
SEMINAL VESICLES WITHOUT FLUID	MEAN±S.D.	1.07 ± 0.21	1.00 ± 0.20	0.99 ± 0.26
EPIDIDYMIS RIGHT	MEAN±S.D.	0.72 ± 0.08	0.68 ± 0.10	0.68 ± 0.09
TESTIS RIGHT	MEAN±S.D.	1.84 ± 0.11	1.76 ± 0.13	1.82 ± 0.16
PROSTATE	MEAN±S.D.	0.95 ± 0.20	0.99 ± 0.26	0.98 ± 0.20

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

[] = NUMBER OF VALUES AVERAGED

a. Excludes values for rats that had abnormal organs (weight affected) or organs damaged (weight affected).

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

000131

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE D12 (PAGE 1): RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - SUMMARY - F1 GENERATION MALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
RATS TESTED	N	25	25	25
TERMINAL BODY WEIGHTS	MEAN±S.D.	533.7 ± 65.2	502.0 ± 42.4	478.1 ± 40.9**
EPIDIDYMIS LEFT	MEAN±S.D.	0.132 ± 0.023 [24]a	0.133 ± 0.014 [24]a	0.140 ± 0.016
TESTIS LEFT	MEAN±S.D.	0.350 ± 0.046 [24]a	0.348 ± 0.033	0.384 ± 0.035**
SEMINAL VESICLES WITH FLUID	MEAN±S.D.	0.318 ± 0.061	0.324 ± 0.065	0.323 ± 0.078
SEMINAL VESICLES WITHOUT FLUID	MEAN±S.D.	0.202 ± 0.044	0.200 ± 0.044	0.207 ± 0.052
EPIDIDYMIS RIGHT	MEAN±S.D.	0.136 ± 0.020	0.134 ± 0.017	0.143 ± 0.017
TESTIS RIGHT	MEAN±S.D.	0.349 ± 0.049	0.352 ± 0.032	0.381 ± 0.036**
PROSTATE	MEAN±S.D.	0.180 ± 0.044	0.199 ± 0.053	0.207 ± 0.045

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

[] = NUMBER OF VALUES AVERAGED

RATIOS (%) = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) x 100.

a. Excludes values for rats that had abnormal organs (weight affected) or organs damaged (weight affected).

** Significantly different from the vehicle control group value (p<0.01).

APPENDIX E
REPORT TABLES – F1 GENERATION FEMALE RATS

000133

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E1 (PAGE 1): CLINICAL OBSERVATIONS - SUMMARY - F1 GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)	I 0 (VEHICLE)	II 1	III 5
<u>PRECOHABITATION (DAY 1 OF STUDY TO THE DAY OF COHABITATION):</u>			
MAXIMUM POSSIBLE INCIDENCE	1861/ 25	1857/ 25	1841/ 25
MORTALITY	0	0	0
PORTION OF TAIL MISSING	0/ 0	0/ 0	62/ 1
INCISORS: TOTAL	0/ 0	0/ 0	31/ 1
MISSING/BROKEN	0/ 0	0/ 0	31/ 1
MISALIGNED	0/ 0	0/ 0	31/ 1
CHROMODACRYORRHEA	0/ 0	0/ 0	24/ 1
SWOLLEN AND PURPLE EAR(S)	0/ 0	6/ 1	23/ 1
LOCALIZED ALOPECIA: TOTAL	30/ 2	0/ 0	20/ 1
BACK	0/ 0	0/ 0	20/ 1
HEAD	7/ 1	0/ 0	0/ 0
LIMBS	23/ 1	0/ 0	0/ 0
PTOSIS	0/ 0	0/ 0	1/ 1
URINE-STAINED ABDOMINAL FUR	0/ 0	1/ 1	0/ 0
HEAD: SCAB	37/ 2	0/ 0	0/ 0
HEAD: LESION	4/ 1	0/ 0	0/ 0

STATISTICAL ANALYSES OF CLINICAL OBSERVATION DATA WERE RESTRICTED TO THE NUMBER OF RATS WITH OBSERVATIONS.
MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP.
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RATS WITH OBSERVATION.

000134

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E1 (PAGE 2): CLINICAL OBSERVATIONS - SUMMARY - F1 GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)	I 0 (VEHICLE)	II 1	III 5
<u>PRESUMED GESTATION: a</u>			
MAXIMUM POSSIBLE INCIDENCE	536/ 24	553/ 25	553/ 25
MORTALITY	0	0	0
SWOLLEN AND PURPLE EAR(S)	40/ 2	43/ 2	44/ 2
INCISORS: TOTAL	24/ 2	0/ 0	23/ 1
MISALIGNED	24/ 2	0/ 0	23/ 1
MISSING/BROKEN	7/ 1	0/ 0	0/ 0
PORTION OF TAIL MISSING	0/ 0	0/ 0	21/ 1
LOCALIZED ALOPECIA: TOTAL	50/ 3	0/ 0**	0/ 0**
HEAD	28/ 2	0/ 0	0/ 0
LIMBS	22/ 1	0/ 0	0/ 0
CHROMODACRYORRHEA	5/ 2	0/ 0	0/ 0

STATISTICAL ANALYSES OF CLINICAL OBSERVATION DATA WERE RESTRICTED TO THE NUMBER OF RATS WITH OBSERVATIONS.
MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP.

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

a. Restricted to rats with a confirmed mating date.

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

000135

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E1 (PAGE 3): CLINICAL OBSERVATIONS - SUMMARY - F1 GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)	I 0 (VEHICLE)	II 1	III 5
<u>LACTATION:</u>			
MAXIMUM POSSIBLE INCIDENCE	483/ 23	525/ 25	487/ 24
MORTALITY	0	0	0
SWOLLEN AND PURPLE EAR(S)	42/ 2	42/ 2	42/ 2
INCISORS: MISALIGNED	21/ 1	0/ 0	21/ 1
PORTION OF TAIL MISSING	0/ 0	0/ 0	21/ 1
CHROMODACRYORRHEA	0/ 0	0/ 0	2/ 1
LOCALIZED ALOPECIA: LIMBS	21/ 1	8/ 1	0/ 0

STATISTICAL ANALYSES OF CLINICAL OBSERVATION DATA WERE RESTRICTED TO THE NUMBER OF RATS WITH OBSERVATIONS.
MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP.
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RATS WITH OBSERVATION.

000136

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E2 (PAGE 1): BODY WEIGHTS - PRECOHABITATION - SUMMARY - F1 GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
RATS TESTED	N	25	25	25
BODY WEIGHT (G)				
DAY 1	MEAN±S.D.	49.4 ± 4.8	48.1 ± 5.1	41.6 ± 7.3**
DAY 8	MEAN±S.D.	88.3 ± 7.1	85.4 ± 5.9	76.5 ± 11.0**
DAY 15	MEAN±S.D.	129.4 ± 9.4	125.5 ± 7.7	114.2 ± 13.5**
DAY 22	MEAN±S.D.	159.8 ± 9.4	156.6 ± 9.5	147.0 ± 13.8**
DAY 29	MEAN±S.D.	182.4 ± 12.9	178.0 ± 10.2	169.6 ± 13.3**
DAY 36	MEAN±S.D.	204.0 ± 14.4	199.2 ± 9.2	188.3 ± 15.4**
DAY 43	MEAN±S.D.	222.0 ± 17.3	216.1 ± 13.5	204.9 ± 15.9**
DAY 50	MEAN±S.D.	236.5 ± 17.4	228.6 ± 12.8	216.8 ± 16.7**
DAY 57	MEAN±S.D.	249.9 ± 19.1	242.3 ± 14.5	227.2 ± 18.4**
PRECOHABITATION a	MEAN±S.D.	272.0 ± 22.9	258.7 ± 14.9*	243.8 ± 18.9**

DAY = DAY POSTWEANING

a. Precohabitation body weights were recorded on the day cohabitation was begun for the F1 generation rats; at that time these rats were 84 to 98 days of age.

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

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

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E3 (PAGE 1): BODY WEIGHT CHANGES - PRECOHABITATION - SUMMARY - F1 GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
RATS TESTED	N	25	25	25
BODY WEIGHT CHANGE (G)				
DAYS 1 - 8	MEAN±S.D.	+38.9 ± 3.8	+37.3 ± 2.8	+34.9 ± 4.3**
DAYS 8 - 15	MEAN±S.D.	+41.2 ± 3.8	+40.0 ± 4.2	+37.7 ± 4.7**
DAYS 15 - 22	MEAN±S.D.	+30.4 ± 4.9	+31.2 ± 4.7	+32.8 ± 5.6
DAYS 22 - 29	MEAN±S.D.	+22.6 ± 6.4	+21.4 ± 2.8	+22.6 ± 3.8
DAYS 29 - 36	MEAN±S.D.	+21.6 ± 6.7	+21.2 ± 6.3	+18.7 ± 4.7
DAYS 36 - 43	MEAN±S.D.	+18.0 ± 6.6	+16.8 ± 8.6	+16.6 ± 4.6
DAYS 43 - 50	MEAN±S.D.	+14.5 ± 5.8	+12.5 ± 4.4	+11.9 ± 5.3
DAYS 50 - 57	MEAN±S.D.	+13.4 ± 6.1	+13.7 ± 5.4	+10.4 ± 5.8
DAYS 1 - 57	MEAN±S.D.	+200.5 ± 17.7	+194.2 ± 15.2	+185.6 ± 15.1**
DAY 1 - PRECOHABITATION a	MEAN±S.D.	+222.7 ± 22.2	+210.6 ± 14.0*	+202.2 ± 17.1**

DAYS = DAY POSTWEANING

a. Precohabitation body weights were recorded on the day cohabitation was begun for the F1 generation rats; at that time these rats were 84 to 98 days of age.

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

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

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E4 (PAGE 1): MATERNAL BODY WEIGHTS - GESTATION - SUMMARY - F1 GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
RATS TESTED	N	25	25	25
PREGNANT	N	23	25	24
INCLUDED IN ANALYSES	N	23	24a	24
MATERNAL BODY WEIGHT (G)				
DAY 0	MEAN±S.D.	271.8 ± 23.5	259.4 ± 14.4*	244.6 ± 22.9**
DAY 1	MEAN±S.D.	281.1 ± 24.0	[23]b 267.6 ± 14.7*	253.6 ± 21.3**
DAY 2	MEAN±S.D.	288.4 ± 23.8	[23]b 272.1 ± 15.5**	256.6 ± 22.7**
DAY 3	MEAN±S.D.	292.6 ± 25.6	[23]b 274.4 ± 14.9*	259.0 ± 23.1**
DAY 4	MEAN±S.D.	294.7 ± 27.6	276.3 ± 15.4*	259.7 ± 22.0**
DAY 5	MEAN±S.D.	297.3 ± 28.2	278.4 ± 13.7*	262.2 ± 21.7**
DAY 6	MEAN±S.D.	300.6 ± 27.4	282.1 ± 14.9*	264.4 ± 23.2**
DAY 7	MEAN±S.D.	304.8 ± 27.6	284.6 ± 15.0*	268.5 ± 22.2**
DAY 8	MEAN±S.D.	308.1 ± 27.4	288.4 ± 15.8*	271.6 ± 23.1**
DAY 9	MEAN±S.D.	311.6 ± 28.5	291.8 ± 14.4*	275.0 ± 23.2**
DAY 10	MEAN±S.D.	317.3 ± 28.8	297.0 ± 14.6*	279.6 ± 23.3**
DAY 11	MEAN±S.D.	324.0 ± 28.2	302.5 ± 15.4*	286.0 ± 24.3**
DAY 12	MEAN±S.D.	328.4 ± 29.0	306.2 ± 16.4**	289.8 ± 24.2**
DAY 13	MEAN±S.D.	331.0 ± 29.6	309.7 ± 16.2*	293.4 ± 24.2**

DAY = DAY OF GESTATION

[] = NUMBER OF VALUES AVERAGED

a. Excludes values for dam 12228, which had a litter consisting of two pups.

b. Excludes a value that was not recorded.

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

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

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E4 (PAGE 2): MATERNAL BODY WEIGHTS - GESTATION - SUMMARY - F1 GENERATION FEMALE RATS

DOSAGE GROUP		I	II	III
DOSAGE (MG/KG/DAY)		0 (VEHICLE)	1	5
RATS TESTED	N	25	25	25
PREGNANT	N	23	25	24
INCLUDED IN ANALYSES	N	23	24a	24
MATERNAL BODY WEIGHT (G)				
DAY 14	MEAN+S.D.	336.5 ± 31.1	314.8 ± 16.0*	299.1 ± 24.3**
DAY 15	MEAN+S.D.	344.1 ± 31.2	322.2 ± 17.0*	307.2 ± 23.6**
DAY 16	MEAN+S.D.	354.2 ± 33.3	332.1 ± 17.3*	319.1 ± 24.6**
DAY 17	MEAN+S.D.	365.3 ± 31.3	346.2 ± 18.4*	333.8 ± 25.1**
DAY 18	MEAN+S.D.	377.8 ± 32.5	361.9 ± 20.2*	348.8 ± 26.1**
DAY 19	MEAN+S.D.	390.4 ± 33.2	375.7 ± 21.2	363.0 ± 27.7**
DAY 20	MEAN+S.D.	403.1 ± 35.8	388.8 ± 21.5	376.0 ± 26.9**

DAY = DAY OF GESTATION

a. Excludes values for dam 12228, which had a litter consisting of two pups.

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

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

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E5 (PAGE 1): MATERNAL BODY WEIGHT CHANGES - GESTATION - SUMMARY - F1 GENERATION FEMALE RATS

DOSAGE GROUP		I	II	III
DOSAGE (MG/KG/DAY)		0 (VEHICLE)	1	5
RATS TESTED	N	25	25	25
PREGNANT	N	23	25	24
INCLUDED IN ANALYSES	N	23	24a	24
MATERNAL BODY WEIGHT CHANGE (G)				
DAYS 0 - 7	MEAN+S.D.	+33.0 ± 13.1	+25.5 ± 6.0* [23]b	+23.9 ± 4.3**
DAYS 7 - 10	MEAN+S.D.	+12.5 ± 3.9	+12.4 ± 4.3	+11.0 ± 5.8
DAYS 10 - 14	MEAN+S.D.	+19.1 ± 7.1	+17.8 ± 4.1	+19.5 ± 4.0
DAYS 14 - 17	MEAN+S.D.	+28.8 ± 6.2	+31.3 ± 6.6	+34.7 ± 4.6**
DAYS 17 - 20	MEAN+S.D.	+37.9 ± 10.6	+42.6 ± 12.3	+42.2 ± 6.7
DAYS 0 - 20	MEAN+S.D.	+131.3 ± 24.5	+130.6 ± 16.8 [23]b	+131.4 ± 14.3

DAYS = DAYS OF GESTATION

[] = NUMBER OF VALUES AVERAGED

a. Excludes values for dam 12228, which had a litter consisting of two pups.

b. Excludes a value that was not recorded.

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

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

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E6 (PAGE 1): MATERNAL BODY WEIGHTS - LACTATION - SUMMARY - F1 GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
RATS TESTED	N	25	25	25
PREGNANT	N	23	25	24
DELIVERED LITTERS	N	23	25	24
INCLUDED IN ANALYSES	N	23	24a	24
MATERNAL BODY WEIGHT (G)				
DAY 1	MEAN+S.D.	316.3 ± 29.1	296.4 ± 14.8*	283.6 ± 25.6**
DAY 4	MEAN+S.D.	325.5 ± 28.7	307.8 ± 14.2	289.4 ± 23.0**
DAY 7	MEAN+S.D.	332.2 ± 30.1	310.4 ± 15.6*	[23]b 294.4 ± 22.7**
DAY 10	MEAN+S.D.	343.5 ± 30.9	330.9 ± 14.5	[23]b 308.4 ± 20.1**
DAY 14	MEAN+S.D.	351.0 ± 22.8	338.4 ± 18.7	[23]b 318.6 ± 25.4**
DAY 21	MEAN+S.D.	335.2 ± 19.1	326.0 ± 15.6	[23]b 310.5 ± 23.6**

DAY = DAY OF LACTATION

[] = NUMBER OF VALUES AVERAGED

a. Excludes values for dam 12228, which had a litter consisting of two pups.

b. Excludes values for a dam that had no surviving pups.

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

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

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E7 (PAGE 1): MATERNAL BODY WEIGHT CHANGES - LACTATION - SUMMARY - F1 GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
RATS TESTED	N	25	25	25
PREGNANT	N	23	25	24
DELIVERED LITTERS	N	23	25	24
INCLUDED IN ANALYSES	N	23	24a	23b
MATERNAL BODY WEIGHT CHANGE (G)				
DAYS 1 - 4	MEAN+S.D.	+9.1 ± 9.1	+11.4 ± 7.7	+8.2 ± 9.8
DAYS 4 - 7	MEAN+S.D.	+6.7 ± 6.6	+2.5 ± 14.9	+5.0 ± 8.9
DAYS 7 - 10	MEAN+S.D.	+11.3 ± 15.2	+20.5 ± 12.6	+14.0 ± 8.4
DAYS 10 - 14	MEAN+S.D.	+7.4 ± 19.2	+7.5 ± 8.4	+10.2 ± 15.1
DAYS 14 - 21	MEAN+S.D.	-15.7 ± 12.6	-12.4 ± 13.1	-8.1 ± 19.4
DAYS 1 - 21	MEAN+S.D.	+18.9 ± 17.8	+29.5 ± 12.0*	+29.3 ± 18.1*

DAYS = DAYS OF LACTATION

a. Excludes values for dam 12228, which had a litter consisting of two pups.

b. Excludes values for a dam that had no surviving pups.

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

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E8 (PAGE 1): ABSOLUTE FEED CONSUMPTION VALUES (G/DAY) - PRECOHABITATION - SUMMARY - F1 GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
RATS TESTED	N	25	25	25
FEED CONSUMPTION (G/DAY)				
DAYS 1 - 8	MEAN±S.D.	12.8 ± 1.4	12.2 ± 0.8	11.5 ± 3.1** [24]a
DAYS 8 - 15	MEAN±S.D.	17.5 ± 1.8	17.2 ± 1.3	17.2 ± 2.0
DAYS 15 - 22	MEAN±S.D.	18.3 ± 2.7	18.2 ± 2.4	19.0 ± 2.2
DAYS 22 - 29	MEAN±S.D.	19.8 ± 1.9	18.9 ± 1.6	19.2 ± 1.6
DAYS 29 - 36	MEAN±S.D.	20.5 ± 2.2 [24]a	19.3 ± 1.7 [24]a	18.7 ± 3.1
DAYS 36 - 43	MEAN±S.D.	22.5 ± 3.9 [24]a	21.5 ± 4.3 [24]a	19.6 ± 2.3** [24]a
DAYS 43 - 50	MEAN±S.D.	21.7 ± 2.7 [24]a	20.2 ± 2.2*	19.4 ± 2.4** [22]a
DAYS 50 - 57b	MEAN±S.D.	22.4 ± 2.0	21.1 ± 2.4* [23]a	20.6 ± 2.2** [23]a
DAYS 1 - 57b	MEAN±S.D.	19.4 ± 1.6	18.4 ± 1.4* [23]a	18.2 ± 1.5** [23]a

DAYS = DAY POSTWEANING

[] = NUMBER OF VALUES AVERAGED

a. Excludes values that were associated with spillage.

b. Because feed consumption was recorded at weekly intervals, based on each rat's day postweaning, days 50-57 postweaning was the last interval in which a feed consumption value was recorded for the youngest rats.

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

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

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E9 (PAGE 1): RELATIVE FEED CONSUMPTION VALUES (G/KG/DAY) - PRECOHABITATION - SUMMARY - F1 GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
RATS TESTED	N	25	25	25
FEED CONSUMPTION (G/KG/DAY)				
DAYS 1 - 8	MEAN±S.D.	186.1 ± 13.0	183.9 ± 13.4	198.1 ± 49.3 [24]a
DAYS 8 - 15	MEAN±S.D.	160.6 ± 11.7	162.9 ± 9.7	181.2 ± 18.7**
DAYS 15 - 22	MEAN±S.D.	126.8 ± 17.9	129.2 ± 15.4	146.4 ± 17.1**
DAYS 22 - 29	MEAN±S.D.	116.0 ± 8.4	112.9 ± 6.6	122.0 ± 11.1*
DAYS 29 - 36	MEAN±S.D.	106.3 ± 8.8 [24]a	102.3 ± 7.6 [24]a	104.7 ± 16.7
DAYS 36 - 43	MEAN±S.D.	105.1 ± 16.5 [24]a	103.6 ± 19.8 [24]a	100.3 ± 12.4 [24]a
DAYS 43 - 50	MEAN±S.D.	94.8 ± 8.9 [24]a	90.7 ± 7.2	92.2 ± 10.3 [22]a
DAYS 50 - 57b	MEAN±S.D.	92.4 ± 6.3	89.5 ± 8.6 [23]a	92.8 ± 8.4 [23]a
DAYS 1 - 57b	MEAN±S.D.	115.0 ± 6.0	112.2 ± 6.3 [23]a	117.9 ± 7.7 [23]a

DAYS = DAY POSTWEANING

[] = NUMBER OF VALUES AVERAGED

a. Excludes values that were associated with spillage.

b. Because feed consumption was recorded at weekly intervals, based on each rat's day postweaning, days 50-57 postweaning was the last interval in which a feed consumption value was recorded for the youngest rats.

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

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

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E10 (PAGE 1): MATERNAL ABSOLUTE FEED CONSUMPTION VALUES (G/DAY) - GESTATION - SUMMARY - F1 GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
RATS TESTED	N	25	25	25
PREGNANT	N	23	25	24
INCLUDED IN ANALYSES	N	23	24a	24
MATERNAL FEED CONSUMPTION (G/DAY)				
DAYS 0 - 7	MEAN±S.D.	26.4 ± 3.9	23.4 ± 2.2* [23]b	22.4 ± 2.2**
DAYS 7 - 10	MEAN±S.D.	27.3 ± 4.2 [22]b	26.2 ± 3.9	24.0 ± 3.5**
DAYS 10 - 14	MEAN±S.D.	27.2 ± 4.6	24.9 ± 2.2	25.1 ± 2.9
DAYS 14 - 17	MEAN±S.D.	27.6 ± 4.3	25.7 ± 3.0	26.8 ± 4.3
DAYS 17 - 20	MEAN±S.D.	26.1 ± 5.3	25.8 ± 3.6	25.7 ± 2.7
DAYS 0 - 20	MEAN±S.D.	26.9 ± 3.9	24.9 ± 2.1 [23]b	24.3 ± 2.4

DAYS = DAYS OF GESTATION

[] = NUMBER OF VALUES AVERAGED

a. Excludes values for dam 12228, which had a litter consisting of two pups.

b. Excludes values that were not recorded, as well as those associated with spillage.

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

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

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E11 (PAGE 1): MATERNAL RELATIVE FEED CONSUMPTION VALUES (G/KG/DAY) - GESTATION - SUMMARY - F1 GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
RATS TESTED	N	25	25	25
PREGNANT	N	23	25	24
INCLUDED IN ANALYSES	N	23	24a	24
MATERNAL FEED CONSUMPTION (G/KG/DAY)				
DAYS 0 - 7	MEAN±S.D.	90.6 ± 9.7	85.3 ± 6.4 { 23}b	86.8 ± 7.6
DAYS 7 - 10	MEAN±S.D.	88.1 ± 9.4 { 22}b	90.1 ± 13.7	87.7 ± 11.4
DAYS 10 - 14	MEAN±S.D.	83.0 ± 10.6	81.5 ± 5.9	86.7 ± 8.9
DAYS 14 - 17	MEAN±S.D.	78.8 ± 9.3	78.2 ± 7.7	85.4 ± 14.0*
DAYS 17 - 20	MEAN±S.D.	67.9 ± 11.2	70.0 ± 8.8	72.3 ± 5.7
DAYS 0 - 20	MEAN±S.D.	82.7 ± 8.4	81.2 ± 5.8 { 23}b	83.7 ± 7.4

DAYS = DAYS OF GESTATION

{ } = NUMBER OF VALUES AVERAGED

a. Excludes values for dam 12228, which had a litter consisting of two pups.

b. Excludes values that were not recorded, as well as those associated with spillage.

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

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E12 (PAGE 1): MATERNAL ABSOLUTE FEED CONSUMPTION VALUES (G/DAY) - LACTATION - SUMMARY - F1 GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
RATS TESTED	N	25	25	25
PREGNANT	N	23	25	24
DELIVERING LITTERS	N	23	25	24
INCLUDED IN ANALYSES	N	23	24a	23b
MATERNAL FEED CONSUMPTION (G/DAY)				
DAYS 1 - 4	MEAN±S.D.	30.2 ± 6.0	28.9 ± 3.6	25.4 ± 6.6*
DAYS 4 - 7	MEAN±S.D.	39.3 ± 4.3	[23]c 37.8 ± 3.4	31.9 ± 5.4**
DAYS 7 - 10	MEAN±S.D.	48.6 ± 5.4	47.8 ± 5.2	39.8 ± 6.4**
DAYS 10 - 14d	MEAN±S.D.	58.9 ± 5.3	56.5 ± 7.5	49.7 ± 8.4**
DAYS 1 - 14d	MEAN±S.D.	45.4 ± 4.1	44.0 ± 4.2	37.7 ± 5.3**

DAYS = DAYS OF LACTATION

[] = NUMBER OF VALUES AVERAGED

a. Excludes values for dam 12228, which had a litter consisting of two pups.

b. Excludes values for a dam that had no surviving pups.

c. Excludes a value that was associated with spillage.

d. Because it is presumed that the pups begin to consume maternal feed after day 14 of lactation, maternal feed consumption values were not tabulated on days 14 to 21 of lactation.

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

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

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E13 (PAGE 1): MATERNAL RELATIVE FEED CONSUMPTION VALUES (G/KG/DAY) - LACTATION - SUMMARY - F1 GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
RATS TESTED	N	25	25	25
PREGNANT	N	23	25	24
DELIVERED LITTERS	N	23	25	24
INCLUDED IN ANALYSES	N	23	24a	23b
MATERNAL FEED CONSUMPTION (G/KG/DAY)				
DAYS 1 - 4	MEAN±S.D.	94.6 ± 19.3	96.0 ± 12.5 [23]c	89.7 ± 24.6
DAYS 4 - 7	MEAN±S.D.	120.1 ± 13.3	122.5 ± 11.0	109.3 ± 17.5*
DAYS 7 - 10	MEAN±S.D.	144.3 ± 14.3	148.9 ± 13.4	132.0 ± 19.8*
DAYS 10 - 14d	MEAN±S.D.	170.6 ± 20.3	168.6 ± 19.1	158.6 ± 24.6
DAYS 1 - 14d	MEAN±S.D.	136.7 ± 14.5	139.0 ± 11.2	126.5 ± 17.0*

DAYS = DAYS OF LACTATION

[] = NUMBER OF VALUES AVERAGED

a. Excludes values for dam 12228, which had a litter consisting of two pups.

b. Excludes values for a dam that had no surviving pups.

c. Excludes a value that was associated with spillage.

d. Because it is presumed that the pups begin to consume maternal feed after day 14 of lactation, maternal feed consumption values were not tabulated on days 14 to 21 of lactation.

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

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E14 (PAGE 1): SEXUAL MATURATION - SUMMARY - F1 GENERATION FEMALE RATS

DOSAGE GROUP		I	II	III
DOSAGE (MG/KG/DAY)		0 (VEHICLE)	1	5
RATS TESTED	N	25	25	25
VAGINA PATENT a	MEAN±S.D.	30.8 ± 1.8	32.4 ± 1.7**	31.8 ± 2.0

a. Average day postpartum that the vagina was patent.

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

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E15 (PAGE 1): PASSIVE AVOIDANCE PERFORMANCE - SUMMARY - F1 GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
SESSION 1a	N	24	24	22
TRIALS TO CRITERION	MEAN±S.D.	5.8 ± 2.4	4.9 ± 2.3	4.9 ± 1.4
LATENCY TRIAL 1b	MEAN±S.D.	8.8 ± 6.0	7.0 ± 3.7	8.9 ± 5.1
LATENCY TRIAL 2b	MEAN±S.D.	25.4 ± 19.2	22.6 ± 19.0	39.5 ± 20.5*
FAILED TO LEARN c	N(%)	0(0.0)	1(4.2)	0(0.0)
SESSION 2a	N	24	23	22
TRIALS TO CRITERION	MEAN±S.D.	3.9 ± 3.0	3.0 ± 1.0	3.9 ± 2.8
LATENCY TRIAL 1b	MEAN±S.D.	36.3 ± 22.4	37.6 ± 24.9	37.7 ± 20.2

- a. Sessions 1 (Learning Phase) and 2 (Retention Phase) of testing were separated by a one-week interval.
b. The latency was recorded in seconds.
c. Number of rats that did not meet the criterion in Session 1 (Learning Phase); Session 2 (Retention Phase) values for these rats were excluded from group averages and statistical analyses.
* Significantly different from the vehicle control group value ($p \leq 0.05$).

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E16 (PAGE 1): WATERMAZE PERFORMANCE - SUMMARY - F1 GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
SESSION 1a	N	24	24	22
TRIALS TO CRITERION	MEAN±S.D.	8.2 ± 2.1	7.9 ± 2.0	8.4 ± 2.3
ERRORS PER TRIAL	MEAN±S.D.	0.52 ± 0.70	0.30 ± 0.12	0.32 ± 0.16
LATENCY TRIAL 2b	MEAN±S.D.	13.7 ± 12.0	11.0 ± 4.6	13.2 ± 7.6
FAILED TO LEARN c	N(%)	0(0.0)	0(0.0)	0(0.0)
SESSION 2a	N	24	24	22
TRIALS TO CRITERION	MEAN±S.D.	7.5 ± 3.4	7.2 ± 2.9	6.3 ± 2.0
ERRORS PER TRIAL	MEAN±S.D.	0.13 ± 0.18	0.15 ± 0.18	0.09 ± 0.16
LATENCY TRIAL 1b	MEAN±S.D.	8.7 ± 4.7	10.8 ± 9.5	6.6 ± 2.2

- a. Session 1 (Learning Phase) and Session 2 (Retention Phase) of testing were separated by a one-week interval.
b. The latency was recorded in seconds.
c. Number of rats that did not meet the criterion in Session 1 (Learning Phase); Session 2 (Retention Phase) values for these rats were excluded from group averages and statistical analyses.

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E17 (PAGE 1): MATING AND FERTILITY - SUMMARY - F1 GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
RATS IN COHABITATION	N	25	25	25
DAYS IN COHABITATION a	MEAN±S.D.	4.7 ± 3.3	3.4 ± 2.3	3.2 ± 2.6
RATS THAT MATED	N(%)	24 (96.0)	25 (100.0)	25 (100.0)
FERTILITY INDEX b	N/N (%)	23/24 (95.8)	25/25 (100.0)	24/25 (96.0)
RATS WITH CONFIRMED MATING DATES	N	24	25	25
MATED BY FIRST MALE c DAYS 1-7	N(%)	21 (87.5)	22 (88.0)	24 (96.0)
MATED BY SECOND MALE c DAYS 8-14	N(%)	3 (12.5)	3 (12.0)	1 (4.0)
RATS PREGNANT/RATS IN COHABITATION	N/N (%)	23/25 (92.0)	25/25 (100.0)	24/25 (96.0)

- a. Restricted to rats with a confirmed mating date and rats that did not mate.
b. Number of pregnancies/number of rats that mated.
c. Restricted to rats with a confirmed mating date.

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E18 (PAGE 1): NECROPSY OBSERVATIONS - SUMMARY - F1 GENERATION FEMALE RATS

DOSAGE GROUP		I	II	III
DOSAGE (MG/KG/DAY)		0 (VEHICLE)	1	5
RATS EXAMINED a	N	25	25	25
MORTALITY	N	0	0	0
APPEARED NORMAL	N	25	24	25
KIDNEYS:				
RIGHT, PELVIS,				
MODERATE DILATION	N	0	1	0

a. Refer to the individual clinical observations table (Table E23) for external observations confirmed at necropsy.

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E19 (PAGE 1): NATURAL DELIVERY OBSERVATIONS - SUMMARY - F1 GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
RATS ASSIGNED TO NATURAL DELIVERY	N	25	25	25
PREGNANT	N(%)	23 (92.0)	25 (100.0)	24 (96.0)
DELIVERED LITTERS	N(%)	23 (100.0)	25 (100.0)	24 (100.0)
INCLUDED IN ANALYSES	N	23	24a	24
DURATION OF GESTATION b	MEAN±S.D.	22.9 ± 0.3 [23]	22.8 ± 0.4 [24]	22.6 ± 0.6* [24]
IMPLANTATION SITES PER DELIVERED LITTER	N MEAN±S.D.	353 15.3 ± 2.0 [23]	361 15.0 ± 2.0 [24]	355 14.8 ± 2.3 [24]
DAMS WITH STILLBORN PUPS	N(%)	2 (8.7)	2 (8.3)	8 (33.3)**
DAMS WITH NO LIVEBORN PUPS	N	0	0	0
GESTATION INDEX	% N/N	100.0 23/ 23	100.0 24/ 24	100.0 24/ 24
DAMS WITH ALL PUPS DYING DAYS 1-4 POSTPARTUM	N(%)	0 (0.0)	0 (0.0)	1 (4.2)
DAMS WITH ALL PUPS DYING DAYS 5-21 POSTPARTUM	N(%)	0 (0.0)	0 (0.0)	0 (0.0)

[] = NUMBER OF VALUES AVERAGED

GESTATION INDEX = (NUMBER OF DAMS WITH LIVEBORN PUPS/NUMBER OF PREGNANT RATS) X 100.

a. Excludes values for dam 12228, which had a litter consisting of two pups.

b. Calculated as the time (in days) elapsed between confirmed mating (arbitrarily defined as 0 hour) and the time (in days) the first pup was delivered.

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

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

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E20 (PAGE 1): LITTER OBSERVATIONS (NATURALLY DELIVERED PUPS) - SUMMARY - F2 GENERATION LITTERS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
DELIVERED LITTERS WITH ONE OR MORE LIVEBORN PUPS		N	23	25
INCLUDED IN ANALYSES		N	23	24a
PUPS DELIVERED (TOTAL)		N	331	349
		MEAN±S.D.	14.4 ± 2.5	14.5 ± 2.1
LIVEBORN		MEAN±S.D. N(%)	14.1 ± 2.8 325(98.2)	14.4 ± 2.0 347(99.4)
STILLBORN		MEAN±S.D. N(%)	0.3 ± 1.0 6(1.8)	0.1 ± 0.3 2(0.6)
CULLED		N	138	145
PUPS FOUND DEAD OR PRESUMED CANNIBALIZED				
DAY 1	N/N(%)	2/325(0.6)	1/347(0.3)	12/323(3.7)**
DAYS 2- 4	N/N(%)	2/323(0.6)	9/346(2.6)	36/311(11.6)**
DAYS 5- 7	N/N(%)	0/183(0.0)	0/192(0.0)	1/176(0.6)
DAYS 8-14	N/N(%)	0/183(0.0)	0/192(0.0)	3/175(1.7)**
DAYS 15-21	N/N(%)	0/183(0.0)	0/192(0.0)	0/172(0.0)
VIABILITY INDEX b	% N/N	98.8 321/325	97.1 337/347	85.1** 275/323
LACTATION INDEX c	% N/N	100.0 183/183	100.0 192/192	97.7** 172/176

DAY(S) = DAY(S) POSTPARTUM

a. Excludes values for litter 12228, which had consisted of two pups.

b. Number of live pups on day 4 postpartum(preculling)/number of liveborn pups on day 1 postpartum.

c. Number of live pups on day 21 postpartum/number of live pups on day 4 postpartum(postculling);

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

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-ETFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E20 (PAGE 2): LITTER OBSERVATIONS (NATURALLY DELIVERED PUPS) - SUMMARY - F2 GENERATION LITTERS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
DELIVERED LITTERS WITH ONE OR MORE LIVEBORN PUPS	N	23	25	24
INCLUDED IN ANALYSES	N	23	24a	24
SURVIVING PUPS/LITTER ^b				
DAY 1 ^c	MEAN±S.D.	14.1 ± 2.8	14.4 ± 2.0	13.4 ± 2.5
DAY 4 PRECULLING	MEAN±S.D.	14.0 ± 2.8	14.0 ± 1.9	11.4 ± 4.2*
DAY 4 POSTCULLING	MEAN±S.D.	8.0 ± 0.2	8.0 ± 0.0	7.3 ± 1.8
DAY 7	MEAN±S.D.	8.0 ± 0.2	8.0 ± 0.0	7.3 ± 1.9
DAY 14	MEAN±S.D.	8.0 ± 0.2	8.0 ± 0.0	7.2 ± 1.9
DAY 21	MEAN±S.D.	8.0 ± 0.2	8.0 ± 0.0	7.2 ± 1.9
PERCENT MALE PUPS PER NUMBER OF PUPS SEXED				
DAY 1 ^c	MEAN±S.D.	44.7 ± 14.4	51.5 ± 12.7	49.4 ± 13.4
DAY 4 PRECULLING	MEAN±S.D.	44.6 ± 14.4	52.0 ± 12.9	48.9 ± 13.2
DAY 4 POSTCULLING	MEAN±S.D.	48.5 ± 5.1	51.6 ± 7.6	[23]d 49.7 ± 8.2
DAY 7	MEAN±S.D.	48.5 ± 5.1	51.6 ± 7.6	[23]d 49.4 ± 7.2
DAY 14	MEAN±S.D.	48.5 ± 5.1	51.6 ± 7.6	[23]d 48.4 ± 7.5
DAY 21	MEAN±S.D.	48.5 ± 5.1	51.6 ± 7.6	[23]d 48.4 ± 7.5

DAY = DAY POSTPARTUM

[] = NUMBER OF VALUES AVERAGED

a. Excludes values for litter 12228, which had consisted of two pups.

b. Average number of live pups per litter, including litters with no surviving pups.

c. Includes pups born alive, found dead day 1 postpartum.

d. Excludes values for dams that had no surviving pups.

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

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E20 (PAGE 3): LITTER OBSERVATIONS (NATURALLY DELIVERED PUPS) - SUMMARY - F2 GENERATION LITTERS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 1	III 5
DELIVERED LITTERS WITH ONE OR MORE LIVEBORN PUPS		N		
		23	25	24
INCLUDED IN ANALYSES		N		
		23	24a	24
LIVE LITTER SIZE AT WEIGHING				
DAY 1	MEAN±S.D.	14.0 ± 2.9	14.4 ± 2.0	13.0 ± 2.7
DAY 4 PRECULLING	MEAN±S.D.	14.0 ± 2.8	14.0 ± 1.9	12.0 ± 3.5
DAY 4 POSTCULLING	MEAN±S.D.	8.0 ± 0.2	8.0 ± 0.0	[23]b 7.6 ± 1.0
DAY 7	MEAN±S.D.	8.0 ± 0.2	8.0 ± 0.0	[23]b 7.6 ± 1.2
DAY 14	MEAN±S.D.	8.0 ± 0.2	8.0 ± 0.0	[23]b 7.5 ± 1.2
DAY 21	MEAN±S.D.	8.0 ± 0.2	8.0 ± 0.0	[23]b 7.5 ± 1.2
PUP WEIGHT/LITTER (GRAMS)				
DAY 1	MEAN±S.D.	6.2 ± 0.4	6.1 ± 0.4	5.4 ± 0.5**
DAY 4 PRECULLING	MEAN±S.D.	8.3 ± 1.0	8.1 ± 0.7	6.9 ± 1.1**
DAY 4 POSTCULLING	MEAN±S.D.	8.5 ± 1.0	8.2 ± 0.7	[23]b 7.0 ± 1.1**
DAY 7	MEAN±S.D.	14.2 ± 1.3	13.7 ± 1.2	[23]b 11.0 ± 1.9**
DAY 14	MEAN±S.D.	30.6 ± 2.0	29.5 ± 2.7	[23]b 24.2 ± 3.8**
DAY 21	MEAN±S.D.	48.0 ± 3.8	46.5 ± 4.4	[23]b 38.7 ± 5.6**

DAY = DAY POSTPARTUM

[] = NUMBER OF VALUES AVERAGED

a. Excludes values for litter 12228, which had consisted of two pups.

b. Excludes values for dams that had no surviving pups.

** Significantly different from the vehicle control group value (p<0.01).

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E21 (PAGE 1): CLINICAL OBSERVATIONS FROM BIRTH TO DAY 21 POSTPARTUM - SUMMARY - F2 GENERATION PUPS

MATERNAL DOSAGE GROUP		I	II	III
MATERNAL DOSAGE (MG/KG/DAY)		0 (VEHICLE)	1	5
LITTERS EXAMINED (N)		23	25	24
TRANSIENT CLINICAL OBSERVATIONS: a		TOTAL FREQUENCY (DAYS x PUPS)/LITTERS WITH OBSERVATIONS		
NOT NURSING	N/N	0/ 0	1/ 1	3/ 3
COLD TO TOUCH	N/N	0/ 0	0/ 0	1/ 1
LEFT EYE, TRAUMATIZED CORNEA	N/N	7/ 1	0/ 0	0/ 0
LEFT EYE, EXOPHTHALMOS	N/N	1/ 1	0/ 0	0/ 0
PERSISTENT CLINICAL OBSERVATIONS: a		TOTAL FREQUENCY (DAYS x PUPS)/LITTERS WITH OBSERVATIONS		
PORTION OF TAIL BLACK	N/N	1/ 1	0/ 0	0/ 0

STATISTICAL ANALYSES WERE RESTRICTED TO THE NUMBER OF LITTERS WITH OBSERVATIONS.

N/N = TOTAL FREQUENCY (DAYS x PUPS)/LITTERS WITH OBSERVATIONS

a. Tabulation restricted to adverse observations; all other pups appeared normal.

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PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF
N-EtFOSE IN RATS (SPONSOR'S STUDY NUMBER: 6316.5)

TABLE E22 (PAGE 1): NECROPSY OBSERVATIONS - SUMMARY - F2 GENERATION PUPS

MATERNAL DOSAGE GROUP		I	II	III
MATERNAL DOSAGE (MG/KG/DAY)		0 (VEHICLE)	1	5
LITTERS EXAMINED (N)		23	25	24
TOTAL PUPS STILLBORN				
OR FOUND DEAD a,b	N	3	5	38
STILLBORN	N	1	1	13
FOUND DEAD	N	2	4	25
NO MILK IN STOMACH c	N(%)	2(100.0)	2(50.0)	13(52.0)
PUPS SACRIFICED AND NECROPSIED ON DAYS 4 OR 21 POSTPARTUM a				
LITTERS EVALUATED	N	23	25	23
PUPS EVALUATED	N	321	339	271
APPEARED NORMAL				
LITTER INCIDENCE	N(%)	22(95.6)	25(100.0)	23(100.0)
PUP INCIDENCE	N(%)	320(99.7)	339(100.0)	271(100.0)
EYES: LEFT, ABSENT				
LITTER INCIDENCE	N(%)	1(4.3)	0(0.0)	0(0.0)
PUP INCIDENCE	N(%)	1(0.3)	0(0.0)	0(0.0)

- a. Complete necropsies were not performed on pups in which autolysis or cannibalization precluded evaluation.
b. Refer to the individual pup clinical observations table (Table E39) for external clinical observations confirmed at necropsy.
c. Analysis restricted to pups found dead and necropsied.

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APPENDIX F
PROTOCOL AND AMENDMENTS



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

PROTOCOL 418-009

SPONSOR'S STUDY NUMBER: 6316.5

STUDY TITLE: Combined Oral (Gavage) Fertility, Developmental and Perinatal/Postnatal Reproduction Toxicity Study of N-EtFOSE in Rats.

PURPOSE: The purpose of this study is to test for toxic effects/disturbances resulting from N-EtFOSE treatment of Crl:CD®BR VAF/Plus® male and female rats before cohabitation through mating, gestation and lactation. This study evaluates ICH Harmonised Tripartite Guideline stages A through F of the reproductive process and should detect effects on the estrous cycle, tubal transport, implantation, gestation, parturition, lactation and maternal behavior in female rats, on the development of the offspring of the treated male and female rats, and permit detection of functional effects (e.g., effects on libido or epididymal sperm maturation) that may not be detected by histological examinations of male rat reproductive organs. Because manifestations of effects induced during this period may be delayed in the offspring, observations will be continued through production of F2 generation litters.

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

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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:

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

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

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

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

REGULATORY COMPLIANCE:

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

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

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

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

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:

0.5% 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 dosage 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.

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:**Stability:**

Stability data for prepared formulations bracketing the range of concentrations and conditions of this study are on file with the Sponsor and will not be determined during the conduct of this study. Suspensions will be prepared daily at the Testing Facility.

Homogeneity Analyses:

Homogeneity of the test article in prepared suspensions will be verified during the course of this study. A syringe will be used to withdraw samples (5 mL each) from the top, middle and bottom of the highest concentration on the first day of preparation. Each sample (5 mL) will be divided into two aliquots, one of 2 mL and one of 3 mL. One aliquot (2 mL) will be shipped for analysis; the other aliquot (3 mL) will be retained at the Testing Facility as a backup sample. Backup samples will be stored under the previously cited conditions and discarded at the Testing Facility upon the request of the Sponsor.

Concentration Analyses:

Concentration of the prepared test article suspensions will be verified during the course of this study. A syringe will be used to withdraw samples (5 mL each) from each concentration during the first and sixth week of dosage administration. Each sample (5 mL each) will be divided into two aliquots, one of 2 mL and one of 3 mL. One aliquot (2 mL) will be shipped for analysis; the other aliquot (3 mL) will be retained at the Testing Facility as a backup sample. Backup samples will be stored under the previously cited conditions and discarded at the Testing Facility upon the request of the Sponsor.

Shipping Instructions:

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

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

Both the recipient and the Study Monitor will be notified in advance of sample shipment.

DISPOSITION:

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

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

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

Number:

Initial population acclimated: 195 virgin male and 205 virgin female rats.
Population selected for study: 175 male rats (35 per dosage group) and 175 female rats (35 per dosage group).

Ten mated female rats per dosage group will be assigned to Cesarean-sectioning on day 10 of presumed gestation; the remaining female rats will be permitted to deliver litters.

A total of 250 F1 generation pups (25 per sex per dosage group) will be selected at weaning on day 21 postpartum for continued postnatal observation.

Body Weight and Age:

Male rats will be ordered to weigh from 300 g to 325 g each at receipt, at which time they will be expected to be at least 60 days of age. Female rats will be ordered to weigh from 200 g to 225 g each at receipt, at which time they will be expected to be at least 60 days of age. Actual body weights will be recorded the day after receipt and will be documented in the raw data. The weight ranges will be included in the final report.

Sex:

Both Fo and F1 generation male and female rats will be evaluated. Only Fo generation male and female rats will be given the test article.

Source:

Charles River Laboratories, Inc., Raleigh, North Carolina.

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

Identification:**Fo Generation:**

Rats are permanently identified using Monel® self-piercing ear tags (Gey Band and Tag Co., Inc., No. MSPT 20101). Male and female rats are assigned temporary numbers at receipt and given unique permanent identification numbers when assigned to the study before administration of the first dosage of the test article.

F1/F2 Generations:

Pups will not be individually identified during lactation; all parameters will be evaluated in terms of the litter. At weaning, each rat selected for continued observation will be identified with a Monel® self-piercing ear tag.

ANIMAL HUSBANDRY:

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

Housing:**Fo Generation Rats/F1 Generation Litters:**

Fo generation rats will be individually housed in stainless steel wire-bottomed cages except during the cohabitation and postpartum periods. During cohabitation, each pair of rats will be housed in the male rat's cage. Beginning no later than day 20 of presumed gestation, Fo generation female rats assigned to natural delivery will be individually housed in nesting boxes. Each dam and delivered litter will be housed in a common nesting box during the postpartum period.

F1 Generation Rats/F2 Generation Litters:

After weaning, the F1 generation rats will be individually housed before cohabitation, housed in pairs (one male rat per female rat) during cohabitation, and individually housed after cohabitation. The same type of caging will be used as described for the Fo generation rats. Beginning no later than day 20 of presumed gestation, F1 generation female rats will be individually housed in nesting boxes. Each dam and delivered litter will be housed in a common nesting box during the postpartum period.

Nesting Material:

Bedding material (bed-o'cobs®) will be supplied to female rats assigned to natural delivery.

Bedding will be changed as often as necessary to keep the animals dry and clean. Analyses for possible contamination are conducted annually and documented in the raw data.

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, the drinking water or the nesting material 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:**Fo Generation:**

Upon arrival, rats will be assigned to individual housing on the basis of computer-generated random units. After acclimation, male and female rats will be selected for study on the basis of physical appearance and body weights recorded during acclimation. The rats will be assigned to dosage groups based on computer-generated (weight-ordered) randomization procedures.

Within each dosage group, consecutive order will be used to assign rats to cohabitation, one male rat per female rat. The cohabitation period will consist of a maximum of 14 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. Female rats not mated within the first 7 days of cohabitation will be assigned alternate male rats that have mated (same dosage group) and will remain in cohabitation for a maximum of seven additional days.

The first ten female rats per dosage group with a confirmed date of mating will be assigned to Caesarean-sectioning on day 10 of presumed gestation. The remaining female rats will be permitted to naturally deliver litters.

Five rats per sex per dosage group will be assigned to a pharmacokinetic sample collection at scheduled sacrifice. A table of random units will be used to select five male rats per dosage group from among those that successfully mated a female rat assigned to natural delivery (scheduled for sacrifice after completion of the cohabitation period) and to select five female rats per group from among those that delivered a litter (scheduled for sacrifice on day 21 postpartum).

F1/F2 Generation Pups:

Day 1 of lactation (postpartum) is defined as the day of birth and is also the first day on which all pups in a litter are individually weighed (pup body weights will be recorded after all pups in a litter are delivered and groomed by the dam).

On day 4 postpartum, a table of random units will be used to select pups to be culled, and litters will be reduced to eight pups each. Whenever possible, the same number of male and female pups per litter will be continued on study.

At weaning of the F1 generation pups on day 21 postpartum, a table of random units will be used to select 25 male and 25 female pups per group, resulting in a total of 250 F1 generation rats (125 per sex) chosen for continued evaluation. At least one male pup and one female pup per litter, when possible, will be selected.

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:

Dosages will be adjusted for the most recently recorded body weight and given at approximately the same time each day.

Fo Generation Male Rats:

Male rats will be given the test article once daily beginning 28 days before cohabitation (maximum 14 days) and continuing through the day before sacrifice. Male rats will be sacrificed after completion of the cohabitation period.

Fo Generation Female Rats:

Female rats will be given the test article once daily beginning 28 days before cohabitation (maximum of 14 days) and continuing through day 9 of presumed gestation (rats assigned to Cesarean-sectioning), day 24 of presumed gestation (rats assigned to natural delivery that do not deliver a litter) or day 20 postpartum (rats that deliver a litter).

F1 Generation:

F1 generation pups will not be directly given the test article, but may be possibly exposed to the test article during maternal gestation (*in utero* exposure) or via maternal milk during the lactation period.

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 Per Sex	Dosage (mg/kg/day)	Concentration (mg/mL)	Dosage Volume (mL/kg)	Argus Batch Number
I	35	0 (Vehicle)	0	5	B-418-009-A(Day.Month.Year)
II	35	1	0.2	5	B-418-009-B(Day.Month.Year)
III	35	5	1	5	B-418-009-C(Day.Month.Year)
IV	35	10	2	5	B-418-009-D(Day.Month.Year)
V	35	15	3	5	B-418-009-E(Day.Month.Year)

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

TESTS, ANALYSES AND MEASUREMENTS - F₀ GENERATION:**Viability - Male and Female Rats:**

All Periods: At least twice daily.

Clinical Observations and/or General Appearance - Male and Female Rats:

Acclimation Period: At least once.

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

Maternal Behavior: Days 1, 4, 7, 14 and 21 postpartum. Any observed abnormal behavior will be recorded daily.

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

Body Weights - Male Rats:

Acclimation Period: At least once.

Dosage Period: Weekly.

Sacrifice: Terminal weight.

Body Weights - Female Rats:

Acclimation Period: At least once.

Dosage Period: Weekly to cohabitation. Daily during presumed gestation and on Days 1, 4, 7, 10 and 14 postpartum (rats assigned to natural delivery).

Sacrifice: Terminal weight.

Feed Consumption Values - Male Rats (recorded and tabulated):

Dosage Period: Weekly.

Feed Consumption Values - Female Rats (recorded and tabulated):

Dosage Period: Weekly to cohabitation. Daily during presumed gestation. Days 1, 4, 7, 10 and 14 postpartum (rats assigned to natural delivery).

Feed consumption will not be tabulated after day 14 postpartum, when it is expected that pups will begin to consume maternal feed.

Feed Consumption Values - Male and Female Rats:

Feed consumption values may be recorded more frequently than cited above if it is necessary to replenish the feed. During cohabitation, when two rats occupy the same cage with one feed jar, replenishment of the feed jars will be documented. Individual values will not be recorded or tabulated.

Estrous Cycling and Mating:

A table of random units will be used to select 15 female rats per dosage group for evaluation of estrous cycling by examination of vaginal cytology for 14 days before the start of the cohabitation period.

During cohabitation, all female rats will be evaluated daily until spermatozoa are observed in a smear of the vaginal contents and/or a copulatory plug is observed *in situ*.

Duration of Gestation:

The duration of gestation is calculated from day 0 of presumed gestation to the day the first pup is observed.

Fertility Parameters:

Fertility Index (percentage of matings that result in pregnancies).

Gestation Index (percentage of pregnancies that result in birth of live litters).

Number of offspring per litter (live and dead pups).

Number of implantation sites.

General condition of dam and litter during the postpartum period.

Viability Indices (percentage of pups born that survive 4 and 7 days).

Lactation Index (percentage of pups born that survive 21 days).

Caesarean-Sectioning Observations:

Rats will be Caesarean-sectioned on day 10 of presumed gestation. Placentae that appear abnormal (size, color or shape) will be noted in the raw data. The rats will be examined for number and distribution of:

Corpora Lutea.

Implantation Sites.

Viable and Nonviable Embryos.

(A viable embryo is oval or crescent shaped, pink, firm and enclosed in an amniotic sac filled with clear fluid. A nonviable embryo is amorphous, small, pale pink to tan or deep red to black, soft and enclosed in an amniotic sac filled with clear, cloudy, or opaque fluid.)

Natural Delivery:

Female rats will be evaluated for:

Clinical Observations During Parturition.

Duration of Gestation (day 0 of presumed gestation to the time the first pup is observed).

Length of Parturition (time of delivery of last pup minus the time of delivery of the first pup divided by N-1 pups in each litter).

Litter Size (defined as all pups delivered).

Pup Viability at Birth.**METHOD OF SACRIFICE:**

Rats will be sacrificed by carbon dioxide asphyxiation. Embryos will be discarded after examination.

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 of each sex 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.

Male and Female Rats Assigned to Pharmacokinetic Sample Collection:

In addition to the appropriate evaluations described below, five rats per sex per dosage group will be assigned to a pharmacokinetic sample collection. Male rats will be selected from among those that successfully mated a female rat assigned to natural delivery; female rats will be selected from among those that delivered a litter. At scheduled sacrifice after completion of the cohabitation period (male rats) and on day 21 postpartum (female rats) blood samples (approximately 4 mL per rat) will be collected from the inferior vena cava into serum separator tubes and centrifuged. The resulting serum will be immediately frozen on dry ice and maintained frozen (-70°C) until shipment to the Sponsor for analysis. The liver will be excised, weighed, and a sample section (lateral lobe) frozen and retained at -70°C until shipment to the Sponsor for analysis.

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

Scheduled Sacrifice of Male Rats:

After completion of the cohabitation period, male rats will be sacrificed and a gross necropsy of the thoracic, abdominal and pelvic viscera will be performed. The following organs will be excised and individually weighed and retained for possible histologic evaluation: testes, epididymides, prostate and seminal vesicles (weighed with and without fluid). The testes will be fixed in Bouin's solution for 48 to 96 hours and then retained in neutral buffered 10% formalin for possible histopathological evaluation. The remaining organs will be retained in neutral buffered 10% formalin.

Scheduled Sacrifice - Female Rats Assigned to Cesarean-Sectioning:

On day 10 of presumed gestation, female rats will be sacrificed, Cesarean-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⁾. All ovaries will be retained in neutral buffered 10% formalin for possible future evaluation.

Scheduled Sacrifice - Female Rats Assigned to Natural Delivery:

Rats that do not deliver a litter will be sacrificed on day 25 of presumed gestation and examined for gross lesions. Uteri will be stained with 10% ammonium sulfide to confirm the absence of implantation sites⁽⁵⁾.

After completion of the 21-day postpartum period, female rats will be sacrificed, and a gross necropsy of the thoracic, abdominal and pelvic viscera will be performed. The number and distribution of implantation sites will be recorded.

Dams with No Surviving Pups:

Dams with no surviving pups will be sacrificed after the last pup is found dead, missing or presumed cannibalized. A gross necropsy of the thoracic, abdominal and pelvic viscera will be performed. Postpartum data for these dams will be excluded from summary tables.

Rats Found Dead or Moribund:

Rats that die or are sacrificed because of moribund condition or abortion 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. Testes, epididymides, prostate and seminal vesicles of male rats will be excised and individual organ weights will be recorded (seminal vesicles weighed with and without fluid). The testes will be fixed in Bouin's solution for 48 to 96 hours and then retained in neutral buffered 10% formalin. The remaining organs will be retained in neutral buffered 10% formalin. Pregnancy status and uterine contents of female rats will be recorded. Aborted fetuses and/or delivered pups will be examined to the extent possible. Ovaries will be retained in neutral buffered 10% formalin. Uteri of apparently nonpregnant rats will be stained with 10% ammonium sulfide to confirm the absence of implantation sites⁽⁵⁾.

TESTS, ANALYSES AND MEASUREMENTS - F1 GENERATION:**Viability:**

Preweaning Period: Litters will be observed for dead pups at least twice daily. The pups in each litter will be counted once daily.

Postweaning Period: Twice daily.

Clinical Observations and/or General Appearance:

Preweaning Period: Once daily.

Postweaning Period: Once weekly.

Maternal Behavior: Days 1, 4, 7, 14 and 21 postpartum. Any observed abnormal behavior will be recorded daily.

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

Body Weights:

Preweaning Period: Days 1 (birth), 4, 7, 14 and 21 postpartum.

Postweaning Period: Weekly.

Presumed Gestation Period: Days 0, 7, 10, 14, 17 and 20 (female rats only).

Lactation Period: Days 1, 4, 7, 10 and 14 (female rats only).

Sacrifice: Terminal weight.

Feed Consumption Values (recorded and tabulated):

Preweaning Period: Not recorded.

Postweaning Period: Weekly except during cohabitation.

Presumed Gestation Period: Days 0, 7, 10, 14, 17 and 20 (female rats only).

Lactation Period: Days 1, 4, 7, 10 and 14 (female rats only).

Feed consumption values may be recorded more frequently if it is necessary to replenish the feed. During cohabitation, when two rats occupy the same cage with one feed jar, values will be documented when feed jars are filled. These intervals will not be tabulated.

Prewaning Developmental Observations:

The number of pups meeting the criterion is recorded on each day of testing. Testing continues until the day the criterion is attained by all pups in the litter.

Surface Righting Reflex (ability to right in 5 seconds): From day 1 postpartum.

Pinna Unfolding: From day 2 postpartum.

Eye Opening: From day 12 postpartum.

Acoustic Startle Response: From day 13 postpartum.

Air Righting Reflex: From day 14 postpartum.

Pupil constriction is evaluated once, on day 21 postpartum.

Postweaning Developmental Observations:

Sexual Maturation:

Female rats will be evaluated for the age of vaginal patency, beginning on day 28 postpartum. Male rats will be evaluated for the age of preputial separation, beginning on day 39 postpartum.

Passive Avoidance Testing:

Beginning at 24 ± 1 day postpartum, one male rat and one female rat from each litter, where possible, will be evaluated in a passive avoidance test for learning, short-term retention and long-term retention.

The passive avoidance apparatus consists of a two-compartment chamber with hinged Plexiglas® lids. One compartment is fitted with a bright light and Plexiglas® floor. The other compartment is fitted with a grid floor to which a brief (1 sec) pulse of mild electric current (1 mA) can be delivered. The two compartments are separated by a sliding door. On each test trial, the rat is placed into the "bright" compartment, the sliding door is opened and the light is turned on. The rat is allowed to explore the apparatus until it enters the "dark" compartment. The sliding door is then immediately closed, the light is turned off and the brief pulse of current is delivered to the grid floor. The rat is then removed from the apparatus and placed into a holding cage for 30 seconds before the start of the next trial. Trials are repeated until the rat remains in the "bright"

compartment for 60 seconds on two consecutive trials (the criterion for learning) or until 15 trials have been completed. The latency to enter the dark compartment or the maximum 60-second interval is recorded for each trial.

Each rat is tested twice. The test sessions are separated by a one-week interval, and the criterion is the same for both days of testing.

Dosage groups are compared for the following dependent measures:

The number of trials to the criterion in the first session—this measure will be used to compare groups for overall learning performance.

The latency (in seconds) to enter the "dark" compartment from the "bright" compartment on trial 1 in the first test session—this measure will be used to compare groups for activity levels and exploratory tendencies in a novel environment.

The latency (in seconds) to enter the "dark" compartment from the "bright" compartment on trial 2 in the first test session—this measure will be used to compare groups for short-term retention.

The number of trials to the criterion in the second test session—this measure will be used to compare groups for long-term retention.

The latency (in seconds) to enter the "dark" compartment from the "bright" compartment on trial 1 in the second session—this value is another indication of long-term retention.

Watermaze Testing:

Beginning at approximately 70 days postpartum, one male rat and one female rat from each litter will be evaluated in a water-filled M-maze for overt coordination, swimming ability, learning and memory.

Each rat is tested in a watertight 16-gauge stainless steel modified M-maze. The maze is filled with water to a depth of approximately nine inches, and the water is monitored for temperature (range of $21^{\circ}\text{C} \pm 1^{\circ}\text{C}$).

On each test trial, the rat will be placed into the starting position (base of the M-maze stem farthest from the two arms) and required to swim to one of the two goals of the M-maze, in order to be removed from the water. On the first trial, the rat is required to enter both arms of the maze before being removed from the water. The initial arm chosen on trial 1 is designated the incorrect goal during the remaining trials. Rats that fail to make a correct goal choice within 60 seconds in any given trial are guided to the correct goal and are then removed from the water. A 15-second intertrial interval will separate each trial. Each rat is required to reach a criterion of five consecutive errorless trials to terminate the test session. The maximum number of trials in any test

session is 15. Latency (measured in seconds) to choose the correct goal or the maximum 60-second interval is recorded for each trial, as is the number of errors (incorrect turns in the maze) during each trial.

Each rat is tested twice. The test sessions are separated by a one-week interval, and the correct goal and the criterion are the same for both test sessions.

Dosage groups are compared for the following dependent measures:

The number of trials to criterion on the first day of testing--this measure will be used to compare groups for overall learning performance.

The average number of errors (incorrect turns in the maze) for each trial on the first day of testing--this measure will also be used to compare groups for overall learning performance.

The latency (in seconds) to reach the correct goal on trial 2 of the first day of testing--this measure will be used to compare groups for short-term retention.

The number of trials to criterion on the second day of testing--this measure will be used to compare groups for long-term retention.

The average number of errors for each trial on the second day of testing--this measure will also be used to compare groups for long-term retention.

The latency (in seconds) to reach the correct goal on trial 1 of day 2 of testing--this is another indicator of long-term retention.

Reproductive Capacity:

At approximately 90 days of age, the F1 generation rats within each dosage group will be assigned to cohabitation, one male rat per female rat, based on computer-generated random units or random unit tables, with the exclusion of sibling matings. The cohabitation period will consist of a maximum of 14 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. Female rats that do not mate within the first 7 days of cohabitation will be assigned alternate male rats from the same dosage group that have mated. Female rats will be allowed to naturally deliver and maintain litters through a 21-day postpartum period.

Mating Performance:

As cited above for Fo generation rats.

Duration of Gestation:

As cited above for Fo generation rats.

Fertility Parameters:

As cited above for Fo generation rats.

F2 Generation Litter Data:

Viability, clinical observations and body weights for F2 generation pups will be recorded as cited above for F1 generation litters.

METHOD OF SACRIFICE - F1 GENERATION RATS/F2 GENERATION PUPS:

As previously cited for Fo generation rats.

NECROPSY - F1 GENERATION RATS:

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 of each sex 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 - F1 Generation Male Rats:

Rats will be sacrificed after completion of the 14-day cohabitation period. A gross necropsy of the thoracic, abdominal and pelvic visceral will be performed. Testes, epididymides, prostate and seminal vesicles of male rats will be excised and individual organ weights will be recorded (seminal vesicles weighed with and without fluid). The epididymides will be retained in neutral buffered 10% formalin. The testes will be fixed in Bouin's solution for 48 to 96 hours and then retained in neutral buffered 10% formalin.

Scheduled Sacrifice - F1 Generation Female Rats:

Female rats will be sacrificed after completion of the 21-day postpartum period. The number and distribution of implantation sites will be recorded. Rats that do not deliver a litter will be sacrificed on day 25 of presumed gestation and uteri will be stained with 10% ammonium sulfide to confirm the absence of implantation sites⁽⁵⁾. A gross necropsy of the thoracic, abdominal and pelvic viscera will be performed. Female rats without a confirmed mating date that do not deliver a litter will be sacrificed on an estimated day 25 of presumed gestation.

F1 Generation Rats Found Dead or Moribund:

Rats that die or are sacrificed because of moribund condition or abortion 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. Testes, epididymides, prostate and seminal vesicles of male rats will be excised and individual organ weights will be recorded (seminal vesicles weighed with and without fluid). The testes will be fixed in Bouin's solution for 48 to 96 hours and then retained in neutral buffered 10% formalin. The remaining organs will be retained in neutral buffered 10% formalin. Pregnancy status and uterine contents of female rats will be recorded. Aborted fetuses and/or delivered pups will be examined to the extent possible. Ovaries will be retained in neutral buffered 10% formalin. Uteri of apparently nonpregnant rats will be stained with 10% ammonium sulfide to confirm the absence of implantation sites⁽⁵⁾.

F1 Generation Dams with No Surviving Pups:

Dams with no surviving pups will be sacrificed after the last pup is found dead, missing or presumed cannibalized. A gross necropsy of the thoracic, abdominal and pelvic viscera will be performed. Postpartum data for these dams will be excluded from summary tables.

F1/F2 Generation Pups Found Dead on Day 1 Postpartum:

Pups that die before examination of the litter for pup viability will be evaluated for vital status at birth. The lungs will be removed and immersed in water. Pups with lungs that sink will be identified as stillborn; pups with lungs that float will be identified as liveborn, and to have died shortly after birth. Pups with gross lesions will be preserved in Bouin's solution for possible future evaluation. Should postmortem autolysis preclude these evaluations, it will be noted in the necropsy data.

F1/F2 Generation Pups Found Dead or Moribund on Days 2 to 21 Postpartum:

Pups found dead or sacrificed due to moribund condition will be examined for gross lesions and for the cause of the moribund condition or death. Pups with gross lesions found on days 2 to 4 postpartum will be preserved in Bouin's solution for possible future evaluation; gross lesions of pups found on days 5 to 21 postpartum will be preserved in neutral buffered 10% formalin. Should postmortem autolysis preclude these evaluations it will be noted in the necropsy data.

F1/F2 Generation Pups Not Selected for Continued Observation:

F1 and F2 generation pups culled on day 4 postpartum will be sacrificed and examined for gross lesions; pups with gross lesions will be preserved in Bouin's solution. Necropsy will include a single cross-section of the head at the level of the frontal-parietal suture and examination of the cross-sectioned brain for apparent hydrocephaly.

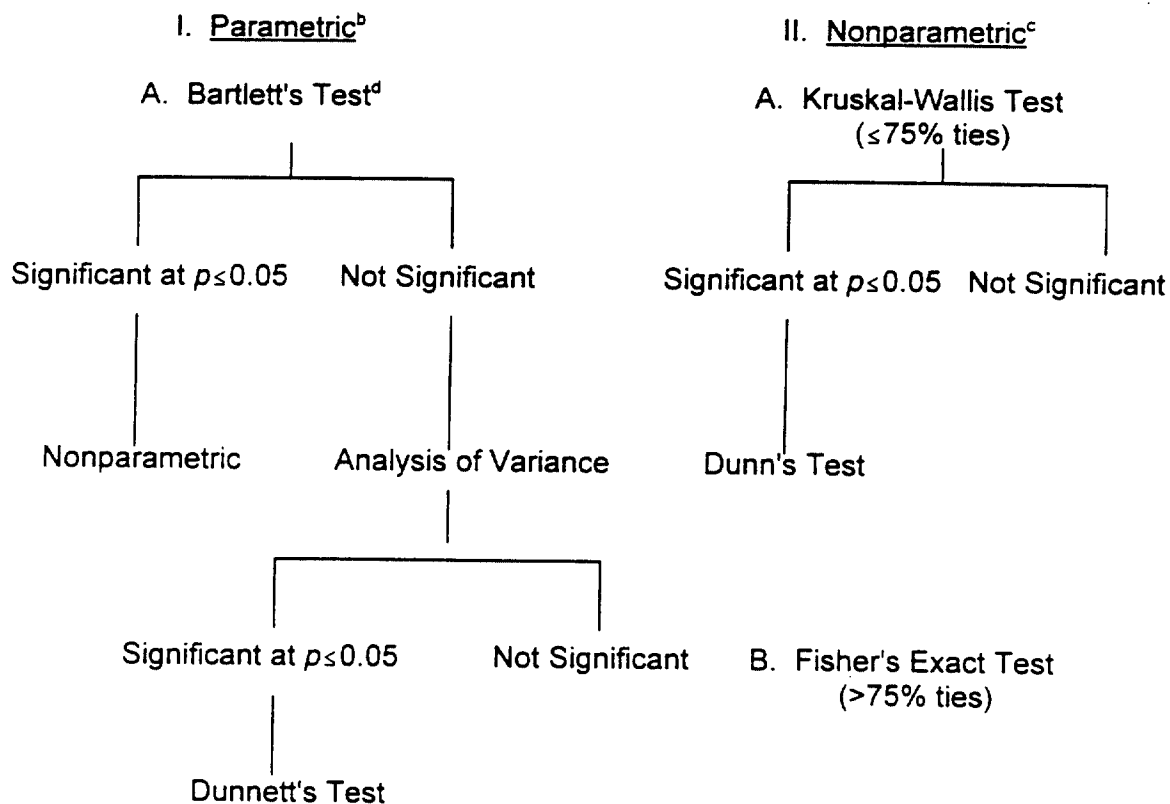
All F1 generation pups culled on day 21 postpartum will be sacrificed and examined for gross lesions; gross lesions will be preserved in neutral buffered 10% formalin. Necropsy will include a single cross-section of the head at the level of the frontal-parietal suture and examination of the cross-sectioned brain for apparent hydrocephaly.

Scheduled Sacrifice - F2 Generation Pups:

On day 21 postpartum, pups will be sacrificed and examined for gross lesions. Necropsy will include a single cross-section of the head at the level of the frontal-parietal suture and examination of the cross-sectioned brain for apparent hydrocephaly.

PROPOSED STATISTICAL METHODS⁽⁶⁻¹²⁾:

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

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

Variance Test for Homogeneity
of the Binomial Distribution

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

DATA ACQUISITION, VERIFICATION AND STORAGE:

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

RECORDS TO BE MAINTAINED:

Protocol and Amendments.
Test Article, Vehicle and/or Reagent Receipt, Preparation and Use.
Animal Acquisition.
Randomization Schedules.
Mating History.
Treatment (if prescribed by Staff Veterinarian).
General Comments.
Clinical Observations and/or General Appearance.
Blood Sample Collection, Processing and Shipment.
Body Weights.
Feed Consumption Values.
Caesarean-Sectioning Observations.
Natural Delivery Observations.
Litter Observations.
Reflex and Physical Development and Behavioral Observations - F1 Generation Pups.
Gross Necropsy Observations.
Organ Weights (if required).
Photographs (if required).
Study Maintenance (room and environmental records).
Feed, Water and Bedding 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

FINAL REPORT:

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

Summary and Conclusion.

Experimental Design and Method.

Evaluation of Test Results.

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

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE STATEMENT:

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

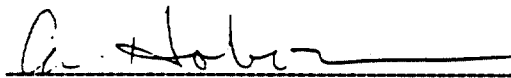
The Sponsor's signature below documents the fact that information concerning the necessity for conducting this study and the fact that this is not an unnecessarily duplicative study may be obtained from the Sponsor. No alternative (*in vitro*) procedures were available for meeting the stated purposes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

REFERENCES:

1. Christian, M.S. and Voytek, P.E. (1982). *In Vivo Reproductive and Mutagenicity Tests*. Environmental Protection Agency, Washington, D.C. National Technical Information Service, U.S. Department of Commerce, Springfield, VA 22161.
2. Christian, M.S. (1984). Reproductive toxicity and teratology evaluations of naltrexone (Proceedings of Naltrexone Symposium, New York Academy of Sciences, November 7, 1983), *J. Clin. Psychiat.* 45(9):7-10.
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PROTOCOL APPROVAL:

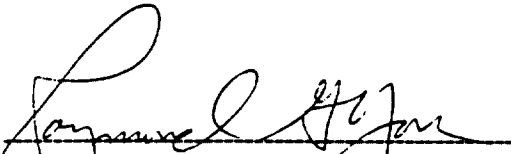
FOR THE TESTING FACILITY



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

28 May 98

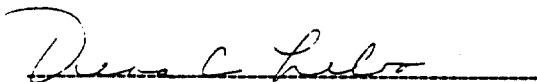
Date



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

28 May 98

Date



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

28 May 98

Date

FOR THE SPONSOR



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

29 May 98

Date

ATTACHMENT 1
STUDY SCHEDULE

ATTACHMENT 1

Protocol 418-009
Page 1 of 2**SCHEDULE***

02 JUN 98	Animal Receipt - Acclimation Begins (Fo generation rats).
08 JUN 98	Start of Dosage Period - Fo Generation Male Rats (28 days before cohabitation and continuing through a 14-day cohabitation period until sacrifice after successful mating has been determined).
08 JUN 98 - 29 JUL 98	Dosage Period - Female Rats Assigned to Caesarean-Sectioning (28 days before cohabitation and continuing through day 09 of presumed gestation).
08 JUN 98 - 01 SEP 98	Dosage Period - Female Rats Assigned to Natural Delivery [28 days before cohabitation through day 24 of presumed gestation (rats that do not deliver a litter) or day 20 postpartum (rats that deliver a litter)].
23 JUN 98 - 06 JUL 98	Dosage Period Estrous Cycle Evaluation.
06 JUL 98 PM - 13 JUL 98 AM	Cohabitation Period (Maximum of 14 days).
13 JUL 98 PM - 20 JUL 98 AM	Male 1 (07 days) Male 2 (07 days)
07 JUL 98	First Possible Day 0 of Presumed Gestation.
20 JUL 98	Last Possible Day 0 of Presumed Gestation.
03 AUG 98	Fo Generation Male Rats Sacrificed after Completion of the Cohabitation Period (Earliest possible date).

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

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ATTACHMENT 1

Protocol 418-009
Page 2 of 2

17 JUL 98	First Possible Day 10 of Presumed Gestation Caesarean-sectioning.
30 JUL 98	Last Possible Day 10 of Presumed Gestation Caesarean-sectioning.
28 JUL 98	First Possible Delivery (Day 21 of presumed gestation).
14 AUG 98	Last Possible Delivery (Day 25 of presumed gestation).
01 AUG 98	First Possible Day 25 of Presumed Gestation Female Sacrifice.
14 AUG 98	Last Possible Day 25 of Presumed Gestation Female Sacrifice.
17 AUG 98	First Possible Day 21 Weaning (Dams and F1 generation pups not selected for continued observation sacrificed).
03 SEP 98	Last Possible Day 21 Weaning.
18 AUG 98	F1 Generation Postweaning Observations Begin (Details of tests cited in protocol).
02 NOV 98 - 16 NOV 98	F1 Generation Cohabitation Period (Initiated when rats are approximately 90 days of age - approximate initial date).
30 NOV 98	F1 Generation Male Rats Sacrificed after Completion of Cohabitation Period - Approximate Earliest Possible Date.
24 NOV 98 - 11 DEC 98	Delivery Period - F1 Generation Dams/F2 Generation Litters (Approximate dates).
14 DEC 98 - 31 DEC 98	Sacrifice of F1 Generation Dams and F2 Generation Litters on Day 21 Postpartum (Approximate dates).
20 APR 99	Draft Final Report.

000191

ATTACHMENT 2
MATERIAL SAFETY DATA SHEET

MATERIAL SAFETY
DATA SHEET

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

N-E+FOSE

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distributed with the intention of earning a profit thereon.

DIVISION: 3M CHEMICALS

TRADE NAME:

FC-10 FLUORAD Brand Fluorochemical Alcohol

ID NUMBER/U.P.C.:

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

ISSUED: January 29, 1998

SUPERSEDES: November 05, 1997

DOCUMENT: 10-3778-7

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

2. PHYSICAL DATA

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

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

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2. PHYSICAL DATA (continued)

APPEARANCE AND ODOR:

Amber waxy solid

3. FIRE AND EXPLOSION HAZARD DATA

FLASH POINT:..... > 148 C Setflash

FLAMMABLE LIMITS - LEL:..... N/A

FLAMMABLE LIMITS - UEL:..... N/A

AUTOIGNITION TEMPERATURE:..... N/A

EXTINGUISHING MEDIA:

Water, Carbon dioxide, Dry chemical, Foam

SPECIAL FIRE FIGHTING PROCEDURES:

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

UNUSUAL FIRE AND EXPLOSION HAZARDS:

See Hazardous Decomposition section for products of combustion.

4. REACTIVITY DATA

STABILITY: Stable

INCOMPATIBILITY - MATERIALS/CONDITIONS TO AVOID:

Not applicable.

HAZARDOUS POLYMERIZATION: Hazardous polymerization will not occur.

HAZARDOUS DECOMPOSITION PRODUCTS:

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

5. ENVIRONMENTAL INFORMATION

SPILL RESPONSE:

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

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

PAGE 3

5. ENVIRONMENTAL INFORMATION (continued)

RECOMMENDED DISPOSAL:

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

ENVIRONMENTAL DATA:

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

REGULATORY INFORMATION:

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

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

EPCRA HAZARD CLASS:

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

6. SUGGESTED FIRST AID

EYE CONTACT:

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

SKIN CONTACT:

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

INHALATION:

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

IF SWALLOWED:

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

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

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7. PRECAUTIONARY INFORMATION

EYE PROTECTION:

Avoid eye contact. Wear safety glasses with side shields.

SKIN PROTECTION:

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

RECOMMENDED VENTILATION:

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

RESPIRATORY PROTECTION:

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

PREVENTION OF ACCIDENTAL INGESTION:

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

RECOMMENDED STORAGE:

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

FIRE AND EXPLOSION AVOIDANCE:

Nonflammable.

OTHER PRECAUTIONARY INFORMATION:

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

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

EXPOSURE LIMITS

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

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

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

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EXPOSURE LIMITS (continued)

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

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

SOURCE OF EXPOSURE LIMIT DATA:

- 3M: 3M Recommended Exposure Guidelines

8. HEALTH HAZARD DATA

EYE CONTACT:

No adverse health effects are expected from eye contact.

SKIN CONTACT:

Product is not expected to be irritating to the skin.

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

INHALATION:

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

IF SWALLOWED:

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

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

MUTAGENICITY:

Not mutagenic in in-vitro assays.

REPRODUCTIVE/DEVELOPMENTAL TOXINS:

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

OTHER HEALTH HAZARD INFORMATION:

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

A Product Toxicity Summary Sheet is available.

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

PAGE 6

SECTION CHANGE DATES

HEADING SECTION CHANGED SINCE November 05, 1997 ISSUE

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

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

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000198

ATTACHMENT 3
TEST ARTICLE PREPARATION PROCEDURE

ATTACHMENT 3

Protocol 418-009
Version: 418-009 (23 MAY 98)
Page 1 of 2

TEST ARTICLE PREPARATION PROCEDURE

Test Article: N-EtFOSE.

Vehicle: 0.5% 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 418-009.

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.
2. Suspensions will be prepared:
☒ Daily ___ Weekly ___ For ___ days of use
3. Suspensions will be prepared at a final dosage volume of 5 mL/kg.
4. Safety:
☒ Gloves, lab coat, goggles or safety glasses and faceshield
☒ 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 ☒ No (Calculations based on 100%)
___ Free Base ___ Purity
6. Sampling requirements: Cited in protocol.
7. Storage: Cited in protocol.

000200

ATTACHMENT 3

Protocol 418-009
Version: 418-009 (23 MAY 98)
Page 2 of 2

TEST 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 dosage administration.

C. Test Article Suspension Preparation:

1. To prepare the 3-mg/mL, group V suspension, add the required amount of test article (See TEST ARTICLE CALCULATIONS) into an appropriately sized, labeled container.
2. Q. S. to the final desired value with the vehicle and mix by inversion.
3. To prepare the 2-mg/mL, group IV suspension, remove the required amount of stock suspension (group V), add an equal volume of vehicle and mix by inversion.
4. To prepare the 1-mg/mL, group III suspension, remove the required amount of stock suspension (group IV), add an equal volume of vehicle and mix by inversion.
5. To prepare the 0.2-mg/mL, group II suspension, remove the required amount of stock suspension (group III), add an equal volume of vehicle and mix by inversion.

D. Preparation of the Control Group:

1. Add the required amount of vehicle to an appropriate vessel.

Written by: *Stephen G. Galt*Approved by: *Stephen G. Galt* Date: 28-MAY-98Clarification: ☒ No ☒ Yes (See attached clarification form.)

(A) CR 1/13/99

Initial/Date: *Christopher K. Ruppert* 1/2/99

000201

ARGUS

TEST ARTICLE/SUBSTANCE PREPARATION
PROCEDURE CLARIFICATIONProtocol: 418-009Version: 418-009 R3.May.98

Date of Clarification	Preparation Step #	Clarification
<u>6/30/98</u>	<u>C.5</u>	<u>Due to spillage, more</u> <u>group 2 needed to be</u> <u>prepared from group 3.</u> <u>see calculation 6/30/98</u>
_____	_____	_____ _____ _____ _____ _____ Study Director _____ Date _____
_____	_____	_____ _____ _____ _____ _____ Study Director _____ Date _____
_____	_____	_____ _____ _____ _____ _____ Study Director _____ Date _____
_____	_____	_____ _____ _____ _____ _____ Study Director _____ Date _____

Reviewed by: MCDate: 7-3-98
08.15.97 TASPPM-01-02

000202



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905 Sheehy Drive, Building A
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PROTOCOL 418-009

COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND
PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-ETFOSE IN
RATS.

SPONSOR'S STUDY NUMBER: 6316.5

Amendment 1 - July 17, 1998

1. Concentration Analyses (page 5 of the protocol):

Samples (5 mL each) from each concentration will be taken during the first and last week of the F1 dosage administration to verify concentrations of the prepared test article formulations.

Reason for Change:

This change was made because dosage administration was extended to include the F1 generation male and female rats.

2. Sex (page 6 of the protocol):

The F1 generation male and female pups will be given the test article or vehicle.

Reason for Change:

These changes were made at the request of the Sponsor in order to provide information about the effects of the test article on the second generation.

3. Method and Frequency (page 10 of the protocol):

The F1 generation male and female pups will be administered the test article orally (gavage) on day 1 postweaning through the day before sacrifice. F2 generation pups will not be directly given the test article, but may be possibly exposed to the test article during maternal gestation (*in utero* exposure) or via maternal milk during the lactation period.

Reason for Change:

These changes were made at the request of the Sponsor and follow the method of exposure to Fo generation.

4. Dosage Levels, Concentrations and Volumes (page 11 of the protocol):

Dosage Group	Number of Fo Generation Rats Per Sex	Number of F1 Generation Rats Per Sex	Dosage (mg/kg/day)	Concentration (mg/mL)	Dosage Volume (mL/kg)	Argus Batch Number
I	35	25	0 (Vehicle)	0	5	B-418-008-A(Day.Month.Year)
II	35	25	1	0.2	5	B-418-008-B(Day.Month.Year)
III	35	25	5	1	5	B-418-008-C(Day.Month.Year)
IV	35	25	10	2	5	B-418-008-D(Day.Month.Year)
V	35	25	15	3	5	B-418-008-E(Day.Month.Year)

Reason for Change:

This change was made because dosage administration was extended to include the F1 generation male and female rats.

5. Tests, Analyses and Measurements - F1 Generation (page 16 of the protocol):Clinical Observations and/or General Appearance:

Prewaning Period: Once daily.

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

Maternal Behavior: Days 1, 4, 7, 14 and 21 postpartum. Any observed abnormal behavior will be recorded daily.

Body Weights - Male Rats:

Prewaning Period: Days 1 (birth), 4, 7, 14 and 21 postpartum.

Dosage Period: Weekly.

Sacrifice: Terminal weight.

Body Weights - Female Rats:

Prewaning Period: Days 1 (birth), 4, 7, 14 and 21 postpartum.

Dosage Period: Weekly to cohabitation. Daily during presumed gestation and on Days 1, 4, 7 and 14 postpartum (rats assigned to natural delivery).

Sacrifice: Terminal weight.

Reason for Change:

These changes were made because dosage administration was extended to include the F1 generation male and female rats.

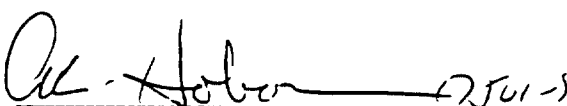
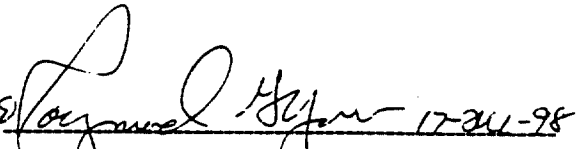
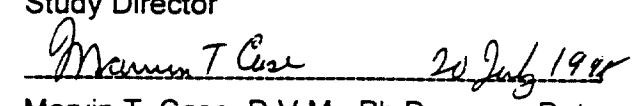
6. F1/F2 Generation Pups Not Selected for Continued Observation (page 22 of the protocol):

On day 4 postpartum, the stomach contents (milk curd) will be collected from culled pups from Groups I, II and V (or highest dosage group available). Samples will be collected from all pups from four to five of the largest litters in these three dosage groups. Individual pup samples will be combined by litter into polypropylene tubes and frozen at -20°C. After completion of sample collection, samples will be shipped (frozen on dry ice) to Kris J. Hansen, Ph.D. at 3M Environmental Technology and Safety Services, 935 Bush Avenue, Building 2-3E-09, St. Paul, Minnesota 55133-3331 for analysis. Both the recipient and the Study Monitor will be notified in advance of sample shipment.

Protocol 418-009
Amendment 1
Page 4

Reason for Change:

Collection of milk samples were requested by the Sponsor to determine if the test article is reaching the pups via lactation.

 Alan M. Hoberman, Ph.D., DABT Date 12/01/98 Director of Research	 Raymond G. York, Ph.D., DABT Date 12/21/98 Associate Director of Research and Study Director
 Dena C. Lebo, V.M.D. Date Member, Institutional Animal Care and Use Committee	 Marvin T. Case, D.V.M., Ph.D. Date 20 July 1998 Study Monitor

000206



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PROTOCOL 418-009

COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND
PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF N-ETFOSE IN
RATS

SPONSOR'S STUDY NUMBER: 6316.5

Amendment 2 - 13 August 1998

1. Necropsy (page 20 of the protocol):

On postpartum day 21, the 10 mg/kg/day dosage group (Group IV) dams and litters will be sacrificed.

Reason for Change:

Group IV was terminated at weaning because of the severe pup toxicity during lactation (mortality and reduced body weights and delayed development).

2. Male and Female Rats Assigned to Pharmacokinetic Sample Collection (page 14 of the protocol):

On postpartum Day 21, the livers of the pups from five litters in each of the remaining groups will be excised, pooled per litter, frozen and retained at -70°C until shipment to the Sponsor.

Reason for Change:

This change was made at the request of the Sponsor for possible analysis.

3. Scheduled Sacrifice - Female Rats Assigned to Natural Delivery and Dams with No Surviving Pups (page 15 of the protocol):

Ovaries will be retained in neutral buffered 10% formalin.

000207

Protocol 418-009
Amendment 2
Page 2

Reason for Change:

This change was made to clarify the protocol

George DeBulac 13-AUG-98
for Alan M. Hoberman, Ph.D., DABT Date
Director of Research

Raymond G. York 13-AUG-98
Raymond G. York, Ph.D., DABT Date
Associate Director of Research and
Study Director

Dena C. Lebo 13-AUG-1998
for Dena C. Lebo, V.M.D. Date
Member, Institutional Animal Care
and Use Committee

Marvin T. Case 27 Aug 1998
Marvin T. Case, D.V.M., Ph.D. Date
Study Monitor

000208



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PROTOCOL 418-009

COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND
PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY
OF N-ETFOSE IN RATS

SPONSOR'S STUDY NUMBER: 6316.5

Amendment 3 - 24 November 1998

1. Natural Delivery (page 13 of the protocol):

The Length of Parturition (time of delivery of last pup minus the time of delivery of the first pup divided by N-1 pups in each litter) will not be calculated.

Reason for Change:

A litter watch was not required by the Sponsor.

 24-Nov-98

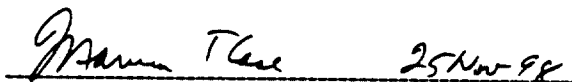
Alan M. Hoberman, Ph.D., DABT Date
Director of Research

 24-Nov-98

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

 24/Nov 98

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

 25 Nov 98

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

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PROTOCOL 418-009

COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND
PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY
OF N-ETFOSE IN RATS

SPONSOR'S STUDY NUMBER: 6316.5

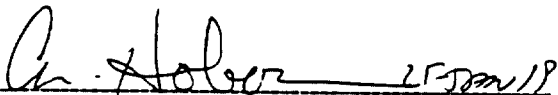
Amendment 4 - 25 January 1999

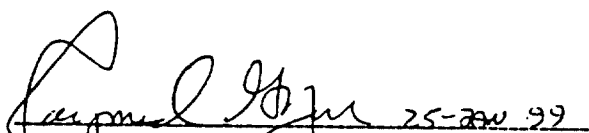
1. Test Article Preparation Procedure (Attachment 3 to the protocol):

The attached preparation procedure has been clarified to eliminate preparation for Groups IV and V.

Reason for Change:

Groups IV and V contained no animals in the second generation, therefore these dosage formulations were discontinued to reserve test article usage.


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


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


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


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

000210

ATTACHMENT 3

Protocol 418-009
Version: 418-009 (16 DEC 98)
Page 1 of 2

TEST ARTICLE PREPARATION PROCEDURE

Test Article: N-EtFOSE.

Vehicle: 0.5% 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 418-009.

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.
2. Suspensions will be prepared:
 X Daily 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.

000211

ATTACHMENT 3

Protocol 418-009
Version: 418-009 (16 DEC 98)
Page 2 of 2

TEST ARTICLE PREPARATION PROCEDURE

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

C. Test Article Suspension Preparation:

1. To prepare the 1-mg/mL, group III suspension, add the required amount of test article (See TEST ARTICLE CALCULATIONS) into an appropriately sized, labeled container.
2. Q. S. to the final desired value with the vehicle and mix by inversion.
3. To prepare the 0.2-mg/mL, group II suspension, remove the required amount of stock suspension (group III), add an equal volume of vehicle and mix by inversion.

D. Preparation of the Control Group:

1. Add the required amount of vehicle to an appropriate vessel.

Written by: Christopher R. RuppertApproved by: [Signature] Date: 21-DEC-98Clarification: X No Yes (See attached clarification form.)Initial/Date : Christopher R. Ruppert 1/7/99

000212



Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
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PROTOCOL 418-009

COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND
PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY
OF N-ETFOSE IN RATS

SPONSOR'S STUDY NUMBER: 6316.5

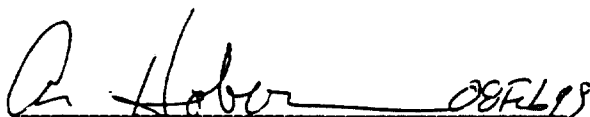
Amendment 5 - 8 February 1999

1. Test Article and Vehicle (page 3 of the protocol):

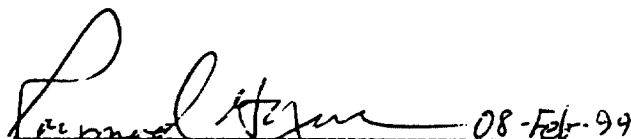
[Effective Date: 7 June 1998] The vehicle was identified as 2.0% Tween® 80 in R. O. deionized water, rather than 0.5% Tween® 80 in R. O. deionized water.

Reason for Change:

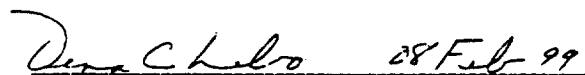
This change was made to obtain an adequate emulsion for the test article.

 08 Feb 99

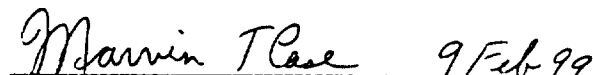
Alan M. Hoberman, Ph.D., DABT Date
Director of Research

 08 Feb 99

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

 08 Feb 99

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

 9 Feb 99

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

000213



Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
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Telefax: (215) 443-8587

PROTOCOL 418-009

COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND
PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY
OF N-EtFOSE IN RATS

SPONSOR'S STUDY NUMBER: 6316.5

Amendment 6 - 19 May 1999

1. Concentration Analyses (page 5 of the protocol):

The concentration samples were sent to the Sponsor. Sample analyses will be conducted at the discretion of the Sponsor and no report will be sent to the Testing Facility.

Reason for Change:

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

2. Male and Female Rats Assigned to Pharmacokinetic Sample Collection (page 14 of the protocol):

The liver and serum samples were sent to the Sponsor. Samples will be analyzed at the discretion of the Sponsor.

Reason for Change:

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

3. F1/F2 Generation Pups Not Selected for Continued Observation (page 22 and Amendment 1 of the protocol):

The stomach contents of these pups were sent to the Sponsor for analysis. Stomach contents will be analyzed at the discretion of the Sponsor.

000214

Protocol 418-009
Amendment 6
Page 2

Reason for Change:

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

for George E. Dearbe 19-May-99 Raymond G. York 19-May-99
Alan M. Hoberman, Ph.D., DABT Date Raymond G. York, Ph.D., DABT Date
Director of Research Associate Director of Research and
Study Director

Dena C. Lebo 19-May-99 Marvin T. Case 21-May-99
Dena C. Lebo, V.M.D. Date Marvin T. Case, D.V.M., Ph.D. Date
Chairperson, Institutional Animal Care and Use Committee Study Monitor

000215

PRIMEDICA

Argus Research Laboratories, Inc.
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PROTOCOL 418-009

COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND
PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY
OF N-EtFOSE IN RATS

SPONSOR'S STUDY NUMBER: 6316.5

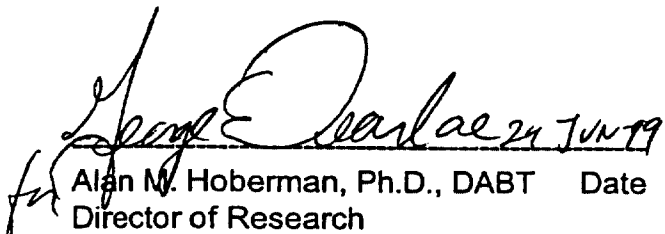
Amendment 7 - 24 June 1999

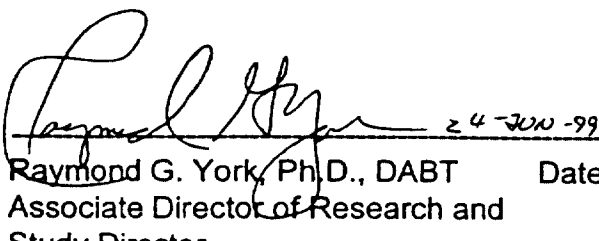
1. Sponsor (page 1 of the protocol):

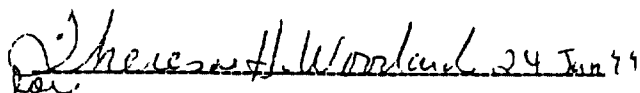
The Sponsor is 3M Corporate Toxicology, rather than 3M Toxicology Services.

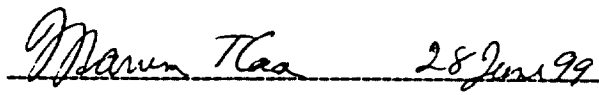
Reason for Change:

The name of the Sponsor has changed.

 24 JUN 99
for Alan M. Hoberman, Ph.D., DABT Date
Director of Research

 24 JUN 99
Raymond G. York, Ph.D., DABT Date
Associate Director of Research and
Study Director

 24 JUN 99
for Dena C. Lebo, V.M.D. Date
Chairperson, Institutional Animal Care
and Use Committee

 28 JUN 99
Marvin T. Case, D.V.M., Ph.D. Date
Study Monitor

000216

APPENDIX G

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

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

- From 16 June 1998 to 18 June 1998 [days 9 to 11 of study (DSs 9 to 11)], the Fo generation rats were administered the volume of test article based on the body weight recorded on DS 1 rather than DS 8. The following table summarizes the average percent of correct dosage that the rats were administered.

<u>Dosage Group</u>	<u>Dosage (mg/kg/day)</u>	<u>Sex</u>	<u>Rat Numbers</u>	<u>Group Average of Daily % of Correct Dosage Received</u>
I	0 (Vehicle)	Male	9901 - 9935	89.80
		Female	10076 - 10110	92.47
II	1	Male	9936 - 9970	89.40
		Female	10111 - 10124, 16400, 10126 - 10145	92.78
III	5	Male	9971 - 10005	89.83
		Female	10146 - 10180	93.63
IV	10	Male	10006 - 10040	90.43
		Female	10181 - 10215	95.53
V	15	Male	10041 - 10075	90.16
		Female	10216 - 10250	96.75

These deviations did not adversely affect the outcome or interpretation of the study because the male rats received approximately 90% of the intended dosage and the female rats received approximately 92% to 97% of the intended dosage. This is within the analytical variability ($\pm 10\%$).

- On 3 October 1998 (observation day 44), the following F1 generation male rats were administered the test article dosage volume based on the previous weekly body weight rather than the current body weight. The following table summarizes the average percent of correct dosage that the rats were administered.

<u>Dosage Group</u>	<u>Dosage (mg/kg/day)</u>	<u>Rat Numbers</u>	<u>Group Average of % of Correct Dosage Received</u>
I	0 (Vehicle)	12089 - 12093	87.50
II	1	12112 - 12119	88.73
III	5	12135 - 12142	89.47

These deviations did not adversely affect the outcome or interpretation of the study because the event occurred on a single day and all of the rats received most of the intended dosage (at least 85% of the intended dosage).

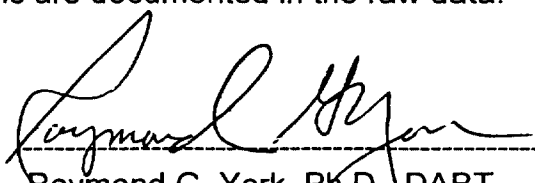
3. On 9 July 1998 (DS 32), ten F0 generation male rats in the 15 mg/kg/day dosage group (Group V) were administered the test article twice, once with the correct volume and once with an incorrect volume.

Rat Number	Mated Prior to Misdosing	Correct Volume (mL)	Extra Volume (mL)	Total Volume (mL)	Total Dosage (mg/kg)	Amount of Test Article (mg/kg)
10041	Yes	2.1	2.2	4.3	10.26	30.79
10042	Yes	2.1	2.2	4.3	10.24	30.71
10043	No	2.0	2.2	4.2	10.37	31.11
10044	Yes	1.9	2.2	4.1	10.79	32.37
10045	Yes	2.1	2.2	4.3	10.29	30.86
10046	Yes	2.2	2.0	4.2	9.59	28.77
10047	Yes	1.8	2.1	3.9	10.57	31.71
10048	Yes	1.9	2.2	4.1	10.99	32.98
10049	Yes	1.9	2.3	4.2	11.02	33.07
10050	Yes	1.9	2.3	4.2	10.82	32.47

These deviations did not adversely affect the outcome or interpretation of the study because there were no additional adverse clinical observations noted in these rats and the event occurred on a single day.

4. On 20 September 1998 (DSs 20, 27, 28, 29, 30, 31, 32, 33 or 34), all F1 generation rats were administered PFOS, the test article for another study. This deviation did not adversely affect the outcome or interpretation of the study because the test article administered (PFOS) is a metabolite of the test article for this study (N-EtFOSE) and this was a single event. There were no adverse clinical observations for the rats administered the incorrect test article.
5. On 14 October 1998 (DS 53), one F1 generation female rat (12249) in the 1 mg/kg/day dosage group (Group II) was not dosed because it was missing from the cage at the time of dosing. This deviation did not adversely affect the outcome or interpretation of the study because the rat received sufficient test article to evaluate the parameter.
6. On 28 August 1998 (observation day 7), the vaginal patency observation was not performed for one F1 generation female rat (12223) in the 0 mg/kg/day dosage group (Group I). This deviation did not adversely affect the outcome or interpretation of the study because sufficient data were available to evaluate this parameter.

All deviations are documented in the raw data.


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

30-JUN-99

Date

000219

APPENDIX H
TEMPERATURE AND RELATIVE HUMIDITY REPORTS

ARGUS

Temperature and Relative Humidity Report Location: Room 04 Protocol Number: 418-009			
Range of Dates: 02-Jun-1998 15:30 to 03-Jun-1998 09:30			
Target Range: Species: Rat Total Number of Days: Total Number of Hours: Total Number of Data Points:	Temperature 64°F to 79°F 2 17.75 19		Relative Humidity 30% to 70% 2 17.75 19
Mean (± SD):	70.1	(± 0.7)	55.3 (± 2.4)
Maximum:	72.3		62.3
Median:	69.8		55.5
Minimum:	69.6		51.8
Number of Points in Range (%):	19	(100.0)	19 (100.0)
Number of Points High (%):	0	(0.0)	0 (0.0)
Number of Points Low (%):	0	(0.0)	0 (0.0)

Report Generated: 09-Sep-1998 at 12:36

COMMENTS: _____

REVIEWED BY: llh DATE: 9/9/98

000221

ARGUS

Temperature and Relative Humidity Report Location: Room 02 Protocol Number: 418-009			
Range of Dates: 03-Jun-1998 09:30 to 27-Jul-1998 14:30			
Target Range: Species: Rat Total Number of Days: Total Number of Hours: Total Number of Data Points:	Temperature 64°F to 79°F 55 1300.75 1298		Relative Humidity 30% to 70% 55 1300.75 1298
Mean (± SD):	69.0	(± 0.9)	62.5 (± 5.6)
Maximum:	72.8		88.4
Median:	69.1		61.5
Minimum:	66.1		51.4
Number of Points in Range (%):	1298	(100.0)	1142 (88.0)
Number of Points High (%):	0	(0.0)	156 (12.0)
Number of Points Low (%):	0	(0.0)	0 (0.0)

Report Generated: 09-Sep-1998 at 12:41

COMMENTS: _____

REVIEWED BY: DATE: 9/9/98

000222

ARGUS

Temperature and Relative Humidity Report Location: Room 02 Protocol Number: 418-009			
Range of Dates: 27-Jul-1998 14:30 to 17-Sep-1998 11:25			
Target Range: Species: Rat Total Number of Days: Total Number of Hours: Total Number of Data Points:	Temperature 64°F to 79°F 53 1244.74 1244	Relative Humidity 30% to 70% 53 1244.74 1244	
Mean (± SD):	68.9 (± 0.9)	57.7 (± 4.4)	
Maximum:	72.4	79.0	
Median:	68.8	57.4	
Minimum:	66.5	46.7	
Number of Points in Range (%):	1244 (100.0)	1231 (99.0)	
Number of Points High (%):	0 (0.0)	13 (1.0)	
Number of Points Low (%):	0 (0.0)	0 (0.0)	

Report Generated: 28-Jan-1999 at 14:22

COMMENTS: _____

REVIEWED BY: anne z. m. h. DATE: 1/28/99

000223

ARGUS

Temperature and Relative Humidity Report Location: Room 04 Protocol Number: 418-009			
Range of Dates: 27-Jul-1998 14:30 to 30-Jul-1998 18:00			
Target Range: Species: Rat Total Number of Days: Total Number of Hours: Total Number of Data Points: Mean ($\pm$ SD): Maximum: Median: Minimum: Number of Points in Range (%): Number of Points High (%): Number of Points Low (%):	Temperature 64°F to 79°F 4 75.25 76 68.8 ($\pm$ 0.3) 69.6 68.8 68.1 76 (100.0) 0 (0.0) 0 (0.0)		Relative Humidity 30% to 70% 4 75.25 76 48.2 ($\pm$ 2.1) 53.3 47.9 42.5 76 (100.0) 0 (0.0) 0 (0.0)

Report Generated: 28-Jan-1999 at 14:17

COMMENTS: _____

REVIEWED BY: Alan R. H. DATE: 1/28/99

000224

ARGUS

Temperature and Relative Humidity Report Location: Room 14 Protocol Number: 418-009			
Range of Dates: 17-Sep-1998 11:25 to 29-Dec-1998 12:00			
Target Range: Species: Rat Total Number of Days: Total Number of Hours: Total Number of Data Points:	Temperature 64°F to 79°F 104 2472.25 2461	Relative Humidity 30% to 70% 104 2472.25 2461	
Mean (± SD):	69.3 (± 1.3)	55.9 (± 3.6)	
Maximum:	72.1	68.0	
Median:	69.5	56.1	
Minimum:	62.4	37.7	
Number of Points in Range (%):	2438 (99.1)	2461 (100.0)	
Number of Points High (%):	0 (0.0)	0 (0.0)	
Number of Points Low (%):	23 (0.9)	0 (0.0)	

Report Generated: 28-Jan-1999 at 14:41

COMMENTS: _____

REVIEWED BY: Ann Smith DATE: 1/28/99

000225

ARGUS

Relative Humidity Deviations Report
Location: Room 02

Protocol Number: 418-009

Range of Dates: 03-Jun-1998 09:30 to 27-Jul-1998 14:30

Humidity Target Range:
Species: Rat

30% to 70%

Date	Time	R.H.	Date	Time	R.H.
03-Jun-1998	09:00	78.5 H	12-Jun-1998	01:00	72.4 H
09-Jun-1998	17:00	71.0 H	12-Jun-1998	03:00	73.3 H
10-Jun-1998	03:00	71.7 H	12-Jun-1998	06:00	71.3 H
10-Jun-1998	05:00	72.2 H	12-Jun-1998	09:00	72.1 H
10-Jun-1998	06:00	71.3 H	12-Jun-1998	10:00	75.5 H
10-Jun-1998	09:00	70.4 H	12-Jun-1998	11:00	71.6 H
10-Jun-1998	10:00	70.2 H	12-Jun-1998	12:00	70.6 H
11-Jun-1998	00:00	70.5 H	12-Jun-1998	13:00	73.1 H
11-Jun-1998	03:00	71.3 H	12-Jun-1998	14:00	74.5 H
11-Jun-1998	06:00	72.6 H	12-Jun-1998	15:00	74.4 H
11-Jun-1998	07:00	70.9 H	12-Jun-1998	16:00	74.6 H
11-Jun-1998	11:00	70.3 H	12-Jun-1998	17:00	70.5 H
11-Jun-1998	17:00	71.4 H	12-Jun-1998	18:00	71.4 H
11-Jun-1998	18:00	71.3 H	12-Jun-1998	20:00	72.7 H
11-Jun-1998	19:00	70.2 H	12-Jun-1998	21:00	70.5 H
11-Jun-1998	20:00	75.7 H	12-Jun-1998	22:00	71.0 H
11-Jun-1998	23:00	70.1 H	13-Jun-1998	03:00	72.8 H

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

Report Generated: 09-Sep-1998 at 12:48

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

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

Study Director: _____

Date: 10/5/98

000226

ARGUS

Relative Humidity Deviations Report
Location: Room 02

Protocol Number: 418-009

Range of Dates: 03-Jun-1998 09:30 to 27-Jul-1998 14:30

Humidity Target Range:
Species: Rat

30% to 70%

Date	Time	R.H.	Date	Time	R.H.
13-Jun-1998	04:00	71.0 H	14-Jun-1998	10:00	72.9 H
13-Jun-1998	05:00	70.9 H	14-Jun-1998	11:00	73.3 H
13-Jun-1998	06:00	70.4 H	14-Jun-1998	12:00	73.4 H
13-Jun-1998	07:00	71.9 H	14-Jun-1998	13:00	73.4 H
13-Jun-1998	10:00	72.7 H	14-Jun-1998	17:00	70.7 H
13-Jun-1998	11:00	74.6 H	14-Jun-1998	19:00	70.5 H
13-Jun-1998	12:00	70.1 H	14-Jun-1998	22:00	70.7 H
13-Jun-1998	13:00	71.5 H	14-Jun-1998	23:00	70.4 H
13-Jun-1998	14:00	70.9 H	15-Jun-1998	01:00	73.1 H
13-Jun-1998	19:00	70.1 H	15-Jun-1998	05:00	70.2 H
14-Jun-1998	00:00	71.1 H	15-Jun-1998	06:00	73.1 H
14-Jun-1998	02:00	72.6 H	15-Jun-1998	12:00	71.7 H
14-Jun-1998	03:00	72.5 H	15-Jun-1998	16:00	70.3 H
14-Jun-1998	04:00	72.4 H	15-Jun-1998	18:00	74.1 H
14-Jun-1998	05:00	74.0 H	15-Jun-1998	19:00	78.3 H
14-Jun-1998	06:00	71.9 H	15-Jun-1998	20:00	71.1 H
14-Jun-1998	08:00	72.0 H	15-Jun-1998	21:00	70.7 H

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

Report Generated: 09-Sep-1998 at 12:48

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

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

Study Director: C. H. Date: 10/5/98

000227

ARGUS

Relative Humidity Deviations Report

Location: Room 02

Protocol Number: 418-009

Range of Dates: 03-Jun-1998 09:30 to 27-Jul-1998 14:30

Humidity Target Range:

30% to 70%

Species: Rat

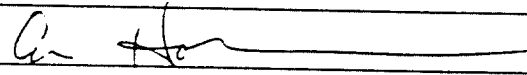
Date	Time	R.H.	Date	Time	R.H.
15-Jun-1998	22:00	78.8 H	16-Jun-1998	16:00	73.3 H
15-Jun-1998	23:00	88.4 H	16-Jun-1998	17:00	74.5 H
16-Jun-1998	00:00	73.2 H	16-Jun-1998	18:00	73.5 H
16-Jun-1998	01:00	83.9 H	16-Jun-1998	19:00	75.1 H
16-Jun-1998	02:00	76.7 H	16-Jun-1998	20:00	77.7 H
16-Jun-1998	03:00	86.1 H	16-Jun-1998	21:00	78.7 H
16-Jun-1998	04:00	73.7 H	16-Jun-1998	22:00	73.9 H
16-Jun-1998	05:00	75.1 H	16-Jun-1998	23:00	81.0 H
16-Jun-1998	06:00	76.8 H	17-Jun-1998	00:00	74.7 H
16-Jun-1998	07:00	78.5 H	17-Jun-1998	01:00	75.5 H
16-Jun-1998	08:00	70.2 H	17-Jun-1998	02:00	70.9 H
16-Jun-1998	09:00	74.3 H	17-Jun-1998	03:00	71.0 H
16-Jun-1998	11:00	73.4 H	17-Jun-1998	04:00	71.2 H
16-Jun-1998	12:00	75.6 H	17-Jun-1998	05:00	76.2 H
16-Jun-1998	13:00	72.6 H	17-Jun-1998	06:00	73.1 H
16-Jun-1998	14:00	73.1 H	17-Jun-1998	08:00	74.3 H
16-Jun-1998	15:00	72.7 H	17-Jun-1998	10:00	74.4 H

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

Report Generated: 09-Sep-1998 at 12:48

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

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

Study Director:  Date: 10/17/98

000228

ARGUS

Relative Humidity Deviations Report
Location: Room 02

Protocol Number: 418-009

Range of Dates: 03-Jun-1998 09:30 to 27-Jul-1998 14:30

Humidity Target Range:
Species: Rat

30% to 70%

Date	Time	R.H.	Date	Time	R.H.
17-Jun-1998	11:00	73.2 H	18-Jun-1998	06:00	74.2 H
17-Jun-1998	12:00	70.5 H	18-Jun-1998	07:00	72.5 H
17-Jun-1998	13:00	74.2 H	18-Jun-1998	08:00	79.2 H
17-Jun-1998	14:00	78.3 H	18-Jun-1998	09:00	71.5 H
17-Jun-1998	15:00	71.5 H	18-Jun-1998	12:00	72.7 H
17-Jun-1998	16:00	70.2 H	20-Jun-1998	20:00	72.0 H
17-Jun-1998	18:00	73.1 H	21-Jun-1998	01:00	70.8 H
17-Jun-1998	19:00	76.6 H	21-Jun-1998	08:00	71.8 H
17-Jun-1998	20:00	73.3 H	21-Jun-1998	20:00	72.9 H
17-Jun-1998	21:00	75.0 H	22-Jun-1998	01:00	72.3 H
17-Jun-1998	22:00	72.8 H	22-Jun-1998	05:00	71.2 H
17-Jun-1998	23:00	71.6 H	22-Jun-1998	06:00	74.7 H
18-Jun-1998	00:00	76.0 H	23-Jun-1998	09:00	70.4 H
18-Jun-1998	01:00	71.3 H	23-Jun-1998	21:00	70.1 H
18-Jun-1998	02:00	72.9 H	25-Jun-1998	00:00	70.1 H
18-Jun-1998	03:00	71.8 H	25-Jun-1998	11:00	73.0 H
18-Jun-1998	04:00	79.3 H	26-Jun-1998	02:00	74.9 H

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

Report Generated: 09-Sep-1998 at 12:49

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

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

Study Director: C. H. Date: 10/17/98

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ARGUS

Relative Humidity Deviations Report
Location: Room 02

Protocol Number: 418-009

Range of Dates: 03-Jun-1998 09:30 to 27-Jul-1998 14:30

Humidity Target Range:
Species: Rat

30% to 70%

Date	Time	R.H.	Date	Time	R.H.
26-Jun-1998	04:00	71.3 H	24-Jul-1998	09:00	71.5 H
26-Jun-1998	09:00	73.0 H			
26-Jun-1998	15:00	74.9 H			
09-Jul-1998	10:00	70.4 H			
10-Jul-1998	02:00	70.6 H			
15-Jul-1998	03:00	71.5 H			
15-Jul-1998	09:00	72.5 H			
15-Jul-1998	13:00	74.2 H			
20-Jul-1998	21:00	72.5 H			
23-Jul-1998	03:00	71.6 H			
23-Jul-1998	06:00	70.5 H			
23-Jul-1998	07:00	72.6 H			
23-Jul-1998	12:00	75.1 H			
23-Jul-1998	16:00	76.5 H			
23-Jul-1998	18:00	75.6 H			
24-Jul-1998	00:00	70.5 H			
24-Jul-1998	06:00	73.8 H			

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

Report Generated: 09-Sep-1998 at 12:51

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

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

Study Director: CH Date: 10/1/98

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ARGUS

Relative Humidity Deviations Report
Location: Room 02**Protocol Number: 418-009**

Range of Dates: 27-Jul-1998 14:30 to 17-Sep-1998 11:25

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

Date	Time	R.H.	Date	Time	R.H.
16-Aug-1998	13:00	72.6 H			
17-Aug-1998	03:00	70.8 H			
17-Aug-1998	07:00	74.0 H			
17-Aug-1998	12:00	71.2 H			
17-Aug-1998	14:00	73.4 H			
17-Aug-1998	15:00	70.4 H			
17-Aug-1998	17:00	76.2 H			
17-Aug-1998	18:00	75.3 H			
17-Aug-1998	21:00	79.0 H			
17-Aug-1998	22:00	72.6 H			
18-Aug-1998	01:00	75.6 H			
18-Aug-1998	04:00	77.2 H			
18-Aug-1998	07:00	76.6 H			

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

Report Generated: 28-Jan-1999 at 14:29

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

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

Study Director: _____

Date: _____

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ARGUS

Temperature Deviations Report
Location: Room 14
Protocol Number: 418-009

Range of Dates: 17-Sep-1998 11:25 to 29-Dec-1998 12:00

Temperature Target Range:
Species: Rat

64°F to 79°F

Date	Time	Temp.	Date	Time	Temp.
07-Dec-1998	05:00	63.9 L	08-Dec-1998	15:00	63.6 L
07-Dec-1998	06:00	63.9 L	08-Dec-1998	16:00	63.6 L
07-Dec-1998	22:00	63.8 L	08-Dec-1998	17:00	63.4 L
07-Dec-1998	23:00	63.6 L	08-Dec-1998	18:00	63.9 L
08-Dec-1998	00:00	63.5 L	08-Dec-1998	19:00	63.8 L
08-Dec-1998	01:00	63.3 L	08-Dec-1998	23:00	63.9 L
08-Dec-1998	02:00	63.1 L			
08-Dec-1998	03:00	63.0 L			
08-Dec-1998	04:00	62.8 L			
08-Dec-1998	05:00	62.7 L			
08-Dec-1998	06:00	62.4 L			
08-Dec-1998	07:00	63.1 L			
08-Dec-1998	08:00	63.5 L			
08-Dec-1998	11:00	63.9 L			
08-Dec-1998	12:00	63.5 L			
08-Dec-1998	13:00	63.5 L			
08-Dec-1998	14:00	63.5 L			

H = Value out of range - High L = Value out of range - Low
 Temp. = Temperature °F

Report Generated: 28-Jan-1999 at 14:48

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

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

Study Director: _____

Date: 18-Feb-99

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APPENDIX I
STATEMENT OF THE STUDY DIRECTOR

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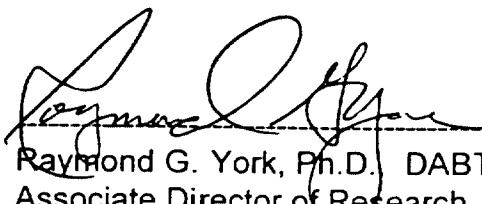


Argus Research Laboratories, Inc.
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Telefax: (215) 443-8587

PROTOCOL 418-009: COMBINED ORAL (GAVAGE) FERTILITY,
DEVELOPMENTAL AND PERINATAL/POSTNATAL
REPRODUCTION TOXICITY STUDY OF N-EtFOSE
IN RATS
SPONSOR'S STUDY NUMBER: 6316.5

STATEMENT OF THE STUDY DIRECTOR

This final report accurately reflects the raw data obtained during the performance of the study. No 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.

 30-Jul-99
Raymond G. York, Ph.D. DABT Date
Associate Director of Research
and Study Director
Argus Research Laboratories, Inc.

- a. U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58.
- b. Japanese Ministry of Health and Welfare (1997). *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.

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APPENDIX J
QUALITY ASSURANCE UNIT FINAL REPORT STATEMENT

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Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
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QUALITY ASSURANCE UNIT FINAL REPORT STATEMENT

Study Director: Raymond G. York, Ph.D., DABT

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

Protocol 418-009: Combined Oral (Gavage) Fertility, Developmental and
Perinatal/Postnatal Reproduction Toxicity Study of
N-EtFOSE in Rats
Sponsor's Study Number: 6316.5

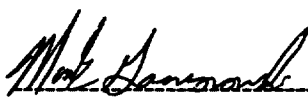
The draft protocol for this study was audited for adherence to U.S. Food and Drug Administration (FDA) Good Laboratory Practice Regulations, Japanese Ministry of Health and Welfare (MHW); Good Laboratory Practice Standard for Safety Studies on Drugs, and European Economic Community (1989) council decision 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 26 MAY 98.

Critical phases of this study were inspected 29 times; study information and raw data were audited seven times (see tables 1 and 2 for dates and phases/data).

The draft final report and the raw data for this study were compared and audited for accuracy, for adherence to protocol requirements, and for adherence to U.S. Food and Drug Administration (FDA) Good Laboratory Practice Regulations, Japanese Ministry of Health and Welfare (MHW); Good Laboratory Practice Standard for Safety Studies on Drugs, and European Economic Community (1989) council decision on 28 July 1989 on the acceptance by the European Economic Community of an OECD decision/recommendation on compliance with principles of good laboratory practice between 05 JAN 99 and 11 MAY 99, and 09 APR 99 and 19 MAY 99, and for revisions requested by the Sponsor 14 JUN 99 and 16 JUN 99 and for finalization on 30 JUN 99.

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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.

 30 JUN 99
for Nancy J. Gongliwski Date
Quality Assurance Manager

 for 30 Jun 99
Heather L. Rabuttino, M.S. Date
Quality Assurance Supervisor
and Principal Auditor

TABLE 1
CRITICAL PHASES INSPECTED

Test Article Administration - Gavage

Dates of inspection: 16 JUN 98, 16 JUN 98, 25 AUG 98

Dates results reported to the Study Director and Management:
19 JUN 98, 19 JUN 98, 26 AUG 98

Estrous Cycle Evaluation

Date of inspection: 25 JUN 98

Date results reported to the Study Director and Management:
25 JUN 98

Cohabitation

Dates of inspection: 09 JUL 98, 03 NOV 98

Dates results reported to the Study Director and Management:
14 JUL 98, 06 NOV 98

Caesarean-Sectioning

Date of inspection: 17JUL 98

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

Test Article Preparation

Dates of inspection: 29 JUL 98, 28 AUG 98

Dates results reported to the Study Director and Management:
31 JUL 98, 02 SEP 98

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Natural Delivery and Litter Observations

Dates of inspection: 29 JUL 98, 25 NOV 98

Dates results reported to the Study Director and Management:
31 JUL 98, 02 DEC 98

Male Necropsy

Dates of Inspection: 30 JUL 98, 18 NOV 98

Dates results reported to the Study Director and Management:
31 JUL 98, 23 NOV 98

Milk Collection

Date of inspection: 04 AUG 98

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

Surface Righting Reflex, Pinna Unfolding, Eye Opening, Acoustic Startle Response, Air Righting Reflex, Pupil Constriction, Sexual Maturation

Dates of inspection:
04 AUG 98, 12 AUG 98, 12 AUG 98, 12 AUG 98, 12 AUG 98,
18 AUG 98, 28 AUG 98, 14 SEP 98

Dates results reported to the Study Director and Management:
07 AUG 98, 20 AUG 98, 14 AUG 98, 14 AUG 98, 14 AUG 98,
19 AUG 98, 02 SEP 98, 15 SEP 98

Culling

Date of inspection: 04 AUG 98

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

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Weaning

Date of inspection: 19 AUG 98

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

Blood Collection

Date of inspection: 19 AUG 98

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

Necropsy - Dam and Litter Sacrifice

Dates of inspection: 19 AUG 98, 15 DEC 98

Dates results reported to the Study Director and Management:
20 AUG 98, 18 DEC 98

Passive Avoidance, Watermaze

Dates of inspection: 27 AUG 98, 26 OCT 98

Dates results reported to the Study Director and Management:
28 AUG 98, 30 OCT 98

TABLE 2

RAW DATA AUDIT(S)

The following study information and raw data were audited
on 15 SEP 98, 17 SEP 98, 18 SEP 98, 22 SEP 98 TO 26 SEP 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.
- Necropsy.
- Organ weights.
- Tissue packing lists.
- Key for testing facility computer backup record abbreviations.
- Edit requests.
- Blood collection data and packing lists.

The results of this audit were reported to the Study Director and Management
on 28 SEP 98.

The following study information and raw data were audited
from 28 SEP 98 to 05 OCT 98:

- In-life transaction record.

The results of this audit were reported to the Study Director and Management
on 13 NOV 98.

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The following study information and raw data were audited
from 29 SEP 98 to 04 OCT 98:

- Animal receipt, randomization, physical examination and acclimation.
- In-life transaction record.
- Feed consumption.
- Estrous cycle evaluation.
- Cohabitation.
- Caesarean-sectioning.
- Maternal gross observations.
- Natural delivery observations.
- Litter observations, including reflex and development.
- Pup body weights and status.
- Table of random units.
- Organ weights.
- Tissue packing lists.
- General comments.
- Study maintenance records.
- Temperature and relative humidity reports.
- Feed, water and bedding analyses.
- Edit requests.
- Dosage volumes.
- Deviations.
- Data review pages.
- Blood collection data and packing lists.

The results of this audit were reported to the Study Director and Management
on 05 OCT 98.

The following study information and raw data were audited
from 06 OCT 98 to 07 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 08 OCT 98.

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The following study information and raw data were audited from 18 JAN 99 to 21 JAN 99:

- In-life transaction record.
- Feed consumption.
- Passive avoidance.
- Watermaze.
- Genealogy chart.
- Necropsy.
- Organ weights.
- Tissue packing lists.
- Edit requests.
- Sexual maturation.

The results of this audit were reported to the Study Director and Management on 21 JAN 99.

The following study information and raw data were audited on 26 JAN 99:

- Vehicle receipt, preparation and use.
- Test article preparation and use.
- Vehicle packing list.

The results of this audit were reported to the Study Director and Management on 28 JAN 99.

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The following study information and raw data were audited
from 21 JAN 99, 04 FEB 99, 05 FEB 99, 08 FEB 99, 09 FEB 99, 11 FEB 99:

- Randomization.
- In-life transaction record.
- Feed consumption.
- Cohabitation.
- Natural delivery observations.
- Litter observations.
- Pup body weights and status.
- Passive avoidance.
- Watermaze.
- Table of random units.
- Necropsy.
- Tissue packing lists.
- General comments.
- Study maintenance records.
- Temperature and relative humidity reports.
- Feed and water analyses.
- Edit requests.
- Dosage volumes.
- Data review pages.
- Sexual maturation.

The results of this audit were reported to the Study Director and Management
on 11 FEB 99.

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WMM