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FYI-1205-01503

December 22, 2005

TSCA Document Processing Center (7407M)
U.S. Environmental Protection Agency
Room 6428 Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
1201 Constitution Ave. NW
Washington, D.C. 20004-3302

Contain NO CBI

Dear Coordinator:

We are reporting these results as a "For Your Information" under the TSCA sec. 8(e) guidance. At this time we are not able to reach the conclusion that the results observed in this study constitute a "significant risk". We have initiated a second phase to this study to possibly expand and clarify the current results, which we currently believe are not biologically significant or would constitute a significant risk.

Hexion conducted an OECD 422 "Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test" on CAS# 51000-52-3, Neodecanoic acid, ethenyl ester. This study was conducted as part of the SIDS data package for the OECD/ICCA HPV Program for submission through the United Kingdom.

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The testing was conducted using three oral gavage dose levels and a control. The high dose level was nominally 1000 mg/kg/day, the "limit dose" for the OECD 422 study. This limit dose was chosen so that we would see at least some toxic effects at the highest dose level, as the preliminary screening study and previous acute toxicity tests indicated low toxicity.

While the OECD 422 protocol includes a large number of endpoints we believe the only remarkable observation were renal observations in the male high dose (1000 mg/kg/day) kidneys. In four of five males examined histopathological change was characterized by nephrosis and the appearance of birefringent crystals. Necrosis/degeneration was not a major change, and the nephrosis was sometimes accompanied by other indicators of renal effects. The nephrosis was also substantiated by increased renal weights and some changes in serum clinical chemistry parameters, most notably BUN.



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In contrast, the pathologist judged that only one of ten high dose females exhibited renal changes due to the test compound, and in this female the renal effect was judged to be "mild".

Similar effects were not observed in the male or female kidneys at the mid-dose of 250 mg/kg/day or the low dose of 100 mg/kg/day.

Liver weights were significantly increased in the high dose males and females, and in the mid-dose males, but there were no histopathological evidence of liver abnormality.

We believe that the pattern of male rat nephropathy at the very high dose of 1000 mg/kg/day, with the concurrent absence of equivalent effects in the female high dose group and lower dose groups is indicative of the well-described phenomena of "male rat nephropathy". However, both the testing laboratory and their contract pathology laboratory were unfamiliar with previous research in this area and they did not specifically examine the male kidneys using more conclusive techniques.

Consequently, we have asked them to re-examine the high dose male kidneys, this time specifically staining them for alpha-2-microglobulin, an indicator protein for this phenomena. However, since the kidneys were not originally "fixed" and prepared for this type of analysis it is not certain that this method will work.

However, At his time we believe the male rat kidney results are probably not biologically significant.

While there were many papers and considerable EPA correspondence and discussion on the issue of alpha-2-microglobulin in the 1980's and early 1990's we refer to the so-called "purple book" which is the summary of an EPA symposium ("Report of the EPA Peer Review Workshop on Alpha-2-microglobulin: Association with Renal Toxicity and Neoplasia in the Male Rat", EPA/625/3-91/021, August 1991). We believe that it is now generally accepted amongst toxicologists that nephropathy of this type is a male rat-specific phenomena, and if a chemical acts on male rat kidneys through the accumulation of this protein, the observed renal effects are generally not meaningful in terms of human risk.

We expect results from the additional pathological examinations in early 2006, and we will provide those results to EPA as an "FYI" or TSCA 8(e) submission pending the findings.

If you have any questions please feel free to call me on (832) 486-6652 or email me at charlie.keller@hexionchem.com.

Sincerely,

A handwritten signature in black ink, appearing to read "Charles A. Keller". The signature is fluid and cursive, with a long horizontal stroke at the end.

Charles A. Keller, Ph.D.
Global Manager, Product Safety and Compliance
Epoxy and Phenolic Resins Division
Hexion Specialty Chemicals, Inc.

Attachment: Final Report "Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test, OECD Guideline 422", Stillmeadow Inc.

STILLMEADOW

I N C O R P O R A T E D

AMENDED FINAL REPORT

**COMBINED REPEATED DOSE TOXICITY STUDY WITH THE REPRODUCTION /
DEVELOPMENTAL TOXICITY SCREENING TEST**
(OECD Guideline 422)

Veova 10

AUTHOR:

Janice O. Kuhn, Ph.D., D.A.B.T.

STUDY INITIATION DATE: 01 December 04
STUDY COMPLETION DATE: 19 September 05
AMENDED STUDY COMPLETION DATE: 19 December 05

CONDUCTED BY:

STILLMEADOW, Inc.
12852 Park One Drive
Sugar Land, TX 77478

LABORATORY STUDY NUMBER:

8419-04

PAGE 1 OF 173

SUBMITTED TO:

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Houston, TX 77082-3101

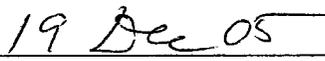
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STILLMEADOW, Inc. GLP COMPLIANCE STATEMENT

This study was designed and performed at STILLMEADOW, Inc. and was conducted in compliance with the OECD: C(98)17 Good Laboratory Practice Standards.



Janice O. Kuhn, Ph.D., DABT
Study Director
STILLMEADOW, Inc.



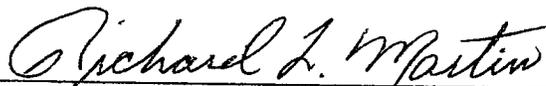
Date (Original date 19Sep05)

QUALITY ASSURANCE STATEMENT

Test Article: Veova 10
 Study Title: Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test

The study report and data have been audited in accordance with STILLMEADOW, Inc. Standard Operating Procedures (SOPs). The final report accurately reflects the study data. The findings from the inspection and audit were reported to the Study Director and management as follows:

Phase of Study Inspected	Type of Inspection	Date Inspected	Date Reported to Study Director	Date Reported to Management
Protocol Review	Study-based	08 Nov 04	08 Nov 04	08 Nov 04
Range Finder Dosing	Study-based	17 Dec 04	17 Dec 04	17 Dec 04
Facility Inspection	Facility-based	06 Jan 05	06 Jan 05	06 Jan 05
Body Weights	Study-based	10 May 05	10 May 05	10 May 05
Facility Inspection	Facility-based	02 Jun 05	02 Jun 05	02 Jun 05
Final Body Weights, Necropsy and Organ Weights	Study-based	17 Jun 05	17 Jun 05	17 Jun 05
Report/Data Audit	Study-based	29 Aug 05	29 Aug 05	29 Aug 05
Amended Report/Data Audit	Study-based	19 Dec 05	19 Dec 05	19 Dec 05



Richard L. Martin, B.S., M.S., C.Ph.T.
 Quality Assurance Unit
 STILLMEADOW, Inc.

19 Dec 05
 Date (Original date 19Sep05)

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SUMMARY

This study was conducted to evaluate the potential toxic effects of the test article, Veova 10 (CAS # 51000-52-3), when administered to rats for a minimum of 28 days. It was also conducted to determine the potential of the test article to affect male and female reproductive performance such as gonadal function, mating behavior, conception, parturition and early postnatal development.

A range finder was conducted using five males and five females per dose level (untreated control, 2000 mg/kg, 1000 mg/kg, 250 mg/kg and 100 mg/kg). The animals were selected by a weight-stratified randomization procedure. They were dosed five days/week for two weeks. The animals were observed daily and food consumption measured daily through study termination (Day 14). Body weights were recorded before dosing on Day 0 and on Days 7 and 14. The dose levels for the definitive portion of the study were selected from the data collected in the range finder.

Eighty rats were equally divided into four groups (Groups I, II, III and IV) with ten males and ten females per group using a weight-stratified randomization procedure. The test material was mixed with the vehicle (corn oil) and samples were collected for homogeneity and stability analysis. Beginning on Day 0, Group I animals were dosed daily with the vehicle only and served as a vehicle control group. The animals of Groups II, III and IV were dosed daily with the test article for 14 days at dose rates of 1000 mg/kg, 250 mg/kg and 100 mg/kg, respectively. All animals were dosed orally by gavage. On Day 14, each male from each group was put with a female from the same group for mating for a period of 14 days maximum. After confirmation of mating, the animals were returned to their individual cages, and all animals continued to be dosed.

Observations for mortality were made twice daily and observations for signs of pharmacologic and/or toxicologic effects were made once daily. Body weights were recorded weekly throughout the study. Food consumption was monitored weekly throughout the study except during the mating period. A functional observational battery (FOB), as well as an evaluation of motor activity, was conducted on the animals before sacrifice.

On Day 29, the males were sacrificed and necropsied. A complete necropsy with organ weight determination was conducted and selected tissues were saved in 10% neutral buffered formalin. Organs weighed were testes and epididymides, liver, kidneys, thymus, spleen, brain and heart. Organs collected but not weighed were: spinal cord, stomach, small and large intestine (duodenum, jejunum, ileum, cecum and colon including Peyer's patches), thyroid, trachea and lungs (including bronchi, preserved by inflation with fixative and then immersion), urinary bladder, lymph nodes (mesenteric and submandibular), peripheral nerve (sciatic or tibial) in close proximity to the muscle, and a sample of bone marrow.

Blood was collected for determination of certain hematology and serum chemistry parameters. Hematology parameters evaluated were erythrocyte count, hemoglobin, hematocrit, total and differential leukocyte counts, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and mean corpuscular volume. Serum chemistry parameters analyzed were blood urea nitrogen, creatinine, serum alanine aminotransferase, serum aspartate aminotransferase, total bilirubin, total protein, total cholesterol, globulin, albumin, A/G ratio, glucose, inorganic phosphorus, calcium, sodium, potassium, and chloride.

SUMMARY (cont.)

The pregnant females were dosed daily through the gestation period and through Day 4 of the lactation period. At that time, they were sacrificed and necropsied in the same manner as the males, with the uterus, ovaries and oviducts, as well as all the other non-reproductive organs listed for the males, collected and weighed and the same blood parameters analyzed.

At birth, each litter was examined and the pups were sexed. The pups were sexed again and weighed on Day 1. They were reweighed and sacrificed on lactation Day 4.

The homogeneity analysis validated the test article mixing procedure. The weekly dose confirmations determined that the mean concentrations of the dosing solutions were 202.9 mg/mL (Group II), 43.8 mg/mL (Group III) and 20.6 mg/mL (Group IV). The resulting dose levels were, on average, 1014 mg/kg, 219 mg/kg and 103 mg/kg, respectively.

One control group (Group I) female exhibited piloerection and activity decrease on Day 17 and died on Day 18; a dosing injury was confirmed at necropsy. The only other observable in-life abnormalities noted during the study were in Group II animals. One female had a red muzzle, piloerection and emaciation on Days 4-8; one male was sensitive to touch on Days 20-28 and another male was emaciated on Days 27-28. No abnormalities were noted in the weekly physical exams that were not observed during the general health observations.

Body weight and food consumption measurements revealed no meaningful differences among male or female group means.

Analysis of litter data revealed little difference in conception rates, number of pups delivered or incidence of stillborn pups. There were, however, four deaths among Group II pups between Day 0 and Day 1. Mean pup body weights on Day 1 were not significantly different among groups. Total litter weights on Day 1 were lower in Group II, but the deaths of the four pups would have contributed to this. There were no abnormal or malformed pups observed.

No differences among the groups were seen in any of the parameters scored in the functional observational battery in either males or females. Motor activity data collected with the Flex-field photobeam activity apparatus revealed no differences among the females. Considerable variability was seen among male groups, but with no apparent dose relationship.

Serum chemistry analysis results revealed that BUN was elevated in the high-dose males (Group II); this elevation would possibly be consistent with the signs of nephrosis seen in the kidneys of this group in histopathology. Cholesterol levels were significantly higher in Groups II and III than control; however, they were within normal limits and are not considered adverse or treatment-related effects. Creatinine levels were within normal limits (although low) in all groups, yet slightly but significantly higher in Group II, which is consistent with the histopathologic findings of kidney lesions. There were no statistically significant differences in any female serum chemistry parameter analyzed.

Individual hematology values were largely within normal limits and there were no statistically significant differences among groups in any male or female hematology parameter analyzed.

SUMMARY (cont.)

The only abnormal findings at necropsy in males were in the Group II males (enlarged and/or pale enlarged kidneys in three animals) and they are consistent with the histopathology findings. Group II kidney weights were also larger than control but the difference was not statistically significant despite histopathologic indications of nephrosis. There were no dose-related findings in females. The following organs were collected at necropsy: adrenal glands, urinary bladder, thymus, spine, peripheral nerve, lymph nodes, lungs, trachea/pharynx/larynx, liver, kidneys, heart, thyroid/parathyroid, spleen, stomach, duodenum, jejunum, ileum, colon, cecum, rectum, airta, brain, bone marrow/sternum, esophagus, ovaries, uterus, testes, seminal vesicles, prostate and epididymides. The number of corpora lutea was recorded.

Liver weights of Group II (high-dose) and Group III (mid-dose) males were significantly greater than control. However, no histopathologic evidence of liver abnormality was identified and the origin of the difference is not clear. Liver weights of Group II females were greater than control, however the difference did not reach statistical significance. All other organ weights were within the expected ranges and mean organ weights did not vary significantly among the four groups.

Histopathologic examination of the saved organs showed no test article-related findings except lesions that were limited to the kidneys of Group II rats treated with 1000 mg/kg. Four of the five males and one in ten females were affected. The primary lesion was nephrosis characterized by the deposition of birefringent oxalate crystals within the renal tubules.

The effects of the administration of the test article on mortality, body weights, food consumption, in-life observations, toxicological effects, reproductive and litter performance, hematology and clinical chemistry, organ weights and necropsy findings were used to determine the no effect level (NOEL). Since there were significant findings in the high-dose level, the mid-dose level of 250 mg/kg was the NOEL in both males and females.

INTRODUCTION

This study was conducted to evaluate the potential toxic effects of the test article, Veova 10, when administered to rats for a minimum of 28 days. It was also conducted to determine the potential of the test article to affect male and female reproductive performance such as gonadal function, mating behavior, conception, parturition and early postnatal development. The study was conducted for Hexion Specialty Chemicals, Inc. It was initiated on 01 Dec 04, first data was recorded on 06 Dec 04, and the in-life portion of the study was terminated on 17 Jun 05. Protocol deviations included: PT and APTT values were not determined for the males (B.11.b.); the number of implantation sites was not recorded (B.11.c.2.); organs were collected from only five females in the control and high dose groups (B.11.c.3.); and adrenal glands were not weighed (B.11.c.4.). The protocol, raw data and this report are on file in the STILLMEADOW, Inc. archives.

TEST SYSTEM (cont.)Animal Husbandry

Cage Type:	Suspended, wire bottom, stainless steel; pregnant females were housed in plastic shoebox-type cages. The nesting material was NES3600-Nestlets, Mfg Ancare, Lot 0408050815-117.
Housing:	Individual
Environmental Controls Set to Maintain:	<ul style="list-style-type: none"> · Temperature of 22°C± 3° · Humidity Range of 30-70% · 12-hour light/dark cycle (dark phase was 12 noon to 12 midnight) · 10-12 air changes per hour
Food:	PMI Feeds, Inc. TM Formulab #5008, available <i>ad libitum</i> . Analyzed by manufacturer for nutritional content.
Water:	Municipal water supply analyzed by TNRCC Water Utilities Division; tap water, available <i>ad libitum</i> (automatic system)

Animal husbandry and housing at STILLMEADOW, Inc. comply with Animal Welfare Act Regulations. No contaminants were expected to have been present in the feed or water that would have interfered with or affected the results of the study.

PROCEDURESRange Finder

A range finder was conducted using five males and five females per dose level (untreated control, 2000 mg/kg, 1000 mg/kg, 250 mg/kg and 100 mg/kg). The animals were selected by a weight-stratified randomization procedure. They were dosed five days/week for two weeks. The animals were observed daily and food consumption was measured daily through study termination (Day 14). Body weights were recorded before dosing on Day 0, and on Days 7 and 14. The data tables for the range-finding portion of the study are seen in Appendices J – M.

The definitive dose levels were selected from the data collected from the range finder. The levels selected took into account any existing toxicity and (toxico-) kinetic data available for the test article or related materials. It was also taken into account that there may be differences in sensitivity between pregnant and non-pregnant animals. The highest dose level was chosen with the aim of inducing toxic effects but not death or obvious suffering. Thereafter, a descending sequence of dose levels was selected with a view to demonstrating any dosage related response and no adverse effects at the lowest level. The doses selected for the definitive study were 1000 mg/kg, 250 mg/kg and, 100 mg/kg, each dosed at a constant volume of 5 mL/kg. The final dose solution concentrations were 200 mg/mL, 50 mg/mL and 20 mg/mL.

PROCEDURES (cont.)

Pretest

Body weights were recorded on Day -7 and Day -1, and food consumption was determined from Day -7 to Day -1. Detailed clinical observations were made once before dosing. They were made outside the home cage. Signs noted included, but were not limited to, changes in skin, fur, eyes, mucous membranes, occurrence of secretions and excretions, and autonomic activity (e.g. lacrimation, piloerection, pupil size, unusual respiratory pattern). Changes in gait, posture and response to handling as well as the presence of clonic or tonic movements, stereotypies (e.g. excessive grooming, repetitive circling) difficult or prolonged parturition or bizarre behavior (e.g. self-mutilation, walking backwards) were also be recorded. Normal weight gain, appearance/behavior, detailed clinical observations results and food consumption values were factors used to select healthy animals for testing. Only naive animals were selected.

On Day -1, animals were assigned to four groups using a weight-stratified randomization procedure in an attempt to equalize the mean body weight and weight range of the males and females of each group. Ten males and ten females were assigned to the control group (Group I), and ten males and ten females were assigned to each of the treatment groups (Groups II-IV).

Test Article Analysis

The dosing formulations for the first week of dosing were prepared on Day 0. Homogeneity was checked in each dosing concentration to validate the mixing procedure. Three samples were collected from top, middle or bottom locations in the mixing container and analyzed for test article content. Since the samples were homogeneous, further homogeneity testing was not conducted for batches prepared weekly. Dose concentrations were verified in one sample taken from the center of each dosing formulation prepared weekly during the in-life phase of the study.

Test Article Administration

The animals were dosed by oral gavage with an appropriately sized stainless steel ball-tipped dosing needle and syringe since gavage dosing assures the proper dose presentation. Three groups (Groups II, III and IV) of ten males and ten females each were dosed daily at 1000 mg/kg, 250 mg/kg and 100 mg/kg, respectively. A concurrent vehicle control group (Group I, ten males and ten females) was dosed with the vehicle, corn oil. Groups were dosed daily at approximately the same time each day and dose amounts were adjusted weekly based on the latest body weight. All animals were dosed at a constant volume of 5 mL/kg.

Males and females were dosed for 14 days prior to mating. Males were dosed for another 14 days during mating, for a total of 28 days. Females were dosed through mating and until one day prior to termination (lactation Day 4 for those that delivered and post-mating Day 23 or post-cohabitation Day 23 for those that did not deliver).

PROCEDURES (cont.)

Observations

Observations for morbidity and mortality were made twice daily, and observations for pharmacologic and/or toxicologic effects were made once daily until study termination. General clinical observations included but were not necessarily limited to evaluation of skin, fur, eyes and mucous membranes, respiratory and circulatory effects, autonomic effects (salivation, lacrimation, excessive urination and diarrhea), central nervous system effects (tremors and convulsions), changes in the level of activity, gait and posture, reactivity to handling or sensory stimuli, altered strength and stereotypies or bizarre behavior (e.g., self mutilation, walking backwards). The nature, onset, severity, and duration of all gross or visible pharmacologic and/or toxicologic effects were recorded. Detailed clinical observations were made weekly in the same manner as pretest.

Body Weights

Body weights were recorded weekly (Days 7, 14, 21 and 28 for the males). Body weights for females were recorded on Days 7, 14, 21 and 28, and/or on gestation Days 0, 4, 7, 11, 14, 17 and 20, and on lactation Days 1 and 4. Body weights for the pups were recorded on lactation Days 1 and 4. Body weights were recorded at the time of discovery after death for animals that died on study.

Food Consumption

Food consumption was recorded weekly through the termination of the study with the exception of the cohabitation period.

Mating Procedures

After fourteen days of treatment, each female was cohabited with one male from the same group for a period of two weeks or until signs of pregnancy were observed. Each morning, the female was examined for the presence of sperm or a vaginal plug. Day 0 of pregnancy was the day the plug or sperm was found. A maximum of fourteen days was allowed for mating. After confirmation of mating, the males were returned to their home cages, and females were put in plastic cages and nesting materials were added.

Parturition and Litter Observations

The day parturition was complete was considered lactation Day 0. When birth was completed, the litters were sexed, examined for gross malformations, and the number of stillbirths and live pups was recorded. The pups were individually marked for identification. Any changes or abnormalities in nesting or nursing behavior were recorded. Body weights for the pups were recorded on lactation Days 1 and 4, and they were re-sexed at that time. Pups were observed daily for general appearance, behavior and survival.

PROCEDURES (cont.)

Functional Observational Battery and Motor Activity

An assessment of motor activity, grip strength, and sensory reactivity to stimuli of different types (e.g., visual, auditory, and proprioceptive stimuli) was conducted. The following parameters were evaluated: posture, involuntary motor movement, vocalization, palpebral closure, ease of removal from home cage, handling reactivity, number of rears, arousal, mobility, gait and gait score, number of fecal boluses and urine pools, approach, touch, click, tail pinch and pupil response, righting reflex and bizarre behavior. Grip strength was measured.

The Flex-Field/Open-Field Activity System by SD Instruments (San Diego, CA) was used for more detailed assessment of motor activity. Males (5/group) were evaluated following 28 days of dosing, just prior to sacrifice. Females (5/group) were evaluated on lactation Day 4, just prior to sacrifice. One male from each group was tested at the same time in three 15-minute increments for a total of forty-five minutes. They were placed in plastic cages in the photocell framework. Females were tested in the same manner except their home cages (nesting cages) were placed in the test compartments. All animals were tested during the dark phase of the light cycle in the animal room in which all the animals on the study were housed.

Euthanasia

Animals were sacrificed by an overdose of carbon dioxide. Males were sacrificed after the mating period on Day 29. Each female and her litter were euthanized on their lactation Day 4, and females that did not deliver were euthanized on approximately Day 51 of the study. Females with total litter loss were sacrificed within 24 hours of litter loss. Body weights were recorded at time of sacrifice.

Blood Collection and Analysis

One mL blood was drawn from the vena cava at necropsy into a purple-topped Vacuette® tube (Lot B030501, Exp Sep 06); one mL was drawn into a red-topped Vacutainer® tube (Lot 4154193, Exp May 06) or similar with clot activator (Lot 4222481, Exp Nov 05); and three mL were drawn into blue-topped tubes (Lot 5024978, Exp Nov 05). The red- and blue-topped Vacutainer® tubes were used to separate serum or plasma. The females' prothrombin times and activated partial thromboplastin times were analyzed at STILLMEADOW, Inc. Hematology and serum chemistry parameters were analyzed at Antech Diagnostics (507 Airport Boulevard, Suite 113, Morrisville, NC 27560). The hematology parameters analyzed were erythrocyte count, hemoglobin, hematocrit, total and differential leukocyte counts, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and mean corpuscular volume. The serum chemistry parameters analyzed were blood urea nitrogen, creatinine, serum alanine aminotransferase, serum aspartate aminotransferase, total bilirubin, total protein, total cholesterol, globulin, albumin, A/G ratio, glucose, inorganic phosphorus, calcium, sodium, potassium, and chloride. Antech Diagnostics is a GLP-compliant analytical laboratory.

PROCEDURES (cont.)

Necropsy and Organ Weights

A gross necropsy examination was conducted on each adult animal at the time of discovery after death or at time of sacrifice. Pups sacrificed on lactation Day 4 were carefully examined externally for gross abnormalities. The necropsy included gross observations of external surfaces and all orifices, and gross observations of thoracic and abdominal cavities and their viscera. Special attention was paid to the organs of the reproductive system. The number of corpora lutea was recorded. The testes and epididymides of all sacrificed males and ovaries with oviducts of the sacrificed females were carefully removed, trimmed, and weighed. Ovaries with oviducts, testes, epididymides and accessory sex organs, and all organs showing macroscopic lesions were preserved. Tissues were weighed as soon as possible to avoid dehydration of the tissues.

The liver, kidneys, thymus, spleen, brain and heart from five adult males and females randomly selected from each group were carefully removed, trimmed and weighed.

The following tissues were preserved in 10% neutral buffered formalin: all gross lesions or tissues showing abnormalities, brain (cerebrum, cerebellum and pons), spinal cord, stomach, small and large intestine (duodenum, jejunum, ileum, caecum and colon including Peyer's patches), liver (sections of 2 lobes), kidneys, adrenals, spleen, heart and aorta, thymus, thyroid, trachea and lungs (including bronchi, preserved by inflation with fixative and then immersion), ovaries with oviducts, uterus, urinary bladder, lymph nodes (mesenteric and submandibular), peripheral nerve (sciatic or tibial) in close proximity to the muscle, and bone marrow.

Preserved samples of the above organs were sent to Pathology Solutions, Inc., Clearwater, FL, GLP-compliant pathologists, for analysis.

Histopathology

Lawrence F. Fisher, DVM, PhD, DACVP of Pathology Solutions, Inc. performed a full histopathologic examination on all tissues saved from five males and all females from the control (Group I) and high-dose (Group II) groups. Special emphasis was put on the stages of spermatogenesis in the male gonads and histopathology of interstitial testicular cell structure. Since treatment related changes were noted in some Group II animals, tissues of five males and five females from the low and intermediate dose groups were also examined. All gross lesions were examined.

Evaluation of Results

The findings were evaluated in terms of the observed effects, necropsy, and microscopic findings. The evaluation includes the relationship between the dose of the test article and the presence or absence, incidence and severity of abnormalities, including gross lesions, identified target organs, infertility, clinical abnormalities, affected reproductive and litter performance, body weight changes, effects on mortality and any other toxic effects. Accepted statistical methods were employed where appropriate, including one-way analysis of variance (ANOVA) and Dunnett's t-test to identify differences from control when identified by ANOVA.

RESULTS AND DISCUSSION

Mortality

Animal 80-F (Group I) was found dead on Day 18. Activity decrease, piloerection, and difficulty standing upright were noted the previous day and she was moved to a separate cage. Necropsy revealed red stain on muzzle and a small hole on the left side of the lung. Death was probably due to a dosing injury. This control female was replaced with animal 87-F.

Test Article Analysis

Homogeneity was checked in each dosing concentration prepared on Day 0 to validate the mixing procedure. Three samples were collected from top, middle or bottom locations in the mixing container and analyzed for test article content. The results demonstrate acceptable homogeneity. Results are presented in Table 1.

Dose concentrations were verified weekly. One sample for analysis was taken from the center of each dosing formulation prepared weekly during the in-life phase of the study. The mean concentrations for the 200 mg/mL (Group II), 50 mg/mL (Group III), and 20 mg/mL (Group IV) solutions were 202.9 mg/mL, 43.8 mg/mL, and 20.6 mg/mL, respectively, indicating the average doses delivered were 1014 mg/kg, 219 mg/kg and 103 mg/kg, respectively.

Observations

Daily in-life observations are presented in Table 4. In the vehicle control group (Group I), one female (80-F) had slight piloerection and moderate activity decrease on Day 17 and was found dead on Day 18 (see Mortality, above). In Group II, (1000 mg/kg), one female (59-F) had slight to extreme red discharge around the muzzle as well as very slight to extreme piloerection and emaciation on Days 4-8. A Group II male (2-M) was sensitive to the touch on Days 20-28 and another Group II male (31-M) was emaciated on Days 27-28. There were no observable abnormalities in any Group III (250 mg/kg) or Group IV (100 mg/kg) animal during the study.

Detailed clinical observations were conducted weekly. No abnormalities were noted that were not observed during the general health observations.

Body Weights

Body weights are presented in Table 2 and Figures 1 (males) and 2 (females). There were no apparent treatment-related differences in group mean body weights through Day 28 when Groups I-IV, males or females, were compared by analysis of variance. Males were euthanized on Day 29. Body weights of females are listed in Table 2 until a female was identified as pregnant, after which the body weights are given as gestational body weights in Table 3. Table 2 also has a separate section with body weights of only those females that were thought to have conceived but did not eventually deliver.

Body weights of females during gestation and lactation are presented in Table 3 and Figures 3 and 4. Females of all control and treated groups exhibited similar weight profiles during the gestation and lactation periods, suggesting that the pregnancies of the treated animals progressed similarly to those of the controls.

RESULTS AND DISCUSSION (cont.)

Figures 4 (control), 5 (high dose) and 6 (mid and low dose) contain body weights of those females that were thought to have conceived but did not deliver. There were three such females in Group I, three in Group II, and two each in Groups III and IV. In one animal (86-F of Group IV), the weight profile suggested that a pregnancy was initiated but not completed. Otherwise, weight gain in these animals seemed quite typical of normal, non-pregnant female Sprague-Dawley rats.

Food Consumption

Food consumption data are presented in Table 5. There were no apparent dose related differences in group mean food consumption among males or females.

Parturition and Litter Observations

Lactation Day 0 litter observations are presented in Table 6. There were 7, 6, 8 and 8 females in Groups I – IV, respectively, that had successful births. One Group II female (59-F) lost her litter either just prior to or immediately following parturition. Group birthing information is summarized in the following table.

Group	% Conception	% Successful Delivery	Mean # Pups	Mean Live Pups	Mean Stillborn
I	70	70	13.7	13.6	0.1
II	70	60	13.4	12.8	0.5
III	80	80	14.0	13.3	0.8
IV	80	80	14.1	13.9	0.3

Little difference is apparent in conception rates, number of pups delivered or incidence of stillborn pups when control and high-, mid- and low-dose groups are compared. Overall, the treated groups showed a greater incidence of stillborn pups than control although there was no clear dose relationship. However, some pups were lost from two high-dose litters soon after birth (see below). Corpora lutea counts at necropsy are presented in Table 16. There were no significant differences in corpora lutea counts among groups.

Individual body weights for the pups were recorded on lactation Days 1 and 4 and the data are presented in Table 7 (summary) and Appendix A. Group means are summarized in the following table.

Group	Day 1 Means	Day 4 Means	Gain
I	6.8	11.7	4.9
II	6.4	9.4	3.0
III	7.5	10.4	2.9
IV	6.9	9.7	2.7

Weights are in grams

Mean pup body weights on Day 1 were not significantly different among groups. Day 4 mean pup weights were significantly lower than control in Groups II and IV, but not in Group III, so the dose response is weak. It is also worth noting that pups in two of the control litters gained much more weight than did the other controls, leading to a higher mean pup weight, and this may bias the analysis unfairly. The same is true in the case of the group mean pup weight gains, where the average weight gains of the pups in the three treated groups are nearly the same, while the control mean weight gain is considerably larger.

RESULTS AND DISCUSSION (cont.)Parturition and Litter Observations (cont.)

Total litter weight group means are summarized in the following table.

Group	Day 1 Means	Day 4 Means	Gain
I	93.8	160.0	66.2
II	75.4	110.3	34.9
III	98.7	134.6	36.0
IV	95.6	132.4	36.8

Weights are in grams

Mean total litter weight in Group II was significantly lower than control on both Day 1 and Day 4, while neither the mid-dose nor the low-dose groups was significantly different from control at Day 1 or Day 4. The loss of four Group II pups before the Day 1 weights may be responsible at least in part for the differences.

Daily observations of the litters revealed no observable abnormalities except for four Group II pups (two pups from two litters) that disappeared between Day 0 and Day 1. Observations are presented in Table 8.

Functional Observational Battery and Motor Activity

The FOB data are presented in Table 9 (summary) and Appendix B, and the legend to the tables is in Appendix C.

The evaluations were conducted the day before sacrifice (on Day 28 of the study for the males and on lactation Day 4 for females). Motor activity analysis with the Flex-field automated apparatus is separate from the FOB itself but is another more quantitative measure of motor activity.

No differences among the groups were seen in any of the parameters scored in the functional observational battery in either males or females.

Motor activity results are presented in Table 10 and Appendix D. Analysis of the motor activity results revealed no statistical differences among female groups in fine movements, ambulatory movements, or their total, for both the center of the cage and the periphery and no difference in the number of rears. The male movements in the center of the cage could not be statistically analyzed due to a photocell that was not functioning during the control group testing. Considerable variability was seen among male fine, ambulatory and total movements as well as in the number of rears, but there was no apparent dose relationship. It is worth noting that whereas the females were tested in their home plastic cages, the males had been housed in stainless steel wire-bottom cages and were placed in plastic cages only for the purpose of the motor activity measurements. Therefore, their greater activity levels likely are related to their having been placed into an unfamiliar setting.

RESULTS AND DISCUSSION (cont.)

Serum Chemistry

Serum chemistry data are presented in Table 11 and Appendix E. There were no statistically significant differences in male albumin, alanine aminotransferase, aspartate aminotransferase, total bilirubin, calcium, glucose, inorganic phosphorus, total protein, sodium, potassium, chloride, globulin, or A/G ratio. BUN was elevated in males of the high-dose group; mean value was approximately 30 mg/dL vs. 18.5-20 mg/dL for the other groups. However, all the female groups had BUN values near 30 mg/dL, yet only one Group II female (56-F) was noted with histopathologic signs of nephrosis. Urea clearance is an indicator of overall renal function, and elevation of BUN in Group II males would possibly be consistent with the signs of nephrosis seen in the kidneys of this group in histopathology. It is unclear why all females including control would appear to have elevated BUN levels. Cholesterol levels were significantly higher in Group II and III males than controls, however they were still within normal limits. Creatinine levels were low normal in all male groups, yet slightly but significantly higher in Group II. The cholesterol and creatinine findings are considered incidental effects.

There were no statistically significant differences in female blood urea nitrogen, creatinine, serum alanine aminotransferase, serum aspartate aminotransferase, total bilirubin, total protein, total cholesterol, globulin, albumin, A/G ratio, glucose, inorganic phosphorus, calcium, sodium, potassium, or chloride.

Hematology

Hematology data are given in Table 12 and Appendix F. Individual values were mainly within normal limits, and there were no statistically significant differences in male group mean RBC, hemoglobin, hematocrit, total leukocyte counts, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, neutrophils, lymphocytes, eosinophils, monocytes or basophils.

Similarly, individual values were largely within normal limits and there were no statistically significant differences among groups in any female hematology parameter analyzed. The female PT and APTT values were similar in all groups.

RESULTS AND DISCUSSION (cont.)

Necropsy Findings

Male necropsy findings are presented in Table 13 and female necropsy findings in Table 14.

There were no abnormalities observed in any Group I, III or IV male. The only findings in the Group II males were enlarged or pale enlarged kidneys in three animals. In females, one Group I animal had a pale, enlarged left kidney. One Group III female had ovaries full of clear liquid and in another, the right adrenal gland was not found. There were no abnormalities observed in Group II or Group IV females. The kidney findings at necropsy in Group II males are consistent with the histopathology findings (see Histopathology below)

Organ Weights

Male organ weights are presented in Table 15 and female organ weights in Table 16. There were no statistically significant differences among groups in weights of male thymus, heart, spleen, brain, testes or epididymides. Liver weights of Group II (high-dose) and Group III (mid-dose) males were significantly greater than control. However, no histopathologic evidence of liver abnormality was identified and the origin of the difference is not clear. Group II kidney weights were also larger than control and while the difference was not statistically significant there were clearly histopathologic indications of nephrosis.

In females, there were no statistically significant differences in the weights of the thymus, kidneys, heart, spleen, brain, ovaries or corpora lutea. Liver weights of Group II females were greater than control, however again the difference did not reach statistical significance.

All other organ weights were within the expected ranges and mean organ weights did not vary significantly among groups.

RESULTS AND DISCUSSION (cont.)

Histopathology

The Pathology Report is presented in Appendix I. Miscellaneous non-test article-related findings included: renal hyaline casts, mineralization and a nephroblastoma (in a control female); pulmonary inflammation and/or edema; and urinary bladder and uterine distention, the latter likely a normal cyclical change.

Test article-related lesions were limited to the kidneys of Group II rats treated with 1000 mg/kg. Four of the five males and one in ten females were affected. The primary lesion was nephrosis, characterized by the deposition of birefringent (brightly evident under polarized light) crystals that resembled oxalates within the renal tubules. Necrosis/degeneration of the adjacent epithelial cells was dependent upon the amount of crystalline deposition but was not a major change. The nephrosis was sometimes accompanied by chronic interstitial nephritis, increased basophilic cortical tubules (a regenerative indicator), and papillary necrosis in one male. Other secondary non-renal lesions included thymic lymphoid depletion in two affected males and a mild gastric ulcer in one affected male.

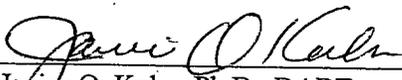
In addition to toxic effects, this study was also intended to determine effects of the test article upon reproductive performance. However, no histopathologic changes were observed upon microscopic examination of the male or female reproductive organs.

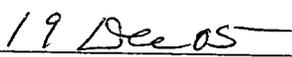
Summary Table

Observation	Group I (Control)	Group II (High)	Group III (Mid)	Group IV (Low)
Pairs started (N)	10	10	10	10
Females showing evidence of copulation (N)	10	10	10	9
Females achieving pregnancy (N)	7	7	8	8
Conceiving days 1 – 5 (N)	3	2	3	2
Conceiving days 6 – 14 (N)	4	5	5	6
Dams with live young born (N)	7	6	8	9
Dams with live young at Day 4 (N)	7	6	8	8
Corpora lutea/dam (mean)	20.25	14.7	16.6	17.25
Live pups/dam at birth (mean)	13.6	12.7	13.3	13.9
Live pups/dam at Day 4 (mean)	13.6	12.7	13.3	13.8
Sex ratio (m/f) at birth (mean)	1.24	2.71	1.06	0.73
Sex ratio (m/f) at Day 4 (mean)	1.24	2.71	1.06	0.73
Litter weight at birth (mean)	93.8	75.4	98.6	95.6
Litter weight at Day 4 (mean)	160.0	110.3	134.6	132.4
Pup weight at birth (mean)	6.8	6.47	7.59	6.9
Pup weight at Day 4 (mean)	11.7	9.4	10.48	9.7
Dams with abnormal pups	None	None	None	None

CONCLUSION

This study was conducted to evaluate the effects of the test article, Veova 10 (CAS # 51000-52-3), when administered to rats. The effects of the administration of the test article on mortality, body weights, food consumption, in-life observations, toxicological effects, reproductive and litter performance, hematology and clinical chemistry, organ weights and necropsy findings indicate the no effect level (NOEL) to be 250 mg/kg in both males and females.


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Date (Original date 19Sep05)

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Table 1 - Homogeneity and Dose Confirmation

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

Homogeneity - Day 0

	Sample	Concentration	Mean	S.D.
20 mg/mL	Top	20.024	16.9	3.0
	Middle	16.478		
	Bottom	14.062		
50 mg/mL	Top	47.827	44.5	3.3
	Middle	44.417		
	Bottom	41.170		
200 mg/mL	Top	183.387	167.2	22.0
	Middle	142.172		
	Bottom	175.935		

Dose Confirmation

	Day of Study								Mean	S.D.
	0	7	14	21	28	35	42	49		
20 mg/mL	16.85	18.47	18.93	16.23	22.61	23.12	21.21	27.34	20.6	3.7
50 mg/mL	44.47	46.95	54.29	44.81	43.06	51.53	31.11	34.28	43.8	7.9
200 mg/mL	167.16	258.47	202.86	194.12	145.59	238.30	183.04	233.33	202.9	38.4

Note: dose confirmation values are the means of the samples tested in triplicate

Table 2 - Body Weights

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

Animal Number	Body Weights (g)								
	Pretest		Day of Study						
	-7	-1	7	14	21	28	35	42	49
Group I									
1-M	262	280	310	337	355	370			
8-M	267	292	319	334	349	358			
9-M	252	275	301	318	334	338			
12-M	260	289	320	330	342	356			
13-M	276	310	332	351	353	364			
15-M	262	288	313	319	333	342			
17-M	263	299	338	354	367	378			
30-M	254	289	315	332	343	354			
36-M	257	283	302	316	321	331			
40-M	260	298	333	348	365	377			
Mean	261	290	318	334	346	357			
S.D.	7	10	13	14	15	16			
47-F	205	214	220	230	236				
49-F	191	207	225	222					
54-F	195	209	213	228					256
58-F	188	199	208	217					248
65-F	194	212	224	231	253				
67-F	194	209	217	224					
68-F	200	218	222	235					
77-F	178	198	207	205					
78-F	195	212	224	235	255				
80-F *	201	216	223	231					
87-F *					253				256
Mean	194	209	218	226	249				
S.D.	8	7	7	9	9				

M - Male; F - Female; S.D. - Standard deviation; * - Animal 80-F was found dead on Day 18 and was replaced with 87-F
 Note: as females were bred successfully, their body weights were recorded as gestation weights (see Table 3).

Table 2 - Body Weights (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

Animal Number	Body Weights (g)								
	Pretest		Day of Study						
	-7	-1	7	14	21	28	35	42	49
Group II									
2-M	260	281	308	321	331	335			
10-M	259	293	313	325	344	356			
16-M	264	291	309	321	334	341			
21-M	263	299	332	338	348	350			
23-M	263	304	326	343	360	361			
27-M	255	286	311	323	355	349			
28-M	262	294	320	338	352	353			
31-M	256	262	272	279	282	272			
35-M	257	289	313	323	334	336			
37-M	258	286	301	314	330	327			
Mean	260	289	311	323	337	338			
S.D.	3	11	16	18	22	25			
45-F	191	212	216	229					298
53-F	184	194	227	216					260
55-F	200	215	226	219					257
56-F	188	205	235	225	240	250	282	356	*
59-F	208	217	195	235					
61-F	190	210	225	236					
63-F	212	222	228	239					
64-F	193	209	222	226	253	251	320	*	
66-F	188	206	208	222	247				
69-F	193	210	224	241					
Mean	195	210	221	229	247	251			
S.D.	9	8	12	9	7	1			

M - Male; F - Female; S.D. - Standard deviation; * - Gave birth

Note: as females were bred successfully, their body weights were recorded as gestation weights (see Table 3).

Table 2 - Body Weights (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
 Test Article: Veova 10

Animal Number	Body Weights (g)								
	Pretest		Day of Study						
	-7	-1	7	14	21	28	35	42	49
Group III									
5-M	266	293	316	329	345	334			
6-M	268	302	329	345	359	372			
14-M	251	279	299	312	325	344			
20-M	258	291	310	330	343	364			
24-M	253	287	313	332	346	360			
25-M	257	296	315	331	343	331			
26-M	250	285	303	321	338	342			
29-M	252	268	282	304	319	325			
32-M	266	299	318	330	346	351			
34-M	250	289	301	313	324	341			
Mean	257	289	309	325	339	346			
S.D.	7	10	13	12	12	15			
42-F	200	215	220	238					
43-F	199	208	222	225	242				
50-F	196	206	213	227	246				
51-F	185	205	211	207					
57-F	200	218	224	227	239				264
70-F	193	210	218	225					
71-F	180	198	216	220					
73-F	195	211	226	231					263
74-F	196	213	214	225					
79-F	196	217	229	238	252				
Mean	194	210	219	226	245				
S.D.	7	6	6	9	6				

M - Male; F - Female; S.D. - Standard deviation

Note: as females were bred successfully, their body weights were recorded as gestation weights (see Table 3).

Table 2 - Body Weights (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

Animal Number	Body Weights (g)								
	Pretest		Day of Study						
	-7	-1	7	14	21	28	35	42	49
Group IV									
3-M	270	307	337	354	368	388			
4-M	260	292	325	339	350	361			
7-M	262	291	315	325	346	355			
11-M	271	300	332	345	358	360			
18-M	267	294	324	347	351	354			
19-M	263	288	316	330	317	341			
22-M	259	276	300	306	313	320			
33-M	248	273	300	310	329	337			
38-M	256	289	319	335	343	348			
39-M	249	284	301	291	307	329			
Mean	261	289	317	328	338	349			
S.D.	8	10	13	20	21	19			
44-F	200	217	232	236	253				
46-F	198	216	199	236	252				
48-F	180	198	223	220					
52-F	194	207	224	231	235	248	268	273	271
60-F	205	220	234	241					
62-F	200	209	232	233	242				
72-F	188	203	211	209					
75-F	191	208	218	214					
76-F	196	212	226	230	242				
86-F	208	213	230	245					250
Mean	196	210	223	230	245	NA			
S.D.	8	7	11	12	8	NA			

M - Male; F - Female; S.D. - Standard deviation

Note: as females were bred successfully, their body weights were recorded as gestation weights (see Table 3).

Table 2 - Body Weights (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
 Test Article: Veova 10

Animal Number	Body Weights (g) **						
	Gestation Day						
	0	4	7	11	14	17	20
Group I							
54-F	245	247	262	239	238	249	273
58-F	225	230	249	234	237	240	242
87-F	248	264	257	260	261	273	287
Group II							
45-F	234	247	264	279	275	296	300
53-F	241	252	248	269	254	254	260
55-F	253	269	259	275	260	270	279
Group III							
57-F	243	249	248	253	255	259	
73-F	237	254	241	261	258	249	259
Group IV							
52-F			235	248	268	273	271
86-F	234	249	274	293	262	257	260

F - Female

** - Females that were thought to have conceived but did not deliver. Their body weights were recorded on the Gestation Body Weight data sheet according to the estimated Gestation Day.

Table 3 - Gestation Body Weights

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

Animal Number	Body Weights (g)							Lactation Day	
	Gestation Day							1	4
	0	4	7	11	14	17	20		
Group I									
47-F	239	255	263	283	300	350	368	276	295
49-F	219	236	244	261	274	336	346	266	271
65-F	261	268	279	289	365	407		279	268
67-F	256	274	282	320	385			290	281
68-F	256	269	281	318	353	396		296	301
77-F	216	231	251	248	271	283	301	253	265
78-F	260	270	282	379				277	291
Group II									
56-F						322	353	281	273
59-F	251	258	270	278	286	294	314	277 *	
61-F	244	268	273	294	301	327	371	285	280
63-F	258	272	289	295	348	386		288	269
64-F								297	303
66-F	256	272	274	325	371			276	279
69-F	271	288	294	347	374			293	291
Group III									
42-F	242	256	273	285	303	321		292	295
43-F	242	266	271	302	326	340		294	283
50-F	251	278	278	299	361	392		281	290
51-F	224	239	253	268	291	326		257	265
70-F	230	245	269	271	283	319	328	261	287
71-F	236	247	263	287	314	311		275	288
74-F	259	273	296	305	382	401		290	280
79-F	264	281	294	386	402			294	300
Group IV									
44-F	257	266	291	308	374			282	284
46-F	258	270	286	301	368			300	305
48-F	229	255	254	278	298	340		265	245
60-F	231	266	277	258	300	343	356	292	309
62-F	251	268	269	289	322	402		281	288
72-F	225	244	256	270	284	348	361	287	283
75-F	233	250	255	269	340			256	256
76-F	250	270	285	325	361			283	287

F - Female; * - Lost litter

Table 4 - General Health Observations
 Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
 Test Article: Veova 10

Animal Number	Pretest Day						
	-7	-6	-5	-4	-3	-2	-1
Group I Males							
All							
Group I Females							
All							
Group II Males							
All							
Group II Females							
All							
Group III Males							
All							
Group III Females							
All							
Group IV Males							
All							
Group IV Females							
All							

NOA - No observable abnormalities

Table 4 - General Health Observations (cont.)
 Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
 Test Article: Veova 10

Animal Number	Observation	Day of Study														
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Group I Males																
All	NOA															
Group I Females																
All	NOA															
Group II Males																
All	NOA															
Group II Females																
59-F	Red discharge around muzzle	-	-	-	-	m	e	e	s	s	s	-	-	-	-	-
	Piloerection	-	-	-	-	e	e	m	v	v	v	-	-	-	-	-
	Emaciated	-	-	-	-	p	p	p	p	p	p	-	-	-	-	-
	NOA															
Rest																
Group III Males																
All	NOA															
Group III Females																
All	NOA															
Group IV Males																
All	NOA															
Group IV Females																
All	NOA															

M - Male; F - Female; NOA - no observable abnormalities; e - extreme; m - moderate; s - slight; v - very slight; p - observation present; (-) - observation not present

Table 4 - General Health Observations (cont.)
Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
Test Article: Veova 10

Animal Number	Observation	Day of Study													
		15	16	17	18	19	20	21	22	23	24	25	26	27	28
Group I Males															
All	NOA														
Group I Females															
80-F	Piloerection	-	-	s											
	Activity decrease	-	-	m											
	Death	-	-	-	p										
	NOA														
Group II Males															
2-M	Sensitivity to touch	-	-	-	-	-	p	p	p	p	p	p	p	p	p
31-M	Emaciation	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	NOA														
Group II Females															
All	NOA														
Group III Males															
All	NOA														
Group III Females															
All	NOA														
Group IV Males															
All	NOA														
Group IV Females															
All	NOA														

M - Male; F - Female; NOA - no observable abnormalities; m - moderate; s - slight; p - observation present; (-) - observation not present

Table 4 - General Health Observations (cont.)
Combined Repeated Dose, Toxicity Study with Reproduction/Developmental Toxicity Screening Test
Test Article: Veova 10

Animal Number	Observation	29	30	31	32	33	34	35	36	37	38	39	40	41	42
Group I Females															
All	NOA														
Group II Females															
All	NOA														
Group III Females															
All	NOA														
Group IV Females															
All	NOA														

Animal Number	Observation	43	44	45	46	47	48	49	50	51
Group I Females										
All	NOA									
Group II Females										
All	NOA									
Group III Females										
All	NOA									
Group IV Females										
All	NOA									

NOA - no observable abnormalities

Table 5 - Food Consumption

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
 Test Article: Veova 10

Pre-Cohabitation

Animal Number	Food Consumed (g)				
	Pretest Day			Day of Study	
	-7	-4	0	7	14
Group I - Control					
1-M	96	76	28	157	163
8-M	78	85	17	169	173
9-M	63	76	20	194	147
12-M	78	85	27	173	167
13-M	81	95	30	172	176
15-M	72	82	30	163	147
17-M	72	87	28	181	163
30-M	73	81	28	150	149
36-M	68	72	23	138	127
40-M	73	84	23	163	167
Mean	75	82	25	166	158
S.D.	9	7	4	16	15
47-F	58	65	18	114	133
49-F	61	76	19	119	81
54-F	81	73	19	201	70
58-F	50	81	7	176	110
65-F	51	67	16	127	109
67-F	48	63	22	112	118
68-F	60	71	18	122	86
77-F	48	61	23	110	149
78-F	61	67	20	134	117
80-F	62	62	15	98	98
Mean	58	69	18	131	107
S.D.	10	7	4	32	24
Overall Mean	67	75	22	149	133
Overall S.D.	13	9	6	30	33

M - Male; F - Female; S.D. - Standard deviation

Table 5 - Food Consumption (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
 Test Article: Veova 10

Pre-Cohabitation

Animal Number	Food Consumed (g)				
	Pretest Day			Day of Study	
	-7	-4	0	7	14
Group II					
2-M	74	79	25	146	161
10-M	70	85	24	154	142
16-M	70	79	23	176	148
21-M	82	93	33	171	168
23-M	71	88	31	161	165
27-M	76	85	26	152	155
28-M	75	86	29	167	161
31-M	81	74	21	149	132
35-M	77	89	28	189	242
37-M	79	88	27	160	159
Mean	76	85	27	163	163
S.D.	4	6	4	13	30
45-F	50	73	18	114	133
53-F	46	61	22	148	129
55-F	64	68	20	107	123
56-F	245	122	32	158	142
59-F	52	65	26	106	188
61-F	52	63	20	125	132
63-F	58	66	18	163	146
64-F	55	67	17	232	122
66-F	53	66	18	115	119
69-F	64	70	23	240	231
Mean	74	72	21	151	147
S.D.	60	18	5	49	36
Overall Mean	75	78	24	157	155
Overall S.D.	42	14	5	36	33

M - Male; F - Female; S.D. - Standard deviation

Table 5 - Food Consumption (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
 Test Article: Veova 10

Pre-Cohabitation

Animal Number	Food Consumed (g)				
	Pretest Day			Day of Study	
	-7	-4	0	7	14
Group III					
5-M	67	80	26	157	142
6-M	76	89	23	169	160
14-M	71	82	23	149	136
20-M	154	84	27	166	159
24-M	100	85	25	165	168
25-M	78	83	26	148	154
26-M	69	82	26	169	162
29-M	63	69	24	193	255
32-M	76	90	29	171	149
34-M	72	86	26	171	188
Mean	83	83	26	166	167
S.D.	27	6	2	13	34
42-F	53	71	10	118	142
43-F	59	77	16	132	122
50-F	60	67	17	124	127
51-F	64	75	18	116	108
57-F	54	74	18	117	122
70-F	52	62	19	108	108
71-F	189	62	20	115	111
73-F	51	61	19	160	116
74-F	55	69	18	118	113
79-F	57	67	21	121	120
Mean	69	69	18	123	119
S.D.	42	6	3	14	10
Overall Mean	76	76	22	144	143
Overall S.D.	35	9	5	26	35

M - Male; F - Female; S.D. - Standard deviation

Table 5 - Food Consumption (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

Pre-Cohabitation

Animal Number	Food Consumed (g)				
	Pretest Day			Day of Study	
	-7	-4	0	7	14
Group IV					
3-M	78	85	25	173	156
4-M	74	83	28	173	154
7-M	76	87	25	225	157
11-M	69	77	24	165	143
18-M	68	81	22	173	159
19-M	106	82	27	164	155
22-M	60	78	22	167	144
33-M	70	79	22	156	143
38-M	78	86	24	191	158
39-M	78	90	32	147	125
Mean	76	83	25	173	149
S.D.	12	4	3	22	11
44-F	72	76	25	130	120
46-F	59	75	15	254	126
48-F	63	68	20	141	113
52-F	57	65	18	126	131
60-F	49	63	21	137	123
62-F	46	58	16	126	109
72-F	54	61	24	104	96
75-F	52	64	19	123	104
76-F	90	84	14	123	125
86-F	48	66	21	145	143
Mean	59	68	19	141	119
S.D.	13	8	4	41	14
Overall Mean	67	75	22	157	134
Overall S.D.	15	10	4	36	20

M - Male; F - Female; S.D. - Standard deviation

Table 5 - Food Consumption (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
 Test Article: Veova 10

Females, Post-Cohabitation

Animal Number	Food Consumed (g)			
	Gestation Day			
	7	14	21	28
Group I - Control				
47-F	109	78	93	104
49-F	124	175	145	22
54-F	114	117	198	194
58-F	24	168	178	194
65-F	117	115	144	2
67-F	109	134	111	-
68-F	125	229	131	11
77-F	13	219	113	115
78-F	224	88	131	-
80-F	82	36	82	104
Mean	104	136	133	93
S.D.	58	62	36	77
Group II				
45-F	148	134	29	180
53-F	114	124	35	109
55-F	118	124	45	86
56-F	110	118	112	114
59-F	188	268	80	1
61-F	122	154	78	61
63-F	44	120	99	2
64-F	165	96	86	-
66-F	123	151	80	23
69-F	122	200	69	-
Mean	125	149	71	72
S.D.	38	50	27	63

F - Female; S.D. - Standard deviation; - = No longer on study

Table 5 - Food Consumption (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

Females, Post-Cohabitation

Animal Number	Food Consumed (g)			
	Gestation Day			
	7	14	21	28
Group III				
42-F	20	86	19	-
43-F	86	144	70	29
50-F	94	141	52	3
51-F	109	138	63	3
57-F	175	105	39	36
70-F	9	183	109	110
71-F	244	174	117	13
73-F	13	78	128	123
74-F	227	78	215	123
79-F	198	202	73	-
Mean	118	133	89	55
S.D.	89	45	56	54
Group IV				
44-F	67	235	84	-
46-F	133	152	253	3
48-F	109	131	104	70
52-F	176	144	89	-
60-F	42	127	151	52
62-F	123	134	125	15
72-F	135	168	119	54
75-F	97	119	157	-
76-F	233	140	139	-
86-F	127	98	39	71
Mean	124	145	126	44
S.D.	53	37	57	29

F - Female; S.D. - Standard deviation; - = No longer on study

Table 6 - Lactation Day 0 Litter Information

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
 Test Article: Veova 10

Dam Number	Number of Pups	Number of Males	Number of Females	Number Born Live	Number Stillborn	General Observations
Group 1						
49	12	5	7	12	0	NOA
67	13	10	3	13	0	NOA
68	13	8	5	12	1	One male dead, rest NOA
78	15	5	10	15	0	NOA
77	15	7	8	15	0	NOA
65	15	5	10	15	0	NOA
47	13	7	6	13	0	NOA
Mean	13.7	6.7	7.0	13.6	0.1	
Group 2						
63	17	10	7	17	0	NOA
69	12	11	1	12	0	NOA
66	13	6	6	12	1	One male dead, partially eaten, rest NOA
64	13	5	5	10 *	1	One male dead, rest NOA
61	12	4	7	11	1	One male dead, rest NOA
56	12	5	7	12	0	NOA
Mean	13.4	6.8	5.5	12.8	0.5	
Group 3						
71	12	5	6	11	1	One male dead, rest NOA
79	14	7	7	14	0	NOA
74	13	6	7	13	0	NOA
42	15	7	6	13	2	Two dead males, rest NOA
50	17	6	9	15	2	One male, one female dead, rest NOA
70	14	7	6	13	1	One male blue/dead, rest NOA
43	15	8	7	15	0	NOA
51	12	7	5	12	0	NOA
Mean	14.0	6.6	6.6	13.3	0.8	
Group 4						
75	14	6	8	14	0	NOA
44	14	2	11	13	1	One male dead, rest NOA
46	14	6	8	14	0	NOA
76	16	7	9	16	0	NOA
72	15	8	7	15	0	One female pale, rest NOA
60	12	3	9	12	0	NOA
48	14	7	6	13	1	One female dead, rest NOA
62	14	6	8	14	0	NOA
Mean	14.1	5.6	8.3	13.9	0.3	

NOA - No observable abnormalities; * - Pups were not sexed until the next day, and two had disappeared

Table 7 - Litter Weights Summary

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

Dam Number	Litter Total		Change	Mean		Change
	Day 1	Day 4		Day 1	Day 4	
Group 1						
49	75.9	117.3	41.4	6.3	9.8	3.5
67	85.7	123.1	37.4	6.6	10.3	3.7
68	98.0	145.1	47.1	7.5	11.2	3.7
78	107.0	233.0	126.0	7.1	15.5	8.4
77	107.4	198.5	91.1	7.2	13.2	6.0
65	93.0	152.5	59.5	6.2	10.2	4.0
47	89.6	150.8	61.2	6.9	11.6	4.7
Mean	93.8	160.0	66.2	6.8	11.7	4.9
S.D.	11.4	41.6	31.8	0.5	2.0	1.8
Group 2						
63	90.0	123.2	33.2	5.3	7.2	1.9
69	70.8	105.3	34.5	5.9	8.8	2.9
66	89.4	130.3	40.9	7.5	10.9	3.4
64	64.4	98.0	33.6	6.4	9.8	3.4
61	58.1	82.0	23.9	6.5	9.1	2.6
56	79.6	123.0	43.4	6.6	10.3	3.7
Mean	75.4	110.3	34.9	6.4	9.4	3.0
S.D.	13.2	18.5	6.8	0.7	1.3	0.7
Group 3						
71	86.5	116.5	30.0	7.9	10.6	2.7
79	117.1	136.4	19.3	8.4	11.4	3.0
74	113.6	136.1	22.5	8.7	10.5	1.8
42	90.2	130.3	40.1	6.9	10.0	3.1
50	103.9	154.6	50.7	6.9	10.3	3.4
70	84.0	125.2	41.2	6.5	9.6	3.1
43	104.9	151.4	46.5	7.0	10.1	3.1
51	89.0	126.4	37.4	7.4	10.5	3.1
Mean	98.7	134.6	36.0	7.5	10.4	2.9
S.D.	12.9	13.0	11.1	0.8	0.5	0.5
Group 4						
75	84.1	109.8	25.7	6.0	7.8	1.8
44	86.8	142.0	55.2	6.7	10.9	4.2
46	98.8	126.1	27.3	7.1	9.0	1.9
76	95.7	135.1	39.4	6.0	8.4	2.4
72	124.1	171.9	47.8	8.3	11.5	3.2
60	85.3	128.3	43.0	7.1	10.7	3.6
48	91.1	116.1	25.0	7.0	8.9	1.9
62	98.7	129.6	30.9	7.1	10.0	2.9
Mean	95.6	132.4	36.8	6.9	9.7	2.7
S.D.	12.9	18.9	11.3	0.7	1.3	0.9

Refer to Appendix A for individual weights.

S.D. - standard deviation; All weights are in grams; Change is Day 4 weights minus Day 1 weights

Table 8 - Litter Observations

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
 Test Article: Veova 10

Dam Number	Number of Pups	Observation	Day of Observation				
			0	1	2	3	4
Group 1							
49	12	NOA					
67	13	NOA		*			
68	13	NOA					
78	15	NOA					
77	15	NOA					
65	15	NOA					
47	13	NOA					
Group 2							
63	17	NOA					
69	12	NOA					
66	12	NOA					
64	12	Two pups missing	-	p	-	-	-
61	11/9	Two pups missing	-	p	-	-	-
56	12	NOA					
Group 3							
71	11	NOA					
79	14	NOA					
74	13	NOA					
42	13	NOA	*	*			
50	15	NOA					
70	13	NOA					
43	15	NOA					
51	12	NOA					
Group 4							
75	14	NOA					
44	13	NOA					
46	14	NOA					
76	16	NOA					
72	15	NOA					
60	12	NOA					
48	13	NOA					
62	14	NOA					

NOA - No observable abnormalities; * - observations not recorded; p - observation present; (-) - observation not present

Table 9 - Functional Observational Battery Summary

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

Males

		Group			
		I	II	III	IV
Home-Cage Observations	Posture	1.0	1.0	1.0	1.0
	Involuntary Motor Movements	0/0	0/0	0/0	0/0
	Vocalization	-	-	-	-
	Palpebral Closure	1.0	1.0	1.0	1.0
Handling	Ease of Removing Rat	2.2	1.0	1.0	1.0
	Reaction to being handled	1.0	1.6	1.6	3.2
Open-Field Measurements	Number of Rears	8.8	10.2	4.6	6.0
	Arousal	4.2	4.2	4.0	3.0
	Mobility	0	0	0	0
	Gait / Gait Score	0/0	0/0	0/0	0/0
Excretion	Fecal Boluses	0.8	1.6	0.4	0.6
	Pools of Urine	0.4	0	0	0.2
Stimulus Reactivity	Approach Response	1.0	1.0	1.0	1.0
	Touch Response	1.0	0.6	1.0	0.6
	Click Response	1.0	1.0	1.0	0.6
	Tail Pinch Response	1.4	1.0	1.0	1.6
	Pupil Response	+	+	+	+
	Righting Reflex	1	1	1	1
Other Parameters	Grip Strength (units: kg)	0.718/0.365	0.674/0.525	0.715/0.595	0.308/0.767
	Bizarre Behavior	0	0	0	0

Refer to Appendix B for individual data and Appendix C for legend

Table 9 - Functional Observational Battery Summary (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
 Test Article: Veova 10

Females

		Group			
		I	II	III	IV
Home-Cage Observations	Posture	1.2	1.0	1.0	1.0
	Involuntary Motor Movements	0/0	0/0	0/0	0/0
	Vocalization	-	-	-	-
	Palpebral Closure	1.0	1.0	0.8	1.0
Handling	Ease of Removing Rat	1.2	1.4	1.2	1.0
	Reaction to being handled	1.0	1.4	1.2	1.0
Open-Field Measurements	Number of Rears	14.6	8.0	16.2	16.2
	Arousal	4.6	4.2	4.6	4.6
	Mobility	0	0	0	0
	Gait / Gait Score	0/0	0/0	0/0	0/0
Excretion	Fecal Boluses	0	0.8	0.6	1.2
	Pools of Urine	0.2	0	0.2	0.6
Stimulus Reactivity	Approach Response	1.0	0.6	0.8	1.0
	Touch Response	1.0	1.0	0.8	0.6
	Click Response	1.0	0.2	1.2	1.0
	Tail Pinch Response	1.4	1.2	1.0	1.0
	Pupil Response	+	+	+	+
	Righting Reflex	1	1	1	1
Other Parameters	Grip Strength (units: kg)	0.646/0.409	0.713/0.569	0.765/0.490	0.671/0.508
	Bizarre Behavior	0	0	0	0

Refer to Appendix B for individual data and Appendix C for legend

Table 10 - Motor Activities Summary

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
 Test Article: Veova 10

Males	Cen FS	Cen AS	Cen TS	Per FS	Per AS	Per TS	Rear S
Group I							
Mean	NA	NA	NA	223	775	998	279
S.D.	NA	NA	NA	17	125	136	42
Group II							
Mean	238	609	846	246	707	953	290
S.D.	19	77	67	25	137	153	27
Group III							
Mean	304	935	1240	159	400	559	258
S.D.	60	373	432	23	148	133	79
Group IV							
Mean	164	649	813	341	1230	1571	292
S.D.	36	194	218	80	222	272	21
Females							
Group I							
Mean	241	602	843	183	519	702	203
S.D.	47	190	225	32	158	162	122
Group II							
Mean	278	629	907	188	560	748	182
S.D.	80	340	373	62	250	281	109
Group III							
Mean	260	691	951	203	604	808	193
S.D.	57	298	305	90	307	384	92
Group IV							
Mean	226	558	784	177	511	688	178
S.D.	109	278	372	63	205	261	115

Cen - center of cage; Per - periphery of cage; FS - summary of fine movements; AS - summary of ambulatory movements
 TS - total of fine and ambulatory movements; NA - not applicable; S.D. - standard deviation
 Refer to Appendix D for individual data

Table 11 - Serum Chemistry Summary
 Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
 Test Article: Veova 10

	ALB	ALT	AST	T Bil	BUN	CA	Chol	Creat	Gluc	Phos	TP	Na	K	Cl	Glob	A/G Ratio
Group I Male																
Mean	2.9	46	73	0.1	19	9.8	73	0.3	111	6.7	5.5	135	5.4	92	2.6	1.1
S.D.	0.3	8	20	0.0	2	0.9	12	0.1	15	0.9	0.6	7	0.3	4	0.3	0.1
Group I Female																
Mean	3.1	71	85	0.1	32	10.8	86	0.5	126	6.8	5.5	143	6.1	102	2.4	1.28
S.D.	0.2	20	19	0.1	7	0.4	10	0.1	19	2.0	0.3	2	0.4	2	0.2	0.14
Group I Overall																
Mean	3.0	59	79	0.1	26	10.3	80	0.4	119	6.8	5.5	139	5.7	97	2.5	1.19
S.D.	0.3	20	20	0.0	8	0.8	13	0.1	19	1.6	0.5	7	0.5	6	0.3	0.15
Group II Male																
Mean	2.9	37	59	0.1	30	9.7	99	0.4	120	6.9	5.6	132	5.7	88	2.7	1.07
S.D.	0.1	7	6	0.0	5	0.4	11	0.1	28	1.1	0.3	4	0.3	3	0.2	0.10
Group II Female																
Mean	3.2	65	117	0.1	31	10.7	95	0.4	139	6.8	5.7	143	6.0	100	2.4	1.34
S.D.	0.3	19	69	0.0	6	0.5	22	0.1	22	1.7	0.5	1	0.7	3	0.3	0.09
Group II Overall																
Mean	3.1	52	90	0.1	30	10.2	97	0.4	130	6.8	5.6	138	5.9	95	2.6	1.22
S.D.	0.3	20	57	0.0	6	0.7	17	0.1	26	1.4	0.4	6	0.6	7	0.3	0.17

S.D. - Standard deviation; Refer to Appendix E for individual data and Appendix G for units

Table 11 - Serum Chemistry Summary (cont.)
 Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
 Test Article: Veova 10

	ALB	ALT	AST	T Bil	BUN	CA	Chol	Creat	Gluc	Phos	TP	Na	K	Cl	Glob	A/G Ratio
Group III Male																
Mean	3.0	49	68	0.1	21	10.2	88	0.3	115	7.1	5.9	137	5.5	93	2.9	1.07
S.D.	0.4	11	15	0.0	4	1.2	13	0.1	13	0.9	1.0	9	0.5	5	0.6	0.09
Group III Female																
Mean	3.2	62	121	0.1	28	10.9	103	0.5	135	7.3	5.8	144	5.9	102	2.5	1.29
S.D.	0.3	13	79	0.1	3	0.4	15	0.1	10	1.5	0.5	2	0.3	3	0.3	0.14
Group III Overall																
Mean	3.1	53	85	0.1	23	10.4	93	0.4	121	7.2	5.8	139	5.7	96	2.7	1.14
S.D.	0.4	13	51	0.0	5	1.0	15	0.1	15	1.1	0.8	8	0.5	7	0.5	0.15
Group IV Male																
Mean	3.0	45	71	0.1	19	10.0	79	0.3	121	7.3	5.7	137	5.6	92	2.7	1.11
S.D.	0.3	9	15	0.0	2	1.1	9	0.1	21	0.8	0.7	7	0.6	5	0.4	0.07
Group IV Female																
Mean	3.0	75	117	0.1	35	10.8	81	0.4	139	7.7	5.2	145	6.3	104	2.2	1.36
S.D.	0.2	13	52	0.1	10	0.6	16	0.1	35	3.1	0.3	1	0.3	1	0.3	0.20
Group IV Overall																
Mean	3.0	55	86	0.1	24	10.3	80	0.4	127	7.5	5.5	139	5.9	96	2.6	1.19
S.D.	0.3	17	38	0.0	9	1.0	11	0.1	27	1.8	0.6	7	0.6	7	0.4	0.17

S.D. - Standard deviation; Refer to Appendix E for individual data and Appendix G for units

Table 12 - Hematology Summary

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

	WBC	RBC	Hgb	Hct	MCV	MCH	MCHC	Neut	Lymp	Mono	Eos	Baso	PT	APTT
Group I Male														
Mean	10.15	8.58	15.9	52.3	61.0	18.6	30.5	11.5	84.5	1.2	1.2	0.5		
S.D.	2.39	0.28	0.5	1.3	1.3	0.4	0.5	1.2	1.7	0.3	0.4	0.2		
Group I Female														
Mean	5.98	6.68	13.4	43.1	64.9	20.2	31.2	27.8	65.9	1.5	4.1	0.2	13.8	24.9
S.D.	2.37	0.85	1.3	4.3	3.1	0.9	0.5	11.9	14.6	0.5	3.0	0.1	0.5	18.9
Group I Overall														
Mean	8.18	7.68	14.8	48.0	62.8	19.4	30.8	19.2	75.7	1.4	2.6	0.4		
S.D.	3.15	1.14	1.6	5.6	3.0	1.1	0.6	11.6	13.7	0.4	2.5	0.2		
Group II Male														
Mean	11.918	7.944	14.58	47.59	59.95	18.37	30.64	14.84	80.73	1.9	0.9	0.51		
S.D.	2.19	0.38	0.6	2.2	1.7	0.4	0.5	4.0	4.7	0.7	0.3	0.3		
Group II Female														
Mean	6.20	6.54	12.9	41.6	63.9	19.9	31.1	33.5	61.8	1.6	2.4	0.2	13.9	23.0
S.D.	2.23	1.11	2.0	6.4	3.1	0.8	0.5	12.9	14.3	0.3	1.9	0.1	0.6	5.8
Group I I Overall														
Mean	9.38	7.32	13.8	44.9	61.7	19.0	30.9	23.1	72.3	1.8	1.6	0.4		
S.D.	3.62	1.05	1.6	5.4	3.1	1.0	0.5	13.0	13.7	0.6	1.4	0.3		
Group III Male														
Mean	11.96	8.21	15.6	50.6	61.7	19.0	30.8	12.9	82.7	1.8	1.1	0.5		
S.D.	2.46	0.30	0.4	1.3	1.0	0.4	0.4	3.0	2.7	0.5	0.3	0.2		
Group III Female														
Mean	3.41	6.66	13.0	42.2	63.4	19.5	30.8	28.7	67.1	1.0	2.7	0.3	14.4	23.1
S.D.	1.42	0.64	1.1	3.6	1.2	0.5	0.3	14.9	15.4	0.4	1.0	0.3	1.0	15.5
Group III Overall														
Mean	9.11	7.69	14.7	47.8	62.3	19.2	30.8	18.1	77.5	1.5	1.6	0.4		
S.D.	4.68	0.86	1.4	4.6	1.3	0.5	0.3	11.4	11.4	0.6	1.0	0.2		
Group IV Male														
Mean	10.00	8.37	15.5	51.4	61.5	18.6	30.2	14.4	82.0	1.3	1.0	0.5		
S.D.	2.11	0.30	0.5	1.8	1.2	0.4	0.4	7.2	7.2	0.3	0.4	0.2		
Group IV Female														
Mean	5.64	6.11	12.7	40.7	67.0	20.8	31.1	35.0	59.4	1.8	2.9	0.1	14.1	20.5
S.D.	2.22	0.72	1.1	2.8	3.8	0.8	0.7	14.1	14.3	0.8	1.6	0.1	0.9	12.2
Group IV Overall														
Mean	8.55	7.61	14.6	47.8	63.3	19.3	30.5	21.3	74.5	1.5	1.6	0.4		
S.D.	2.96	1.19	1.6	5.6	3.5	1.2	0.6	13.9	14.6	0.6	1.3	0.3		

S.D. - Standard deviation; Refer to Appendix F for individual data and Appendix G for units

Note: PT and APTT values were not determined for males.

Table 13 - Male Necropsy Findings

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
 Test Article: Veova 10

Animal Number	Day 29 Necropsy	
	External Findings	Internal Findings
Group I		
1-M	NOA	NOA
8-M	NOA	NOA
9-M	NOA	NOA
12-M	NOA	NOA
13-M	NOA	NOA
15-M	NOA	NOA
17-M	NOA	NOA
30-M	NOA	NOA
36-M	NOA	NOA
40-M	NOA	NOA
Group II		
2-M	NOA	NOA
10-M	NOA	Large kidneys
16-M	NOA	NOA
21-M	NOA	Pale, enlarged kidneys
23-M	NOA	Pale, enlarged kidneys
27-M	NOA	NOA
28-M	NOA	NOA
31-M	NOA	NOA
35-M	NOA	NOA
37-M	NOA	NOA

M - Male; NOA - no observable abnormalities.

Table 13 - Male Necropsy Findings (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
Test Article: Veova 10

Animal Number	Day 29 Necropsy	
	External Findings	Internal Findings
Group III		
5-M	NOA	NOA
6-M	NOA	NOA
14-M	NOA	NOA
20-M	NOA	NOA
24-M	NOA	NOA
25-M	NOA	NOA
26-M	NOA	NOA
29-M	NOA	NOA
32-M	NOA	NOA
34-M	NOA	NOA
Group IV		
3-M	NOA	NOA
4-M	NOA	NOA
7-M	NOA	NOA
11-M	NOA	NOA
18-M	NOA	NOA
19-M	NOA	NOA
22-M	NOA	NOA
33-M	NOA	NOA
38-M	NOA	NOA
39-M	NOA	NOA

M - Male; NOA - no observable abnormalities.

Table 14 - Female Necropsy Findings

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

Animal Number	External Findings	Internal Findings
Group I		
47-F	NOA	NOA
49-F	NOA	NOA
54-F	NOA	NOA
58-F	NOA	NOA
65-F	NOA	NOA
67-F	NOA	NOA
68-F	NOA	NOA
77-F	NOA	NOA
78-F	NOA	NOA
87-F	NOA	Left kidney pale and enlarged
Group II		
45-F	NOA	NOA
53-F	NOA	NOA
55-F	NOA	NOA
56-F	NOA	NOA
59-F	NOA	NOA
61-F	NOA	NOA
63-F	NOA	NOA
64-F	NOA	NOA
66-F	NOA	NOA
69-F	NOA	NOA

F - Female; NOA - no observable abnormalities.

Table 14 - Female Necropsy Findings (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

Animal Number	External Findings	Internal Findings
Group III		
42-F	NOA	NOA
43-F	NOA	NOA
50-F	NOA	NOA
51-F	NOA	NOA
57-F	NOA	Ovaries full of clear liquid
70-F	NOA	NOA
71-F	NOA	NOA
73-F	NOA	NOA
74-F	NOA	Right adrenal gland not found
79-F	NOA	NOA
Group IV		
44-F	NOA	NOA
46-F	NOA	NOA
48-F	NOA	NOA
52-F	NOA	NOA
60-F	NOA	NOA
62-F	NOA	NOA
72-F	NOA	NOA
75-F	NOA	NOA
76-F	NOA	NOA
86-F	NOA	NOA

F - Female; NOA - no observable abnormalities.

Table 15 - Male Organ Weights

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

Animal Number	Organ Weights (g)							
	Day 29							
	Thymus	Liver	Kidneys	Heart	Spleen	Brain	Testes	Epididymides
Group I								
1-M	0.4169	13.7630	2.5360	1.3206	0.6305	1.6696	3.6519	1.2781
12-M	0.5232	14.0853	3.0016	1.4542	0.7371	1.7399	4.2228	1.1431
15-M	0.3680	13.9252	2.5774	1.1660	0.7892	1.8018	4.6821	0.8252
30-M	0.3140	15.5730	2.9197	1.1992	*	1.9650	3.2248	0.8981
36-M	0.4177	11.4937	2.3596	1.2275	0.7003	1.6738	3.8042	0.8599
Mean	0.4080	13.7680	2.6789	1.2735	0.7143	1.7700	3.9172	1.0009
S.D.	0.0773	1.4625	0.2715	0.1163	0.0667	0.1217	0.5570	0.1990
Group II								
10-M	0.2489	22.9132	4.4099	1.3306	0.7411	1.8438	3.9297	0.8985
21-M	0.3535	20.2533	3.9453	1.1700	0.9358	1.5963	3.3421	1.3513
23-M	0.2239	19.6534	5.0900	1.3276	0.9973	1.8792	4.2045	1.4777
31-M	0.3081	16.3912	3.4863	1.1584	0.7341	1.6163	3.6917	0.9369
37-M	0.3819	18.8303	3.1509	1.3440	0.9026	1.8541	3.4547	1.5032
Mean	0.3033	19.6083	4.0165	1.2661	0.8622	1.7579	3.7245	1.2335
S.D.	0.0671	2.3609	0.7653	0.0933	0.1187	0.1392	0.3509	0.2943
Group III								
6-M	0.2094	22.1693	3.3830	1.2630	0.7423	1.9339	3.7125	1.1785
14-M	0.4625	16.0727	2.6925	1.2517	0.6763	1.7552	3.9058	1.3830
25-M	0.1608	17.5710	2.7557	1.1095	0.7192	1.7041	3.5117	1.5013
29-M	0.3540	14.1716	2.3659	1.1028	0.9126	1.7308	3.3907	1.2755
34-M	0.5742	16.5504	2.8240	1.2380	0.7627	1.7743	3.4408	1.2893
Mean	0.3522	17.3070	2.8042	1.1930	0.7626	1.7797	3.5923	1.3255
S.D.	0.1721	2.9849	0.3682	0.0798	0.0898	0.0902	0.2138	0.1221
Group IV								
3-M	0.6000	17.4090	3.2260	1.4965	1.0147	1.8870	3.8064	0.7680
11-M	0.3686	15.4844	2.7576	1.1941	0.8094	1.6740	4.0871	0.9205
19-M	0.4227	15.6435	2.8258	1.3054	0.7371	1.7883	4.6874	0.9413
33-M	0.3136	18.5106	2.6569	1.2961	0.7028	1.8661	3.2121	1.5772
38-M	0.3365	15.6738	2.3584	1.3818	0.7077	1.4571	3.7170	1.2665
Mean	0.4083	16.5443	2.7649	1.3348	0.7943	1.7345	3.9020	1.0947
S.D.	0.1147	1.3515	0.3136	0.1124	0.1303	0.1761	0.5409	0.3252

M - Male; S.D. - Standard deviation; * - inadvertently not recorded.

Table 16 - Female Organ Weights

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
 Test Article: Veova 10

Animal Number	Organ Weights (g)							Corpora Lutea (Count)
	Thymus	Liver	Kidneys	Heart	Spleen	Brain	Ovaries	
Group I								
47-F	0.3031	15.3304	2.0441	1.0955	0.7069	1.7035	0.2695	40
49-F	0.2930	13.5655	2.0380	0.9180	0.7467	1.6245	0.2901	21
54-F	0.2293	9.0833	1.9406	1.0776	0.6785	1.8166	0.2746	*
58-F	0.1298	9.5538	1.7026	0.8344	0.6291	1.7578	0.5309	10
65-F	0.1566	13.1346	1.9704	1.0854	0.6750	1.3445	0.2881	15
67-F	0.2311	12.6238	2.1781	1.1802	0.8270	1.7079	0.3054	30
68-F	0.1819	12.8924	1.9843	1.0449	0.6755	1.7854	0.2613	*
77-F	0.1817	10.5075	1.8165	0.9314	0.6458	1.7117	0.2453	22
78-F	0.1538	14.7229	1.9715	0.9651	0.6146	1.6881	0.2669	13
87-F	0.2193	7.4900	2.8882	0.9370	0.5174	1.4902	0.1936	11
Mean	0.2080	11.8904	2.0534	1.0070	0.6717	1.6630	0.2926	20.3
S.D.	0.0582	2.5899	0.3203	0.1057	0.0821	0.1441	0.0891	10.4
Group II								
45-F	0.2163	15.3384	2.0963	0.9866	0.7288	1.7731	0.2451	15
53-F	0.2863	12.8663	1.7408	1.1440	0.6175	1.9201	0.3005	8
55-F	0.2120	11.8214	1.7081	0.9902	0.5237	1.7665	0.4254	15
56-F	0.2348	17.6414	2.0743	1.2481	0.7112	1.7221	0.2492	16
59-F	0.4071	13.5039	2.0702	1.0370	0.8027	1.4324	1.8081	9
61-F	0.2258	13.8422	1.5763	0.9118	0.7182	1.7030	0.3995	10
63-F	0.2357	16.7067	2.0293	1.0665	0.4822	1.7732	0.2876	22
64-F	0.1780	17.0860	2.4202	1.0832	0.7006	1.8278	2.0909	17
66-F	0.2223	16.2745	1.8755	1.2034	0.8106	1.7411	0.1938	22
69-F	0.3249	19.2213	2.1944	0.9533	0.6207	1.7092	0.5000	13
Mean	0.2543	15.4302	1.9785	1.0624	0.6716	1.7369	0.6500	14.7
S.D.	0.0675	2.3613	0.2534	0.1094	0.1094	0.1248	0.6944	4.9

F - Female; S.D. - Standard deviation; * - inadvertently not recorded.

Table 16 - Female Organ Weights (cont.) (g)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
 Test Article: Veova 10

Animal Number	Organ Weights (g)							Corpora Lutea (Count)
	Thymus	Liver	Kidneys	Heart	Spleen	Brain	Ovaries	
Group III								
42-F	0.3752	12.0420	1.7440	0.9250	0.6083	1.7257	0.2876	22
51-F	0.3075	12.6119	1.7363	1.0515	0.4588	1.7098	0.3290	11
57-F	0.2706	11.4305	1.7063	0.9758	0.5821	1.6828	0.4819	27
73-F	0.2352	9.7359	1.7385	0.9934	0.6214	1.7237	0.2574	11
74-F	0.2529	13.8852	1.8328	1.0916	0.8766	1.8216	0.5253	12
Mean	0.2883	11.9411	1.7516	1.0075	0.6294	1.7327	0.3762	16.6
S.D.	0.0555	1.5300	0.0477	0.0652	0.1524	0.0526	0.1200	7.4
Group IV								
46-F	0.3115	14.9573	2.1174	1.2237	0.8118	1.7798	0.2600	*
48-F	0.2755	9.9587	1.6951	0.9720	0.4819	1.6915	0.2892	26
60-F	0.2161	13.9355	2.0114	1.0845	0.7139	1.6786	0.2382	14
72-F	0.1720	11.8886	1.6348	1.1621	0.4686	1.6773	0.2519	17
86-F	0.2222	10.9555	1.7357	0.8849	0.5802	1.6513	0.2189	12
Mean	0.2395	12.3391	1.8389	1.0654	0.6113	1.6957	0.2516	17.3
S.D.	0.0545	2.0729	0.2123	0.1379	0.1490	0.0492	0.0261	6.2

F - Female; S.D. - Standard deviation; * - inadvertently not recorded.

Appendix A - Individual Pup Sex and Weights
Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
Test Article: Veova 10

Group 1

Pup Number	Dam Number														
	49			68			77			65			47		
	Sex	Weight Day 1	Sex Day 4												
1	M	6.4	M	8.4	M	7.1	M	6.8	M	7.5	M	6.9	M		
2	F	7.2	M	6.1	M	6.9	M	7.2	M	6.3	M	6.5	M		
3	M/F	6.4	M	7.8	M	7.0	M	7.1	M	6.4	M	6.7	M		
4	F	6.3	M	8.8	M	7.2	M	7.2	M	6.8	M	7.1	M		
5	M	6.3	M	8.4	M	6.5	M	6.9	M	4.8	M	7.2	M		
6	M	7.0	F	7.5	M	7.7	F	7.5	M	5.8	M	6.3	M		
7	F	6.6	F	7.7	F	7.6	F	7.3	F	6.4	F	6.9	F		
8	F/M	6.0	F	8.4	M	7.4	F	7.5	F	6.1	F	6.8	F		
9	F	7.2	F	7.5	F	6.2	F	7.2	F	6.8	F	7.0	F		
10	F	6.1	F	5.7	F	6.7	F	6.9	F	6.3	F	7.1	F		
11	F	7.1	F	6.8	F	6.6	F	6.8	F	5.8	F	7.2	F		
12	F	6.3	F	8.3	F	8.0	F	7.1	F	6.0	F	6.8	F		
13	F	6.8	F	6.6	F	7.5	F	7.0	F	5.9	F	7.1	F		
14						7.4	F	7.5	F	6.3	F				
15						7.2	F	7.4	F	5.8	F				
Total		85.7		98.0		107.0		107.4		93.0		89.6			
Mean		6.6		7.5		7.1		7.2		6.2		6.9			
SD		0.4		1.0		0.5		0.2		0.6		0.3			

M - Male; F - Female; S.D. - Standard deviation; * - Pup not found; Note: All weights are in grams

Appendix A - Individual Pup Sex and Weights (cont.)
Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
Test Article: Veova 10

Pup Number	Dam Number																	
	63			69			66			64			61			56		
	Sex	Weight Day 1	Weight Day 4	Sex	Weight Day 1	Weight Day 4	Sex	Weight Day 1	Weight Day 4	Sex	Weight Day 1	Weight Day 4	Sex	Weight Day 1	Weight Day 4	Sex	Weight Day 1	Weight Day 4
1	F	5.5	7.0	M	6.4	8.0	M	7.9	10.7	M	6.6	10.3	M	6.6	8.6	M	6.5	9.5
2	M	5.8	6.8	M	6.2	8.8	M	7.1	11.0	M	6.8	8.7	M	6.4	10.0	M	5.6	10.4
3	M	5.8	7.1	M	5.9	9.6	F	7.5	11.0	M	6.7	10.2	M	6.6	10.0	M	6.7	10.6
4	F	5.2	5.2	M	5.3	8.7	F	7.3	10.7	M	6.4	9.1	F	5.7	8.9	M	6.6	11.0
5	M	6.0	7.7	M	6.0	9.6	F	7.0	10.7	M	6.6	10.4	F	6.3	7.7	M	6.7	9.8
6	F	4.9	6.5	M	6.0	8.5	F	7.1	10.9	F	6.5	9.3	F	6.5	9.5	F	7.0	10.6
7	F	5.0	7.7	M	5.5	9.4	F	7.2	10.4	F	5.5	11.3	F	6.6	8.7	F	6.9	9.1
8	F	5.3	6.9	M	5.5	8.0	F	7.6	10.8	F	6.9	8.7	F	6.4	9.2	F	6.8	10.4
9	F	4.9	6.6	M	6.1	8.0	M	7.7	10.7	F	6.0	9.5	F	7.0	9.4	F	6.7	10.2
10	F	5.0	7.9	M	6.0	9.1	M	7.3	10.9	F	6.4	10.5	F	6.6	11.4	F	6.6	11.4
11	M	4.8	8.2	M	6.3	8.7	M	7.7	11.1	F	6.3	8.7	M	6.8	10.1	F	6.8	10.1
12	M	5.3	7.9	F	5.6	8.9	M	8.0	11.4	F	6.4	10.5	F	6.7	9.9	F	6.7	9.9
13	M	5.9	7.2															
14	M	4.8	8.2															
15	M	5.7	7.9															
16	M	5.0	7.7															
17	M	5.1	6.7															
Total		90.0	123.2		70.8	105.3		89.4	130.3		64.4	98.0		58.1	82.0		79.6	123.0
Mean		5.3	7.2		5.9	8.8		7.5	10.9		6.4	9.8		6.5	9.1		6.6	10.3
SD		0.4	0.8		0.3	0.6		0.3	0.3		0.4	0.9		0.3	0.7		0.4	0.6

M - Male; F - Female; S.D. - Standard deviation; Note: All weights are in grams

Appendix A - Individual Pup Sex and Weights (cont.)
Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
Test Article: Veova 10

Group 3

Pup Number	Dam Number																							
	79		74		50		70		43		51		42											
	Sex	Weight Day 1	Sex	Weight Day 4	Sex	Weight Day 1	Sex	Weight Day 4	Sex	Weight Day 1	Sex	Weight Day 4	Sex	Weight Day 1										
1	F	8.0	10.7	F	8.6	12.0	F	9.9	10.6	M	8.1	11.5	M	6.1	10.4	M	6.8	10.5	M	7.8	11.0	M	7.0	10.7
2	F	7.7	10.2	F	9.0	11.0	F	8.2	9.8	M	6.8	10.9	M	6.8	7.5	M	6.7	9.2	M	7.6	9.4	M	7.1	10.6
3	F	7.1	11.3	F	8.8	12.1	F/M	8.5	10.9	M	6.9	10.0	M	6.9	10.8	M	7.1	11.0	M	7.6	10.8	M	6.8	10.3
4	F	7.3	9.9	F	9.3	10.0	F/M	8.6	9.9	M	6.5	10.1	M	7.0	9.7	M	7.5	8.3	M	7.4	11.1	M	6.5	10.0
5	F	7.8	10.6	F	7.1	10.6	F	8.4	10.2	M	7.1	9.9	M	6.8	9.2	M	7.4	9.8	M	7.7	10.7	M	7.2	9.5
6	F	8.3	9.4	F	7.9	*	F	9.1	10.9	M	6.6	10.3	M	7.0	10.2	M	7.1	10.3	M	7.6	10.4	M	7.0	9.4
7	M	8.1	11.2	F	8.3	*	F	8.6	10.1	F	7.4	10.4	M	6.9	10.7	M	6.3	11.4	M	7.7	11.1	M	6.8	9.9
8	M	8.3	10.4	M	8.6	10.2	M	8.7	10.5	F	6.8	10.3	F	6.4	10.4	M	7.4	9.5	M	7.3	10.9	F	6.9	10.5
9	M	8.1	11.4	M	7.1	12.5	M/F	9.0	10.3	F	7.0	10.2	F	6.8	9.2	F/M	6.9	10.6	F	6.7	10.3	F	6.5	8.8
10	M	7.8	11.3	M	7.8	9.8	M	8.1	11.7	F	6.4	10.5	F	5.3	10.3	F	6.7	9.1	F	7.1	10.6	F	7.1	10.0
11	M	8.0	10.1	M	7.5	10.2	M	9.1	10.7	F	7.1	9.7	F	6.2	9.7	F	7.6	10.2	F	7.3	9.7	F	7.0	10.1
12				M	9.6	13.1	M	8.3	10.9	F	7.0	9.9	F	5.4	7.7	F	7.1	10.9	F	7.2	10.4	F	7.2	10.4
13				M	8.3	12.4	M	9.1	9.6	F	6.8	11.0	F	6.4	9.4	F	7.0	9.8	F			F	7.1	10.1
14				M	9.2	12.5				F	6.6	10.3	F	7.2	10.5									
15										F	6.8	9.6	F	6.1	10.3									
Total		86.5	116.5		117.1	136.4		113.6	136.1		103.9	154.6		84.0	125.2		104.9	151.4		89.0	126.4		90.2	130.3
Mean		7.9	10.6		8.4	11.4		8.7	10.5		6.9	10.3		6.5	9.6		7.0	10.1		7.4	10.5		6.9	10.0
SD		0.4	0.7		0.8	1.2		0.5	0.6		0.4	0.5		0.6	1.0		0.4	0.8		0.3	0.5		0.2	0.5

M - Male; F - Female; S.D. - Standard deviation; * - Pup not found; Note: All weights are in grams

Appendix A - Individual Pup Sex and Weights (cont.)
Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
Test Article: Veova 10

Pup Number	Sex	75				76				72				60				48				62			
		Weight		Sex	Weight		Sex	Weight		Sex	Weight		Sex	Weight											
		Day 1	Day 4		Day 1	Day 4		Day 1	Day 4		Day 1	Day 4		Day 1	Day 4	Day 1									
1	F	6.1	8.5	F/M	6.4	10.9	F	7.1	9.1	M	5.8	8.5	M	9.5	11.8	M	7.7	11.4	M	6.4	8.3	M	7.1	9.7	
2	F	6.3	8.3	F	6.5	9.7	F	7.2	9.6	M	6.4	8.6	M	8.2	12.8	M	7.2	12.1	M	7.3	8.5	M	6.8	11.2	
3	F	5.3	7.0	F	6.5	10.5	F	6.5	9.5	M	6.2	9.3	M	8.5	10.1	M	7.1	10.8	M	7.1	9.8	M	7.8	10.1	
4	F	6.4	8.5	F	6.6	10.7	F	7.1	9.5	M	6.3	9.6	M	7.9	12.9	F/M	6.6	9.7	M	7.4	9.5	M	6.8	10.2	
5	F	5.9	7.8	F	5.9	10.2	F	5.9	9.4	M	6.0	8.8	M	9.3	11.7	F/M	7.1	10.9	M	7.0	9.2	M	7.1	9.8	
6	F	6.0	7.5	F	6.5	10.8	F	6.9	7.4	M	5.8	8.2	M	8.6	11.6	F/M	7.0	10.3	M	6.8	8.6	M	7.7	11.0	
7	F	6.2	7.8	F	6.7	11.4	F	7.2	9.3	M	6.3	8.2	M	8.2	11.5	F	7.5	10.0	M/F	7.5	8.6	F	6.8	9.5	
8	F	5.7	7.0	M	6.6	11.1	F	6.3	8.9	F	6.0	8.6	M	7.8	11.6	F	8.0	10.5	F	6.4	8.2	F	6.7	8.8	
9	M	6.2	7.8	M	7.2	11.7	M	7.2	10.2	F	6.1	9.2	F/M	8.4	11.7	F	7.0	10.2	F	7.0	9.3	F	7.0	9.8	
10	M	5.8	7.8	M	7.2	11.4	M	7.7	9.1	F	5.6	9.1	F	5.4	11.8	F	6.5	11.0	F	7.1	8.8	F	7.1	9.9	
11	M	5.6	7.5	M	6.6	11.5	M	7.1	9.4	F	6.2	7.7	F	8.8	11.9	F	7.1	10.1	F	7.2	9.4	F	6.9	10.0	
12	M	6.1	8.4	M	7.0	11.2	M	7.3	8.4	F	5.3	6.1	F	8.5	12.2	F	6.5	11.3	F	6.9	9.1	F	6.8	10.3	
13	M	6.6	8.7	M	7.1	10.9	M	7.6	7.2	F	6.2	8.5	F	8.3	6.7	F	7.0	8.8	F	7.0	8.8	F	7.0	9.3	
14	M	5.9	7.2	M	7.7	9.1	M	7.7	9.1	F	6.3	8.1	F	8.0	11.5	F	8.0	11.5	F	7.0	8.8	F	7.1	*	
15										F	6.2	8.8	F	8.7	12.1	F									
16										F	5.0	7.8	F												
Total		84.1	109.8		86.8	142.0		98.8	126.1		95.7	135.1		124.1	171.9		85.3	128.3		91.1	116.1		98.7	129.6	
Mean		6.0	7.8		6.7	10.9		7.1	9.0		6.0	8.4		8.3	11.5		7.1	10.7		7.0	8.9		7.1	10.0	
SD		0.3	0.6		0.4	0.6		0.5	0.8		0.4	0.8		0.9	1.5		0.5	0.7		0.3	0.5		0.3	0.6	

M - Male; F - Female; S.D. - Standard deviation; * - Pup not found; Note: All weights are in grams

Appendix B - Functional Observational Battery Individual Data

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

	Group I Males	1-M	12-M	15-M	30-M	36-M
Home-Cage Observations	Posture	1	1	1	1	1
	Involuntary Motor Movements	0/0	0/0	0/0	0/0	0/0
	Vocalization	-	-	-	+	-
	Palpebral Closure	1	1	1	1	1
Handling	Ease of Removing Rat	1	1	3	3	3
	Reaction to being handled	1	1	1	1	1
Open-Field Measurements	Number of Rears	9	4	16	6	9
	Arousal	4	3	6	4	4
	Mobility	0	0	0	0	0
	Gait / Gait Score	0/0	0/0	0/0	0/0	0/0
Excretion	Fecal Boluses	4	0	0	0	0
	Pools of Urine	2	0	0	0	0
Stimulus Reactivity	Approach Response	1	1	1	1	1
	Touch Response	1	1	1	1	1
	Click Response	1	1	1	1	1
	Tail Pinch Response	2	1	2	1	1
	Pupil Response	+	+	+	+	+
	Righting Reflex	1	1	1	1	1
Other Parameters	Grip Strength (units: kg)	0.465/0.330	0.705/0.365	0.680/0.559	0.740/0.510	1.000/0.059
	Bizarre Behavior	0	0	0	0	0

Refer to Appendix C for Legend

Appendix B - Functional Observational Battery Individual Data (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

	Group II Males	10-M	21-M	23-M	31-M	37-M
Home-Cage Observations	Posture	1	1	1	1	1
	Involuntary Motor Movements	0/0	0/0	0/0	0/0	0/0
	Vocalization	-	-	-	-	-
	Palpebral Closure	1	1	1	1	1
Handling	Ease of Removing Rat	1	1	1	1	1
	Reaction to being handled	1	1	3	2	1
Open-Field Measurements	Number of Rears	5	25	13	2	6
	Arousal	4	5	4	4	4
	Mobility	0	0	0	0	0
	Gait / Gait Score	0/0	0/0	0/0	0/0	0/0
Excretion	Fecal Boluses	3	0	0	5	0
	Pools of Urine	0	0	0	0	0
Stimulus Reactivity	Approach Response	1	1	1	1	1
	Touch Response	1	1	1	0	0
	Click Response	2	1	1	0	1
	Tail Pinch Response	2	1	0	1	1
	Pupil Response	+	+	+	+	+
	Righting Reflex	1	1	1	1	1
Other Parameters	Grip Strength (units: kg)	0.515/0.560	0.999/0.550	0.718-0.515	0.550/0.505	0.590/0.495
	Bizarre Behavior	0	0	0	0	0

Refer to Appendix C for Legend

Appendix B - Functional Observational Battery Individual Data (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

	Group III Males	6-M	14-M	25-M	29-M	34-M
Home-Cage Observations	Posture	1	1	1	1	1
	Involuntary Motor Movements	0/0	0/0	0/0	0/0	0/*
	Vocalization	-	-	-	-	-
	Palpebral Closure	1	1	1	1	1
Handling	Ease of Removing Rat	1	1	1	1	1
	Reaction to being handled	1	1	1	4	1
Open-Field Measurements	Number of Rears	7	6	3	4	3
	Arousal	4	4	4	4	4
	Mobility	0	0	0	0	0
	Gait / Gait Score	0/0	0/0	0/0	0/0	0/0
Excretion	Fecal Boluses	0	0	2	0	0
	Pools of Urine	0	0	0	0	0
Stimulus Reactivity	Approach Response	1	1	1	1	1
	Touch Response	1	1	1	1	1
	Click Response	1	1	1	1	1
	Tail Pinch Response	1	1	1	1	1
	Pupil Response	+	+	+	+	+
	Righting Reflex	1	1	1	1	1
Other Parameters	Grip Strength (units: kg)	0.715/0.510	0.930/0.385	0.560/0.680	0.480/0.700	0.890/0.700
	Bizarre Behavior	0	0	0	0	*

* - inadvertently not recorded.

Refer to Appendix C for Legend

Appendix B - Functional Observational Battery Individual Data (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

	Group IV Males	3-M	11-M	19-M	33-M	38-M
Home-Cage Observations	Posture	1	1	1	1	1
	Involuntary Motor Movements	0/0	0/0	0/0	0/0	0/0
	Vocalization	-	-	-	-	-
	Palpebral Closure	1	1	1	1	1
Handling	Ease of Removing Rat	1	1	1	1	1
	Reaction to being handled	3	2	4	3	4
Open-Field Measurements	Number of Rears	7	2	7	4	10
	Arousal	4	2	4	3	2
	Mobility	0	0	0	0	0
	Gait / Gait Score	0/0	0/0	0/0	0/0	0/0
Excretion	Fecal Boluses	0	0	0	3	0
	Pools of Urine	0	0	0	1	0
Stimulus Reactivity	Approach Response	1	1	1	1	1
	Touch Response	1	0	0	1	1
	Click Response	1	0	0	1	1
	Tail Pinch Response	2	1	1	2	2
	Pupil Response	+	+	+	+	+
	Righting Reflex	1	1	1	1	1
Other Parameters	Grip Strength (units: kg)	0.995/0.610	0.485/0.790	0.895/0.625	0.315/0.695	1.040/1.115
	Bizarre Behavior	0	0	0	0	0

Refer to Appendix C for Legend

Appendix B - Functional Observational Battery Individual Data (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

	Group I Females	67-F	49-F	68-F	54-F	87-F
Home-Cage Observations	Posture	2	1	1	1	1
	Involuntary Motor Movements	0/0	0/0	0/0	0/0	0/0
	Vocalization	+	-	-	-	-
	Palpebral Closure	1	1	1	1	1
Handling	Ease of Removing Rat	2	1	1	1	1
	Reaction to being handled	1	1	1	1	1
Open-Field Measurements	Number of Rears	15	20	9	14	15
	Arousal	5	5	4	5	4
	Mobility	0	0	0	0	0
	Gait / Gait Score	0/0	0/0	0/0	0/0	0/0
Excretion	Fecal Boluses	0	0	0	0	0
	Pools of Urine	0	0	0	1	0
Stimulus Reactivity	Approach Response	1	1	1	1	1
	Touch Response	1	1	1	1	1
	Click Response	0	1	1	3	0
	Tail Pinch Response	1	1	1	3	1
	Pupil Response	+	+	+	+	+
	Righting Reflex	1	1	1	1	1
Other Parameters	Grip Strength (units: kg)	0.530/0.465	0.615/0.305	0.755/0.515	0.610/0.265	0.720/0.495
	Bizarre Behavior	0	0	0	0	0

Refer to Appendix C for Legend

Appendix B - Functional Observational Battery Individual Data (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
 Test Article: Veova 10

	Group II Females	63-F	69-F	53-F	61-F	XXX-F
Home-Cage Observations	Posture	1	1	1	1	1
	Involuntary Motor Movements	0/0	0/0	0/0	0/0	0/0
	Vocalization	-	+	-	-	-
	Palpebral Closure	1	1	1	1	1
Handling	Ease of Removing Rat	3	1	1	1	1
	Reaction to being handled	3	1	1	1	1
Open-Field Measurements	Number of Rears	7	7	13	8	5
	Arousal	5	4	4	4	4
	Mobility	0	0	0	0	0
	Gait / Gait Score	0/0	0/0	0/0	0/0	0/0
Excretion	Fecal Boluses	0	1	3	0	0
	Pools of Urine	0	0	0	0	0
Stimulus Reactivity	Approach Response	1	1	1	0	0
	Touch Response	2	1	1	1	0
	Click Response	0	0	1	0	0
	Tail Pinch Response	2	1	2	1	0
	Pupil Response	+	+	+	+	+
	Righting Reflex	1	1	1	1	1
Other Parameters	Grip Strength (units: kg)	0.520/0.510	0.530/0.490	0.810-0.660	0.640/0.565	1.065/0.620
	Bizarre Behavior	0	0	0	0	0

Refer to Appendix C for Legend

Appendix B - Functional Observational Battery Individual Data (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

	Group III Females	42-F	51-F	57-F	73-F	74-F
Home-Cage Observations	Posture	1	1	1	1	1
	Involuntary Motor Movements	0/0	0/0	0/0	0/0	0/0
	Vocalization	-	-	-	-	-
	Palpebral Closure	1	1	1	1	0
Handling	Ease of Removing Rat	1	1	1	1	2
	Reaction to being handled	1	1	1	1	2
Open-Field Measurements	Number of Rears	14	19	24	14	10
	Arousal	4	5	5	5	4
	Mobility	0	0	0	0	0
	Gait / Gait Score	0/0	0/0	0/0	0/0	0/0
Excretion	Fecal Boluses	0	0	3	0	0
	Pools of Urine	0	0	0	1	0
Stimulus Reactivity	Approach Response	1	0	1	1	1
	Touch Response	1	1	0	1	1
	Click Response	0	0	1	4	1
	Tail Pinch Response	1	1	1	1	1
	Pupil Response	+	+	+	+	+
	Righting Reflex	1	1	1	1	1
Other Parameters	Grip Strength (units: kg)	0.610/0.540	0.915/0.365	0.580/0.560	0.665/0.560	1.055/0.425
	Bizarre Behavior	0	0	0	0	*

Refer to Appendix C for Legend

Appendix B - Functional Observational Battery Individual Data (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

	Group IV Females	46-F	72-F	60-F	48-F	86-F
Home-Cage Observations	Posture	1	1	1	1	1
	Involuntary Motor Movements	0/0	0/0	0/0	0/0	0/0
	Vocalization	-	-	-	-	-
	Palpebral Closure	1	1	1	1	1
Handling	Ease of Removing Rat	1	1	1	1	1
	Reaction to being handled	1	1	1	1	1
Open-Field Measurements	Number of Rears	16	25	15	11	14
	Arousal	6	5	4	4	4
	Mobility	0	0	0	0	0
	Gait / Gait Score	0/0	0/0	0/0	0/0	0/0
Excretion	Fecal Boluses	3	3	0	0	0
	Pools of Urine	2	1	0	0	0
Stimulus Reactivity	Approach Response	1	1	1	1	1
	Touch Response	1	0	1	0	1
	Click Response	1	1	1	1	1
	Tail Pinch Response	2	1	1	0	1
	Pupil Response	+	+	+	+	+
	Righting Reflex	1	1	1	1	1
Other Parameters	Grip Strength (units: kg)	0.510/0.390	0.580/0.560	0.850/0.505	0.710/0.510	0.705/0.575
	Bizarre Behavior	0	0	0	0	0

Refer to Appendix C for Legend

Appendix C - Functional Observational Battery Legend
 Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
 Test Article: Veova 10

Observation	Possible Values
Posture	1. Sitting or standing normal 2. Rearing 3. Asleep or curled up 4. Flattened limbs in air 5. Lying on side, limbs in air 6. Crouched over 7. Head Bobbing
Involuntary Motor Movements	Clonic 0: Normal 1: Repetitive movements 2: Quivering 3: Mild Tremors 4: Whole Body Tremors 5: Shocklike jerks 6: Clonic convulsions 7: Wet Dog Shakes
Tonic	0: Normal 1: Contraction of extensors 2: Opisthotonos 3: Emprostotonos 4: Explosive jumps 5: Prolonged convulsions
Vocalization	+ / -
Palpebral Closure	1. Eyelids wide open 2. Eyelids slightly drooping 3. Eyelids half drooping completely shut 4. Eyelids completely shut
Ease of Removing Rat	1. Very easy 2. Easy 3. Moderately difficult 4. Difficult 5. Very Difficult
Reaction to being handled	1. Low 2. Moderately low 3. Moderately high 4. High
Number of Rears	Number of time the front legs of the rat come off the surface with or without support.
Arousal	1. Very low (stupor) 2. Low 3. Somewhat low 4. Alert (normal) 5. Somewhat high 6. Very high (hyperactive)
Mobility	0: No impairment 1: Slightly impaired 2: Somewhat impaired 3: Totally impaired
Gait	0: Normal gait 1: Ataxia 2: Drags hindlimbs from body 3: Feet point away 4: Drags forelimbs from body 5: Walks on tiptoes 6: Hunched posture 7: Drags body
Gait Score	0: No abnormal gait 1: Slightly abnormal gait 2: Moderately abnormal gait 3: Severely abnormal gait
Fecal Boluses	D: Diarrhea Number of fecal boluses in 3 minutes
Pools of Urine	X: Polyuria Number of pools of urine in 3 minutes
Approach Response	0: No reaction 1: Rat slowly approaches 2: Rat flinches 3: Energetic flinch 4: Jumps, bites or attacks
Touch Response	0: No reaction 1: Rat turns or walk away 2: Rat flinches 3: Energetic flinch 4: Jumps, bites or attacks
Click Response	0: No reaction 1: Slight reaction 2: Rat flinches 3: Energetic flinch 4: Exaggerated reaction
Tail Pinch Response	0: No reaction 1: Rat turns or walk away 2: Rat flinches 3: Energetic flinch 4: Exaggerated reaction
Pupil Response	+ / -
Righting Reflex	1. Lands on feet 2. Slightly uncoordinated 3. Lands on side 4. Lands on back
Grip Strength (kg)	Measure using strain gauges. Two measures are taken for front and rear limbs.
Bizarre Behavior	1. Circling 2. Stereotypic grooming 3. Pacing 4. Repetitive sniffing 5. Head weaving

Appendix D - Motor Activities Individual Data

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
 Test Article: Veova 10

Males	Cen FS	Cen AS	Cen TS	Per FS	Per AS	Per TS	Rear S
Group I	0*	0*	0*	221	616	837	256
	0*	0*	0*	227	832	1059	266
	0*	0*	0*	218	727	945	292
	0*	0*	0*	248	950	1198	345
	0*	0*	0*	202	751	953	238
Mean	NA	NA	NA	223	775	998	279
SD	NA	NA	NA	17	125	136	42
Group II	241	623	864	235	606	841	279
	258	559	817	256	663	919	290
	248	637	885	222	790	1012	306
	235	512	747	233	573	806	252
	207	712	919	286	902	1188	322
Mean	238	609	846	246	707	953	290
SD	19	77	67	25	137	153	27
Group III	200	321	521	189	140	329	134
	321	895	1216	137	421	558	245
	354	1306	1660	137	507	644	333
	327	1074	1401	161	462	623	321
	319	1081	1400	172	469	641	259
Mean	304	935	1240	159	400	559	258
SD	60	373	432	23	148	133	79
Group IV	192	518	710	300	931	1231	273
	105	370	475	437	1226	1663	301
	191	787	978	392	1427	1819	290
	171	791	962	346	1461	1807	323
	162	777	939	232	1105	1337	271
Mean	164	649	813	341	1230	1571	292
SD	36	194	218	80	222	272	21

* - Photocell was not functioning; discovered after completion of measurements.

Cen - center of cage; Per - periphery of cage; FS - summary of fine movements; AS - summary of ambulatory movements
 TS - total of fine and ambulatory movements; NA - not applicable; S.D. - standard deviation

Appendix D - Motor Activities Individual Data (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
 Test Article: Veova 10

Females	Cen FS	Cen AS	Cen TS	Per FS	Per AS	Per TS	Rear S
Group I							
	159	408	567	200	399	599	118
	273	921	1194	185	792	977	300
	250	542	792	171	503	674	88
	258	565	823	221	470	691	142
	265	574	839	137	430	567	365
Mean	241	602	843	183	519	702	203
SD	47	190	225	32	158	162	122
Group II							
	321	1063	1384	157	715	872	355
	164	250	414	251	426	677	179
	228	752	980	210	870	1080	127
	361	317	678	95	226	321	63
	315	764	1079	227	565	792	187
Mean	278	629	907	188	560	748	182
SD	80	340	373	62	250	281	109
Group III							
	294	807	1101	156	509	665	227
	322	391	713	176	356	532	109
	191	820	1011	361	1104	1465	149
	285	1059	1344	139	674	813	338
	207	377	584	185	378	563	144
Mean	260	691	951	203	604	808	193
SD	57	298	305	90	307	384	92
Group IV							
	143	197	340	78	229	307	51
	117	382	499	152	441	593	57
	393	858	1251	229	630	859	284
	257	552	809	215	479	694	267
	222	800	1022	212	774	986	229
Mean	226	558	784	177	511	688	178
SD	109	278	372	63	205	261	115

Cen - center of cage; Per - periphery of cage; FS - summary of fine movements; AS - summary of ambulatory movements
 TS - total of fine and ambulatory movements; S.D. - standard deviation

Appendix E - Serum Chemistry Individual Data
 Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
 Test Article: Veova 10

Animal Number	ALB	ALT	AST	T Bil	BUN	CA	Chol	Creat	Gluc	Phos	TP	Na	K	Cl	Glob	A/G Ratio
Group I																
1-M	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
8-M	2.8	38	54	0.1	18	9.5	72	0.3	103	6.1	5.2	132	5.2	91	2.4	1.17
9-M	3.0	50	73	0.1	21	10.1	73	0.3	114	6.8	5.9	139	6.0	96	2.9	1.03
12-M	3.0	57	75	0.1	17	9.8	79	0.3	106	7.0	5.7	137	5.5	94	2.7	1.11
13-M	2.6	45	61	0.1	18	9.4	71	0.3	106	6.5	5.1	131	5.1	90	2.5	1.04
15-M	2.2	30	39	0.1	19	7.9	50	0.2	89	5.8	4.2	121	5.2	84	2.0	1.10
17-M	3.2	50	68	0.1	17	11.4	94	0.4	143	8.8	6.4	148	5.3	96	3.2	1.00
30-M	2.8	44	100	0.1	19	9.9	75	0.3	118	6.6	5.4	137	5.7	94	2.6	1.08
36-M	3.1	50	92	0.1	22	9.9	63	0.3	106	6.0	5.6	136	5.0	93	2.5	1.24
40-M	3.0	47	96	0.1	16	10.1	84	0.3	113	7.1	5.9	134	5.3	90	2.9	1.03
Mean	2.9	46	73	0.1	19	9.8	73	0.3	111	6.7	5.5	135	5.4	92	2.6	1.1
S.D.	0.3	8	20	0.0	2	0.9	12	0.1	15	0.9	0.6	7	0.3	4	0.3	0.1
47-F	2.9	71	67	0.1	33	11.2	100	0.5	129	4.5	5.1	142	5.9	105	2.2	1.32
49-F	2.9	87	96	0.2	32	10.4	83	0.5	114	4.7	5.6	142	5.8	102	2.7	1.07
54-F	3.5	40	87	0.1	27	11.2	76	0.5	153	10.5	5.8	147	6.1	104	2.3	1.52
58-F	3.4	40	129	0.2	23	11.2	92	0.5	156	9.1	6.2	145	6.1	103	2.8	1.21
65-F	3.0	81	72	0.2	33	10.3	96	0.5	96	7.7	5.5	142	5.9	98	2.5	1.20
67-F	3.0	78	77	0.1	27	10.9	76	0.4	117	6.1	5.7	142	6.2	100	2.7	1.11
68-F	2.9	73	79	0.1	31	10.7	95	0.4	108	5.7	5.2	143	5.6	102	2.3	1.26
77-F	3.3	80	69	0.1	31	11.0	85	0.4	117	7.0	5.7	146	5.7	100	2.4	1.38
78-F	3.0	102	77	0.2	34	10.7	86	0.4	130	8.3	5.1	141	7.1	102	2.1	1.43
87-F	3.1	57	96	0.1	48	10.2	68	0.6	141	4.8	5.5	143	6.2	99	2.4	1.29
Mean	3.1	71	85	0.1	32	10.8	86	0.5	126	6.8	5.5	143	6.1	102	2.4	1.28
S.D.	0.2	20	19	0.1	7	0.4	10	0.1	19	2.0	0.3	2	0.4	2	0.2	0.14
Overall																
Mean	3.0	59	79	0.1	26	10.3	80	0.4	119	6.8	5.5	139	5.7	97	2.5	1.19
S.D.	0.3	20	20	0.0	8	0.8	13	0.1	19	1.6	0.5	7	0.5	6	0.3	0.15

M - Male; F - Female; S.D. - Standard deviation; * - Quantity not sufficient; Refer to Appendix G for units

Appendix E - Serum Chemistry Individual Data (cont.)
Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
Test Article: Veova 10

Animal Number	ALB	ALT	AST	T Bil	BUN	CA	Chol	Creat	Gluc	Phos	TP	Na	K	Cl	Glob	A/G Ratio
Group II																
2-M	2.9	31	53	0.1	33	9.4	97	0.5	101	6.1	5.6	127	5.2	83	2.7	1.07
10-M	2.9	43	63	0.1	27	10.3	92	0.5	162	7.6	5.5	137	5.4	91	2.6	1.12
16-M	2.9	28	64	0.1	38	9.3	93	0.5	103	5.0	5.4	128	6.2	84	2.5	1.16
21-M	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
23-M	2.6	33	52	0.1	28	9.1	92	0.5	97	6.1	5.3	130	5.5	86	2.7	0.96
27-M	2.9	44	55	0.1	34	10.2	106	0.5	119	6.8	*	138	5.8	92	*	*
28-M	2.9	41	62	0.1	36	10.0	125	0.5	106	7.2	6.0	133	6.1	88	3.1	0.94
31-M	3.0	30	69	0.2	26	9.7	92	0.3	106	7.8	5.4	129	5.8	88	2.4	1.25
35-M	3.1	38	59	0.1	30	9.8	104	0.4	173	8.5	6.0	131	5.8	91	2.9	1.07
37-M	2.8	46	57	0.1	21	9.8	88	0.3	109	7.3	5.6	133	5.7	90	2.8	1.00
Mean	2.9	37	59	0.1	30	9.7	99	0.4	120	6.9	5.6	132	5.7	88	2.7	1.07
S.D.	0.1	7	6	0.0	5	0.4	11	0.1	28	1.1	0.3	4	0.3	3	0.2	0.10
45-F	3.6	73	276	0.2	29	11.3	84	0.6	130	8.8	6.3	143	5.5	98	2.7	1.33
53-F	3.5	52	82	0.1	25	10.7	92	0.5	187	9.0	6.0	144	5.6	99	2.5	1.40
55-F	3.5	59	79	0.1	23	10.6	46	0.4	147	5.8	6.1	141	5.8	94	2.6	1.35
56-F	2.8	59	69	0.1	38	10.2	90	0.4	131	5.7	4.8	143	5.7	102	2.0	1.40
59-F	3.5	36	155	0.1	31	11.7	102	0.4	152	8.0	6.2	144	5.5	100	2.7	1.30
61-F	2.9	47	190	0.2	40	10.4	98	0.5	158	8.1	4.8	145	8.0	106	1.9	1.53
63-F	3.1	103	85	0.1	29	10.2	89	0.4	115	6.3	5.6	145	6.1	102	2.5	1.24
64-F	3.1	69	83	0.1	26	10.2	97	0.4	124	5.8	5.4	143	5.8	100	2.3	1.35
66-F	3.1	85	75	0.1	38	10.8	127	0.4	124	3.5	5.7	142	6.2	100	2.6	1.19
69-F	3.2	67	73	0.1	26	10.5	120	0.4	125	6.6	5.6	142	5.8	102	2.4	1.33
Mean	3.2	65	117	0.1	31	10.7	95	0.4	139	6.8	5.7	143	6.0	100	2.4	1.34
S.D.	0.3	19	69	0.0	6	0.5	22	0.1	22	1.7	0.5	1	0.7	3	0.3	0.09
Overall																
Mean	3.1	52	90	0.1	30	10.2	97	0.4	130	6.8	5.6	138	5.9	95	2.6	1.22
S.D.	0.3	20	57	0.0	6	0.7	17	0.1	26	1.4	0.4	6	0.6	7	0.3	0.17

M - Male; F - Female; S.D. - Standard deviation; * - Quantity not sufficient; Refer to Appendix G for units

Appendix E - Serum Chemistry Individual Data (cont.)
Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
 Test Article: Veova 10

Animal Number	ALB	ALT	AST	T Bil	BUN	CA	Chol	Creat	Gluc	Phos	TP	Na	K	Cl	Glob	A/G Ratio
Group III																
5-M	2.8	42	51	0.1	24	10.3	96	0.3	115	6.3	5.6	136	5.3	91	2.8	1.00
6-M	3.1	62	75	0.2	21	9.6	94	0.3	129	7.7	5.8	140	6.0	98	2.7	1.15
14-M	2.8	37	61	0.1	22	9.3	73	0.3	101	5.9	5.1	127	5.3	86	2.3	1.22
20-M	4.0	71	97	0.2	26	13.1	109	0.5	138	8.8	8.3	158	6.6	103	4.3	0.93
24-M	2.9	41	68	0.1	20	10.0	103	0.3	106	7.1	5.7	133	5.6	88	2.8	1.04
25-M	2.7	52	55	0.1	19	9.2	81	0.3	101	6.5	5.0	132	5.0	93	2.3	1.17
26-M	3.4	51	86	0.1	25	10.9	76	0.3	122	7.5	6.6	143	6.0	97	3.2	1.06
29-M	2.7	39	68	0.1	18	9.5	73	0.3	100	6.5	5.2	129	5.1	89	2.5	1.08
32-M	3.0	39	56	0.1	17	10.5	88	0.3	122	7.9	6.0	138	5.1	91	3.0	1.00
34-M	2.8	52	58	0.1	15	9.6	84	0.3	111	7.0	5.4	132	5.4	91	2.6	1.08
Mean	3.0	49	68	0.1	21	10.2	88	0.3	115	7.1	5.9	137	5.5	93	2.9	1.07
S.D.	0.4	11	15	0.0	4	1.2	13	0.1	13	0.9	1.0	9	0.5	5	0.6	0.09
42-F	3.2	51	57	0.1	32	10.4	100	0.4	129	5.5	5.8	142	6.1	102	2.6	1.23
51-F	3.0	72	149	0.2	30	10.6	85	0.5	126	7.7	5.0	146	6.3	107	2.0	1.50
57-F	3.4	50	75	0.1	25	10.8	93	0.4	134	6.0	6.1	141	5.6	100	2.7	1.26
73-F	3.6	59	248	0.2	24	11.2	114	0.5	135	8.1	6.3	146	5.6	104	2.7	1.33
74-F	3.0	80	76	0.1	28	11.5	121	0.5	151	9.1	5.7	144	5.8	99	2.7	1.11
Mean	3.2	62	121	0.1	28	10.9	103	0.5	135	7.3	5.8	144	5.9	102	2.5	1.29
S.D.	0.3	13	79	0.1	3	0.4	15	0.1	10	1.5	0.5	2	0.3	3	0.3	0.14
Overall Mean	3.1	53	85	0.1	23	10.4	93	0.4	121	7.2	5.8	139	5.7	96	2.7	1.14
S.D.	0.4	13	51	0.0	5	1.0	15	0.1	15	1.1	0.8	8	0.5	7	0.5	0.15

M - Male; F - Female; S.D. - Standard deviation; Refer to Appendix G for units

Appendix E - Serum Chemistry Individual Data (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
Test Article: Veova 10

Animal Number	ALB	ALT	AST	T Bil	BUN	CA	Chol	Creat	Gluc	Phos	TP	Na	K	Cl	Glob	A/G Ratio
Group IV																
3-M	2.9	50	73	0.1	20	8.1	83	0.3	118	6.6	5.7	139	6.9	97	2.8	1.04
4-M	3.4	61	78	0.1	21	11.1	88	0.4	116	7.5	6.7	143	5.8	93	3.3	1.03
7-M	3.5	46	98	0.2	23	12.1	75	0.4	180	8.9	6.7	151	5.6	102	3.2	1.09
11-M	2.5	42	64	0.1	18	9.4	84	0.5	115	6.5	4.8	134	5.6	91	2.3	1.09
18-M	3.0	46	86	0.1	20	10.0	72	0.3	114	7.8	5.7	138	5.6	93	2.7	1.11
19-M	2.6	46	64	0.1	17	9.8	71	0.3	116	8.5	4.7	128	6.0	86	2.1	1.24
22-M	2.8	38	52	0.1	17	9.3	74	0.3	106	6.9	5.3	127	4.5	85	2.5	1.12
33-M	3.2	50	61	0.1	16	10.5	73	0.3	122	6.9	6.0	136	5.7	86	2.8	1.14
38-M	2.9	44	79	0.1	19	10.0	74	0.3	111	7.2	5.7	136	5.7	92	2.8	1.04
39-M	3.1	28	52	0.1	23	9.9	99	0.3	110	6.6	5.7	136	5.0	92	2.6	1.19
Mean	3.0	45	71	0.1	19	10.0	79	0.3	121	7.3	5.7	137	5.6	92	2.7	1.11
S.D.	0.3	9	15	0.0	2	1.1	9	0.1	21	0.8	0.7	7	0.6	5	0.4	0.07
46-F	2.8	92	196	0.2	34	10.9	103	0.4	143	8.8	5.3	143	6.4	102	2.5	1.12
48-F	3.1	62	83	0.1	44	10.1	87	0.4	113	4.6	5.5	144	6.3	104	2.4	1.29
72-F	2.9	72	117	0.2	41	11.4	75	0.6	193	8.6	4.8	145	6.5	105	1.9	1.53
75-F	3.0	64	61	0.1	35	10.1	82	0.4	102	4.6	5.4	145	5.8	104	2.4	1.25
86-F	3.2	84	127	0.1	19	11.3	59	0.4	144	11.8	5.2	147	6.5	104	2.0	1.60
Mean	3.0	75	117	0.1	35	10.8	81	0.4	139	7.7	5.2	145	6.3	104	2.2	1.36
S.D.	0.2	13	52	0.1	10	0.6	16	0.1	35	3.1	0.3	1	0.3	1	0.3	0.20
Overall																
Mean	3.0	55	86	0.1	24	10.3	80	0.4	127	7.5	5.5	139	5.9	96	2.6	1.19
S.D.	0.3	17	38	0.0	9	1.0	11	0.1	27	1.8	0.6	7	0.6	7	0.4	0.17

M - Male; F - Female; S.D. - Standard deviation; Refer to Appendix G for units

Appendix F - Hematology Individual Data

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

Animal Number	WBC	RBC	Hgb	Hct	MCV	MCH	MCHC	Neut	Lymp	Mono	Eos	Baso	PT	APTT
Group I														
1-M	4.96	8.35	16.3	53.3	63.8	19.5	30.6	11.8	81.8	1.1	1.5	0.6		
8-M	10.38	8.46	16.0	52.2	61.8	18.9	30.6	9.9	86.0	1.2	1.6	0.4		
9-M	11.40	9.22	16.7	54.5	59.1	18.2	30.7	11.3	84.3	1.4	0.8	0.9		
12-M	8.08	8.28	15.1	50.2	60.7	18.3	30.1	12.2	84.7	1.2	0.9	0.3		
13-M	11.89	8.67	16.2	52.0	59.9	18.6	31.1	12.4	82.2	1.8	2.0	0.5		
15-M	10.29	8.35	15.7	50.6	60.6	18.8	31.1	10.6	86.7	1.2	0.6	0.4		
17-M	12.90	8.65	15.8	52.6	60.8	18.3	30.0	11.2	85.6	0.8	0.9	0.5		
30-M	11.61	8.73	16.1	53.0	60.6	18.4	30.4	13.5	82.9	0.8	1.2	0.7		
36-M	8.28	8.40	15.3	52.0	61.9	18.2	29.4	12.2	84.9	1.3	0.9	0.2		
40-M	11.71	8.64	16.2	52.8	61.1	18.8	30.8	9.7	85.6	1.6	1.5	0.6		
Mean	10.15	8.58	15.9	52.3	61.0	18.6	30.5	11.5	84.5	1.2	1.2	0.5		
S.D.	2.39	0.28	0.5	1.3	1.3	0.4	0.5	1.2	1.7	0.3	0.4	0.2		
47-F	8.28	5.80	11.7	36.3	62.6	20.1	32.2	27.4	68.4	2.2	1.1	0.2	12.9	16.9
49-F	5.65	6.61	13.2	42.4	64.2	20.0	31.1	27.4	66.8	1.3	2.5	0.3	13.5	16.6
54-F	3.98	7.49	14.6	46.4	62.0	19.4	31.4	18.7	76.4	1.3	3.0	0.3	14.4	19.8
58-F	5.98	7.64	15.2	49.0	64.1	19.9	31.1	11.9	83.1	1.1	3.0	0.4	13.7	19.5
65-F	*	*	*	*	*	*	*	*	*	*	*	*	13.9	78.3
67-F	11.12	5.58	12.3	40.0	71.7	22.1	30.8	22.5	74.2	1.1	1.5	0.2	13.9	24.3
68-F	5.01	6.09	12.2	39.7	65.2	20.0	30.7	25.6	68.9	1.0	4.1	0.1	13.5	14.9
77-F	4.08	6.67	13.4	43.8	65.6	20.0	30.5	54.9	31.7	2.2	11.0	0.1	13.6	18.6
78-F	5.91	6.25	13.2	41.8	67.0	21.1	31.6	32.9	59.9	1.7	4.8	0.3	13.3	20.0
87-F	3.84	7.95	15.2	48.7	61.3	19.1	31.2	29.1	63.4	1.5	5.6	0.2	14.8	19.8
Mean	5.98	6.68	13.4	43.1	64.9	20.2	31.2	27.8	65.9	1.5	4.1	0.2	13.8	24.9
S.D.	2.37	0.85	1.3	4.3	3.1	0.9	0.5	11.9	14.6	0.5	3.0	0.1	0.5	18.9
Overall														
Mean	8.18	7.68	14.8	48.0	62.8	19.4	30.8	19.2	75.7	1.4	2.6	0.4		
S.D.	3.15	1.14	1.6	5.6	3.0	1.1	0.6	11.6	13.7	0.4	2.5	0.2		

M - Male; F - Female; S.D. - Standard deviation; * - No sample submitted; Refer to Appendix G for units

Note: PT and APTT values were not determined for males.

Appendix F - Hematology Individual Data (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

Animal Number	WBC	RBC	Hgb	Hct	MCV	MCH	MCHC	Neut	Lymp	Mono	Eos	Baso	PT	APTT
Group II														
2-M	11.42	7.71	14.2	46.4	60.3	18.5	30.6	20.9	73.5	3.1	1.0	0.7		
10-M	9.70	7.35	13.9	45.4	61.8	19.0	30.7	14.3	82.6	1.0	0.9	0.2		
16-M	7.72	7.40	13.7	44.1	59.6	18.5	31.1	13.7	78.2	2.2	1.4	1.2		
21-M	14.33	8.02	14.6	48.1	60.0	18.2	30.3	15.6	79.3	2.3	1.1	0.4		
23-M	11.00	8.09	15.3	50.1	61.9	18.9	30.5	14.1	82.8	1.6	0.4	0.5		
27-M	13.97	8.05	15.1	48.7	60.5	18.7	31.0	16.1	80.3	1.2	1.2	0.4		
28-M	13.20	8.29	14.9	47.1	56.9	18.0	31.6	20.0	75.3	2.9	0.7	0.4		
31-M	11.79	7.76	14.2	46.7	60.2	18.3	30.4	16.2	79.6	1.2	1.1	0.5		
35-M	11.39	8.48	15.4	51.7	60.9	18.1	29.8	9.8	87.5	1.4	0.5	0.3		
37-M	14.66	8.29	14.5	47.6	57.4	17.5	30.4	7.7	88.2	2.1	0.7	0.5		
Mean	11.92	7.94	14.6	47.6	60.0	18.4	30.6	14.8	80.7	1.9	0.9	0.5		
S.D.	2.19	0.38	0.6	2.2	1.7	0.4	0.5	4.0	4.7	0.7	0.3	0.3		
45-F	*	*	*	*	*	*	*	*	*	*	*	*	*	*
53-F	6.30	7.95	15.0	48.1	60.5	18.9	31.3	13.3	83.4	1.1	1.6	0.1	14.5	24.0
55-F	4.12	8.19	16.0	50.9	62.1	19.5	31.4	22.6	73.3	1.3	2.0	0.5	14.7	27.2
56-F	7.06	5.80	11.3	35.6	61.4	19.6	31.9	30.2	66.4	1.9	0.8	0.1	13.1	18.4
59-F	3.32	4.79	9.5	30.7	64.2	19.9	31.0	32.3	64.2	2.0	1.1	0.1	13.5	12.9
61-F	*	*	*	*	*	*	*	*	*	*	*	*	†	†
63-F	6.02	6.69	12.8	41.5	62.1	19.1	30.8	50.5	44.7	1.8	2.5	0.3	14.7	32.7
64-F	5.42	6.34	13.2	42.2	66.6	20.8	31.3	51.7	39.4	1.4	6.7	0.1	13.6	23.4
66-F	10.74	6.03	12.8	42.1	69.9	21.2	30.4	33.0	62.7	1.9	1.5	0.2	13.9	21.8
69-F	6.65	6.50	12.8	41.7	64.1	19.8	30.8	34.6	60.6	1.4	2.7	0.1	13.5	23.4
Mean	6.20	6.54	12.9	41.6	63.9	19.9	31.1	33.5	61.8	1.6	2.4	0.2	13.9	23.0
S.D.	2.23	1.11	2.0	6.4	3.1	0.8	0.5	12.9	14.3	0.3	1.9	0.1	0.6	5.8
Overall														
Mean	9.38	7.32	13.8	44.9	61.7	19.0	30.9	23.1	72.3	1.8	1.6	0.4		
S.D.	3.62	1.05	1.6	5.4	3.1	1.0	0.5	13.0	13.7	0.6	1.4	0.3		

M - Male; F - Female; S.D. - Standard deviation; * - No sample submitted; † - No clot detected; Refer to Appendix G for units
 Note: PT and APTT values were not determined for males.

Appendix F - Hematology Individual Data (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

Animal Number	WBC	RBC	Hgb	Hct	MCV	MCH	MCHC	Neut	Lymp	Mono	Eos	Baso	PT	APTT
Group III														
5-M	15.29	8.17	15.4	49.8	61.0	18.9	30.9	19.3	76.2	2.4	1.1	0.4		
6-M	12.68	8.21	15.5	51.6	62.9	18.9	30.0	16.1	80.7	1.2	1.0	0.4		
14-M	9.18	7.98	15.5	50.2	62.9	19.4	30.8	12.6	82.1	2.4	1.3	0.5		
20-M	9.37	8.43	16.0	51.6	61.2	18.9	30.9	10.7	84.5	2.0	1.2	0.6		
24-M	8.78	8.28	15.7	51.2	61.8	19.0	30.7	10.3	85.2	1.4	1.3	0.5		
25-M	11.06	8.21	15.3	50.3	61.3	18.6	30.3	9.0	85.3	1.7	0.9	0.3		
26-M	14.85	8.29	16.0	50.9	61.5	19.3	31.3	11.7	84.0	1.4	1.0	0.7		
29-M	10.66	7.49	14.8	47.5	63.4	19.8	31.2	14.1	81.9	2.4	0.6	0.2		
32-M	13.52	8.61	16.0	51.9	60.3	18.6	30.9	11.4	84.3	1.6	0.8	0.7		
34-M	14.23	8.42	15.6	51.1	60.7	18.6	30.6	13.4	82.3	1.5	1.5	0.5		
Mean	11.96	8.21	15.6	50.6	61.7	19.0	30.8	12.9	82.7	1.8	1.1	0.5		
S.D.	2.46	0.30	0.4	1.3	1.0	0.4	0.4	3.0	2.7	0.5	0.3	0.2		
42-F	4.48	6.02	11.5	37.7	62.6	19.0	30.4	42.3	53.7	1.5	2.0	0.2	15.0	17.2
51-F	4.79	6.39	12.7	40.9	64.0	19.9	31.1	45.1	49.0	1.4	4.1	0.1	12.9	14.8
57-F	3.91	7.72	14.7	47.6	61.7	19.0	30.8	14.1	80.9	0.9	3.3	0.2	14.7	14.8
73-F	1.48	6.68	13.2	42.9	64.2	19.7	30.7	13.9	82.9	0.4	2.5	0.7	15.6	50.8
74-F	2.41	6.49	12.9	41.9	64.6	19.9	30.8	28.2	68.9	0.9	1.7	0.1	14.0	18.0
Mean	3.41	6.66	13.0	42.2	63.4	19.5	30.8	28.7	67.1	1.0	2.7	0.3	14.4	23.1
S.D.	1.42	0.64	1.1	3.6	1.2	0.5	0.3	14.9	15.4	0.4	1.0	0.3	1.0	15.5
Overall														
Mean	9.11	7.69	14.7	47.8	62.3	19.2	30.8	18.1	77.5	1.5	1.6	0.4		
S.D.	4.68	0.86	1.4	4.6	1.3	0.5	0.3	11.4	11.4	0.6	1.0	0.2		

M - Male; F - Female; S.D. - Standard deviation; Refer to Appendix G for units

Note: PT and APTT values were not determined for males.

Appendix F - Hematology Individual Data (cont.)

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

Animal Number	WBC	RBC	Hgb	Hct	MCV	MCH	MCHC	Neut	Lymp	Mono	Eos	Baso	PT	APTT
Group IV														
3-M	13.55	8.35	14.8	49.0	58.8	17.7	30.1	18.5	78.6	1.4	0.5	0.5		
4-M	10.42	8.23	15.5	51.5	62.6	18.8	30.1	10.1	85.1	1.1	0.9	0.8		
7-M	10.55	8.18	15.6	50.7	62.1	19.0	30.7	11.7	84.2	1.3	1.1	0.8		
11-M	5.90	8.00	15.0	50.3	62.9	18.8	29.8	8.6	88.8	1.2	0.5	0.3		
18-M	9.73	8.11	15.3	49.6	61.2	18.9	30.9	11.9	84.4	1.7	0.6	0.3		
19-M	11.32	8.45	15.7	52.0	61.5	18.6	30.3	33.4	62.9	1.7	1.1	0.4		
22-M	11.72	8.33	15.3	50.5	60.6	18.4	30.4	14.0	81.0	1.1	1.8	0.4		
33-M	8.02	8.86	16.4	54.5	61.6	18.6	30.1	11.7	85.6	1.0	0.8	0.4		
38-M	8.86	8.26	15.2	51.6	62.5	18.5	29.5	12.7	84.8	1.0	0.8	0.2		
39-M	9.91	8.89	16.4	54.2	61.0	18.5	30.3	11.1	84.6	1.1	1.5	0.8		
Mean	10.00	8.37	15.5	51.4	61.5	18.6	30.2	14.4	82.0	1.3	1.0	0.5		
S.D.	2.11	0.30	0.5	1.8	1.2	0.4	0.4	7.2	7.2	0.3	0.4	0.2		
46-F	6.81	5.84	12.5	40.6	69.6	21.3	30.6	28.6	67.4	2.4	1.0	0.2	*	*
48-F	3.77	6.76	13.3	41.9	62.0	19.6	31.7	44.4	47.1	2.9	5.3	0.1	13.6	14.3
72-F	2.80	5.14	11.0	36.4	70.8	21.3	30.1	33.3	63.3	0.9	2.3	0.1	13.5	12.2
75-F	6.99	5.91	12.7	40.6	68.7	21.5	31.3	52.7	42.4	1.3	3.3	0.1	15.4	38.6
86-F	7.85	6.88	13.9	44.1	64.1	20.2	31.6	16.2	76.7	1.7	2.6	0.2	14.0	16.8
Mean	5.64	6.11	12.7	40.7	67.0	20.8	31.1	35.0	59.4	1.8	2.9	0.1	14.1	20.5
S.D.	2.22	0.72	1.1	2.8	3.8	0.8	0.7	14.1	14.3	0.8	1.6	0.1	0.9	12.2
Overall														
Mean	8.55	7.61	14.6	47.8	63.3	19.3	30.5	21.3	74.5	1.5	1.6	0.4		
S.D.	2.96	1.19	1.6	5.6	3.5	1.2	0.6	13.9	14.6	0.6	1.3	0.3		

M - Male; F - Female; S.D - Standard deviation; * - No clot detected; Refer to Appendix G for units
 Note: PT and APTT values were not determined for males.

Appendix G - Units for Serum Chemistry and Hematology

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

Serum Chemistry Parameters	Units
ALB - Albumin	g/dL
ALT - Alanine Aminotransferase	IU/L
AST - Aspartate Aminotransferase	IU/L
T BIL - Total Bilirubin	mg/dL
BUN - Urea Nitrogen	mg/dL
Calcium	mg/dL
Chol - Cholesterol	
Creat - Creatinine	mg/dL
Glucose	mg/dL
Phos - Phosphorus	mg/dL
T P - Total Protein	g/dL
Na - Sodium	mEq/L
K - Potassium	mEq/L
Cl - Chloride	mEq/L
Glob - Globulin	g/dL
A/G Ratio - Albumin/Globulin Ratio	mEq/L

Hematology Parameters	Units
WBC - White Blood Cells	thous/ μ L
RBC - Erythrocyte Count	mill/ μ L
Hgb - Hemoglobin	g/dL
Hct - Hematocrit	%
MCV - Mean Corpuscular Volume	fL
MCH - Mean Corpuscular Hemoglobin	pg
MCHC - Mean Corpuscular Hemoglobin Concentration	g/dL
Neut - Neutrophils	%
Lymp - Lymphocytes	%
Mono - Monocytes	%
Eos - Eosinophils	%
Baso - Basophils	%
PT - Prothrombin Time	secs
APTT - Activated Partial Thromboplastin Time	secs

Appendix H - Certificate of Analysis

Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test

Test Article: Veova 10

RESOLUTION

PERFORMANCE PRODUCTS

Certificate of AnalysisCustomer:
Stillmeadow Inc.
Dr. Jan KuhnShip-To:
12852 Park One Dr.
Sugar Land, TX 77478Product : VEOVA™ 10
Customer Product : n/a
SQR No. : 1000Sales Order/Item : N/C
Cust PO/Indent : n/aShipping Date : 9-23-2004
Batch No. : ECMV0086Delivery Number : n/a
Cert. Date : March 10, 2004
Expiration Date : March 10, 2007
Shipping Loc : WTC
Mfg. Date : 03/2004

Property	Units	Minimum	Maximum	Result	F	Test Method
Color, Pt-Co	Pt-Co		15	5		ASTM D1209
Density @20C	kg/m3	875	885	880		ASTM D4052
Water	km/m		0.1	0.0		ASTM E203
Acid value as KOH	mg/g		1.0	0.7		ASTM D1639
Refractive Index @25C		1.432	1.437	1.434		ASTM D1218
Appearance, CFFSM	Clear & Free From Suspended Matter			Pass	3	ASTM D4176
Vinyl Unsaturation	mol/kg	4.85	5.10	4.98		SMS 2687

(Footnotes)

1-Guaranteed, 2-Typical, 3-Report Only.

* TRADEMARK: REGISTERED U.S. PATENT OFFICE

Resolution certifies that its product will meet those specifications designated as such herein.



11 Nov 04
Kenneth Washburn, Ph.D., DABT
Product Safety Coordinator

All products purchased from or supplied by Resolution Performance Products are subject to terms and conditions set out in the contract. If you have any questions regarding this certification or the delivery, please call your local account representative.

Appendix I – Protocol and Amendment

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Introduction

The objective of this study was to evaluate the potential toxic effects of the test substance when administered to rats for a minimum of 28 days and to determine the potential of the test substance to affect male and female reproductive performance such as gonadal function, mating behavior, conception, parturition, and early postnatal development. This report, prepared by Pathology Solutions, Inc., for STILLMEADOW, Inc., on behalf of Hefion Specialty Chemicals, Inc., presents and interprets the microscopic pathology data.

Materials and Methods

Eighty rats were equally divided into four groups with ten males and ten females per group. Group 1 rats received the vehicle only and served as a control group. The rats of Groups 2 through 4 received the test substance orally by gavage daily from 14 days. On Day 14, each male from each group was put with a female from the same group for mating for a maximum period of 14 days. After confirmation of mating, the animals were returned to their individual cages, and all animals continued to be treated at least through Day 28. After Day 28, the males were sacrificed and necropsied by Stillmeadow, Inc. personnel. A complete necropsy with organ weight determination was conducted and selected tissues were saved in 10% neutral buffered formalin. The pregnant females were dosed daily through the gestation period and through Day 4 of lactation period. The pregnant females were sacrificed and necropsied on Day 5 by Stillmeadow Inc. personnel in the same manner as the males. Tissues were collected and preserved in formalin for histopathological analysis. Formalin-preserved tissues were trimmed, embedded in paraffin, sectioned and stained with hematoxylin and eosin. A board-certified veterinary pathologist examined all tissues listed. brain – cerebrum, brain – cerebellum, brain – pons, thoracic spinal cord, peripheral nerve, thyroid, trachea, thymus, submandibular lymph node, lungs/bronchus, heart, aorta, liver, spleen, kidney - right, kidney - left, adrenals, stomach, duodenum, jejunum, ileum/Peyer's patch, cecum, colon, mesenteric lymph node, bone marrow, testes, epididymis, seminal vesicle, prostate, ovaries, oviducts, uterus, urinary bladder. Tissue changes were graded as minimal – the smallest degree or amount that might be seen, or involving less than 10% of the tissue; mild – observed following brief search or involving 10-40% of the tissue; moderate – easily seen or involving 40-60% of the tissue; or marked – quite obvious change, involving a majority of the tissue or appearing to be as severe as possible.

Study Design

Group No.	Treatment level	Dose (mg/kg)	No. of Males	No. Females
1	Control	0	5	10
2	High dose	1,000	5	10
3	Mid dose	250	5	5
4	Low dose	100	5	5

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Individual pathology findings for each animal are presented in Table 1.
The summary and incidence of microscopic findings for each group is presented in Table 2.

Unscheduled Deaths.

All rats survived to the scheduled necropsy.

Microscopic Pathology – Terminal Sacrifice

Compound-related lesions were limited to the kidneys of rats treated with the dose of 1,000 mg/kg. Males (4 of 5) were affected more than females (1 of 10). The primary lesion was nephrosis, characterized by the deposition of birefringent (brightly evident under polarized light) crystals that resembled oxalates within the renal tubules. Necrosis/degeneration of the adjacent epithelial cells was dependent upon the amount of crystalline deposition, but was not a major change. The nephrosis was sometimes accompanied by chronic interstitial nephritis, increased basophilic cortical tubules (a regenerative indicator), and papillary necrosis in 1 male. Other secondary non-renal lesions included thymic lymphoid depletion in 2 affected males and a mild gastric ulcer in 1 affected male.

Incidental Findings

Incidental findings included renal hyaline casts, mineralization, and a nephroblastoma (in a control female); pulmonary inflammation and/or edema; and urinary bladder and uterine distention, the latter likely a normal cyclical change.

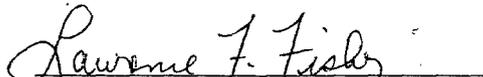
Discussion

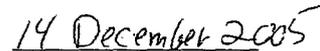
In addition to toxic effects, this study was also intended to determine effects of the test article upon reproductive performance. However, no histopathologic changes were observed upon microscopic examination of the male or female reproductive organs.

Conclusions

Oral administration of the test article to male and female rats for 28 days resulted in oxalate nephrosis at the high dose, and was more severe in males. Primary effects were not seen in other organs. The no-effect dose was the intermediate dose of 250 mg/kg.

Evaluating Pathologist:


Lawrence F. Fisher, DVM, PhD, DACVP


Date

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 1; Group: 1

Sex: Male

Pathologist: LFF

Animal Fate: Scheduled sacrifice on Day 29

Days on Test: 28

Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Kidney, right: Hyaline casts, cortex/medulla – mild, focal

Kidney, left: Hyaline casts, cortex/medulla – mild, focal

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve		Bone Marrow
Thyroid		Testes
Trachea	Adrenals	Epididymis
Thymus	Stomach	Seminal Vesicle
Submandibular Lymph Node	Duodenum	Prostate
Lungs/Bronchus	Jejunum	Urinary Bladder

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 12; Group: 1

Sex: Male

Pathologist: LFF

Animal Fate: Scheduled sacrifice on Day 29

Days on Test: 28

Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Kidney, left: Hyaline casts, cortex/medulla – mild, focal

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid		Testes
Trachea	Adrenals	Epididymis
Thymus	Stomach	Seminal Vesicle
Submandibular Lymph Node	Duodenum	Prostate
Lungs/Bronchus	Jejunum	Urinary Bladder

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 15; Group: 1

Sex: Male

Pathologist: LFF
Days on Test: 28Animal Fate: Scheduled sacrifice on Day 29
Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Illeum/Peyer's Patch: Autolysis – moderate, diffuse, mucosa
Kidney, right: Hyaline casts, cortex/medulla – mild, focal
Kidney, left: Hyaline casts, cortex/medulla – mild, multifocal

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve		Bone Marrow
Thyroid		Testes
Trachea	Adrenals	Epididymis
Thymus	Stomach	Seminal Vesicle
Submandibular Lymph Node	Duodenum	Prostate
Lungs/Bronchus	Jejunum	Urinary Bladder

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 30; Group: 1	Sex: Male
Pathologist: LFF Days on Test: 28	Animal Fate: Scheduled sacrifice on Day 29 Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Illeum/Peyer's Patch: Autolysis – mild, diffuse, mucosa
Kidney, left: Hyaline casts, cortex/medulla: mild, focal

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid		Testes
Trachea	Adrenals	
Thymus	Stomach	Seminal Vesicle
Submandibular Lymph Node	Duodenum	Prostate
Lungs/Bronchus		Urinary Bladder

TISSUES UNAVAILABLE FOR EVALUATION:

Epididymis: Not examined, not found in wet tissue
Jejunum: Not examined, not found in wet tissue

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 36; Group: 1

Sex: Male

Pathologist: LFF

Animal Fate: Scheduled sacrifice on Day 29

Days on Test: 28

Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

None

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	
Brain - Pons	Liver	
Thoracic Spinal Cord	Spleen	
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid	Kidney, left	Testes
Trachea	Adrenals	Epididymis
Thymus	Stomach	Seminal Vesicle
Submandibular Lymph Node	Duodenum	Prostate
Lungs/Bronchus		Urinary Bladder

TISSUES UNAVAILABLE FOR EVALUATION:

Cecum: Not examined, not found in wet tissue

Colon: Not examined, not found in wet tissue

Jejunum: Not examined, not found in wet tissue

Mesenteric Lymph Node: Not examined, not found in wet tissue

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 10; Group: 2

Sex: Male

Pathologist: LFF
Days on Test: 28Animal Fate: Scheduled sacrifice on Day 29
Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Kidney, right: Nephritis, interstitial, chronic – minimal, multifocal; Papillary necrosis - moderate, focal; Basophilic tubules, cortex – mild, multifocal; Nephrosis – moderate, multifocal
Kidney, left: Nephritis, interstitial, chronic – moderate, patchy; Papillary necrosis - moderate, focal; Basophilic tubules, cortex – mild, multifocal; Nephrosis – moderate, multifocal

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colón
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve		Bone Marrow
Thyroid		Testes
Trachea	Adrenals	
Thymus	Stomach	Seminal Vesicle
Submandibular Lymph Node	Duodenum	Prostate
Lungs/Bronchus	Jejunum	Urinary Bladder

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

Epididymis: One of pair present/normal

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 21; Group: 2

Sex: Male

Pathologist: LFF

Animal Fate: Scheduled sacrifice on Day 29

Days on Test: 28

Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Kidney, right: Nephrosis – moderate, multifocal; Nephritis, interstitial, chronic – moderate, multifocal; Hyaline casts, cortex/medulla – moderate, multifocal; Basophilic tubules, cortex – mild, multifocal
Kidney, left: Nephrosis – moderate, multifocal; Nephritis, interstitial, chronic – moderate, multifocal; Basophilic tubules, cortex – mild, multifocal
Stomach: Ulcer – mild, focal, nonglandular

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve		Bone Marrow
Thyroid		Testes
Trachea	Adrenals	Epididymis
Thymus		Seminal Vesicle
Submandibular Lymph Node	Duodenum	Prostate
Lungs/Bronchus	Jejunum	Urinary Bladder

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

Seminal Vesicle: One of pair present/normal
Thyroid: One of pair present/normal

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 23; Group: 2	Sex: Male
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Day 29
Days on Test: 28	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Kidney, right: Nephrosis – moderate, multifocal; Nephritis, interstitial, chronic – moderate, multifocal; Basophilic tubules, cortex – moderate, multifocal
Kidney, left: Nephrosis – moderate, multifocal; Nephritis, interstitial, chronic – moderate, multifocal; Basophilic tubules, cortex – moderate, multifocal
Thymus: Lymphoid depletion: mild
Urinary Bladder: Dilatation - marked

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	
Brain - Cerebellum	Aorta	
Brain - Pons	Liver	
Thoracic Spinal Cord	Spleen	
Peripheral Nerve		Bone Marrow
Thyroid		Testes
Trachea	Adrenals	Epididymis
	Stomach	Seminal Vesicle
Submandibular Lymph Node	Duodenum	Prostate
Lungs/Bronchus	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

Illeum/Peyer's Patch: Not examined, not found in wet tissue
Cecum: Not examined, not found in wet tissue
Colon: Not examined, not found in wet tissue
Mesenteric Lymph Node: Not examined, not found in wet tissue

TISSUE COMMENTS:

Kidney, right: Birefringent oxalate crystals
Kidney, left: Birefringent oxalate crystals

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 31; Group: 2

Sex: Male

Pathologist: LFF

Animal Fate: Scheduled sacrifice on Day 29

Days on Test: 28

Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Kidney, right: Nephrosis – moderate, multifocal; Nephritis, interstitial, chronic – mild, multifocal; Basophilic tubules, cortex – moderate, multifocal
Kidney, left: Nephrosis – moderate, multifocal; Nephritis, interstitial, chronic – mild, multifocal; Basophilic tubules, cortex – moderate, multifocal
Submandibular Lymph Node: Lymphoid depletion - moderate
Thymus: Lymphoid depletion - moderate

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve		Bone Marrow
Thyroid		Testes
Trachea	Adrenals	Epididymis
	Stomach	Seminal Vesicle
	Duodenum	Prostate
Lungs/Bronchus	Jejunum	Urinary Bladder

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

Kidney, right: Birefringent oxalate crystals
Kidney, left: Birefringent oxalate crystals

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 37; Group: 2

Sex: Male

Pathologist: LFF

Animal Fate: Scheduled sacrifice on Day 29

Days on Test: 28

Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Kidney, right: Nephrosis

Kidney, left: Nephrosis; Basophilic tubules, cortex – mild, focal

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve		Bone Marrow
Thyroid		Testes
Trachea	Adrenals	Epididymis
Thymus	Stomach	Seminal Vesicle
Submandibular Lymph Node	Duodenum	Prostate
Lungs/Bronchus	Jejunum	Urinary Bladder

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

Kidney, right: Presumptive – oxalates in pelvis

Kidney, left: Presumptive – oxalates in pelvis

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 6; Group: 3

Sex: Male

Pathologist: LFF

Animal Fate: Scheduled sacrifice on Day 29

Days on Test: 28

Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Lungs/Bronchus: Edema – moderate, diffuse
Heart: Inflammation, chronic: mild, multifocal
Kidney, right: Hyaline casts, cortex/medulla – minimal, focal

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum		Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve		Bone Marrow
Thyroid	Kidney, left	Testes
Trachea	Adrenals	Epididymis
Thymus	Stomach	Seminal Vesicle
Submandibular Lymph Node	Duodenum	Prostate
	Jejunum	Urinary Bladder

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 14; Group: 3

Sex: Male

Pathologist: LFF
Days on Test: 28

Animal Fate: Scheduled sacrifice on Day 29
Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

None

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid	Kidney, left	Testes
Trachea	Adrenals	Epididymis
Thymus	Stomach	Seminal Vesicle
Submandibular Lymph Node	Duodenum	Prostate
Lungs/Bronchus	Jejunum	Urinary Bladder

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 25; Group: 3

Sex: Male

Pathologist: LFF

Animal Fate: Scheduled sacrifice on Day 29

Days on Test: 28

Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Kidney, right: Hyaline casts, cortex/medulla – mild, focal

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	
Brain - Cerebellum	Aorta	
Brain - Pons	Liver	
Thoracic Spinal Cord	Spleen	
Peripheral Nerve		Bone Marrow
Thyroid	Kidney, left	Testes
Trachea	Adrenals	Epididymis
Thymus	Stomach	Seminal Vesicle
Submandibular Lymph Node	Duodenum	Prostate
Lungs/Bronchus	Jejunum	Urinary Bladder

TISSUES UNAVAILABLE FOR EVALUATION:

Ileum/Peyer's Patch: Not examined, not found in wet tissue

Cecum: Not examined, not found in wet tissue

Colon: Not examined, not found in wet tissue

Mesenteric Lymph Node: Not examined, not found in wet tissue

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 29; Group: 3

Sex: Male

Pathologist: LFF
Days on Test: 28Animal Fate: Scheduled sacrifice on Day 29
Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Kidney, left: Basophilic tubules, cortex – minimal, focal

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid		Testes
Trachea	Adrenals	Epididymis
Thymus	Stomach	Seminal Vesicle
Submandibular Lymph Node	Duodenum	Prostate
Lungs/Bronchus	Jejunum	Urinary Bladder

TISSUES UNAVAILABLE FOR EVALUATION:

Thoracic Spinal Cord: Not examined, missing

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 34; Group: 3	Sex: Male
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Day 29
Days on Test: 28	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Kidney, left: Basophilic tubules, cortex – minimal, focal

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Illeum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid		Testes
Trachea	Adrenals	Epididymis
Thymus	Stomach	Seminal Vesicle
Submandibular Lymph Node	Duodenum	Prostate
Lungs/Bronchus	Jejunum	Urinary Bladder

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 3; Group: 4

Sex: Male

Pathologist: LFF
Days on Test: 28Animal Fate: Scheduled sacrifice on Day 29
Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

None

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid	Kidney, left	Testes
Trachea	Adrenals	Epididymis
Thymus	Stomach	Seminal Vesicle
Submandibular Lymph Node	Duodenum	Prostate
Lungs/Bronchus	Jejunum	Urinary Bladder

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 11; Group: 4	Sex: Male
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Day 29
Days on Test: 28	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

None

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid	Kidney, left	Testes
Trachea	Adrenals	Epididymis
Thymus	Stomach	Seminal Vesicle
Submandibular Lymph Node	Duodenum	Prostate
Lungs/Bronchus	Jejunum	Urinary Bladder

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 19; Group: 4

Sex: Male

Pathologist: LFF
Days on Test: 28Animal Fate: Scheduled sacrifice on Day 29
Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

None

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord		Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid	Kidney, left	Testes
Trachea	Adrenals	Epididymis
Thymus	Stomach	Seminal Vesicle
Submandibular Lymph Node	Duodenum	Prostate
Lungs/Bronchus	Jejunum	Urinary Bladder

TISSUES UNAVAILABLE FOR EVALUATION:

Spleen: Not examined, not found in wet tissue

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 33; Group: 4

Sex: Male

Pathologist: LFF
Days on Test: 28Animal Fate: Scheduled sacrifice on Day 29
Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Kidney, left: Mineralization, minimal, focal; Hyaline casts, cortex/medulla – minimal, focal

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid		Testes
Trachea	Adrenals	Epididymis
Thymus	Stomach	Seminal Vesicle
Submandibular Lymph Node		
Lungs/Bronchus	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

Duodenum: Not examined, not found in wet tissue
Prostate: Not examined, not found in wet tissue
Urinary Bladder: Not examined, not found in wet tissue

TISSUE COMMENTS:

Adrenals: Medulla not in section, bilateral/normal

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 38; Group: 4

Sex: Male

Pathologist: LFF

Animal Fate: Scheduled sacrifice on Day 29

Days on Test: 28

Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Kidney, left: Hyaline casts, cortex/medulla – minimal, focal

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid		Testes
Trachea	Adrenals	Epididymis
Thymus	Stomach	Seminal Vesicle
Submandibular Lymph Node	Duodenum	
Lungs/Bronchus	Jejunum	Urinary Bladder

TISSUES UNAVAILABLE FOR EVALUATION:

Prostate: Not examined, not found in wet tissue

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 47; Group: 1	Sex: Female
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Lactation Day 5
Days on Test: Through Lactation Day 4	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Kidney, left: Basophilic tubules, cortex – minimal, focal

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid		Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	Uterus
Submandibular Lymph Node	Duodenum	Urinary Bladder
Lungs/Bronchus	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 49; Group: 1	Sex: Female
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Lactation Day 5
Days on Test: Through Lactation Day 4	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

None

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid	Kidney, left	Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	Uterus
Submandibular Lymph Node	Duodenum	Urinary Bladder
Lungs/Bronchus	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 54; Group: 1	Sex: Female
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Lactation Day 5
Days on Test: Through Lactation Day 4	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Lungs/Bronchus: Inflammation, chronic – mild, multifocal, perivascular
Kidney, right: Mineralization – minimal, focal, medulla
Kidney, left: Mineralization – minimal, focal, medulla

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	
Peripheral Nerve		Bone Marrow
Thyroid		Ovaries
Trachea	Adrenals	Oviducts
	Stomach	Uterus
	Duodenum	Urinary Bladder
	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

Thymus: Not examined, wrong tissue sectioned
Submandibular Lymph Node: Not examined, wrong tissue sectioned
Mesenteric Lymph Node: Not examined, missing

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 58; Group: 1	Sex: Female
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Lactation Day 5
Days on Test: Through Lactation Day 4	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Lungs/Bronchus: Inflammation, chronic – minimal, multifocal
Kidney, right: Hyaline casts, convoluted tubules – minimal, focal
Kidney, left: Hyaline casts, convoluted tubules – minimal, focal

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve		Bone Marrow
Thyroid		Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	Uterus
Submandibular Lymph Node	Duodenum	
	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

Urinary Bladder: Not examined, not found in wet tissue
--

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

**PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test**

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 65; Group: 1	Sex: Female
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Lactation Day 5
Days on Test: Through Lactation Day 4	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Lungs/Bronchus: Inflammation, chronic – mild, multifocal
Kidney, left: Hyaline casts, convoluted tubules – mild, focal

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid		Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	Uterus
	Duodenum	Urinary Bladder
	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

Brain – Cerebellum: Not examined, missing
Submandibular Lymph Node: Not examined, not found in wet tissue
Mesenteric Lymph Node: Not examined, not found in wet tissue

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 67; Group: 1	Sex: Female
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Lactation Day 5
Days on Test: Through Lactation Day 4	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Stomach: Hyperplasia – mild, diffuse, nonglandular
--

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Illeum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid	Kidney, left	Ovaries
Trachea	Adrenals	Oviducts
Thymus		Uterus
Submandibular Lymph Node	Duodenum	Urinary Bladder
Lungs/Bronchus	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 68; Group: 1	Sex: Female
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Lactation Day 5
Days on Test: Through Lactation Day 4	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

None

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid	Kidney, left	Ovaries
Trachea	Adrenals	
Thymus	Stomach	Uterus
Submandibular Lymph Node	Duodenum	Urinary Bladder
Lungs/Bronchus	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

Oviducts: Oviduct missing

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 77; Group: 1	Sex: Female
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Lactation Day 5
Days on Test: Through Lactation Day 4	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

None

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid	Kidney, left	Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	Uterus
Submandibular Lymph Node	Duodenum	Urinary Bladder
Lungs/Bronchus	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 78; Group: 1	Sex: Female
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Lactation Day 5
Days on Test: Through Lactation Day 4	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

None

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum		Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
	Kidney, left	Ovaries
	Adrenals	Oviducts
Thymus	Stomach	Uterus
Submandibular Lymph Node	Duodenum	Urinary Bladder
	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

Thyroid: Not examined, not found in wet tissue
Trachea: Not examined, not found in wet tissue
Lungs/Bronchus: Not examined, not found in wet tissue
Aorta: Not examined, not found in wet tissue

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 87; Group: 1	Sex: Female
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Lactation Day 5
Days on Test: Through Lactation Day 4	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Lungs/Bronchus: Inflammation, chronic – minimal, multifocal
Kidney, right: Hyaline casts, convoluted tubules – mild, multifocal
Kidney, left: Nephroblastoma; Macroscopic observation confirmed

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
	Spleen	
Peripheral Nerve		Bone Marrow
Thyroid		Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	Uterus
Submandibular Lymph Node	Duodenum	Urinary Bladder
	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

Thoracic Spinal Cord: Not examined, not found in wet tissue
Mesenteric Lymph Node: Not examined, wrong tissue sectioned

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 45; Group: 2	Sex: Female
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Lactation Day 5
Days on Test: Through Lactation Day 4	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Liver: Inflammation, chronic – minimal, multifocal
--

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons		Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	
Thyroid	Kidney, left	Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	Uterus
Submandibular Lymph Node	Duodenum	
Lungs/Bronchus	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

Bone Marrow: Not examined, not found in wet tissue
Urinary Bladder: Not examined, not found in wet tissue

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 53; Group: 2

Sex: Female

Pathologist: LFF

Animal Fate: Scheduled sacrifice on Lactation Day
5

Days on Test: Through Lactation Day 4

Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Lungs/Bronchus: Inflammation, chronic – minimal, multifocal

Kidney, left: Hyaline casts, convoluted tubules – minimal focal

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid		Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	Uterus
Submandibular Lymph Node	Duodenum	Urinary Bladder
	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

Thoracic Spinal Cord: Not diagnosis, inadequate section

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 73; Group: 3	Sex: Female
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Lactation Day 5
Days on Test: Through Lactation Day 4	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Lungs/Bronchus: Inflammation, chronic – minimal, multifocal
Kidney, left: Hyaline casts, cortex/medulla – minimal, focal
Uterus: Dilatation – mild, bilateral

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid		Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	
	Duodenum	Urinary Bladder
	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

Thoracic Spinal Cord: No diagnosis, inadequate section
Submandibular Lymph Node: Not examined, wrong tissue sectioned

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 74; Group: 3	Sex: Female
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Lactation Day 5
Days on Test: Through Lactation Day 4	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

None

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid	Kidney, left	Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	Uterus
Submandibular Lymph Node	Duodenum	Urinary Bladder
Lungs/Bronchus	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

Adrenals: One of pair present/normal

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 1; Group: 4

Sex: Female

Pathologist: LFF

Animal Fate: Scheduled sacrifice on Lactation Day
5

Days on Test: Through Lactation Day 4

Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Kidney, right: Hyaline casts/cortex/medulla – mild, focal
Kidney, left: Hyaline casts/cortex/medulla – moderate, focal; Mineralization – mild, multifocal, tubules; Basophilic tubules, cortex – mild, focal

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Illeum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve		Bone Marrow
Thyroid		Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	Uterus
Submandibular Lymph Node	Duodenum	Urinary Bladder
Lungs/Bronchus	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 48; Group: 4	Sex: Female
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Lactation Day 5
Days on Test: Through Lactation Day 4	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Kidney, left: Hyaline casts, cortex/medulla – minimal, focal
--

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid		Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	Uterus
Submandibular Lymph Node	Duodenum	Urinary Bladder
Lungs/Bronchus	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 55; Group: 2	Sex: Female
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Lactation Day 5
Days on Test: Through Lactation Day 4	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Lungs/Bronchus: Inflammation, chronic – minimal, multifocal

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid	Kidney, left	Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	Uterus
	Duodenum	Urinary Bladder
	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

Submandibular Lymph Node: Not examined, not found in wet tissue

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 56; Group: 2	Sex: Female
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Lactation Day 5
Days on Test: Through Lactation Day 4	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Kidney, right: Nephrosis – minimal, focal

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve		Bone Marrow
Thyroid	Kidney, left	Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	Uterus
Submandibular Lymph Node	Duodenum	Urinary Bladder
Lungs/Bronchus	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

Kidney, right: Birefringent crystals in one tubule
Adrenals: One of a pair present/normal

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 59; Group: 2	Sex: Female
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Lactation Day 5
Days on Test: Through Lactation Day 4	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

None

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid	Kidney, left	Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	Uterus
	Duodenum	Urinary Bladder
Lungs/Bronchus	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

Thoracic Spinal Cord: No diagnosis, inadequate section
Submandibular Lymph Node: Not examined, not found in wet tissue

TISSUE COMMENTS:

Ovaries: One of pair present/normal
Oviducts: One of pair present/normal

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 61; Group: 2

Sex: Female

Pathologist: LFF

Animal Fate: Scheduled sacrifice on Lactation Day
5

Days on Test: Through Lactation Day 4

Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Kidney, left: Hyaline casts, cortex/medulla – mild, multifocal

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
		Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	Uterus
Submandibular Lymph Node	Duodenum	Urinary Bladder
Lungs/Bronchus	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

Thoracic Spinal Cord: No diagnosis, inadequate section

Thyroid: Not examined, not found in wet tissue

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 63; Group: 2	Sex: Female
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Lactation Day 5
Days on Test: Through Lactation Day 4	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

None

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid	Kidney, left	Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	Uterus
Submandibular Lymph Node	Duodenum	Urinary Bladder
Lungs/Bronchus	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 64; Group: 2

Sex: Female

Pathologist: LFF

Animal Fate: Scheduled sacrifice on Lactation Day
5

Days on Test: Through Lactation Day 4

Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Lungs/Bronchus: Inflammation, chronic – mild, multifocal

Kidney, left: Basophilic tubules, cortex – minimal, focal

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid		Ovaries
Trachea	Adrenals	
Thymus	Stomach	Uterus
Submandibular Lymph Node	Duodenum	Urinary Bladder
	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

Oviducts: Oviduct missing

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

**PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test**

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 66; Group: 2	Sex: Female
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Lactation Day 5
Days on Test: Through Lactation Day 4	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

None

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid	Kidney, left	Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	Uterus
Submandibular Lymph Node	Duodenum	Urinary Bladder
Lungs/Bronchus	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 69; Group: 2	Sex: Female
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Lactation Day 5
Days on Test: Through Lactation Day 4	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

None

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid	Kidney, left	Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	Uterus
Submandibular Lymph Node	Duodenum	Urinary Bladder
Lungs/Bronchus	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 42; Group: 3	Sex: Female
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Lactation Day 5
Days on Test: Through Lactation Day 4	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

None

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid	Kidney, left	Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	Uterus
Submandibular Lymph Node	Duodenum	Urinary Bladder
Lungs/Bronchus	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 51; Group: 3

Sex: Female

Pathologist: LFF

Animal Fate: Scheduled sacrifice on Lactation Day
5

Days on Test: Through Lactation Day 4

Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Kidney, left: Hyaline casts, cortex/medulla – mild, focal

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid		Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	Uterus
Submandibular Lymph Node	Duodenum	Urinary Bladder
Lungs/Bronchus	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 57; Group: 3	Sex: Female
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Lactation Day 5
Days on Test: Through Lactation Day 4	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Lungs/Bronchus: Inflammation, chronic – minimal, multifocal
Kidney, left: Hyaline casts, cortex/medulla – mild, multifocal
Uterus: Dilatation, uterine horn – moderate, bilateral

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid		Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	
Submandibular Lymph Node	Duodenum	Urinary Bladder
	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 60; Group: 4

Sex: Female

Pathologist: LFF

Animal Fate: Scheduled sacrifice on Lactation Day
5

Days on Test: Through Lactation Day 4

Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Kidney, left: Mineralization – minimal, multifocal, tubules

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid		Ovaries
Trachea		Oviducts
Thymus	Stomach	Uterus
Submandibular Lymph Node	Duodenum	Urinary Bladder
Lungs/Bronchus	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

Adrenals: Not examined, not found in wet tissue

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 72; Group: 4	Sex: Female
Pathologist: LFF	Animal Fate: Scheduled sacrifice on Lactation Day 5
Days on Test: Through Lactation Day 4	Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

Lungs/Bronchus: Inflammation, chronic – mild, multifocal
--

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid	Kidney, left	Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	Uterus
Submandibular Lymph Node	Duodenum	Urinary Bladder
	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Table 1 – Individual Findings

Animal ID: 86; Group: 4

Sex: Female

Pathologist: LFF

Animal Fate: Scheduled sacrifice on Lactation Day
5

Days on Test: Through Lactation Day 4

Probable Cause of Death: Scheduled Sacrifice

MICROSCOPIC OBSERVATIONS:

None

TISSUES WITHIN NORMAL HISTOLOGICAL LIMITS:

Brain - Cerebrum	Heart	Ileum/Peyer's Patch
Brain - Cerebellum	Aorta	Cecum
Brain - Pons	Liver	Colon
Thoracic Spinal Cord	Spleen	Mesenteric Lymph Node
Peripheral Nerve	Kidney, right	Bone Marrow
Thyroid	Kidney, left	Ovaries
Trachea	Adrenals	Oviducts
Thymus	Stomach	Uterus
Submandibular Lymph Node	Duodenum	Urinary Bladder
Lungs/Bronchus	Jejunum	

TISSUES UNAVAILABLE FOR EVALUATION:

None

TISSUE COMMENTS:

None

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

TABLE 2 – Incidence of Microscopic Findings

Tissue/ Finding/ Severity	Males				Females			
	Grp 1	Grp 2	Grp 3	Grp 4	Grp 1	Grp 2	Grp 3	Grp 4
Adrenal	(5)	(5)	(5)	(5)	(10)	(10)	(5)	(4)
Within normal limits	5	5	5	5	10	10	5	4
Aorta	(5)	(5)	(5)	(5)	(9)	(10)	(5)	(5)
Within normal limits	5	5	5	5	9	10	5	5
Bone marrow	(5)	(5)	(5)	(5)	(10)	(9)	(5)	(5)
Within normal limits	5	5	5	5	10	9	5	5
Brain, Cerebrum	(5)	(5)	(5)	(5)	(10)	(10)	(5)	(5)
Within normal limits	5	5	5	5	10	10	5	5
Brain, Cerebellum	(5)	(5)	(5)	(5)	(10)	(10)	(5)	(5)
Within normal limits	5	5	5	5	10	10	5	5
Brain, Pons	(5)	(5)	(5)	(5)	(10)	(10)	(5)	(5)
Within normal limits	5	5	5	5	10	10	5	5
Cecum	(4)	(5)	(4)	(5)	(10)	(10)	(5)	(5)
Within normal limits	4	5	4	5	10	10	5	5
Colon	(4)	(5)	(4)	(5)	(10)	(10)	(5)	(5)
Within normal limits	4	5	4	5	10	10	5	5
Duodenum	(5)	(5)	(5)	(4)	(10)	(10)	(5)	(5)
Within normal limits	5	5	5	4	10	10	5	5
Epididymis	(3)	(5)	(5)	(5)	(0)	(0)	(0)	(0)
Within normal limits	3	5	5	5	-	-	-	-
Heart	(5)	(5)	(5)	(5)	(10)	(10)	(5)	(5)
Within normal limits	5	5	4	5	10	10	5	5
Inflammation, chronic mild	-	-	1	-	-	-	-	-
	-	-	1	-	-	-	-	-
Ileum/Peyer's Patch	(5)	(5)	(4)	(5)	(10)	(10)	(5)	(5)
Within normal limits	3	5	4	5	10	10	5	5
Autolysis	2	-	-	-	-	-	-	-
Minimal	-	-	-	-	-	-	-	-
Mild	1	-	-	-	-	-	-	-
Moderate	1	-	-	-	-	-	-	-

() – numbers in parentheses represent the total number of tissues examined

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

TABLE 2 – Incidence of Microscopic Findings

Tissue/ Finding/ Severity	Males				Females			
	Grp	Grp	Grp	Grp	Grp	Grp	Grp	Grp
	1	2	3	4	1	2	3	4
Jejunum	(3)	(5)	(5)	(5)	(10)	(10)	(5)	(5)
Within normal limits	3	5	5	5	10	10	5	5
Kidney, left	(5)	(5)	(5)	(5)	(10)	(10)	(5)	(5)
Within normal limits	1	0	3	3	5	7	2	2
Hyaline casts, cortex/medulla	4	1	-	2	2	1	3	2
minimal	-	-	-	2	1	-	1	1
mild	4	-	-	-	1	1	2	-
moderate	-	-	-	-	-	-	-	1
Nephrosis	-	4	-	-	-	-	-	-
moderate	-	4	-	-	-	-	-	-
Nephritis, interstitial, chronic	-	4	-	-	-	-	-	-
minimal	-	-	-	-	-	-	-	-
mild	-	2	-	-	-	-	-	-
moderate	-	2	-	-	-	-	-	-
Basophilic tubules, cortex	-	5	2	-	1	1	-	1
minimal	-	-	1	-	1	1	-	-
mild	-	3	-	-	-	-	-	1
moderate	-	2	-	-	-	-	-	-
Papillary necrosis	-	1	-	-	-	-	-	-
moderate	-	1	-	-	-	-	-	-
Mineralization	-	-	-	1	1	-	-	2
minimal	-	-	-	1	1	-	-	1
mild	-	-	-	-	-	-	-	1
Nephroblastoma	-	-	-	-	1	-	-	-
Hyaline casts, convoluted tubules	-	-	-	-	1	1	-	-
minimal	-	-	-	-	1	1	-	-

() – numbers in parentheses represent the total number of tissues examined

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

TABLE 2 – Incidence of Microscopic Findings

Tissue/ Finding/ Severity	Males				Females			
	Grp 1	Grp 2	Grp 3	Grp 4	Grp 1	Grp 2	Grp 3	Grp 4
Kidney, right	(5)	(5)	(5)	(5)	(10)	(10)	(5)	(5)
Within normal limits	3	0	3	5	7	9	5	4
Hyaline casts, cortex/medulla	2	1	2	-	1	-	-	1
minimal	-	-	1	-	1	-	-	-
mild	2	1	1	-	-	-	-	1
moderate	-	1	-	-	-	-	-	-
Nephrosis	-	5	-	-	-	1	-	-
minimal	-	-	-	-	-	1	-	-
moderate	-	5	-	-	-	-	-	-
Nephritis, interstitial, chronic	-	4	-	-	-	-	-	-
minimal	-	1	-	-	-	-	-	-
mild	-	1	-	-	-	-	-	-
moderate	-	2	-	-	-	-	-	-
Basophilic tubules, cortex	-	4	-	-	-	-	-	-
mild	-	1	-	-	-	-	-	-
moderate	-	3	-	-	-	-	-	-
Papillary necrosis	-	1	-	-	-	-	-	-
moderate	-	1	-	-	-	-	-	-
Mineralization	-	-	-	-	1	-	-	-
minimal	-	-	-	-	1	-	-	-
Liver	(5)	(5)	(5)	(5)	(10)	(10)	(5)	(5)
Within normal limits	5	5	5	5	9	9	5	5
Inflammation, chronic	-	-	-	-	1	1	-	-
minimal	-	-	-	-	1	1	-	-
Lungs/Bronchus	(5)	(5)	(5)	(5)	(9)	(10)	(5)	(5)
Within normal limits	5	5	4	5	5	7	3	4
Edema	-	-	1	-	-	-	-	-
moderate	-	-	1	-	-	-	-	-
Inflammation, chronic	-	-	-	-	3	3	2	1
minimal	-	-	-	-	2	2	2	-
mild	-	-	-	-	2	1	-	1
Lymph node, submandibular	(5)	(5)	(5)	(5)	(9)	(8)	(4)	(5)
Within normal limits	5	4	5	5	9	8	4	5
Lymphoid depletion	-	1	-	-	-	-	-	-
mild	-	1	-	-	-	-	-	-

() – numbers in parentheses represent the total number of tissues examined

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

Tissue/ Finding/ Severity	Males				Females			
	Grp 1	Grp 2	Grp 3	Grp 4	Grp 1	Grp 2	Grp 3	Grp 4
Lymph node, mesenteric	(4)	(5)	(4)	(5)	(8)	(10)	(5)	(5)
Within normal limits	4	5	4	5	8	10	5	5
Ovaries	(0)	(0)	(0)	(0)	(10)	(10)	(5)	(5)
Within normal limits	-	-	-	-	10	10	5	5
Oviducts	(0)	(0)	(0)	(0)	(9)	(9)	(5)	(5)
Within normal limits	-	-	-	-	9	9	5	5
Periperal Nerve	(5)	(5)	(5)	(5)	(10)	(10)	(5)	(5)
Within normal limits	5	5	5	5	10	10	5	5
Prostate	(5)	(5)	(5)	(3)	(0)	(0)	(0)	(0)
Within normal limits	5	5	5	3	-	-	-	-
Seminal vesicles	(5)	(5)	(5)	(5)	(0)	(0)	(0)	(0)
Within normal limits	5	5	5	5	-	-	-	-
Spinal cord, thoracic	(5)	(5)	(4)	(5)	(9)	(7)	(4)	(5)
Within normal limits	5	5	4	5	9	7	4	5
Spleen	(5)	(5)	(5)	(4)	(10)	(10)	(5)	(5)
Within normal limits	5	5	5	4	10	10	5	5
Stomach	(5)	(5)	(5)	(5)	(10)	(10)	(5)	(5)
Within normal limits	5	4	5	5	9	10	5	5
Ulcer	-	1	-	-	-	-	-	-
mild	-	1	-	-	-	-	-	-
Hyperplasia	-	-	-	-	1	-	-	-
mild	-	-	-	-	1	-	-	-
Testes	(5)	(5)	(5)	(5)	(0)	(0)	(0)	(0)
Within normal limits	5	5	5	5	-	-	-	-

() – numbers in parentheses represent the total number of tissues examined

Appendix I – Protocol and Amendment (cont.)

PATHOLOGY REPORT – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

STILLMEADOW, Inc. Study No.: 8419-04

TABLE 2 – Incidence of Microscopic Findings

Tissue/ Finding/ Severity	Males				Females			
	Grp	Grp	Grp	Grp	Grp	Grp	Grp	Grp
	1	2	3	4	1	2	3	4
Thymus	(5)	(5)	(5)	(5)	(9)	(10)	(5)	(5)
Within normal limits	5	3	5	5	9	10	5	5
Lymphoid depletion	-	2	-	-	-	-	-	-
mild	-	1	-	-	-	-	-	-
moderate	-	1	-	-	-	-	-	-
Thyroid	(5)	(5)	(5)	(5)	(9)	(9)	(5)	(5)
Within normal limits	5	5	5	5	9	9	5	5
Trachea	(5)	(5)	(5)	(5)	(9)	(10)	(5)	(5)
Within normal limits	5	5	5	5	9	10	5	5
Urinary bladder	(5)	(5)	(5)	(4)	(9)	(9)	(5)	(5)
Within normal limits	5	4	5	4	9	9	5	5
Dilatation	-	1	-	-	-	-	-	-
marked	-	1	-	-	-	-	-	-
Uterus	(0)	(0)	(0)	(0)	(10)	(10)	(5)	(5)
Within normal limits	-	-	-	-	10	10	3	5
Dilatation, uterine horn	-	-	-	-	-	-	2	-
moderate	-	-	-	-	-	-	2	-

() – numbers in parentheses represent the total number of tissues examined

Appendix I – Protocol and Amendment (cont.)

Stillmeadow, Inc. Study No. 8419-04

Stillmeadow Study No. 8419-04

Pathology Report – Combined Repeated Dose Toxicity Study with the
Reproduction/Developmental Toxicity Screening Test

Report Amendment No. 1

Amendment Date: December 14, 2005

1. Materials and Methods**Amend to:** by adding the following at the end of the section:

Tissue changes were graded as minimal – the smallest degree or amount that might be seen; or involving less than 1% of the tissue; mild – observed following brief search or involving 10-40% of the tissue; moderate – easily seen or involving 40-60% of the tissue; or marked – quite obvious change, involving a majority of the tissue or appearing to be as severe as possible.

Reason: To add clarity to the data description.**2. Study Design****Amend from:**

Group No.	Treatment level	Dose (mg/kg)	No. of Males	No. Females
1	Control	0	5	10
2	High dose	1,000	5	10
3	Low dose	250	5	5
4	Mid dose	100	5	5

Amend to:

Group No.	Treatment level	Dose (mg/kg)	No. of Males	No. Females
1	Control	0	5	10
2	High dose	1,000	5	10
3	Mid dose	250	5	5
4	Low dose	100	5	5

Reason: To correctly identify the low, mid, and high dose groups.**3. Microscopic Pathology – Terminal Sacrifice****Amend from:**

The primary lesion was nephrosis, characterized by the deposition of birefringent oxalate crystals within the renal tubules.

Amend to:

The primary lesion was nephrosis, characterized by the deposition of birefringent (brightly evident under polarized light) crystals that resembled oxalates within the renal tubules.”

Reason: To clarify the description of the microscopic findings.

Report Amendment No. 1, December 14, 2005

Appendix I – Protocol and Amendment (cont.)

Stillmeadow, Inc. Study No. 8419-04

4. Discussion**Amend from:**

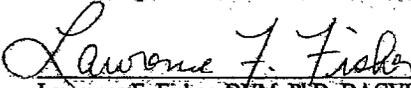
The finding of oxalate nephrosis suggests that the metabolism of the test article following oral administration is similar to that of ethylene glycol. The toxicity of ethylene glycol is primarily a result of its metabolic by-products and not the parent compound which is metabolized by cytosolic enzymes in the liver, the first step catalyzed by the enzyme alcohol dehydrogenase. The by-products include glycolic acid, glyoxylic acid, and oxalic acid, the latter depositing in the renal tubules as insoluble crystals. Since the protocol directed attention to effects upon spermatogenesis, it may have been suspected that the test article metabolites were similar to ethylene glycol monomethyl ether, which affects spermatocytes. In this study, no morphologic effect was observed in the seminiferous tubules.

Amend to:

In addition to toxic effects, this study was also intended to determine effects of the test article upon reproductive performance. However, no histopathologic changes were observed upon microscopic examination of the male or female reproductive organs.

Reason: To remove unnecessary and speculative comparison of the renal lesions to that of ethylene glycol. The test article does not contain ethylene glycol and it does not metabolize to ethylene glycol.

This report amendment No. 1 has been signed by:


Lawrence F. Fisher, DVM, PhD, DACVP
Evaluating Pathologist

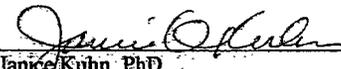
14 December 2005
Date

And reviewed by:


Dayle Lewandowski, Quality Assurance
Pathology Solutions Inc.

December 14, 2005
Date

And approved by:


Janice Kuhn, PhD
Study Director, Stillmeadow, Inc.

16 Dec 05
Date

Report Amendment No. 1, December 14, 2005

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Appendix J - Range Finder Body Weights and Dosing Information

Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test

Test Substance: Veova 10

Animal Number	Day 0 Body Weight	Dose (mL)	Day 7 Body Weight	Dose (mL)	Terminal Body Weight	Change
Group I - Control						
3-M	283	NA	303	NA	320	37
5-M	302	NA	323	NA	346	44
9-M	266	NA	286	NA	300	34
16-M	292	NA	311	NA	325	33
22-M	286	NA	298	NA	310	24
27-F	198	NA	210	NA	214	16
31-F	213	NA	227	NA	231	18
36-F	201	NA	212	NA	222	21
44-F	240	NA	233	NA	245	5
46-F	208	NA	222	NA	232	24
Mean	249		263		275	26
S.D.	41		45		50	12
Group II - 2000 mg/kg						
2-M	296	0.682	301	0.694	312	16
4-M	292	0.673	297	0.685	312	20
13-M	281	0.648	260	0.599	-	-21
14-M	285	0.657	275	0.634	218	-67
15-M	277	0.639	287	0.662	305	28
29-F	203	0.468	218	0.503	232	29
35-F	207	0.477	226	0.521	223	16
38-F	220	0.507	201	0.463	-	-19
42-F	198	0.456	203	0.468	215	17
49-F	215	0.496	218	0.503	238	23
Mean	247		249		257	4
S.D.	42		40		44	31
Group III - 1000 mg/kg						
6-M	295	0.340	310	0.357	326	31
7-M	284	0.327	300	0.346	321	37
17-M	270	0.311	280	0.323	295	25
23-M	292	0.337	302	0.348	307	15
24-M	302	0.348	315	0.363	330	28
28-F	191	0.220	216	0.249	225	34
30-F	215	0.248	220	0.254	232	17
33-F	203	0.234	212	0.244	207	4
34-F	208	0.240	213	0.246	226	18
45-F	218	0.251	219	0.252	234	16
Mean	248		259		270	23
S.D.	44		46		49	10

M - Male; F - Female; S.D. - Standard deviation; Change is terminal (or body weight at death) minus Day 0 body weight

Note: Animals 13-M and 38-F found dead on Day 9; all body weights are in grams

Appendix J - Range Finder Body Weights and Dosing Information (cont.)

Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test

Test Substance: Veova 10

Animal Number	Day 0	Dose (mL)	Day 7	Dose (mL)	Terminal	Change
Group IV - 250 mg/kg						
10-M	296	0.085	303	0.087	322	26
11-M	282	0.081	287	0.083	295	13
19-M	290	0.084	313	0.090	330	40
21-M	292	0.084	305	0.088	316	24
25-M	275	0.079	290	0.084	277	2
26-F	212	0.061	218	0.063	235	23
41-F	179	0.052	200	0.058	212	33
43-F	206	0.059	207	0.060	209	3
47-F	225	0.065	219	0.063	240	15
48-F	213	0.061	228	0.066	238	25
Mean	247		257		267	20
S.D.	44		46		46	12
Group V - 100 mg/kg						
1-M	294	0.034	308	0.036	328	34
8-M	290	0.033	300	0.035	315	25
12-M	284	0.033	302	0.035	319	35
18-M	277	0.032	294	0.034	320	43
20-M	304	0.035	322	0.037	348	44
32-F	210	0.024	216	0.025	224	14
37-F	237	0.027	243	0.028	247	10
39-F	199	0.023	204	0.024	210	11
40-F	186	0.021	208	0.024	212	26
50-F	217	0.025	225	0.026	232	15
Mean	250		262		276	26
S.D.	45		47		55	13

M - Male; F - Female; S.D. - Standard deviation; Change is terminal (or body weight at death) minus Day 0 body weight

Note: all body weights are in grams

Appendix K - Range Finder General Health Observations

Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test

Test Substance: Veova 10

Animal Number	Observations	Day of Study							
		0	1	2	3	4	5	6	7
Group I - Control									
3-M	NOA								
5-M	NOA								
9-M	NOA								
16-M	NOA								
22-M	NOA								
27-F	NOA								
31-F	NOA								
36-F	NOA								
44-F	NOA								
46-F	NOA								
Group II - 2000 mg/kg									
2-M	NOA								
4-M	NOA								
13-M	NOA								
14-M	NOA								
15-M	NOA								
29-F	NOA								
35-F	Activity decrease	-	m	m	-	-	-	-	-
	Piloerection	-	p	p	-	-	-	-	-
38-F	NOA								
42-F	NOA								
49-F	NOA								
Group III - 1000 mg/kg									
6-M	NOA								
7-M	NOA								
17-M	NOA								
23-M	NOA								
24-M	NOA								
28-F	NOA								
30-F	NOA								
33-F	NOA								
34-F	NOA								
45-F	NOA								

M - Male; F - Female; m - moderate; p - present; - = not present; NOA - no observable abnormalities

Appendix K - Range Finder General Health Observations (cont.)

Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test
Test Substance: Veova 10

Animal Number	Observations	Day of Study							
		0	1	2	3	4	5	6	7
Group IV - 250 mg/kg									
10-M	NOA								
11-M	NOA								
19-M	NOA								
21-M	NOA								
25-M	NOA								
26-F	NOA								
41-F	NOA								
43-F	NOA								
47-F	NOA								
48-F	NOA								
Group V - 100 mg/kg									
1-M	NOA								
8-M	NOA								
12-M	NOA								
18-M	NOA								
20-M	NOA								
32-F	NOA								
37-F	NOA								
39-F	NOA								
40-F	NOA								
50-F	NOA								

M - Male; F - Female; NOA - no observable abnormalities

Appendix K - Range Finder General Health Observations (cont.)

Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test
 Test Substance: Veova 10

Animal Number	Observations	Day of Study						
		8	9	10	11	12	13	14
Group I - Control								
3-M	NOA							
5-M	NOA							
9-M	NOA							
16-M	NOA							
22-M	NOA							
27-F	NOA							
31-F	NOA							
36-F	NOA							
44-F	NOA							
46-F	NOA							
Group II - 2000 mg/kg								
2-M	NOA							
4-M	NOA							
13-M	Death	-	D					
14-M	Death	-	-	-	-	-	-	D
15-M	NOA							
29-F	NOA							
35-F	Activity decrease	m	-	-	-	-	-	-
	Piloerection	p	-	-	-	-	-	-
38-F	Activity decrease	-	m					
	Labored breathing	-	m					
	Death	-	D*					
42-F	NOA							
49-F	NOA							
Group III - 1000 mg/kg								
6-M	NOA							
7-M	NOA							
17-M	NOA							
23-M	NOA							
24-M	NOA							
28-F	Diarrhea	-	-	-	p	p	p	p
30-F	NOA							
33-F	NOA							
34-F	NOA							
45-F	NOA							

M - Male; F - Female; m - moderate; p - observation present; - = observation not present; NOA - no observable abnormalities
 D - Death; D* - found dead after observation time

Appendix K - Range Finder General Health Observations (cont.)

Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test

Test Substance: Veova 10

Animal Number	Observations	Day of Study						
		8	9	10	11	12	13	14
Group IV - 250 mg/kg								
10-M	NOA							
11-M	NOA							
19-M	NOA							
21-M	NOA							
25-M	NOA							
26-F	NOA							
41-F	NOA							
43-F	NOA							
47-F	NOA							
48-F	NOA							
Group V - 100 mg/kg								
1-M	NOA							
8-M	NOA							
12-M	NOA							
18-M	NOA							
20-M	NOA							
32-F	NOA							
37-F	NOA							
39-F	NOA							
40-F	NOA							
50-F	NOA							

M - Male; F - Female; NOA - no observable abnormalities

Appendix L - Range Finder Food Consumption

Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test

Test Substance: Veova 10

Animal Number	1	2	3	4	5	6	7
Group I - Control							
3-M	23.9	24.4	25.8	25.0	22.2	24.9	23.2
5-M	7.8	30.2	33.0	30.1	30.9	29.4	27.3
9-M	4.1	28.6	22.7	27.0	29.6	48.3	25.7
16-M	17.4	26.8	26.2	24.5	25.8	39.8	22.6
22-M	20.1	30.5	23.7	27.1	29.6	26.3	30.0
27-F	26.9	25.0	20.0	23.2	25.5	23.6	20.8
31-F	21.4	19.1	21.9	25.9	27.3	28.0	23.0
36-F	21.3	23.0	20.4	21.7	19.6	34.6	21.0
44-F	17.0	17.7	25.3	19.0	23.2	9.5	19.5
46-F	16.8	21.0	23.5	22.6	21.2	26.1	22.0
Mean	17.7	24.6	24.3	24.6	25.5	29.1	23.5
S.D.	7.0	4.5	3.7	3.2	3.9	10.3	3.2
Group II - 2000 mg/kg							
2-M	17.7	19.9	27.1	14.4	22.7	24.8	28.2
4-M	16.8	17.2	7.7	13.9	24.4	28.4	27.8
13-M	23.7	13.5	23.4	25.1	19.5	28.3	16.5
14-M	23.2	11.7	13.0	23.5	24.3	33.8	27.8
15-M	12.8	21.5	11.3	31.3	25.9	29.7	26.0
29-F	31.0	20.5	16.6	11.4	21.0	20.4	20.3
35-F	4.9	19.8	25.4	42.3	24.3	19.6	23.6
38-F	20.6	17.9	29.4	†	16.2	38.1	15.6
42-F	27.0	21.2	17.6	24.6	18.5	20.7	22.1
49-F	83.6	25.3	16.4	25.8	24.1	13.0	22.5
Mean	26.1	18.9	18.8	23.6	22.1	25.7	23.0
S.D.	21.5	4.0	7.2	9.6	3.2	7.5	4.6
Group III - 1000 mg/kg							
6-M	11.3	21.2	23.9	24.8	24.7	41.6	14.5
7-M	18.1	20.6	25.7	27.4	30.4	27.6	†
17-M	23.5	14.9	19.3	24.1	31.9	23.9	60.4
23-M	17.9	11.6	26.5	24.2	21.1	16.3	39.4
24-M	22.8	26.5	27.3	24.7	29.6	4.2	60.6
28-F	26.2	21.6	19.9	22.0	21.1	35.4	6.1
30-F	22.0	8.4	20.1	25.2	26.1	27.0	5.1
33-F	24.9	18.6	20.7	27.2	16.7	25.4	4.1
34-F	24.6	19.6	22.7	20.4	22.0	22.6	†
45-F	22.7	19.8	23.0	24.7	25.3	20.9	2.5
Mean	21.4	18.3	22.9	24.5	24.9	24.5	24.1
S.D.	4.5	5.3	2.9	2.1	4.8	10.1	25.4

M - Male; F - Female; S.D. - Standard deviation; † - No value obtained; All food consumption weights are in grams

Appendix L - Range Finder Food Consumption (cont.)

Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test

Test Substance: Veova 10

Animal Number	1	2	3	4	5	6	7
Group IV - 250 mg/kg							
10-M	18.3	0.0	29.0	28.5	27.5	30.7	27.5
11-M	22.3	0.0	12.0	25.9	28.4	0.0	57.4
19-M	21.1	23.0	25.0	23.3	30.6	0.0	19.0
21-M	34.9	18.0	19.0	25.1	29.4	0.0	38.6
25-M	21.7	19.0	27.0	19.0	29.6	0.0	13.5
26-F	21.1	0.0	31.5	15.3	25.5	0.0	45.7
41-F	26.0	0.0	23.0	22.6	16.2	30.5	20.7
43-F	19.4	7.0	25.0	22.1	22.4	51.5	16.5
47-F	24.0	14.0	29.0	20.7	27.9	5.8	24.4
48-F	15.1	25.0	24.0	22.9	26.8	29.2	19.6
Mean	22.4	10.6	24.5	22.5	26.4	14.8	28.3
S.D.	5.3	10.3	5.6	3.7	4.3	18.9	14.3
Group V - 100 mg/kg							
1-M	18.3	18.0	13.0	8.8	22.9	24.7	25.5
8-M	19.5	25.0	12.0	6.9	27.3	3.1	65.9
12-M	21.7	44.3	25.0	0.9	26.0	15.5	12.1
18-M	27.2	33.0	5.0	18.6	29.2	9.8	27.5
20-M	29.7	25.0	2.3	24.1	29.2	17.7	34.5
32-F	17.6	35.4	25.0	†	18.0	22.3	22.7
37-F	26.9	25.0	18.0	6.7	26.6	26.2	23.1
39-F	23.6	24.0	28.0	20.0	19.3	6.2	22.0
40-F	19.8	25.0	15.0	6.4	22.3	15.1	18.1
50-F	27.4	19.0	17.0	4.0	22.3	29.8	22.2
Mean	23.2	27.4	16.0	10.7	24.3	17.0	27.4
S.D.	4.4	8.0	8.5	8.1	3.9	8.8	14.7

M - Male; F - Female; S.D. - Standard deviation; † - No value obtained; All food consumption weights are in grams

Appendix L - Range Finder Food Consumption (cont.)

Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test

Test Substance: Veova 10

Animal Number	8	9	10	11	12	13	14
Group I - Control							
3-M	25.9	28.7	26.4	25.7	28.2	27.1	27.4
5-M	26.3	26.1	30.3	22.4	30.3	30.2	29.7
9-M	27.6	21.7	30.1	25.2	31.2	28.9	28.2
16-M	29.0	22.3	26.5	26.7	26.9	28.5	24.9
22-M	28.3	27.9	30.0	28.3	27.9	28.0	29.1
27-F	23.7	19.5	20.9	21.7	24.5	24.4	21.3
31-F	23.9	20.1	23.1	24.8	24.4	23.0	19.4
36-F	23.8	21.7	18.0	23.8	23.9	25.0	21.2
44-F	22.5	21.7	21.9	23.2	23.9	23.7	24.5
46-F	25.5	24.2	23.2	25.5	28.1	23.4	18.5
Mean	25.7	23.4	25.0	24.7	26.9	26.2	24.4
S.D.	2.2	3.2	4.3	2.0	2.7	2.6	4.1
Group II - 2000 mg/kg							
2-M	24.5	25.0	28.2	28.8	20.8	34.7	28.7
4-M	25.9	24.2	30.9	26.5	28.4	30.7	29.0
13-M *	1.9	1.9					
14-M **	20.1	11.5	5.6	9.7	6.1	0.8	
15-M	26.5	24.3	24.9	25.4	28.4	31.5	27.9
29-F	21.5	18.8	23.1	18.3	18.1	23.0	22.9
35-F	23.9	19.2	25.4	14.2	24.2	23.3	††
38-F *	6.7	0.9					
42-F	29.4	21.3	23.7	19.8	23.9	29.1	22.0
49-F	27.3	23.2	27.5	20.8	25.2	31.2	††
Mean	20.8	17.0	23.7	20.4	21.9	25.5	26.1
S.D.	9.2	9.1	7.7	6.4	7.3	10.8	3.4
Group III - 1000 mg/kg							
6-M	34.2	25.2	25.2	24.0	31.4	28.3	31.8
7-M	28.8	28.4	26.2	26.7	33.7	31.1	28.4
17-M	31.3	22.4	28.6	25.2	31.4	37.4	30.8
23-M	29.5	22.7	22.3	22.2	34.7	25.9	28.3
24-M	30.8	26.6	28.8	25.4	31.2	31.3	30.0
28-F	25.8	23.2	23.4	19.3	20.6	22.4	23.3
30-F	16.8	21.8	20.3	22.0	23.1	22.1	23.3
33-F	22.9	17.0	21.7	11.0	22.0	18.3	19.6
34-F	21.1	19.0	20.5	19.3	18.9	19.5	25.6
45-F	25.5	23.1	25.2	17.9	24.3	27.3	26.4
Mean	26.7	22.9	24.2	21.3	27.1	26.4	26.8
S.D.	5.3	3.3	3.1	4.7	5.9	6.0	3.9

M - Male; F - Female; S.D. - Standard deviation; †† - Not recorded; All food consumption weights are in grams

* Animal died on Day 9; ** Animal died on Day 14

Appendix L - Range Finder Food Consumption (cont.)

Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test

Test Substance: Veova 10

Animal Number	8	9	10	11	12	13	14
Group IV - 250 mg/kg							
10-M	27.9	28.9	27.4	26.6	29.1	28.6	28.4
11-M	30.1	24.3	23.7	26.1	24.5	28.6	27.1
19-M	28.8	28.0	28.6	29.1	30.1	33.0	27.3
21-M	30.2	26.2	25.4	25.8	24.6	28.5	30.4
25-M	31.2	14.0	0.1	6.7	8.1	23.5	31.8
26-F	23.9	22.8	24.9	21.1	24.5	23.9	28.1
41-F	27.4	19.5	16.1	21.0	18.3	26.3	25.4
43-F	25.7	15.6	20.5	19.3	21.3	20.4	15.8
47-F	24.0	21.1	22.6	21.8	25.1	26.2	26.5
48-F	26.1	22.3	21.0	24.7	25.7	25.9	21.6
Mean	27.5	22.3	21.0	22.2	23.1	26.5	26.2
S.D.	2.6	4.9	8.2	6.3	6.3	3.5	4.6
Group V - 100 mg/kg							
1-M	27.0	25.6	24.5	23.7	26.3	33.3	21.6
8-M	29.6	27.4	28.5	24.4	26.2	30.1	31.6
12-M	27.0	24.5	24.8	24.6	28.6	26.8	27.8
18-M	29.2	26.2	24.8	25.2	30.9	28.5	31.7
20-M	31.0	27.4	30.1	27.0	30.8	35.6	31.7
32-F	21.2	17.8	17.0	19.5	23.9	23.1	23.1
37-F	18.9	24.9	19.7	19.7	16.1	23.2	24.4
39-F	21.7	21.2	19.8	17.6	22.2	24.2	20.2
40-F	19.1	18.4	17.6	20.0	17.8	21.1	22.4
50-F	20.5	23.3	24.3	19.2	23.1	18.3	26.2
Mean	24.5	23.7	23.1	22.1	24.6	26.4	26.1
S.D.	4.7	3.5	4.4	3.2	5.0	5.5	4.4

M - Male; F - Female; S.D. - Standard deviation; all food consumption weights are in grams

Appendix M - Range Finder Necropsy findings

Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test
 Test Substance: Veova 10

Animal Number	Findings	
	External	Internal
Group II - 2000 mg/kg		
13-M	Animal found dead Day 9 almost immediately after dosing. Urogenital area stained yellow; fur on chin wet; red discharge around muzzle; opacity on left eye	Lungs mottled, patches of black tissue noted, lungs full of liquid; liver darkened. Suspect dosing error
14-M	Found dead on Day 14. No external findings recorded	Lungs mottled; stomach, small and large intestines filled with gas
38-F	Found dead on Day 9 approximately 30 minutes following dosing. Opacity on right eye; chin wet; urogenital area stained yellow; dark feces matted around anus	Lungs mottled red, small lobe on right side very dark, fluid in lungs; stomach filled with gas. Suspect dosing error

Appendix N – Protocol and Amendment

STILLMEADOW
INCORPORATED

AMENDMENT #1 FOR PROTOCOL NUMBER 8419-04

Study Title: COMBINED REPEATED DOSE TOXICITY STUDY WITH THE REPRODUCTION / DEVELOPMENTAL TOXICITY SCREENING TEST

Test Substance: Veova 10

Study Number: STILLMEADOW, Inc. 8419-04

Sponsor: Resolution Performance Products
3333 Highway 6 South
Houston, TX 77082-3101

Effective Date: 17 June 2005

The following alteration is being made to the above protocol.

To change:

Sponsor: Resolution Performance Products
3333 Highway 6 South
Houston, TX 77082-3101

Sponsor Contact: Kenneth Washburn, Ph. D., DABT

To read:

Sponsor: Hexion Specialty Chemicals, Inc.
3333 Highway 6 South
Houston, TX 77082-3101

Sponsor Contact: Sattar Alcasey, Ph.D., DABT

Justification for change: Resolution Performance Products has merged to become Hexion Specialty Chemicals, Inc. and Sattar Alcasey has been given responsibility for this study.

Study impact: None

This amendment has been reviewed or approved by the following:

Approved: Janice O. Kuhn 22 Jun 05
Janice O. Kuhn, Ph.D., DABT
Study Director
STILLMEADOW, Inc. Date

Reviewed: B. Lynn Murphy 20 Jun 05
B. Lynn Murphy, B.S., RQAP
Director, Quality Assurance
STILLMEADOW, Inc. Date

Approved: Mark S. Holbert 20 Jun 05
Mark S. Holbert
Vice President
STILLMEADOW, Inc. Date

Approved: Sattar Alcasey June 22 / 2005
Sattar Alcasey, Ph.D., DABT
Product Safety Specialist
Hexion Specialty Chemicals, Inc. Date

Appendix N – Protocol and Amendment (cont.)

STILLMEADOW

INCORPORATED

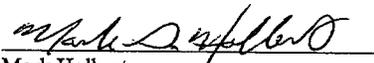
PROTOCOL 8419-04

Study Title: COMBINED REPEATED DOSE TOXICITY STUDY WITH THE
REPRODUCTION / DEVELOPMENTAL TOXICITY SCREENING TEST

Test Substance: Veova 10

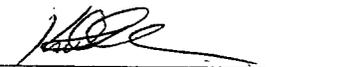
Study Identification: STILLMEADOW, Inc.
12852 Park One Drive
Sugar Land, Texas 77478

Approved:  01 Dec 04
Date
Janice O. Kuhn, Ph.D., DABT
Study Director
STILLMEADOW, Inc.

Approved:  08 Nov 04
Date
Mark Holbert
Vice President
STILLMEADOW, Inc.

Reviewed:  08 Nov 04
Date
B. Lynn Murphy, B.S., RQAP
Director, Quality Assurance Unit
STILLMEADOW, Inc.

Sponsor: Resolution Performance Products
3333 Highway 6 South
Houston, TX 77082-3101

Approved:  01 DEC 04
Date
Kenneth Washburn, Ph. D., DABT

Appendix N – Protocol and Amendment (cont.)

Study Number 8419-04
Page 2 of 12

PROTOCOL FOR STUDY 8419-04

A. GENERAL

1. Study Title: COMBINED REPEATED DOSE TOXICITY STUDY WITH THE REPRODUCTION / DEVELOPMENTAL TOXICITY SCREENING TEST
2. Purpose: To evaluate the potential toxic effects of the test substance when administered to rats for 28 days and to determine the potential of the test substance to affect male and female reproductive performance such as gonadal function, mating behavior, conception, parturition and early postnatal development
3. Regulatory Compliance:

This study will be conducted according to OECD Guideline for Testing of Chemicals: Guideline 422, Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test, 22 March 1996.

This study will be conducted in compliance with OECD: C(98)17 Good Laboratory Practice Standards.

All procedures in this protocol are in compliance with Animal Welfare Act Regulations. All methods can be found in STILLMEADOW, Inc. Standard Operating Procedures (SOPs).
4. Quality Assurance: The Quality Assurance Unit (QAU) will review the protocol. The study information will be entered into the Master Schedule. The study will be inspected at least once during its progress. Further inspections may be scheduled as needed to ensure the integrity of the study. Any deviations from SOPs, the Protocol, or Good Laboratory Practice Standards will be immediately reported to the Study Director and Management. The report will be audited and a statement prepared and signed which shall specify the dates inspections were made and findings reported to Management and to the Study Director.
5. Test Substance: Veova 10 (CAS # 51000-52-3). Test article identification should include the name, batch number and purity. The Sponsor should also provide information regarding safety, stability, storage conditions and disposal. The Sponsor assumes responsibility for purity, stability, identity, synthesis methods and location of documentation
6. Proposed Schedule:

Range finder:
Proposed Start Date: 30 Nov 04
Proposed End Date: 14 Dec 04

Definitive:
Proposed Start Date: 04 Jan 05
Proposed End Date: At least 54 days after start date

Study Duration: At least 54 days.

Appendix N – Protocol and Amendment (cont.)

Study Number 8419-04
Page 3 of 12A. GENERAL (cont.)7. Study Director:

Janice O. Kuhn, Ph.D., DABT

8. Experimental Summary:

Eighty rats will be equally divided into four groups with ten males and ten females per group. The test material will be mixed with the vehicle and samples will be collected for homogeneity and stability analysis. Group I animals will receive the vehicle only and will serve as a vehicle control group. The animals of Groups II – IV will receive the test substance orally by gavage daily for 14 days at dose rates to be determined by a range finder. Concentrations used on the range finding study will be 2000, 1000, 250 and 100 mg/kg. On Day 14, each male from each group will be put with a female from the same group for mating for a period of 14 days maximum. After confirmation of mating, the animals will be returned to their individual cages, and all animals will continue to be treated at least through Day 28. After Day 28, the males will be sacrificed and necropsied. A complete necropsy with organ weight determination will be conducted and selected tissues will be saved in 10% neutral buffered formalin or other appropriate fixative. Blood will be collected for determination of certain hematology and serum chemistry parameters. The pregnant females will be dosed daily through the gestation period and through Day 4 of the lactation period. At that time, they will be sacrificed and necropsied in the same manner as the males. At birth, the litters will be examined and findings observed, and the pups will be sacrificed at the same time as their dams. Observations for mortality will be made twice daily. Observations for signs of pharmacologic and/or toxicologic effects will be made once daily. Body weights will be recorded weekly throughout the study. Food consumption will be monitored weekly throughout the study except for the mating period. A functional observation battery will be conducted on the animals before sacrifice.

9. Protocol Amendments:

Any change or alteration in the protocol will be justified, approved by the Study Director, and recorded in writing. The Sponsor will sign all protocol amendments.

10. Sponsor Audits:

The Sponsor may send an authorized representative to inspect the test system and/or data on the STILLMEADOW, Inc. premises during normal working hours.

Appendix N – Protocol and Amendment (cont.)

Study Number 8419-04
Page 4 of 12B. EXPERIMENTAL DESIGN1. Animals

- a. Species/Strain/Source: Albino rat; Sprague-Dawley; Harlan, Indianapolis, IN (or other suitable supplier)
- b. Justification of Species: The rat is conventionally used to provide an index of toxicity on which human hazard can be judged, and is the species preferred by the regulatory agencies.
- c. Quantity and Sex: Forty males and forty females (nulliparous and non-pregnant)
- d. Age/Weight: Young adult (approximately 8 weeks); males, approximately 225 - 330 g; females, approximately 175 - 250 g. Weight variation should not exceed $\pm 20\%$ of the mean for each sex.
- e. Identification: Ear punch and cage cards
- f. Acclimation and Health Status: Animals will be acclimated for at least 7 days prior to testing. Normal weight gain, appearance and behavior will be factors used to select healthy animals for testing. Only naive animals will be selected.
- g. Randomization: Animals will be selected for testing by Day 0 and will be randomly assigned to four groups, Groups I, II, III or IV, with ten males and ten females in each group. A weight-stratified randomization procedure will be employed.

2. Animal Husbandry

- a. Cages: Stainless steel, suspended, wire bottom
- b. Number per Cage: Animals will be housed individually during the study except for the mating period.
- c. Food: PMI Feeds, Inc.TM Formulab #5008, or equivalent; available *ad libitum*. Analyzed by manufacturer for nutritional content.
- d. Water: Tap water; available *ad libitum* (automatic system). Municipal water supply analyzed by Texas Commission on Environmental Quality (TCEQ) Water Utilities Division.
- e. Contaminants: There are no known contaminants in the feed or water available to laboratory animals that would be expected to interfere with the study.
- f. Environment: Target temperature: approximately $22^{\circ}\text{C} \pm 3^{\circ}$
Target relative humidity: approximately 30 - 70%
12-hour light/dark cycle (regulated automatically)
Room ventilation: approximately 10 - 12 air changes per hour

Appendix N – Protocol and Amendment (cont.)

Study Number 8419-04
Page 5 of 12B. EXPERIMENTAL DESIGN (cont.)3. Pretest

a. Range Finder:

A range finder will be conducted using five males and five females per dose level (untreated control, 2000 mg/kg, 1000 mg/kg, 250 mg/kg and 100 mg/kg). The animals will be selected by a weight-stratified randomization procedure. They will be dosed five days/week for two weeks. The animals will be observed daily and food consumption measured daily through study termination (Day 14). Body weights will be recorded before dosing on Day 0, and on Days 7 and 14. A gross necropsy will be performed on each animal on Day 14.

The definitive dose levels will be selected from the data collected from the range finder. The levels selected will take into account any existing toxicity and (toxico-) kinetic data available for the test substance or related materials. It will also be taken into account that there may be differences in sensitivity between pregnant and non-pregnant animals. The highest dose level will be chosen with the aim of inducing toxic effects but not death or obvious suffering. Thereafter, a descending sequence of dose levels will be selected with a view to demonstrating any dosage related response and no adverse effects at the lowest level. Two- to four-fold intervals are frequently optimum and addition of a fourth test group may be preferable to using very large intervals (e.g. more than a factor of 10) between dosages.

b. Acclimation, General Health Observations and Body Weights:

Animals will be acclimated for a period of at least 7 days. Body weights will be recorded on Day -7 and on Day -1. General health observations will be recorded daily.

c. Food Consumption:

Pretest food consumption (Day -7 through Day -1) will be recorded.

d. Detailed Physical Examination:

Detailed clinical observations will be made once before dosing. They will be made outside the home cage. Signs noted should include, but are not limited to, changes in skin, fur, eyes, mucous membranes, occurrence of secretions and excretions and autonomic activity (e.g. lacrimation, piloerection, pupil size, unusual respiratory pattern). Changes in gait, posture and response to handling as well as the presence of clonic or tonic movements, stereotypies (e.g. excessive grooming, repetitive circling) difficult or prolonged parturition or bizarre behavior (e.g. self-mutilation, walking backwards) should also be recorded.

Appendix N – Protocol and Amendment (cont.)

Study Number 8419-04
Page 6 of 12B. EXPERIMENTAL DESIGN (cont.)3. Pretest (cont.)

- e. Health Status: Normal weight gain, appearance / behavior, detailed clinical observations results and food consumption values will be factors used to select healthy animals for testing. Only naive animals will be selected.
- f. Randomization: Animals will be selected for testing by Day 0 and will be randomly assigned to one of four groups, Groups I, II, III or IV, with ten males and ten females in each group. A weight-stratified randomization procedure will be employed.
- g. Test Substance Analysis and Preparation: Analysis of the test substance to demonstrate stability over the testing period will be conducted before test substance preparation and at study termination. The dosing formulations for the first week of dosing will be prepared on Day -1 or Day 0. Homogeneity will be checked in each dosing concentration to validate the mixing procedure. Six samples will be collected from top, middle or bottom locations in the mixing container and analyzed for test substance content. If samples are homogeneous, further testing will not be conducted for batches prepared weekly. Dose concentrations will be verified.

4. Test Substance Administration

- a. Method: The animals will be dosed by gavage with an appropriately sized stainless steel ball-tipped dosing needle and syringe.
- b. Justification of Method of Treatment: Gavage dosing assures the proper dose presentation.

Appendix N – Protocol and Amendment (cont.)

Study Number 8419-04
Page 7 of 12B. EXPERIMENTAL DESIGN (cont.)4. Test Substance Administration (cont.)c. Test substance
Preparation and
Administration:

The dosing formulations will be prepared weekly with the vehicle.

Dose concentrations of each formulation will be verified. One sample will be taken from the center of each dosing formulation prepared weekly during the in-life phase of the study.

Three groups of ten males and ten females will be dosed daily at doses selected based on data from the range finding portion of the study. A concurrent vehicle control group (Group I, ten males and ten females) will be included in the study and will not receive the test substance. Groups will be dosed daily at approximately the same time each day and dose amounts will be adjusted weekly based on the latest body weight.

Males and females will be dosed for 14 days prior to mating. Males will be dosed for another 14 days during mating, for a minimum of 28 days. Females will be dosed through mating, and until one day prior to termination (lactation Day 4 for those that deliver, and post-mating Day 25 or post-cohabitation Day 25 for those that do not deliver).

5. Observations

a. Clinical Signs:

General clinical observations will be made once daily. Observations will include but not necessarily be limited to evaluation of skin, fur, eyes and mucous membranes, respiratory and circulatory effects, autonomic effects (salivation, lacrimation, excessive urination and diarrhea), central nervous system effects (tremors and convulsions), changes in the level of activity, gait and posture, reactivity to handling or sensory stimuli, altered strength and stereotypies or bizarre behavior (e.g., self mutilation, walking backwards). The nature, onset, severity, and duration of all gross or visible pharmacologic and/or toxicologic effects will be recorded.

b. Mortality Checks:

Animals will be observed twice daily for morbidity and mortality. Moribund animals will be euthanized to minimize suffering and to ensure that tissues will not be lost due to autolysis. These animals will be considered as dying on study.

Appendix N – Protocol and Amendment (cont.)

Study Number 8419-04
Page 8 of 12B. EXPERIMENTAL DESIGN (cont.)5. Observations (cont.)c. Detailed Physical
Examination:

Detailed clinical observations will be made weekly in the same manner as pretest.

6. Body Weights:

Body weights will be recorded on Day 7 and weekly thereafter through sacrifice for males. Body weights for females will be recorded on Days 7 and 14, on gestation Days 0, 4, 7, 11, 14, 17 and 20, and on lactation Days 1 and 4. Body weights for the pups will be recorded on lactation Days 1 and 4. Body weights will also be recorded at the time of discovery after death for animals that die on study.

7. Food Consumption:

Food consumption will be recorded weekly through the termination of the study with the exception of the cohabitation period.

8. Mating Procedures:

After fourteen days of treatment, each female will be cohabited with one male from the same group for a period of two weeks or until pregnancy occurs. Each morning, the female will be examined for the presence of sperm or a vaginal plug. Day 0 of pregnancy will be the day the plug or sperm is found. A maximum of fourteen days will be allowed for mating. After this confirmation of mating, the males will be returned to their home cages, and females will be put in plastic cages and nesting materials will be added.

9. Parturition and Litter Observations:

The day parturition is complete will be lactation Day 0. Any difficulties during birth will be recorded if birth is observed. When birth is completed, the litters will be sexed, examined for gross malformations, and the number of stillbirths and live pups will be recorded. The pups will be individually marked for identification. Any changes or abnormalities in nesting or nursing behavior will be recorded. Body weights for the pups will be recorded on lactation Days 1 and 4, and they will be re-sexed at that time. Pups will be observed daily for general appearance, behavior and survival. A detailed physical examination will be recorded for each pup on lactation Days 1 and 4.

10. Functional Observational Battery:

An assessment of motor activity, grip strength, and sensory reactivity to stimuli of different types (e.g., visual, auditory, and proprioceptive stimuli) will be conducted. Males (5/group) will be evaluated following 28 days of dosing, just prior to sacrifice. Females (5/group) will be evaluated on lactation Day 4, just prior to sacrifice.

Appendix N – Protocol and Amendment (cont.)

Study Number 8419-04
Page 9 of 12B. EXPERIMENTAL DESIGN (cont.)11. Termination of Study

- a. Euthanasia: Animals will be sacrificed by an overdose of CO₂. Males will be sacrificed after the mating period, approximately Day 28. Females with litters and their litters will be euthanized on their lactation Day 4, and females that didn't deliver will be euthanized on approximately Day 53. Females with total litter loss will be sacrificed within 24 hours of litter loss.
- b. Blood Collection: Blood will be drawn from the vena cava at necropsy. Prothrombin time and activated partial thromboplastin time will be analyzed at STILLMEADOW, Inc. The following parameters will be analyzed at Antech Diagnostics (507 Airport Boulevard, Suite 113, Morrisville, NC 27560):
- Hematology: erythrocyte count, hemoglobin, hematocrit, total and differential leukocyte counts, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and mean corpuscular volume.
- Serum Chemistry: blood urea nitrogen, creatinine, serum alanine aminotransferase, serum aspartate aminotransferase, total bilirubin, total protein, total cholesterol, globulin, albumin, A/G ratio, glucose, inorganic phosphorus, calcium, sodium, potassium, and chloride.
- Antech Diagnostics is a GLP-compliant analytical laboratory.
- c. Gross Necropsy: A gross necropsy examination will be conducted on each adult animal at the time of discovery after death or at time of sacrifice. Moribund animals will be sacrificed to lessen the likelihood of unobserved death and subsequent autolysis. The gross necropsy shall include the following:
1. Terminal body weight.
 2. Gross observations of external surfaces, all orifices; cranial, thoracic, abdominal, and pelvic cavities and their contents. Special attention will be paid to the organs of the reproductive system. The number of implantation sites and corpora lutea will be recorded.
 3. The testes and epididymides of all sacrificed males and ovaries with oviducts of the sacrificed females will be carefully removed, trimmed, and weighed. Ovaries with oviducts, testes, epididymides and accessory sex organs and all organs showing macroscopic lesions will be preserved. Tissues will be weighed as soon as possible to avoid dehydration of the tissues.

Appendix N – Protocol and Amendment (cont.)

Study Number 8419-04
Page 10 of 12B. EXPERIMENTAL DESIGN (cont.)11. Termination of Study (cont.)

c. Gross Necropsy (cont.):

4. For five adult males and females randomly selected from each group, the liver, kidneys, adrenals, thymus, spleen, brain and heart will be carefully removed, trimmed, and weighed. Tissues will be weighed as soon as possible to avoid dehydration of the tissues.
5. The following tissues will also be preserved in the most appropriate fixation medium: all gross lesions or tissues showing abnormalities, brain (cerebrum, cerebellum and pons), spinal cord, stomach, small and large intestine (duodenum, jejunum, ileum, caecum and colon including Peyer's patches), liver (sections of 2 lobes), kidneys, adrenals, spleen, heart and aorta, thymus, thyroid, trachea and lungs (including bronchi, preserved by inflation with fixative and then immersion), ovaries with oviducts, uterus, urinary bladder, lymph nodes (mesenteric and submandibular), peripheral nerve (sciatic or tibial) preferably in close proximity to the muscle, and a section of the bone marrow.

Preserved samples of the above organs will be sent to Pathology Solutions, Inc., Clearwater, FL, GLP-compliant pathologists, for analysis.

Stillborn pups or pups dying on study will be necropsied. Pups sacrificed on lactation Day 4 will be carefully examined externally for gross abnormalities.

d. Histopathology:

A full histopathologic examination of all of tissues saved from all animals that die during the course of the study and all animals sacrificed in the control and high-dose groups will be performed. Special emphasis will be put on the stages of spermatogenesis in the male gonads and histopathology of interstitial testicular cell structure. If treatment related changes are noted in these animals, examinations will be made on tissues from the other groups. All gross lesions will also be examined.

12. Evaluation of Results:

The findings will be evaluated in terms of the observed effects, necropsy and microscopic findings. The evaluation will include the relationship between the dose of the test substance and the presence or absence, incidence and severity of abnormalities, including gross lesions, identified target organs, infertility, clinical abnormalities, affected reproductive and litter performance, body weight changes, effects on mortality and any other toxic effects. Accepted statistical methods will be employed where appropriate.

Appendix N – Protocol and Amendment (cont.)

Study Number 8419-04
Page 11 of 12B. EXPERIMENTAL DESIGN (cont.)13. Test Substance
Accountability:

A comprehensive inventory of test substance received and used will be kept. The test substance container(s) will be weighed when received at this facility, and a record of all test substance use will be maintained. Test substance will be stored in the original containers, or in the equivalent thereof, or in glass containers with Teflon-lined caps.

14. Disposal of Unused
Test Substance:

Unused test substance will be disposed of at the Sponsor's expense after the termination of the study. STILLMEADOW, Inc. will retain a reserve sample.

15. Safety Precautions:

General safety precautions as required by laboratory SOPs will be followed. The Sponsor will supply basic toxicity data on the test substance to be used. However, since the toxicity of test substances is often not well characterized, this laboratory will be conservative in setting safety procedures. The Sponsor's Representative shall be notified of any personnel exposures requiring a physician's examination or care.

C. DATA MANAGEMENT

1. Records:

The following records will be maintained during the study and transferred to the STILLMEADOW, Inc. archives upon study termination:

- a. Protocol and Protocol Amendments (if any).
- b. Final report and amendments (if any).
- c. Study correspondence.
- d. Animal receipt data.
- e. Test substance receipt, identification as supplied by Sponsor, preparation, administration, and disposition.
- f. Test animal information: number, sex, source and strain.
- g. Body weight data.
- h. Daily observation data for mortality and observations for signs of pharmacologic and/or toxicologic effects.
- i. Food consumption data.
- j. Physical examination findings (if any).
- k. Hematology and serum chemistry determinations at sacrifice.
- l. Breeding and litter data.
- m. Mortality data, gross necropsy findings, and histopathology findings.
- n. Organ weights.
- o. Other pertinent data.

2. Data Storage:

All raw data, the original protocol and the final report, and a reserved sample of the test substance will be retained at STILLMEADOW, Inc. in the archives.

Appendix N – Protocol and Amendment (cont.)

Study Number 8419-04
Page 12 of 12C. DATA MANAGEMENT (cont.)3. Data Reporting:

The final report will include all data as described in the Good Laboratory Practice Standards, including:

- a. Statement from the Quality Assurance Unit.
- b. Signature of the Study Director.
- c. A GLP Compliance Statement signed by the Study Director.
- d. Names of scientific personnel involved in the study.
- e. Dates of study initiation and termination.
- f. Identification, description, preparation, and storage of the test substance.
- g. All pertinent animal data, animal husbandry, dosing information, and observation methods.
- h. Description of the test procedures.
- i. Individual body weights and means by sex and group.
- j. Individual food consumption data and means by sex and group.
- k. Individual hematology and serum chemistry values and means by sex and group.
- l. Observations on the nature, onset, severity, and duration of all gross or visible pharmacological and/or toxicologic signs.
Nonroutine findings will be addressed in a discussion section in which the relationship to treatment will be evaluated.
- m. Individual organ weights means by sex and group.
- n. Individual mortality data, gross necropsy findings, organ weights and histopathology findings.
- o. Breeding and litter success data.
- p. Methods of statistical analysis and results.
- q. A reference to the Protocol.

4. Report Submission:

A draft report will be submitted to the Sponsor after termination of the in-life portion of the study.

Figure 1 – Male Group Mean Body Weights
Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity
Screening Test
Test Article: Veova 10

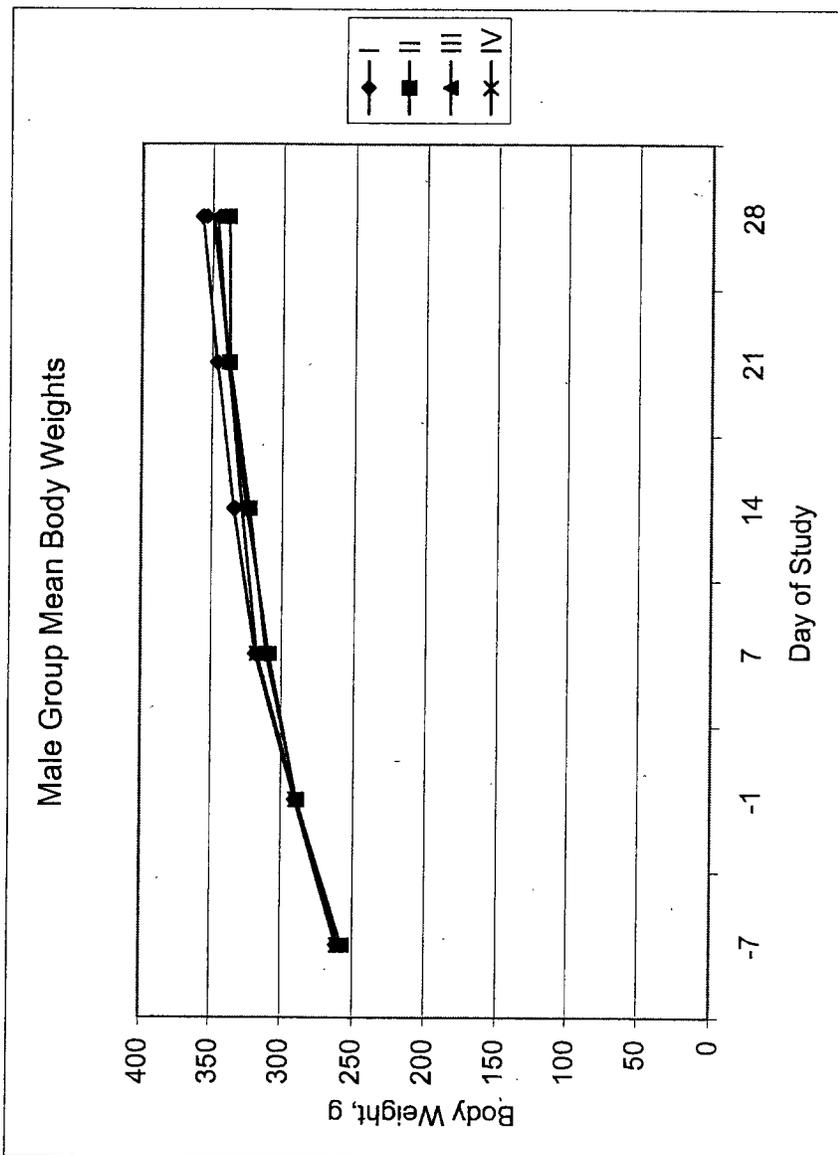


Figure 2 – Female Group Mean Body Weights
Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity
Screening Test
Test Article: Veova 10

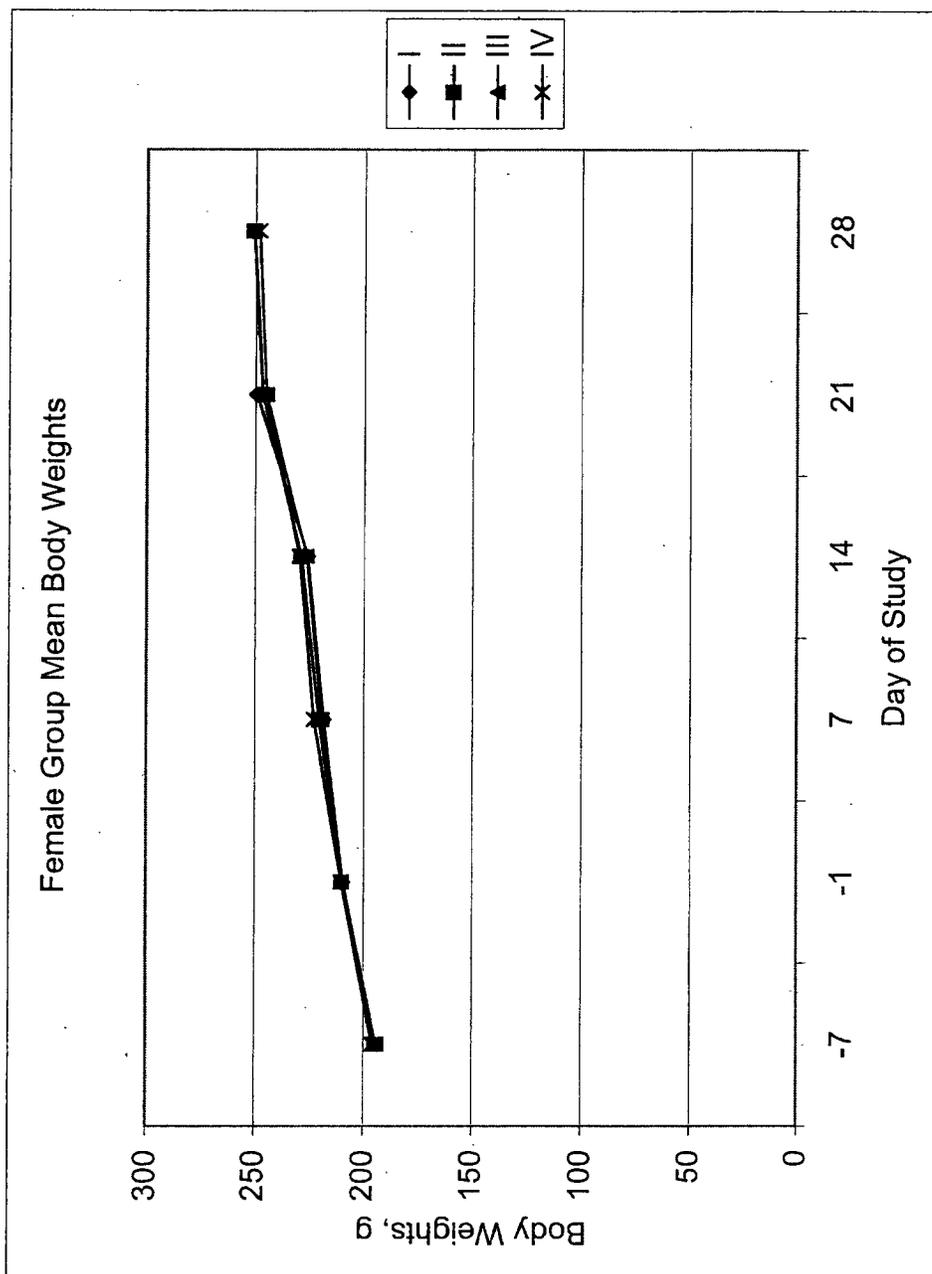


Figure 3 – Female Group Mean Body Weights during Gestation and Lactation
Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity
Screening Test
Test Article: Veova 10

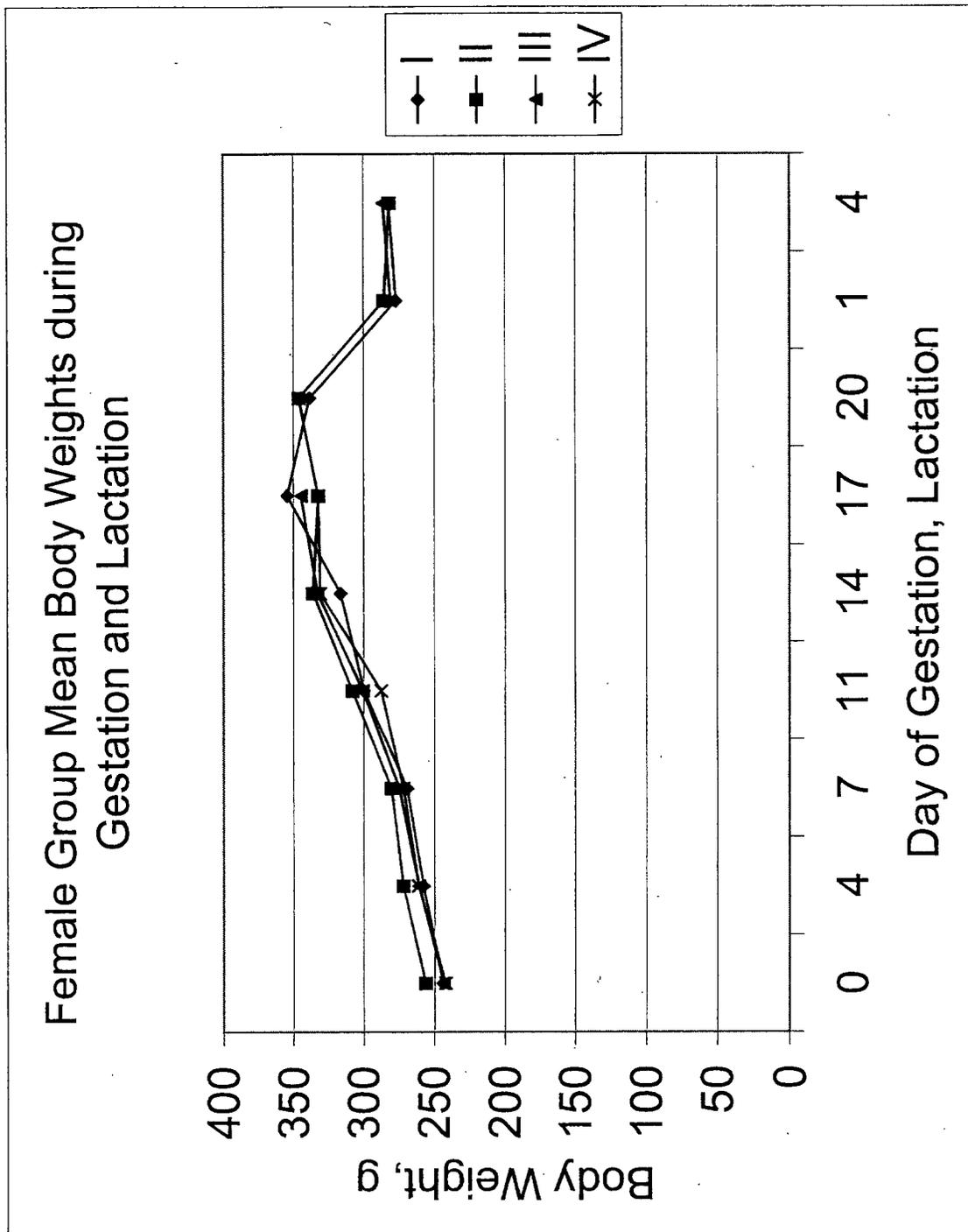


Figure 4 – Individual Body Weights of Controls Failing to Deliver
Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity
Screening Test
Test Article: Veova 10

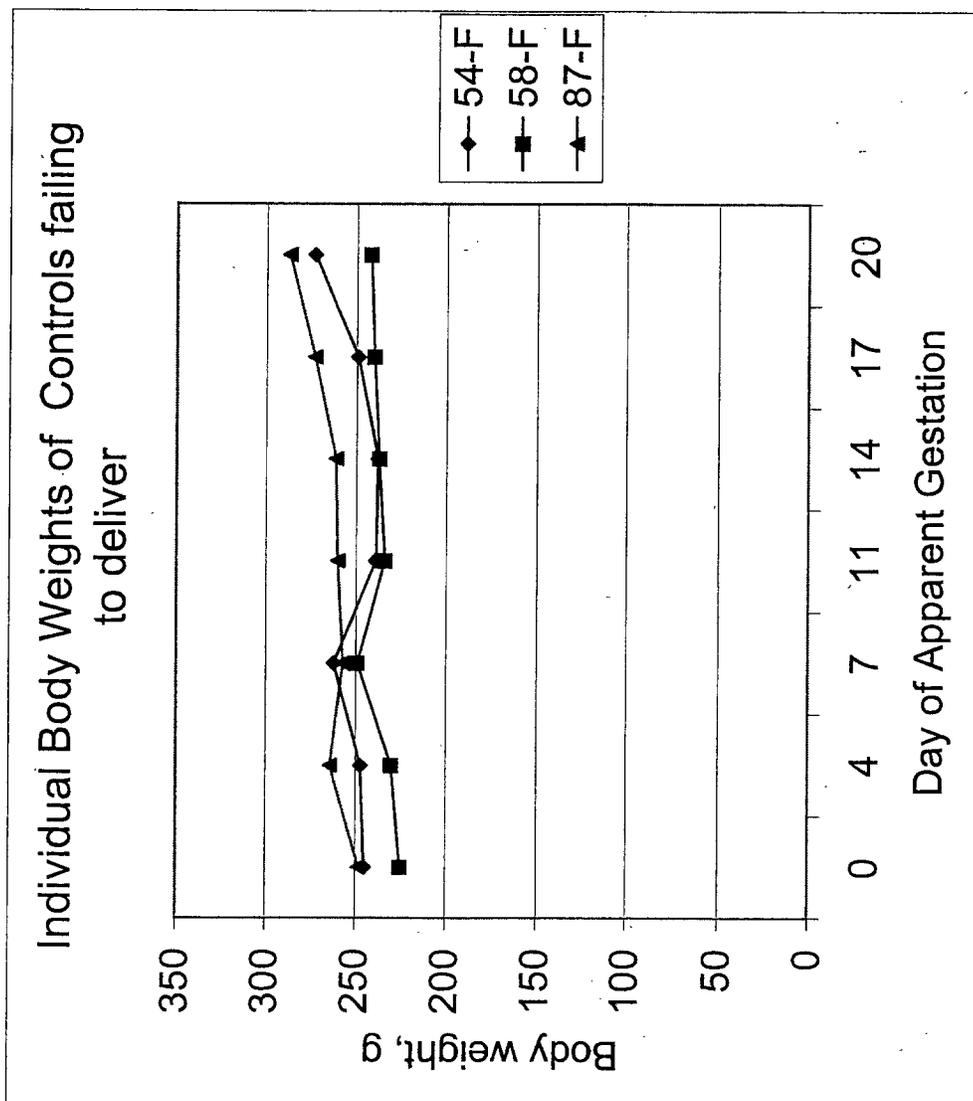


Figure 5 –Body Weights of High-dose Individuals Failing to Deliver
Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity
Screening Test
Test Article: Veova 10

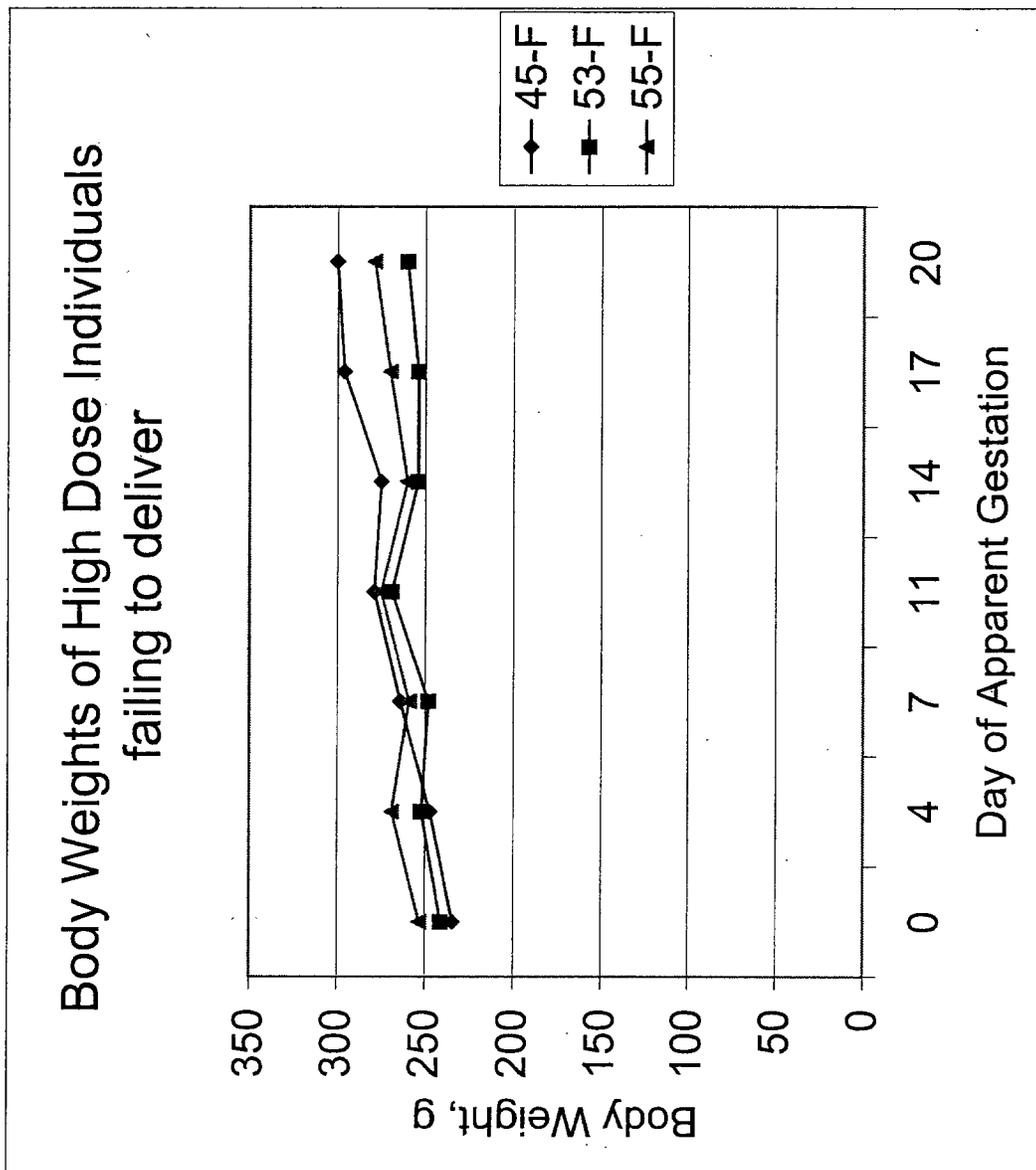
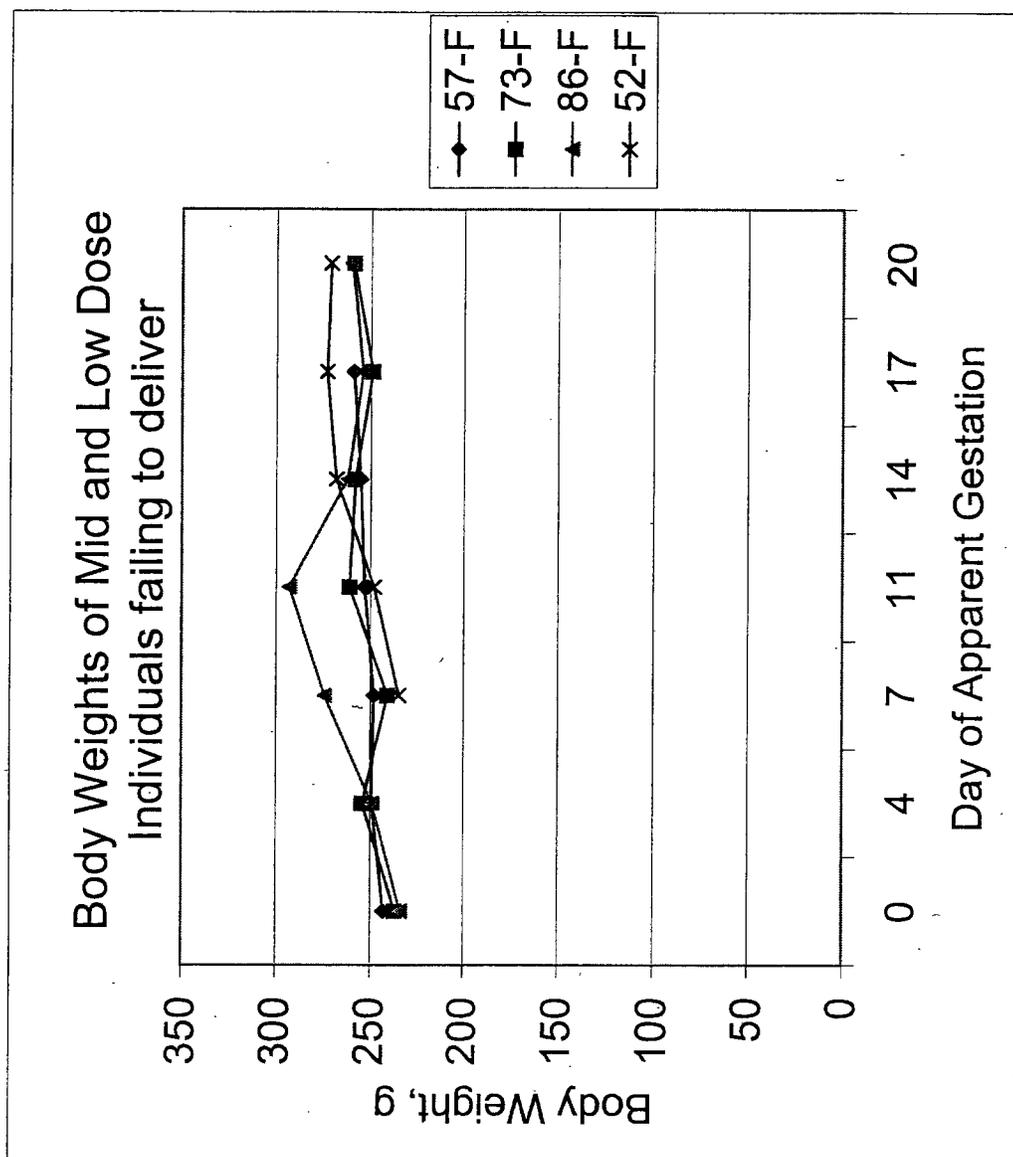


Figure 6 – Body Weights of Mid- and Low-dose Individuals Failing to Deliver
Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity
Screening Test
Test Article: Veova 10



Amendment 1

**COMBINED REPEATED DOSE TOXICITY STUDY WITH THE REPRODUCTION /
DEVELOPMENTAL TOXICITY SCREENING TEST**

Veova 10

Sponsor: Hexion Specialty Chemicals, Inc.
3333 Highway 6 South
Houston, TX 77082-3101

Final Report Amendment No. 1

This amendment modifies page 6 of the final report:

To change: Organs collected but not weighed were: spinal cord, stomach, small and large intestine (duodenum, jejunum, ileum, cecum and colon including Peyer's patches), thyroid, trachea and lungs (including bronchi, preserved by inflation with fixative and then immersion), uterus, urinary bladder, lymph nodes (mesenteric and submandibular), peripheral nerve (sciatic or tibial) in close proximity to the muscle, and a sample of bone marrow.

To read: Organs collected but not weighed were: spinal cord, stomach, small and large intestine (duodenum, jejunum, ileum, cecum and colon including Peyer's patches), thyroid, trachea and lungs (including bronchi, preserved by inflation with fixative and then immersion), urinary bladder, lymph nodes (mesenteric and submandibular), peripheral nerve (sciatic or tibial) in close proximity to the muscle, and a sample of bone marrow.

This amendment modifies page 7 of the final report:

To change: The pregnant females were dosed daily through the gestation period and through Day 4 of the lactation period. At that time, they were sacrificed and necropsied in the same manner as the males, with the ovaries and oviducts and other organs collected and weighed and the same blood parameters analyzed.

To read: The pregnant females were dosed daily through the gestation period and through Day 4 of the lactation period. At that time, they were sacrificed and necropsied in the same manner as the males, with the uterus, ovaries and oviducts, as well as all the other non-reproductive organs listed for the males, collected and weighed and the same blood parameters analyzed.

Amendment 1 (cont.)

This amendment modifies page 8 of the final report:

To add: The following organs were collected at necropsy: adrenal glands, urinary bladder, thymus, spine, peripheral nerve, lymph nodes, lungs, trachea/pharynx/larynx, liver, kidneys, heart, thyroid/parathyroid, spleen, stomach, duodenum, jejunum, ileum, colon, cecum, rectum, aorta, brain, bone marrow/sternum, esophagus, ovaries, uterus, testes, seminal vesicles, prostate and epididymides. The number of corpora lutea was recorded.

This amendment modifies page 8 of the final report:

To change: Liver weights of Group II females were greater than control, however again the difference did not reach statistical significance. All other organ weights were within the expected ranges and mean organ weights did not vary significantly among groups.

To read: Liver weights of Group II females were greater than control, however the difference did not reach statistical significance. All other organ weights were within the expected ranges and mean organ weights did not vary significantly among the four groups.

This amendment modifies pages 4 (Table of Contents) and 15-20 of the final report:

To add: AND DISCUSSION to the RESULTS section.

This amendment modifies page 15 of the final report:

To change: Body weights are presented in Table 2 and Figures 1 (males) and 2 (females). There were no apparent dose-related differences in group mean body weights among males or females through Day 28. Males were euthanized on Day 29.

Body weights of females during gestation and lactation are in Table 3 and Figures 3 and 4. Females of all groups exhibited similar weight profiles during the gestation and lactation periods. Body weights of those females that had not yet, or failed to, conceive or deliver are shown in Table 2 (Days 21-51) and Figures 4 (control), 5 (high dose) and 6 (mid and low dose). In one animal (86-F of Group IV), the weight profile suggested that a pregnancy was initiated but not completed. Otherwise, weight gain in these animals seemed typical of normal, non-pregnant females.

Amendment 1 (cont.)

To read: Body weights are presented in Table 2 and Figures 1 (males) and 2 (females). There were no apparent treatment-related differences in group mean body weights through Day 28 when Groups I-IV, males or females, were compared by analysis of variance. Males were euthanized on Day 29. Body weights of females are listed in Table 2 until a female was identified as pregnant, after which the body weights are given as gestational body weights in Table 3. Table 2 also has a separate section with body weights of only those females that were thought to have conceived but did not eventually deliver.

Body weights of females during gestation and lactation are presented in Table 3 and Figures 3 and 4. Females of all control and treated groups exhibited similar weight profiles during the gestation and lactation periods, suggesting that the pregnancies of the treated animals progressed similarly to those of the controls.

Figures 4 (control), 5 (high dose) and 6 (mid and low dose) contain body weights of those females that were thought to have conceived but did not deliver. There were three such females in Group I, three in Group II, and two each in Groups III and IV. In one animal (86-F of Group IV), the weight profile suggested that a pregnancy was initiated but not completed. Otherwise, weight gain in these animals seemed quite typical of normal, non-pregnant female Sprague-Dawley rats.

This amendment modifies page 20 of the final report:

To change: Test article-related lesions were limited to the kidneys of Group II rats treated with 1000 mg/kg. Four of the five males and one in ten females were affected. The primary lesion was nephrosis, characterized by the deposition of birefringent oxalate crystals within the renal tubules. Necrosis/degeneration of the adjacent epithelial cells was dependent upon the amount of crystalline deposition but was not a major change. The nephrosis was sometimes accompanied by chronic interstitial nephritis, increased basophilic cortical tubules (a regenerative indicator), and papillary necrosis in one male. Other secondary non-renal lesions included thymic lymphoid depletion in two affected males and a mild gastric ulcer in one affected male.

The finding of oxalate nephrosis suggests that the metabolism of the test article following oral administration is similar to that of ethylene glycol. The toxicity of ethylene glycol is primarily a result of its metabolic by-products and not the parent compound that is metabolized by cytosolic enzymes in the liver, the first step catalyzed by the enzyme alcohol dehydrogenase. The by-products include glycolic acid, glyoxylic acid, and oxalic acid, the latter depositing in the renal tubules as insoluble crystals. Since the protocol directed attention to effects upon spermatogenesis, it may have been suspected that the test article metabolites were similar to ethylene glycol monomethyl ether, which affects spermatocytes. In this study, no morphologic effect was observed in the seminiferous tubules.

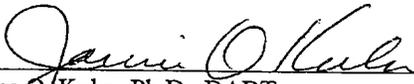
Amendment 1 (cont.)

To read: Test article-related lesions were limited to the kidneys of Group II rats treated with 1000 mg/kg. Four of the five males and one in ten females were affected. The primary lesion was nephrosis, characterized by the deposition of birefringent (brightly evident under polarized light) crystals that resembled oxalates within the renal tubules. Necrosis/degeneration of the adjacent epithelial cells was dependent upon the amount of crystalline deposition but was not a major change. The nephrosis was sometimes accompanied by chronic interstitial nephritis, increased basophilic cortical tubules (a regenerative indicator), and papillary necrosis in one male. Other secondary non-renal lesions included thymic lymphoid depletion in two affected males and a mild gastric ulcer in one affected male.

In addition to toxic effects, this study was also intended to determine effects of the test article upon reproductive performance. However, no histopathologic changes were observed upon microscopic examination of the male or female reproductive organs.

Reason for amendment: To provide clarification of several points discussed in the report and to accurately reflect the amended histopathology report.

Amendment Approval:



Janice O. Kuhn, Ph.D., DABT
Study Director
STILLMEADOW, Inc.

19 Dec 05
Date