

AR 226 - 3321

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## TRADE SECRET

*Study Title*

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

**TEST GUIDELINES:** U.S. EPA Health Effects Test Guidelines  
OPPTS 870.3200 (1998)

OECD Guideline for the Testing of Chemicals  
Section 4: Health Effects, Number 410 (1981)

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**STUDY COMPLETED ON:** November 3, 2004

**PERFORMING LABORATORY:** E.I. du Pont de Nemours and Company  
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**LABORATORY PROJECT ID:** DuPont-13830

**WORK REQUEST NUMBER:** [REDACTED]

**SERVICE CODE NUMBER:** [REDACTED]

**SPONSOR:** E.I. du Pont de Nemours and Company  
Wilmington, Delaware 19898  
U.S.A.

### GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study was conducted in compliance with U.S. EPA TSCA (40 CFR part 792) Good Laboratory Practice Standards, which are consistent with the OECD Principles of Good Laboratory Practice (as revised 1997) published in ENV/MC/CHEM(98)17, except for the item documented below.

Test substance characterization and stability analyses were performed at Regional Analytical Services (RAS), a non-GLP laboratory. The test substance analyses performed were in compliance with regulatory guidelines. None of the aforementioned analyses were performed under Good Laboratory Practice Standards; however, the analyses were conducted in compliance with ISO9002 regulations. All of the analyses are considered valid and sufficient for the purposes of this study.

Applicant / Sponsor: E.I. du Pont de Nemours and Company  
Wilmington, Delaware 19898  
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Study Director: Carol Finlay 63 Nov 2004  
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DuPont Representative Date

## QUALITY ASSURANCE DOCUMENTATION

Work Request Number: [REDACTED]

Study Code Number: [REDACTED]

The conduct of this study has been subjected to periodic Quality Assurance inspections. The dates of inspection are indicated below.

| <i>Phase Audited</i>  | <i>Audit Dates</i>  | <i>Dates Reported to Study<br/>Director and Management</i> |
|-----------------------|---------------------|------------------------------------------------------------|
| Conduct: Evaluation   | 1 Dec 2003          | 1 Dec 2003                                                 |
| Tables and Appendices | 16, 18, 23 Feb 2004 | 23 Feb 2004                                                |
| Tables and Appendices | 23-26 Feb 2004      | 26 Feb 2004                                                |
| Tables and Appendices | 9-12, 16 Mar 2004   | 16 Mar 2004                                                |
| Report/Records:       | 6-8 Oct 2004        | 8 Oct 2004                                                 |

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Date

### CERTIFICATION

We, the undersigned, declare that this report provides an accurate evaluation of data obtained from this study.

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### STUDY INFORMATION

9th Collective Nomenclature:

[REDACTED]

Synonyms/Codes:

[REDACTED]  
• H-25425

Haskell Number: 25425

CAS Registry Number:

[REDACTED]

Purity:

[REDACTED]

Known Impurities:

[REDACTED]

Physical Characteristics:

[REDACTED]

Study Initiated/Completed: November 18, 2003 / (see report cover page)

In-life Initiated/Completed: November 25, 2003 / December 23, 2003

## SUMMARY

The objective of this study was to determine the potential toxicity of H-25425 following repeated dermal exposure. The test substance was applied to the shaved, intact skin of male Crl:CD<sup>®</sup>(SD)IGS BR rats for 6 hours/day for 28 consecutive days. Three groups of 10 male rats were treated dermally with 10, 100, or 1000 mg/kg/day H-25425. A control group of 10 male rats was similarly treated with deionized water. The rats were observed for mortality, clinical signs, dermal effects, and body weight effects during the study. Food consumption was determined weekly during the study. Blood samples for total fluorine were collected on test days 0, 7, 14, 21, and 27. The day 21 samples were analyzed. Blood and urine samples were collected for clinical pathology prior to sacrifice on day 28. Blood samples were collected at necropsy for analysis of concentration of perfluorooctanoic acid (PFOA). All rats underwent necropsy for gross and microscopic pathological evaluation.

No deaths occurred, and no test substance-related effects on body weight or nutritional parameters were observed. No clinical signs attributable to systemic toxicity occurred. No dermal irritation was observed during the study.

PFOA concentrations in plasma from rats in the control group and the 10 mg/kg/day group were below the lower limit of quantitation (10 ppb). The mean concentrations were 13 ppb in the 100 mg/kg/day group and 105 ppb in the 1000 mg/kg/day group.

Fluorine levels in blood from treated and control rats were either not detectable or below the limit of quantification (500 ppb).

No adverse effects were observed on any clinical pathology parameters (hematology, clinical chemistry, coagulation parameters, urinalysis), organ weights, or gross or microscopic pathology parameters.

The no-observed-effect level (NOEL)<sup>a</sup> for male rats was 1000 mg/kg/day, the highest dosage tested. The NOEL is based on a lack of adverse test substance-related effects on any in-life, clinical pathology, or anatomic pathology parameter in male rats treated dermally at dosages up to 1000 mg/kg/day.

---

<sup>a</sup> The no-observed-effect (NOEL) for this study is defined as the highest dose at which toxicologically important effects attributable to the test substance were not detected. Thus, for this study, the NOEL is equivalent to the NOEL as defined by the United States Environmental Protection Agency (1985), and the no-observed-adverse-effect level (NOAEL) as defined by the European Union (1994).

## INTRODUCTION

The test substance, H-25425, is a [REDACTED] It belongs to the group of compounds known as [REDACTED] In a previously conducted 90-day oral gavage study with the test substance, male and female rats were dosed at 0 (control), 10, 100, or 1000 mg/kg for 90 consecutive days.<sup>(1)</sup> No adverse test substance-related effects on body weight, body weight gain, food consumption, food efficiency, or clinical pathology parameters were observed in any male or female dose group. Reversible, minimal to mild thyroid follicular hypertrophy was observed in the 1000 mg/kg/day male and female groups. The no-observed-effect level (NOEL) for subchronic toxicity endpoints in male and female rats was 100 mg/kg/day.

Dose levels for the present study were selected to duplicate the dose levels of the oral gavage study.

## STUDY DESIGN

| Group | Number/Group | Dosage (mg/kg) |
|-------|--------------|----------------|
| IX    | 10           | 0 (Control)    |
| XI    | 10           | 10             |
| XIII  | 10           | 100            |
| XV    | 10           | 1000           |

## MATERIALS AND METHODS

### A. Test Guidelines

The study design complies with the following test guidelines except as noted below:

- Office of Prevention, Pesticides and Toxic Substances (OPPTS) U.S. Environmental Protection Agency (EPA) (1998). OPPTS 870.3200 21/28-Day Dermal Toxicity. *Health Effects Test Guidelines*.
- Organisation for Economic Co-Operation and Development (OECD) (1981). 410 Repeated Dose Dermal Toxicity: 21/28-Day Study. *Guideline for the Testing of Chemicals*.

Exception - The wrappings of 7 rats became dislodged during the exposure period. Therefore, on these occasions they may not have been exposed to the test substance for 6 hours. Four of these rats were in the control group, and three rats were in different test groups. This exception did not affect the objectives or the validity of the study because, considering that no significant toxicological effects were observed at any dosage level, it is not likely that an occasional exposure period of less than 6 hours for some animals would have changed the study results.

Exception - Only male rats were treated because in previous studies with other [REDACTED] males were more sensitive to the toxicological effects than females.

#### B. Test Substance

The test substance, H-25425, was supplied by the sponsor as an [REDACTED] The test substance appeared to be stable under the conditions of the study. No evidence of instability, such as a change in color or physical state, was observed.

#### C. Test Species

On November 18, 2003, 44 male CrI:CD<sup>®</sup>(SD)IGS BR rats, with an assigned birth date of October 6, 2003, were received from Charles River Laboratories, Inc., Raleigh, North Carolina.

The CrI:CD<sup>®</sup>(SD)IGS BR rat was selected based on consistently acceptable health status and on extensive experience with the strain at Haskell Laboratory.

#### D. Animal Husbandry

##### 1. Housing

Rats were housed singly in stainless steel, wire-mesh cages suspended above cage boards.

##### 2. Environmental Conditions

Animal rooms were maintained at a temperature of 18-26°C and a relative humidity of 30-70%. Animal rooms were artificially illuminated (fluorescent light) on an approximate 12-hour light/dark cycle.

##### 3. Feed and Water

Tap water was provided *ad libitum*. PMI<sup>®</sup> Nutrition International, LLC Certified Rodent LabDiet<sup>®</sup> 5002 meal was available *ad libitum* except when the rats were fasted.

##### 4. Identification

Prior to assignment to groups, each rat was temporarily identified by a cage card affixed to the outside of its cage. After assignment to groups, each rat was assigned an animal number which was tattooed on the tail of each rat and included on the cage labels.

##### 5. Animal Health and Environmental Monitoring Program

As specified in the Haskell Laboratory animal health and environmental monitoring program, the following procedures are performed periodically to ensure that contaminant levels are below those that would be expected to impact the scientific integrity of the study:

- Water samples are analyzed for total bacterial counts, and the presence of coliforms, lead, and other contaminants.
- Feed samples are analyzed for total bacterial, spore, and fungal counts.
- Samples from freshly washed cages and cage racks are analyzed to ensure adequate sanitation by the cagewashers.

Certified animal feed is used, guaranteed by the manufacturer to meet specified nutritional requirements and not to exceed stated maximum concentrations of key contaminants, including specified heavy metals, aflatoxin, chlorinated hydrocarbons, and organophosphates. The presence of these contaminants below the maximum concentration stated by the manufacturer would not be expected to impact the integrity of the study.

The animal health and environmental monitoring program is administered by the attending laboratory animal veterinarian. Evaluation of these data did not indicate any conditions that affected the validity of the study.

#### **E. Quarantine and Pretest**

Upon arrival at Haskell Laboratory, the rats were removed from shipping cartons and quarantined for 6 days. The rats were weighed 3 times during the quarantine period and examined daily for any clinically apparent signs of disease or injury. The rats were observed daily for mortality and signs of illness, injury, or abnormal behavior.

On the bases of acceptable body weight gains and freedom from clinically apparent signs of disease or injury, the rats were released from quarantine on test day -1 by the laboratory animal veterinarian.

#### **F. Assignment to Groups and Study Start**

Forty rats were selected for study use on the bases of adequate body weight gain, freedom from clinical signs of disease or injury, and a body weight within  $\pm 20\%$  of the mean. The selected rats were divided by computerized, stratified randomization into 4 groups of 10 rats, so that there were no statistically significant differences among group body weight means.

Dose administration with H-25425 began on test day 0 when the rats were approximately 7 weeks of age.

#### **G. Test Substance Preparation and Administration**

Approximately 24 hours prior to the first treatment, the fur of each rat was closely shaved to expose the skin from the back and trunk. The area to be treated was marked on the back of each rat with a water-insoluble marker. The rats were treated for 28 consecutive days at approximately the same time each day. The exposure period was approximately 6 hours per day.

The test substance was moistened with deionized water to form a thick paste and applied as evenly and thinly as possible to the test site. The amount of test substance needed to treat each rat was based on the most recently determined body weight measurement. The control rats were treated with deionized water. The test site was covered with a 2-ply porous gauze dressing followed by successive layers of stretch gauze (no more than 8 layers) and self-adhesive bandage. After the exposure period, the wrappings were removed and excess test substance was washed off with warm tap water. Each rat was then gently patted dry and returned to the cage. The control animals received the same washing technique as the treated animals.

It was not possible to cover an area of 10% of the total body surface for any dose group without excessively diluting the test substance. The approximate total body surface area covered with the thick paste for the 10, 100, and 1000 mg/kg/day groups was 1%, 1%, and 3.3%, respectively.

Following an evaluation rats were reshaved as needed during the study. The entire area that was originally shaved (including the untreated control skin) was reshaved.

#### **H. Body Weights**

The rats were weighed at 3-4 day intervals throughout the study.

#### **I. Food Consumption and Food Efficiency**

The amount of food consumed by each rat was determined once per week throughout the study. Individual food consumption was determined by weighing the amount of diet in each feeder at the beginning and end of the week and subtracting the final weight and the amount of spillage from the feeder during the week from the initial weight. From these measurements, mean daily food consumption was determined. From the food consumption and body weight data, mean daily food efficiency was calculated.

#### **J. Observations**

The rats were observed for clinical signs and dermal effects after washing. The rats were also observed for clinical signs at each weighing. The Draize Scale was used to score skin irritation. Adjacent areas of untreated skin were used for comparison.

The rats were checked twice daily for mortality and for signs of illness, injury, or abnormal behavior.

#### **K. Total Fluorine and Perfluorooctanoic Acid Level Evaluations**

Blood was collected into EDTA tubes from the orbital sinus of all rats on test days 0, 7, 14, 21, and 27 approximately one hour after removal of the test substance. The blood was refrigerated. The total fluorine content of the day 21 blood samples was determined by using a Wickbold torch combustion method followed by analysis with a fluoride ion selective electrode.<sup>(2)</sup> The limit of

quantification (LOQ) for this method is 500 ppb. Fluorine blood analysis was performed at Stereochem, Newark, Delaware.

Additional blood was collected from the *vena cava* of all rats at necropsy into a tube containing EDTA. Plasma was prepared and stored frozen at -80°C to -20°C until analyzed for concentration of perfluorooctanoic acid (PFOA). PFOA was extracted from the plasma by protein precipitation in acetonitrile. The compound was quantified by liquid chromatography/tandem mass spectrometry (LC/MS/MS) analysis using selected reaction monitoring (SRM). Quantification was performed using extracted calibration standards containing an internal standard. The lower limit of quantitation (LLOQ) for this method is 10 ppb. Plasma samples were analyzed for PFOA at Exygen Research, 3058 Research Drive, State College, PA 16801. See Appendix F for additional details of this analysis.

## L. Clinical Pathology Evaluation

A clinical pathology evaluation was conducted on all animals 28 days after initiation of the study. The day before collection of samples for the clinical pathology evaluation animals were placed in metabolism cages. Animals were fasted overnight (approximately 16 hours) and urine collected from each animal. Blood samples for hematology and clinical chemistry measurements were collected from the orbital sinus of each animal while the animal was under carbon dioxide anesthesia. Blood samples for plasma fluoride, PFOA, and coagulation parameters were collected at sacrifice from the abdominal *vena cava* of each animal while the animal was under carbon dioxide anesthesia. Additional blood collected from the *vena cava* was placed in a serum tube, processed to serum, and frozen at -80°C. Serum was discarded without analysis because further tests were not required to support experimental findings. Bone marrow smears were inadvertently not collected at sacrifice. All blood samples were evaluated for quality by visual examination prior to analysis. Results were maintained in the study records and reported only if the sample was analyzed.

### 1. Hematology and Coagulation

Complete blood counts, including reticulocytes, were determined on a Bayer® Advia 120 hematology analyzer or determined from microscopic evaluation of the blood smear. Wright-Giemsa stained blood smears from all animals were examined microscopically for confirmation of automated results and evaluation of cellular morphology. Blood smears, stained with new methylene blue, were prepared from each animal undergoing a hematology evaluation, but were not needed for examination. Coagulation times were determined on a Sysmex® CA-1000 Coagulation Analyzer.

The following parameters were determined:

red blood cell count  
hemoglobin  
hematocrit  
mean corpuscular volume

platelet count  
white blood cell count  
differential white blood cell count  
microscopic blood smear examination

mean corpuscular hemoglobin  
mean corpuscular hemoglobin concentration  
red cell distribution width  
absolute reticulocyte count

prothrombin time  
activated partial thromboplastin time

## 2. Clinical Chemistry

Serum clinical chemistry parameters were determined on an Hitachi 717 clinical chemistry analyzer. Plasma fluoride concentrations were determined using a Beckman® Φ12 digital pH/ISE meter and a fluoride-selective electrode.

The following parameters were determined:

|                            |                       |
|----------------------------|-----------------------|
| aspartate aminotransferase | glucose               |
| alanine aminotransferase   | total protein         |
| sorbitol dehydrogenase     | albumin               |
| alkaline phosphatase       | globulin              |
| total bilirubin            | calcium               |
| urea nitrogen              | inorganic phosphorus  |
| creatinine                 | sodium                |
| cholesterol                | potassium             |
| triglycerides              | chloride              |
|                            | fluoride <sup>a</sup> |

## 3. Urinalysis

Urine volume and appearance (quality, color, and clarity) were measured and evaluated visually, respectively. Urine constituents were semi-quantitatively measured on a Bayer Clinitek® Atlas™ Automated Urine Chemistry analyzer. Urine protein was measured on an Hitachi 717 clinical chemistry analyzer. Urine osmolality was determined using an Advanced Osmometer 3900. Urine fluoride concentrations were determined using a Beckman® Φ12 digital pH/ISE meter and a fluoride-selective electrode, and total urine fluorides were calculated (volume × concentration). Sediments from all urine specimens were evaluated microscopically.

The following parameters were determined:

|            |              |
|------------|--------------|
| quality    | ketone       |
| color      | bilirubin    |
| clarity    | blood        |
| volume     | urobilinogen |
| osmolality | fluoride     |

<sup>a</sup> Fluoride determination was analyzed on EDTA plasma.

pH  
glucose

protein  
microscopic urine sediment examination

### M. Anatomic Pathology Evaluation

After 28 days of exposure to the test substance (test day 28), groups of 10 male rats from the 0, 10, 100, and 1000 mg/kg/day groups were sacrificed and necropsied.

The rats were fasted overnight on the afternoon before their scheduled sacrifice. The order of sacrifice for scheduled deaths was random among all treatment groups. Rats were euthanized by carbon dioxide anesthesia and exsanguination. Gross examinations were performed on all rats.

The following tissues were collected from all rats.

|               |                                 |
|---------------|---------------------------------|
| liver         | skin (treated)                  |
| kidneys       | skin (untreated)                |
| thyroid gland | gross observations <sup>a</sup> |

a. Gross observations made at necropsy for which histopathology was not appropriate (e.g., fluid, ruffled fur, and missing anatomic parts) were generally not collected.

The following tissues were weighed: liver, kidneys, and thyroid gland (after fixation). Organ weight/final body weight ratios were calculated.

Gross lesions for which a microscopic diagnosis would not be additive (e.g., osteoarthritis, pododermatitis, chronic dermatitis of the tail, urinary calculi, and deformity of the teeth, toe, tail, or pinna) were saved but were generally not processed for microscopic evaluation.

All tissues were fixed in 10% neutral buffered formalin. Processed tissues were embedded in paraffin, cut at a nominal thickness of 5 micrometers, stained with hematoxylin and eosin (H&E), and examined microscopically.

All collected tissues from rats in the control and 1000 mg/kg/day groups were processed to slides and received a full histopathological examination.

### N. Statistical Analyses

Significance was judged at  $p < 0.05$ .

| Parameter        | Preliminary Test                      | Method of Statistical Analysis                                                             |                                           |
|------------------|---------------------------------------|--------------------------------------------------------------------------------------------|-------------------------------------------|
|                  |                                       | If preliminary test is not significant                                                     | If preliminary test is significant        |
| Body Weight      | Test for lack of trend <sup>(3)</sup> | Sequential application <sup>(4)</sup> of the Jonckheere-Terpstra trend test <sup>(5)</sup> | Preliminary tests for pairwise comparison |
| Body Weight Gain |                                       |                                                                                            |                                           |
| Food Consumption |                                       |                                                                                            |                                           |
| Food Efficiency  |                                       | OR <sup>a</sup>                                                                            |                                           |

| Parameter                                         | Preliminary Test                                                                                             | Method of Statistical Analysis                                                                |                                                                               |
|---------------------------------------------------|--------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
|                                                   |                                                                                                              | If preliminary test is not significant                                                        | If preliminary test is significant                                            |
| Organ Weight                                      | Levene's test for homogeneity <sup>(6)</sup> and Shapiro-Wilk test <sup>(7)</sup> for normality <sup>b</sup> | One-way analysis of variance <sup>(8)</sup> followed with Dunnett's test <sup>(9,10,11)</sup> | Kruskal-Wallis test <sup>(12)</sup> followed with Dunn's test <sup>(13)</sup> |
| Clinical Pathology <sup>c</sup>                   | Levene's test for homogeneity <sup>(6)</sup> and Shapiro-Wilk test <sup>(7)</sup> for normality <sup>b</sup> | One-way analysis of variance <sup>(8)</sup> followed with Dunnett's test <sup>(9,10,11)</sup> | Kruskal-Wallis test <sup>(12)</sup> followed with Dunn's test <sup>(13)</sup> |
| Survival<br>Incidence of Clinical<br>Observations | None                                                                                                         | Cochran-Armitage test for trend <sup>(8)d</sup>                                               |                                                                               |

- a Pairwise comparisons and associated preliminary tests were only conducted if the test for lack of trend was significant.
- b If the Shapiro-Wilk test was not significant but Levene's test was significant, a robust version of Dunnett's test was used. If the Shapiro-Wilk test was significant, Kruskal-Wallis test was followed by Dunn's test.
- c When an individual observation was recorded as being less than a certain value, calculations were performed on half the recorded value. For example, if bilirubin was reported as <0.1, 0.05 was used for any calculations performed with that bilirubin data.
- d If the incidence was not significant, but a significant lack of fit occurred, then Fisher's Exact test<sup>(14)</sup> with a Bonferroni correction was used.

## RESULTS AND DISCUSSION

### In-Life Toxicology

#### A. Mean Body Weights and Body Weight Gains (Tables 1-2, Figure 1, Appendix A)

No test substance-related effects on mean body weights or mean body weight gains were observed in any group of male rats. No statistically significant differences in mean body weights were observed. Mean body weight gains in all groups were greater than control over some intervals (not statistically significant). Mean body weight gains in all test groups were statistically decreased compared to control in the interval days 10-14. The differences were not considered test substance-related because they did not exhibit a monotonic dose-response. The mean overall body weight gains in all test groups were lower than control. The differences were not considered to be test substance-related because they were not statistically significant and did not exhibit a monotonic dose-response.

#### B. Food Consumption and Food Efficiency (Tables 3-4, Appendix B)

No effects on food consumption were observed. Mean overall food consumption (test days 0-27) in the 1000 mg/kg/day group was 101% of control (not statistically significant).

No test substance-related effects on food efficiency were observed. Mean food efficiency was statistically decreased in the interval days 7-14 at all dosages. These differences were not considered test substance-related because they did not exhibit a monotonic dose response. Mean overall food efficiency was statistically decreased in the 100 and 1000 mg/kg/day groups. These differences were not considered test substance-related because they were 10% or less than control, mean food efficiency in these groups was greater than control over 1 or 2 weekly intervals (not statistically significant), and the decreased food efficiency did not result in any reduction in final body weight or overall body weight gain.

#### C. Clinical Observations, Dermal Effects, and Mortality (Tables 5-7, Appendices C-E)

No clinical signs resulting from systemic toxicity occurred. Ocular discharge and nasal discharge were not considered test substance-related as they were observed in both treated and control animals. Dark eyes, corneal opacity, or enophthalmus were observed in several rats during the study. These clinical signs were not considered test substance-related because the incidence did not exhibit a monotonic dose response. These signs may be a result of orbital sinus bleeding.

Hair loss, superficial wounds, swollen face, and staining of the fur/skin were present in both treated and control animals and were not considered test substance-related.

No dermal irritation was observed during the study.

No deaths occurred.

**D. Perfluorooctanoic Acid (PFOA) and Total Fluorine Evaluations**  
(Tables 8-9, Appendices F-G)

PFOA concentrations in plasma from rats in the control group and the 10 mg/kg/day group were below the lower limit of quantitation (LLOQ or 10 ppb). The mean concentrations were 13 ppb in the 100 mg/kg/day group and 105 ppb in the 1000 mg/kg/day group. These levels were considerably lower than those observed in the oral study with this test substance.<sup>(1)</sup> The source of the PFOA in the plasma, whether from direct application or metabolism of chemical in the test substance, is unknown.

Fluorine levels in blood from treated and control rats were either not detectable or below the limit of quantification (LOQ or 500 ppb). This is in contrast with the measurable total fluorine evident in animals dosed at all levels (10 mg/kg/day and above) in the oral study.

**E. In-Life Conclusions**

No adverse effects were observed on mean body weight, nutritional parameters, mortality, or clinical signs in male rats treated up to and including 1000 mg/kg/day. PFOA was present in plasma from rats treated at 100 and 1000 mg/kg/day. Blood fluorine levels were not detectable at levels above the LOQ of 500 ppb in any dose group.

**Clinical Pathology Evaluation**

**A. Hematology**  
(Table 10, Appendix H)

There were no adverse changes in hematologic parameters in male rats. The following statistically significant changes in mean hematologic parameters were not related to treatment:

- Mean corpuscular hemoglobin concentration was minimally but statistically increased in males treated with 10 or 1000 mg/kg (both 102% of control mean). These changes did not occur in a dose-related pattern, and were therefore considered to be unrelated to treatment.

**B. Coagulation**  
(Table 11, Appendix H)

There were no treatment-related or statistically significant changes in coagulation parameters in male rats.

**C. Clinical Chemistry**  
(Table 12, Appendix H)

There were no adverse changes in clinical chemistry parameters in male rats. The following statistically significant changes in mean clinical chemistry parameters were either treatment-related and not adverse, or not related to exposure to compound:

- Minimally decreased urea nitrogen and creatinine in males treated with 100 or 1000 mg/kg were considered to be treatment-related. Mean concentrations of urea nitrogen were 83% of controls in both groups, while mean creatinine concentrations were 83% and 76% of controls in rats treated with 100 or 1000 mg/kg, respectively. In addition, with the exception of one rat treated with 10 mg/kg, creatinine concentrations of this group were also decreased. Generally, increases in urea nitrogen and creatinine are considered adverse; minimal decreases in these parameters have no toxicologic significance. The cause of minimally decreased urea nitrogen and creatinine was not addressed in this study.
- Cholesterol and triglyceride concentrations were minimally decreased in males treated with 1000 mg/kg (statistically significant only for cholesterol; means were 81% and 72% of respective controls). These decreases were likely to be treatment-related based on the distribution of the individual animal data in comparison to control rats. However, because the range of individual values was similar between control and 1000 mg/kg groups, these changes were considered to be non-adverse.
- Potassium was minimally decreased (statistically significant) in males treated with 1000 mg/kg (90% of control group mean). This decrease was likely to be treatment-related based on the consistency of the individual animal data. However, in comparison to historical laboratory data, individual animal potassium concentrations in both the control and 100 mg/kg groups of rats were within the historical range for individual animal values (5.1-7.3 mmol/L), with the exception of one outlier in the control group (#902) with a potassium concentration of 7.72 mmol/L. In addition, means for both groups were within the historical range of means (5.7-6.5 mmol/L). Therefore, this change, although treatment-related, was not considered to be adverse.

**D. Urinalyses**  
(Table 13, Appendix H)

There were no adverse changes in urinalysis parameters in male rats. The following statistically significant change was not related to treatment:

- Urine protein was increased in males treated with 10 mg/kg. This change occurred only in the low dose group, and therefore was considered to be unrelated to compound.

**E. Urine and Plasma Fluoride**  
(Tables 12-13, Appendix H)

There were no statistically significant or treatment-related changes in plasma fluoride or urine fluoride at the end of the dosing period.

**F. Clinical Pathology Conclusions**

Treating male rats dermally with H-25425 at dosages up to 1000 mg/kg for 28 days resulted in minimally decreased urea nitrogen and creatinine at 100 and 1000 mg/kg/day and minimally decreased cholesterol, triglycerides, and potassium at 1000 mg/kg/day. None of these changes were considered to be adverse. Therefore, there were no adverse effects on hematology, coagulation, clinical chemistry, or urinalysis parameters in the dermal study which is consistent with the oral study.

**Anatomic Pathology Evaluation**

**A. Cause of Death**  
(Appendix J)

There were no test substance-related deaths. All 40 rats survived until the scheduled 28-day sacrifice.

**B. Organ Weights**  
(Table 14, Appendix I)

There were no dermal exposure-related effects on absolute or relative organ weights. All individual and mean organ weight differences were considered to be spurious and unrelated to test substance administration.

**C. Gross Observations**  
(Table 15, Appendix J)

There were no test substance-related gross observations. The three gross observations made at necropsy were interpreted to be incidental lesions unrelated to test substance administration.

**D. Microscopic Findings**  
(Table 16, Appendix J)

There were no test substance-related microscopic findings. All microscopic findings in this study are known to occur naturally in rats of this stock and age and were not present in a dose-response fashion in either incidence or severity.

**E. Anatomic Pathology Conclusions**

No adverse effects were observed on mortality, organ weights, gross pathology, or histopathology in male rats treated dermally up to and including 1000 mg/kg/day. This is in contrast with the reversible, minimal to mild thyroid follicular hypertrophy observed at 1000 mg/kg/day in the oral study.

## CONCLUSIONS

Under the conditions of this study, the no-observed-effect level (NOEL)<sup>a</sup> for H-25425 in male rats was 1000 mg/kg/day, the highest dosage tested. The NOEL is based on a lack of adverse test substance-related effects on any in-life, clinical pathology, or anatomic pathology parameter in male rats treated dermally at dosages up to 1000 mg/kg/day.

## RECORDS AND SAMPLE STORAGE

All data and records for analytical characterizations conducted by or for the sponsor will be retained by the sponsor. Laboratory-specific or site-specific raw data, such as personnel files and equipment records will be retained by the facility where the work was done.

A sample of the test substance will be collected for archive purposes and retained at Haskell Laboratory, Newark, Delaware. Specimens (if applicable), raw data, and the final report will be retained at Haskell Laboratory, Newark, Delaware or at Iron Mountain Records Management, Wilmington, Delaware.

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<sup>a</sup> The NOEL for this study is defined as the highest dose at which toxicologically important effects attributable to the test substance were not detected. Thus, for this study, the NOEL is equivalent to the NOEL as defined by the United States Environmental Protection Agency<sup>(15)</sup> and to the no-observed-adverse-effect level (NOAEL) as defined by the European Union.<sup>(16)</sup>

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**TABLES**

## TABLES

### EXPLANATORY NOTES

#### Abbreviations

mg/kg = mg/kg/day

g/anm/day = grams/animal/day

#### **Summary of Hematology Values**

RBC - red blood cell count  
HGB - hemoglobin  
HCT - hematocrit  
MCV - mean corpuscular volume  
MCH - mean corpuscular hemoglobin  
MCHC - mean corpuscular hemoglobin concentration  
RDW - red cell distribution width  
ARET - absolute reticulocyte count  
PLT - platelet count  
WBC - white blood cell count  
ANEU - absolute neutrophil (all forms)  
ALYM - absolute lymphocyte  
AMON - absolute monocyte  
AEOS - absolute eosinophil  
ABAS - absolute basophil  
ALUC - absolute large unstained cell  
-- - no data

#### **Summary of Coagulation Values**

PT - prothrombin time  
APTT - activated partial thromboplastin time  
-- - no data

## TABLES

### EXPLANATORY NOTES

#### Summary of Clinical Chemistry Values

|      |   |                            |
|------|---|----------------------------|
| AST  | - | aspartate aminotransferase |
| ALT  | - | alanine aminotransferase   |
| SDH  | - | sorbitol dehydrogenase     |
| ALKP | - | alkaline phosphatase       |
| BILI | - | total bilirubin            |
| BUN  | - | urea nitrogen              |
| CREA | - | creatinine                 |
| CHOL | - | cholesterol                |
| TRIG | - | triglycerides              |
| GLUC | - | glucose                    |
| TP   | - | total protein              |
| ALB  | - | albumin                    |
| GLOB | - | globulin                   |
| CALC | - | calcium                    |
| IPHS | - | inorganic phosphorous      |
| NA   | - | sodium                     |
| K    | - | potassium                  |
| CL   | - | chloride                   |
| PFLU | - | plasma fluoride            |
| --   | - | no data                    |

#### Summary of Urinalysis Values

|      |   |                                                                   |
|------|---|-------------------------------------------------------------------|
| VOL  | - | volume                                                            |
| UOSM | - | urine osmolality                                                  |
| pH   | - | the logarithm of the reciprocal of the hydrogen ion concentration |
| URO  | - | urobilinogen                                                      |
| UFLU | - | urine fluoride                                                    |
| UMTP | - | urine protein                                                     |
| --   | - | no data                                                           |

#### Clinical Pathology Note

When an individual observation was recorded as being less than a certain value, calculations were performed on half the recorded value. For example, if bilirubin was reported as <0.1, 0.05 was used for any calculations performed with that bilirubin data.

TABLE 1  
MEAN BODY WEIGHTS OF MALE RATS (g)

| Group:<br>Dosage (mg/kg) | IX<br>0           | XI<br>10          | XIII<br>100       | XV<br>1000        |
|--------------------------|-------------------|-------------------|-------------------|-------------------|
| Test                     |                   |                   |                   |                   |
| DAY0                     | 206.8<br>9.0(10)  | 202.4<br>9.7(10)  | 204.5<br>8.4(10)  | 207.0<br>6.6(10)  |
| DAY3                     | 219.0<br>13.9(10) | 220.9<br>10.7(10) | 218.6<br>9.1(10)  | 222.4<br>8.9(10)  |
| DAY7                     | 248.2<br>12.8(10) | 255.2<br>11.8(10) | 247.9<br>12.8(10) | 253.5<br>10.0(10) |
| DAY10                    | 271.3<br>16.7(10) | 277.4<br>14.4(10) | 267.3<br>15.2(10) | 274.1<br>10.0(10) |
| DAY14                    | 299.1<br>17.5(10) | 300.9<br>14.9(10) | 283.6<br>23.5(10) | 297.5<br>8.6(10)  |
| DAY17                    | 310.0<br>13.3(10) | 309.5<br>18.5(10) | 294.5<br>24.0(10) | 307.3<br>16.2(10) |
| DAY21                    | 324.2<br>16.4(10) | 319.9<br>20.5(10) | 309.4<br>21.3(10) | 321.4<br>13.0(10) |
| DAY24                    | 339.9<br>16.3(10) | 337.5<br>19.0(10) | 322.9<br>20.8(10) | 333.6<br>15.0(10) |
| DAY27                    | 350.3<br>21.6(10) | 344.0<br>24.4(10) | 331.4<br>24.6(10) | 337.3<br>23.7(10) |
| DAY28                    | 332.6<br>21.0(10) | 326.4<br>22.6(10) | 312.8<br>25.5(10) | 320.3<br>21.6(10) |

Data arranged as: Mean

Standard deviation (Number of values included in calculation)

There were no statistically significant differences from control at  $p < 0.05$ .

TABLE 2  
MEAN BODY WEIGHT GAINS OF MALE RATS (g)

| Group:<br>Dosage (mg/kg) | IX<br>0           | XI<br>10          | XIII<br>100       | XV<br>1000        |
|--------------------------|-------------------|-------------------|-------------------|-------------------|
| Test                     |                   |                   |                   |                   |
| DAY0 -DAY3               | 12.2<br>6.4(10)   | 18.6<br>5.8(10)   | 14.1<br>2.9(10)   | 15.4<br>5.1(10)   |
| DAY3 -DAY7               | 29.2<br>6.3(10)   | 34.3<br>3.6(10)   | 29.3<br>5.7(10)   | 31.1<br>2.1(10)   |
| DAY7 -DAY10              | 23.1<br>6.0(10)   | 22.2<br>4.7(10)   | 19.4<br>5.0(10)   | 20.7<br>1.9(10)   |
| DAY10 -DAY14             | 27.9<br>3.6(10)   | 23.6#<br>4.1(10)  | 16.3#<br>10.7(10) | 23.4#<br>5.1(10)  |
| DAY14 -DAY17             | 10.8<br>6.9(10)   | 8.5<br>10.6(10)   | 10.9<br>7.0(10)   | 9.8<br>10.0(10)   |
| DAY17 -DAY21             | 14.3<br>8.8(10)   | 10.5<br>15.7(10)  | 14.9<br>7.5(10)   | 14.1<br>8.1(10)   |
| DAY21 -DAY24             | 15.7<br>8.4(10)   | 17.6<br>7.6(10)   | 13.5<br>5.4(10)   | 12.2<br>6.5(10)   |
| DAY24 -DAY27             | 10.4<br>10.1(10)  | 6.5<br>16.3(10)   | 8.5<br>8.7(10)    | 3.7<br>13.5(10)   |
| DAY27 -DAY28             | -17.7<br>3.3(10)  | -17.6<br>4.5(10)  | -18.6<br>3.3(10)  | -17.1<br>4.1(10)  |
| DAY0 -DAY28              | 125.7<br>16.3(10) | 124.0<br>19.8(10) | 108.3<br>21.8(10) | 113.3<br>19.8(10) |

Data arranged as: Mean

Standard deviation (Number of values included in calculation)

# Statistically significant difference at  $p < 0.05$  by Jonckheere-Terpstra trend test

TABLE 3

## MEAN DAILY FOOD CONSUMPTION BY MALE RATS (g/day)

| Group:<br>Dosage (mg/kg) | IX<br>0             | XI<br>10            | XIII<br>100         | XV<br>1000          |
|--------------------------|---------------------|---------------------|---------------------|---------------------|
| Test                     |                     |                     |                     |                     |
| DAY0-DAY7                | 21.7<br>1.7(10)     | 23.3<br>1.1(10)     | 22.0<br>1.3(10)     | 22.9<br>1.5(10)     |
| DAY7-DAY14               | 25.8<br>2.0(10)     | 26.4<br>1.6(10)     | 24.2<br>2.6(10)     | 26.1<br>1.2(10)     |
| DAY14-DAY21              | 24.9<br>0.9(10)     | 24.7<br>1.9(10)     | 23.9<br>2.4(10)     | 25.1<br>1.0(10)     |
| DAY21-DAY27              | 27.1<br>1.8(10)     | 27.0<br>2.0(10)     | 25.7<br>2.9(10)     | 26.3<br>2.8(10)     |
| DAY0-DAY27               | 24.792<br>1.230(10) | 25.293<br>1.331(10) | 23.863<br>1.974(10) | 25.053<br>1.303(10) |

Data arranged as: Mean

Standard deviation (Number of values included in calculation)

There were no statistically significant differences from control at  $p < 0.05$ .

TABLE 4

MEAN DAILY FOOD EFFICIENCY OF MALE RATS  
(g body weight gain/g food consumed)

| Group:<br>Dosage (mg/kg) | IX<br>0             | XI<br>10             | XIII<br>100          | XV<br>1000           |
|--------------------------|---------------------|----------------------|----------------------|----------------------|
| Test                     |                     |                      |                      |                      |
| DAY0-DAY7                | 0.272<br>0.042 (10) | 0.324<br>0.055 (10)  | 0.281<br>0.034 (10)  | 0.289<br>0.028 (10)  |
| DAY7-DAY14               | 0.281<br>0.023 (10) | 0.248#<br>0.038 (10) | 0.206#<br>0.075 (10) | 0.241#<br>0.020 (10) |
| DAY14-DAY21              | 0.144<br>0.042 (10) | 0.106<br>0.084 (10)  | 0.156<br>0.050 (10)  | 0.136<br>0.043 (10)  |
| DAY21-DAY27              | 0.156<br>0.080 (10) | 0.145<br>0.090 (10)  | 0.137<br>0.075 (10)  | 0.092<br>0.099 (10)  |
| DAY0-DAY27               | 0.214<br>0.020 (10) | 0.207<br>0.024 (10)  | 0.196#<br>0.022 (10) | 0.192#<br>0.025 (10) |

Data arranged as: Mean  
Standard deviation (Number of values included in calculation)# Statistically significant difference at  $p < 0.05$  by Jonckheere-Terpstra trend test

TABLE 5

SUMMARY OF CLINICAL OBSERVATIONS FOR MALE RATS - PREDOSING

| Treatment Group   | IX<br>0 mg/kg (Control) | XI<br>10 mg/kg | XIII<br>100 mg/kg | XV<br>1000 mg/kg |
|-------------------|-------------------------|----------------|-------------------|------------------|
| Dose              | 0 mg/kg                 | 10 mg/kg       | 100 mg/kg         | 1000 mg/kg       |
| Animal Count      | 10                      | 10             | 10                | 10               |
| Eye Observations  |                         |                |                   |                  |
| Dark              |                         |                |                   |                  |
| Incidence         | 2 ( 20%)                | 0              | 3 ( 30%)          | 1 ( 10%)         |
| Mean onset (Days) | 17                      |                | 14                | 28               |
| Corneal Opacity   |                         |                |                   |                  |
| Incidence         | 0                       | 0              | 1 ( 10%)          | 0                |
| Mean onset (Days) |                         |                | 17                |                  |
| Opaque            |                         |                |                   |                  |
| Incidence         | 1 ( 10%)                | 0              | 0                 | 0                |
| Mean onset (Days) | 28                      |                |                   |                  |
| Enophthalmus      |                         |                |                   |                  |
| Incidence         | 0                       | 0              | 1 ( 10%)          | 0                |
| Mean onset (Days) |                         |                | 21                |                  |
| Discharge         |                         |                |                   |                  |
| Eye               |                         |                |                   |                  |
| Incidence         | 4 ( 40%)                | 2 ( 20%)       | 2 ( 20%)          | 2 ( 20%)         |
| Mean onset (Days) | 15                      | 3              | 7                 | 7                |
| Nose              |                         |                |                   |                  |
| Incidence         | 2 ( 20%)                | 1 ( 10%)       | 3 ( 30%)          | 3 ( 30%)         |
| Mean onset (Days) | 19                      | 17             | 15                | 22               |
| Hair Loss         |                         |                |                   |                  |
| Incidence         | 2 ( 20%)                | 1 ( 10%)       | 1 ( 10%)          | 0                |
| Mean onset (Days) | 21                      | 17             | 24                |                  |

TABLE 5 (Continued)

SUMMARY OF CLINICAL OBSERVATIONS FOR MALE RATS - PREDOSING

| Treatment Group   | IX                | XI       | XIII      | XV         |
|-------------------|-------------------|----------|-----------|------------|
| Dose              | 0 mg/kg (Control) | 10 mg/kg | 100 mg/kg | 1000 mg/kg |
| Animal Count      | 10                | 10       | 10        | 10         |
| Wound             |                   |          |           |            |
| Superficial       |                   |          |           |            |
| Incidence         | 2 ( 20%)          | 3 ( 30%) | 2 ( 20%)  | 1 ( 10%)   |
| Mean onset (Days) | 19                | 21       | 18        | 14         |

Incidence - The number of animals for which an observation was recorded.

Mean onset (Days) - The mean of the first test day an observation was recorded for that group.  
There were no statistically significant differences at  $p < 0.05$  by Cochran-Armitage trend test.

TABLE 6  
SUMMARY OF CLINICAL OBSERVATIONS FOR MALE RATS - POSTDOSING

| Treatment Group   | IX<br>0 mg/kg (Control)<br>10 | XI<br>10 mg/kg<br>10 | XIII<br>100 mg/kg<br>10 | XV<br>1000 mg/kg<br>10 |
|-------------------|-------------------------------|----------------------|-------------------------|------------------------|
| Animal Count      |                               |                      |                         |                        |
| Eye Observations  |                               |                      |                         |                        |
| Dark              |                               |                      |                         |                        |
| Incidence         | 3 ( 30%)                      | 1 ( 10%)             | 4 ( 40%)                | 0                      |
| Mean onset (Days) | 17                            | 8                    | 13                      |                        |
| Corneal Opacity   |                               |                      |                         |                        |
| Incidence         | 0                             | 0                    | 1 ( 10%)                | 0                      |
| Mean onset (Days) |                               |                      | 15                      |                        |
| Opaque            |                               |                      |                         |                        |
| Incidence         | 1 ( 10%)                      | 0                    | 0                       | 0                      |
| Mean onset (Days) | 27                            |                      |                         |                        |
| Enophthalmus      |                               |                      |                         |                        |
| Incidence         | 0                             | 0                    | 1 ( 10%)                | 0                      |
| Mean onset (Days) |                               |                      | 18                      |                        |
| Discharge         |                               |                      |                         |                        |
| Eye               |                               |                      |                         |                        |
| Incidence         | 10 (100%)                     | 10 (100%)            | 10 (100%)               | 10 (100%)              |
| Mean onset (Days) | 0                             | 0                    | 0                       | 0                      |
| Nose              |                               |                      |                         |                        |
| Incidence         | 10 (100%)                     | 10 (100%)            | 10 (100%)               | 10 (100%)              |
| Mean onset (Days) | 11                            | 12                   | 12                      | 12                     |
| Hair Loss         |                               |                      |                         |                        |
| Incidence         | 2 ( 20%)                      | 1 ( 10%)             | 1 ( 10%)                | 0                      |
| Mean onset (Days) | 21                            | 17                   | 24                      |                        |

TABLE 6 (Continued)

SUMMARY OF CLINICAL OBSERVATIONS FOR MALE RATS - POSTDOSING

| Treatment Group      | IX<br>0 mg/kg (Control) | XI<br>10 mg/kg | XIII<br>100 mg/kg | XV<br>1000 mg/kg |
|----------------------|-------------------------|----------------|-------------------|------------------|
| Dose                 | 0 mg/kg                 | 10 mg/kg       | 100 mg/kg         | 1000 mg/kg       |
| Animal Count         | 10                      | 10             | 10                | 10               |
| Wound                |                         |                |                   |                  |
| Superficial          |                         |                |                   |                  |
| Incidence            | 2 ( 20%)                | 3 ( 30%)       | 2 ( 20%)          | 1 ( 10%)         |
| Mean onset (Days)    | 17                      | 18             | 15                | 11               |
| Stain Fur/Skin       |                         |                |                   |                  |
| Incidence            | 2 ( 20%)                | 1 ( 10%)       | 1 ( 10%)          | 2 ( 20%)         |
| Mean onset (Days)    | 19                      | 11             | 11                | 19               |
| Swollen Observations |                         |                |                   |                  |
| Face                 |                         |                |                   |                  |
| Incidence            | 2 ( 20%)                | 2 ( 20%)       | 1 ( 10%)          | 0                |
| Mean onset (Days)    | 1                       | 2              | 0                 |                  |

Incidence - The number of animals for which an observation was recorded.

Mean onset (Days) - The mean of the first test day an observation was recorded for that group.  
There were no statistically significant differences at  $p < 0.05$  by Cochran-Armitage trend test.

TABLE 7

PERCENT SURVIVAL OF MALE RATS

| Group:<br>Dosage (mg/kg) | IX<br>0 | XI<br>10 | XIII<br>100 | XV<br>1000 |
|--------------------------|---------|----------|-------------|------------|
| <u>Days on Test</u>      |         |          |             |            |
| 0                        | 100     | 100      | 100         | 100        |
| 7                        | 100     | 100      | 100         | 100        |
| 14                       | 100     | 100      | 100         | 100        |
| 21                       | 100     | 100      | 100         | 100        |
| 28                       | 100     | 100      | 100         | 100        |
| Number at study start    | 10      | 10       | 10          | 10         |
| Alive on test day 28     | 10      | 10       | 10          | 10         |

Percent Survival = (Number of rats alive/Number of rats at risk)\*100

Number of rats at risk = Number at study start.

There were no statistically significant decreases in survival.

TABLE 8  
MEAN PFOA CONCENTRATIONS IN MALE RATS

| Dosage (mg/kg/day) | PLASMA PFOA (ppb) <sup>a</sup> |      | n  |
|--------------------|--------------------------------|------|----|
|                    | Mean                           | S.D. |    |
| 0                  | < 10                           | 0.0  | 10 |
| 10                 | < 10                           | 0.0  | 10 |
| 100                | 13 <sup>b</sup>                | 2    | 10 |
| 1000               | 105                            | 24   | 10 |

n = number of samples

S.D. = Standard Deviation

a Lower limit of quantitation (LLOQ) = 10 ppb

b Value of 10 was used in the calculation when the concentration was below LLOQ  
(<10 ppb)

TABLE 9  
MEASURED CONCENTRATION (ppb)  
WHOLE BLOOD FLUORINE

| Dosage (mg/kg/day) | Mean            | n |
|--------------------|-----------------|---|
| 0                  | < 500 ppb or ND | 5 |
| 10                 | ND              | 5 |
| 100                | < 500 ppb or ND | 5 |
| 1000               | < 500 ppb or ND | 5 |

n = number of samples

ND = not detectable = values < 200 ppb

Values "less than 500 ppb" are  $\geq 200$  ppb and < 500 ppb. 500 ppb = Limit of quantification (LOQ).

TABLE 10  
SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

|                                    | Group IX<br>0 mg/kg | Group XI<br>10 mg/kg | Group XIII<br>100 mg/kg | Group XV<br>1000 mg/kg |
|------------------------------------|---------------------|----------------------|-------------------------|------------------------|
| RBC ( $\times 10^6/\mu\text{L}$ )  |                     |                      |                         |                        |
| DAY 28                             | 7.31<br>0.15(7)     | 7.16<br>0.28(9)      | 7.07<br>0.26(9)         | 7.18<br>0.36(9)        |
| HGB (g/dL)                         |                     |                      |                         |                        |
| DAY 28                             | 14.6<br>0.4(7)      | 14.7<br>0.4(9)       | 14.3<br>0.5(9)          | 14.5<br>0.4(9)         |
| HCT (%)                            |                     |                      |                         |                        |
| DAY 28                             | 47.3<br>1.5(7)      | 46.7<br>1.4(9)       | 45.7<br>1.7(9)          | 45.7<br>1.4(9)         |
| MCV (fL)                           |                     |                      |                         |                        |
| DAY 28                             | 64.8<br>2.0(7)      | 65.3<br>1.5(9)       | 64.6<br>1.1(9)          | 63.7<br>1.6(9)         |
| MCH (pg)                           |                     |                      |                         |                        |
| DAY 28                             | 20.0<br>0.7(7)      | 20.6<br>0.6(9)       | 20.3<br>0.5(9)          | 20.1<br>0.6(9)         |
| MCHC (g/dL)                        |                     |                      |                         |                        |
| DAY 28                             | 30.9<br>0.6(7)      | 31.5*<br>0.4(9)      | 31.4<br>0.4(9)          | 31.6*<br>0.3(9)        |
| RDW (%)                            |                     |                      |                         |                        |
| DAY 28                             | 11.5<br>0.6(7)      | 11.6<br>0.4(9)       | 11.7<br>0.9(9)          | 11.2<br>0.3(9)         |
| ARET ( $\times 10^3/\mu\text{L}$ ) |                     |                      |                         |                        |
| DAY 28                             | 321.9<br>95.3(7)    | 264.4<br>58.4(9)     | 302.0<br>140.7(9)       | 251.0<br>55.3(9)       |
| PLT ( $\times 10^3/\mu\text{L}$ )  |                     |                      |                         |                        |
| DAY 28                             | 1264<br>260(2)      | 1142<br>117(7)       | 1210<br>81(8)           | 1242<br>112(8)         |
| WBC ( $\times 10^3/\mu\text{L}$ )  |                     |                      |                         |                        |
| DAY 28                             | 14.85<br>3.11(7)    | 13.80<br>2.50(9)     | 14.31<br>2.41(9)        | 13.84<br>2.23(9)       |
| ANEU ( $\times 10^3/\mu\text{L}$ ) |                     |                      |                         |                        |
| DAY 28                             | 2.49<br>0.95(7)     | 2.15<br>0.46(9)      | 2.25<br>1.02(9)         | 1.97<br>0.40(9)        |
| ALYM ( $\times 10^3/\mu\text{L}$ ) |                     |                      |                         |                        |
| DAY 28                             | 11.50<br>2.93(7)    | 10.86<br>2.06(9)     | 11.32<br>1.64(9)        | 11.05<br>1.99(9)       |

TABLE 10 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

|                                    | Group IX<br>0 mg/kg | Group XI<br>10 mg/kg | Group XIII<br>100 mg/kg | Group XV<br>1000 mg/kg |
|------------------------------------|---------------------|----------------------|-------------------------|------------------------|
| AMON ( $\times 10^3/\mu\text{L}$ ) |                     |                      |                         |                        |
| DAY 28                             | 0.39<br>0.08(7)     | 0.32<br>0.13(9)      | 0.36<br>0.11(9)         | 0.42<br>0.11(9)        |
| AEOS ( $\times 10^3/\mu\text{L}$ ) |                     |                      |                         |                        |
| DAY 28                             | 0.20<br>0.10(7)     | 0.15<br>0.06(9)      | 0.13<br>0.07(9)         | 0.15<br>0.04(9)        |
| ABAS ( $\times 10^3/\mu\text{L}$ ) |                     |                      |                         |                        |
| DAY 28                             | 0.08<br>0.04(7)     | 0.09<br>0.05(9)      | 0.07<br>0.04(9)         | 0.06<br>0.02(9)        |
| ALUC ( $\times 10^3/\mu\text{L}$ ) |                     |                      |                         |                        |
| DAY 28                             | 0.20<br>0.14(7)     | 0.23<br>0.12(9)      | 0.17<br>0.10(9)         | 0.19<br>0.05(9)        |

Data arranged as: Mean  
Standard deviation (Number of values included in calculation)

\* Statistically significant difference from control at  $p < 0.05$  by Dunnett/Tamhane-Dunnett test.

TABLE 11  
SUMMARY OF COAGULATION VALUES FOR MALE RATS

|            | Group IX<br>0 mg/kg | Group XI<br>10 mg/kg | Group XIII<br>100 mg/kg | Group XV<br>1000 mg/kg |
|------------|---------------------|----------------------|-------------------------|------------------------|
| PT (sec)   |                     |                      |                         |                        |
| DAY 28     | 15.5<br>0.5(10)     | 15.9<br>0.6(10)      | 15.6<br>0.5(10)         | 16.1<br>0.8(10)        |
| APTT (sec) |                     |                      |                         |                        |
| DAY 28     | 18.0<br>1.6(10)     | 18.7<br>2.2(10)      | 17.5<br>1.2(10)         | 18.8<br>1.9(10)        |

Data arranged as: Mean

Standard deviation (Number of values included in calculation)

There were no statistically significant differences from control at  $p < 0.05$ .

TABLE 12  
SUMMARY OF CLINICAL CHEMISTRY VALUES FOR MALE RATS

|              | Group IX<br>0 mg/kg | Group XI<br>10 mg/kg | Group XIII<br>100 mg/kg | Group XV<br>1000 mg/kg |
|--------------|---------------------|----------------------|-------------------------|------------------------|
| AST (U/L)    |                     |                      |                         |                        |
| DAY 28       | 122<br>30(10)       | 122<br>22(10)        | 106<br>20(10)           | 108<br>23(10)          |
| ALT (U/L)    |                     |                      |                         |                        |
| DAY 28       | 52<br>7(10)         | 51<br>9(10)          | 44<br>9(10)             | 47<br>11(10)           |
| SDH (U/L)    |                     |                      |                         |                        |
| DAY 28       | 18.6<br>7.6(10)     | 15.0<br>7.0(10)      | 11.9<br>2.4(10)         | 12.9<br>4.6(10)        |
| ALKP (U/L)   |                     |                      |                         |                        |
| DAY 28       | 212<br>45(10)       | 220<br>47(10)        | 205<br>43(10)           | 244<br>51(10)          |
| BILI (mg/dL) |                     |                      |                         |                        |
| DAY 28       | 0.05<br>0.00(10)    | 0.06<br>0.02(10)     | 0.05<br>0.00(10)        | 0.06<br>0.02(10)       |
| BUN (mg/dL)  |                     |                      |                         |                        |
| DAY 28       | 18<br>2(10)         | 17<br>2(10)          | 15*<br>2(10)            | 15*<br>2(10)           |
| CREA (mg/dL) |                     |                      |                         |                        |
| DAY 28       | 0.29<br>0.05(10)    | 0.26<br>0.05(10)     | 0.24*<br>0.02(10)       | 0.22*<br>0.03(10)      |
| CHOL (mg/dL) |                     |                      |                         |                        |
| DAY 28       | 48<br>11(10)        | 49<br>7(10)          | 48<br>5(10)             | 39*<br>6(10)           |
| TRIG (mg/dL) |                     |                      |                         |                        |
| DAY 28       | 43<br>18(10)        | 48<br>24(10)         | 36<br>13(10)            | 31<br>13(10)           |
| GLUC (mg/dL) |                     |                      |                         |                        |
| DAY 28       | 113<br>28(10)       | 104<br>12(10)        | 101<br>10(10)           | 107<br>18(10)          |
| TP (g/dL)    |                     |                      |                         |                        |
| DAY 28       | 6.1<br>0.3(10)      | 6.1<br>0.4(10)       | 6.0<br>0.3(10)          | 6.0<br>0.3(10)         |
| ALB (g/dL)   |                     |                      |                         |                        |
| DAY 28       | 4.1<br>0.2(10)      | 4.1<br>0.3(10)       | 4.1<br>0.1(10)          | 4.1<br>0.2(10)         |

TABLE 12 (Continued)

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR MALE RATS

|              | Group IX<br>0 mg/kg | Group XI<br>10 mg/kg | Group XIII<br>100 mg/kg | Group XV<br>1000 mg/kg |
|--------------|---------------------|----------------------|-------------------------|------------------------|
| GLOB (g/dL)  |                     |                      |                         |                        |
| DAY 28       | 2.0<br>0.3(10)      | 2.1<br>0.2(10)       | 2.0<br>0.2(10)          | 1.9<br>0.2(10)         |
| CALC (mg/dL) |                     |                      |                         |                        |
| DAY 28       | 11.4<br>0.7(10)     | 11.2<br>0.6(10)      | 11.1<br>0.3(10)         | 11.2<br>0.2(10)        |
| IPHS (mg/dL) |                     |                      |                         |                        |
| DAY 28       | 11.9<br>2.2(10)     | 11.2<br>1.5(10)      | 10.4<br>0.7(10)         | 10.7<br>0.6(10)        |
| NA (mmol/L)  |                     |                      |                         |                        |
| DAY 28       | 147.2<br>1.7(10)    | 147.6<br>2.3(10)     | 147.7<br>1.6(10)        | 148.2<br>1.8(10)       |
| K (mmol/L)   |                     |                      |                         |                        |
| DAY 28       | 6.41<br>0.65(10)    | 6.25<br>0.42(10)     | 6.05<br>0.45(10)        | 5.80*<br>0.30(10)      |
| CL (mmol/L)  |                     |                      |                         |                        |
| DAY 28       | 102.3<br>2.1(10)    | 102.6<br>1.7(10)     | 103.2<br>1.3(10)        | 104.2<br>2.5(10)       |
| PFLU (μg/mL) |                     |                      |                         |                        |
| DAY 28       | 0.1<br>0.0(10)      | 0.1<br>0.0(10)       | 0.1<br>0.0(10)          | 0.1<br>0.0(10)         |

Data arranged as: Mean

Standard deviation (Number of values included in calculation)

\* Statistically significant difference from control at  $p < 0.05$  by Dunnett/Tamhane-Dunnett test.

TABLE 13  
SUMMARY OF URINALYSIS VALUES FOR MALE RATS

|              | Group IX<br>0 mg/kg | Group XI<br>10 mg/kg | Group XIII<br>100 mg/kg | Group XV<br>1000 mg/kg |
|--------------|---------------------|----------------------|-------------------------|------------------------|
| VOL (mL)     |                     |                      |                         |                        |
| DAY 28       | 9.0<br>5.0(10)      | 7.2<br>4.5(10)       | 11.2<br>5.0(10)         | 8.5<br>3.4(10)         |
| UOSM (mOsm)  |                     |                      |                         |                        |
| DAY 28       | 1069<br>691(10)     | 1461<br>662(10)      | 778<br>407(10)          | 924<br>346(10)         |
| pH           |                     |                      |                         |                        |
| DAY 28       | 7.5<br>0.4(9)       | 7.4<br>0.8(10)       | 7.6<br>0.5(10)          | 7.4<br>0.5(10)         |
| URO (EU/dL)  |                     |                      |                         |                        |
| DAY 28       | 0.2<br>0.0(9)       | 0.2<br>0.0(10)       | 0.2<br>0.0(10)          | 0.2<br>0.0(10)         |
| UMTP (mg/dL) |                     |                      |                         |                        |
| DAY 28       | 62<br>35(10)        | 111*<br>59(9)        | 48<br>33(10)            | 59<br>33(10)           |
| UFLU (μg)    |                     |                      |                         |                        |
| DAY 28       | 8.0<br>2.9(10)      | 7.1<br>2.0(10)       | 8.1<br>1.6(10)          | 8.0<br>1.6(10)         |

Data arranged as: Mean

Standard deviation (Number of values included in calculation)

\* Statistically significant difference from control at  $p < 0.05$  by Dunnett/Tamhane-Dunnett test.

TABLE 14

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS

|                                    |                       | MEAN FINAL BODY, ABSOLUTE AND RELATIVE ORGAN WEIGHTS (GRAMS) |                       |                       |  |
|------------------------------------|-----------------------|--------------------------------------------------------------|-----------------------|-----------------------|--|
| Group:                             | IX                    | XI                                                           | XIII                  | XV                    |  |
| Dosage (mg/kg)                     | 0                     | 10                                                           | 100                   | 1000                  |  |
| Test                               |                       |                                                              |                       |                       |  |
| LIVER                              | 10.405<br>1.287(10)   | 10.571<br>1.087(10)                                          | 9.923<br>1.142(10)    | 10.292<br>0.744(10)   |  |
| KIDNEYS                            | 2.843<br>0.264(10)    | 2.890<br>0.294(10)                                           | 2.818<br>0.246(10)    | 2.815<br>0.146(10)    |  |
| THYROID GLAND                      | 0.016<br>0.003(10)    | 0.017<br>0.004(10)                                           | 0.017<br>0.003(10)    | 0.017<br>0.004(10)    |  |
| FINAL BODY WEIGHT                  | 332.550<br>20.986(10) | 326.380<br>22.630(10)                                        | 312.830<br>25.545(10) | 320.270<br>21.593(10) |  |
| LIVER/<br>FINAL BODY * 100         | 3.120<br>0.215(10)    | 3.236<br>0.199(10)                                           | 3.166<br>0.170(10)    | 3.218<br>0.202(10)    |  |
| KIDNEYS/<br>FINAL BODY * 100       | 0.855<br>0.052(10)    | 0.886<br>0.073(10)                                           | 0.901<br>0.042(10)    | 0.881<br>0.047(10)    |  |
| THYROID GLAND/<br>FINAL BODY * 100 | 0.005<br>0.001(10)    | 0.005<br>0.001(10)                                           | 0.005<br>0.001(10)    | 0.005<br>0.001(10)    |  |

Data summarized as: Mean  
Standard Deviation (n)

Statistical Methods: Trend test (Jonckheere-Terpstra).

There were no statistically significant differences at  $p < 0.05$ .

TABLE 15  
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS

| LESIONS                                               | TREATMENT | LESION INCIDENCE (Numeric) |                   |                      |                     |  |
|-------------------------------------------------------|-----------|----------------------------|-------------------|----------------------|---------------------|--|
|                                                       |           | Males                      |                   |                      |                     |  |
|                                                       |           | 0<br>mg/kg<br>IX           | 10<br>mg/kg<br>XI | 100<br>mg/kg<br>XIII | 1000<br>mg/kg<br>XV |  |
| LIVER                                                 |           | (10)                       | (10)              | (10)                 | (10)                |  |
| NO ABNORMALITY DETECTED<br>DISCOLORATION, BROWN.      |           | 10                         | 9<br>1            | 10                   | 10                  |  |
| KIDNEYS                                               |           | (10)                       | (10)              | (10)                 | (10)                |  |
| NO ABNORMALITY DETECTED<br>DILATATION, RIGHT, PELVIS. |           | 9<br>1                     | 10                | 10                   | 10                  |  |
| THYROID GLAND                                         |           | (10)                       | (10)              | (10)                 | (10)                |  |
| NO ABNORMALITY DETECTED                               |           | 10                         | 10                | 10                   | 10                  |  |
| ORAL CAVITY                                           |           |                            |                   | (1)                  |                     |  |
| ULCER/EROSION.                                        |           |                            |                   | 1                    |                     |  |

Figures in parentheses are the number of animals grossly examined for this tissue  
The absence of a number indicates the finding specified was not identified

TABLE 15 (Continued)  
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS

| LESIONS                 | TREATMENT | LESION INCIDENCE (Numeric) |                   |                      |                     |
|-------------------------|-----------|----------------------------|-------------------|----------------------|---------------------|
|                         |           | Males                      |                   |                      |                     |
|                         |           | 0<br>mg/kg<br>IX           | 10<br>mg/kg<br>XI | 100<br>mg/kg<br>XIII | 1000<br>mg/kg<br>XV |
| SKIN, TREATED           |           | (10)                       | (10)              | (10)                 | (10)                |
| NO ABNORMALITY DETECTED |           | 10                         | 10                | 10                   | 10                  |
| SKIN, UNTREATED         |           | (10)                       | (10)              | (10)                 | (10)                |
| NO ABNORMALITY DETECTED |           | 10                         | 10                | 10                   | 10                  |

Figures in parentheses are the number of animals grossly examined for this tissue  
The absence of a number indicates the finding specified was not identified

TABLE 16

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS

| LESIONS                                              | LESION INCIDENCE (NUMERIC) |                  |                   |                      |                     |  |
|------------------------------------------------------|----------------------------|------------------|-------------------|----------------------|---------------------|--|
|                                                      | TREATMENT                  | Males            |                   |                      |                     |  |
|                                                      |                            | 0<br>mg/kg<br>IX | 10<br>mg/kg<br>XI | 100<br>mg/kg<br>XIII | 1000<br>mg/kg<br>XV |  |
| LIVER                                                |                            | (10)             | (1)               |                      | (10)                |  |
| NECROSIS, FOCAL.<br>minimal                          |                            | 1                |                   |                      | 1                   |  |
| Total observations per lesion                        |                            | 1                |                   |                      | 1                   |  |
| INFLAMMATION, SUBACUTE/CHRONIC.<br>minimal           |                            | 7                |                   |                      | 6                   |  |
| mild                                                 |                            | 3                |                   |                      | 4                   |  |
| Total observations per lesion                        |                            | 10               |                   |                      | 10                  |  |
| HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED.<br>minimal |                            | 2                |                   |                      |                     |  |
| Total observations per lesion                        |                            | 2                |                   |                      |                     |  |
| FIBROSIS, FOCAL, CENTRILOBULAR.<br>mild              |                            |                  | 1                 |                      |                     |  |
| Total observations per lesion                        |                            |                  | 1                 |                      |                     |  |
| KIDNEYS                                              |                            | (10)             |                   |                      | (10)                |  |
| NO ABNORMALITY DETECTED                              |                            | 1                |                   |                      | 7                   |  |
| CHRONIC PROGRESSIVE NEPHROPATHY.<br>minimal          |                            | 5                |                   |                      | 3                   |  |

Figures in parentheses are number of animals microscopically examined for this tissue  
The absence of a number indicates the lesion specified was not identified

TABLE 16 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS

| LESIONS                          | LESION INCIDENCE (NUMERIC) |                  |                   |                      |                     |
|----------------------------------|----------------------------|------------------|-------------------|----------------------|---------------------|
|                                  | Males                      |                  |                   |                      |                     |
|                                  | TREATMENT                  | 0<br>mg/kg<br>IX | 10<br>mg/kg<br>XI | 100<br>mg/kg<br>XIII | 1000<br>mg/kg<br>XV |
| KIDNEYS                          |                            | (10)             |                   |                      | (10)                |
| CHRONIC PROGRESSIVE NEPHROPATHY. |                            |                  |                   |                      |                     |
| Total observations per lesion    |                            | 5                |                   |                      | 3                   |
| HYDRONEPHROSIS, UNILATERAL.      |                            |                  |                   |                      |                     |
| minimal                          |                            | 1                |                   |                      |                     |
| Total observations per lesion    |                            | 1                |                   |                      |                     |
| AGGREGATES, LYMPHOID.            |                            |                  |                   |                      |                     |
| minimal                          |                            | 5                |                   |                      | 1                   |
| Total observations per lesion    |                            | 5                |                   |                      | 1                   |
| THYROID GLAND                    |                            | (10)             |                   |                      | (10)                |
| NO ABNORMALITY DETECTED          |                            | 8                |                   |                      | 8                   |
| HYPERTROPHY, FOLLICULAR CELL.    |                            |                  |                   |                      |                     |
| minimal                          |                            | 2                |                   |                      | 2                   |
| Total observations per lesion    |                            | 2                |                   |                      | 2                   |
| ECTOPIC THYMUS TISSUE.           |                            | 1                |                   |                      |                     |

Figures in parentheses are number of animals microscopically examined for this tissue  
The absence of a number indicates the lesion specified was not identified

TABLE 16 (Continued)

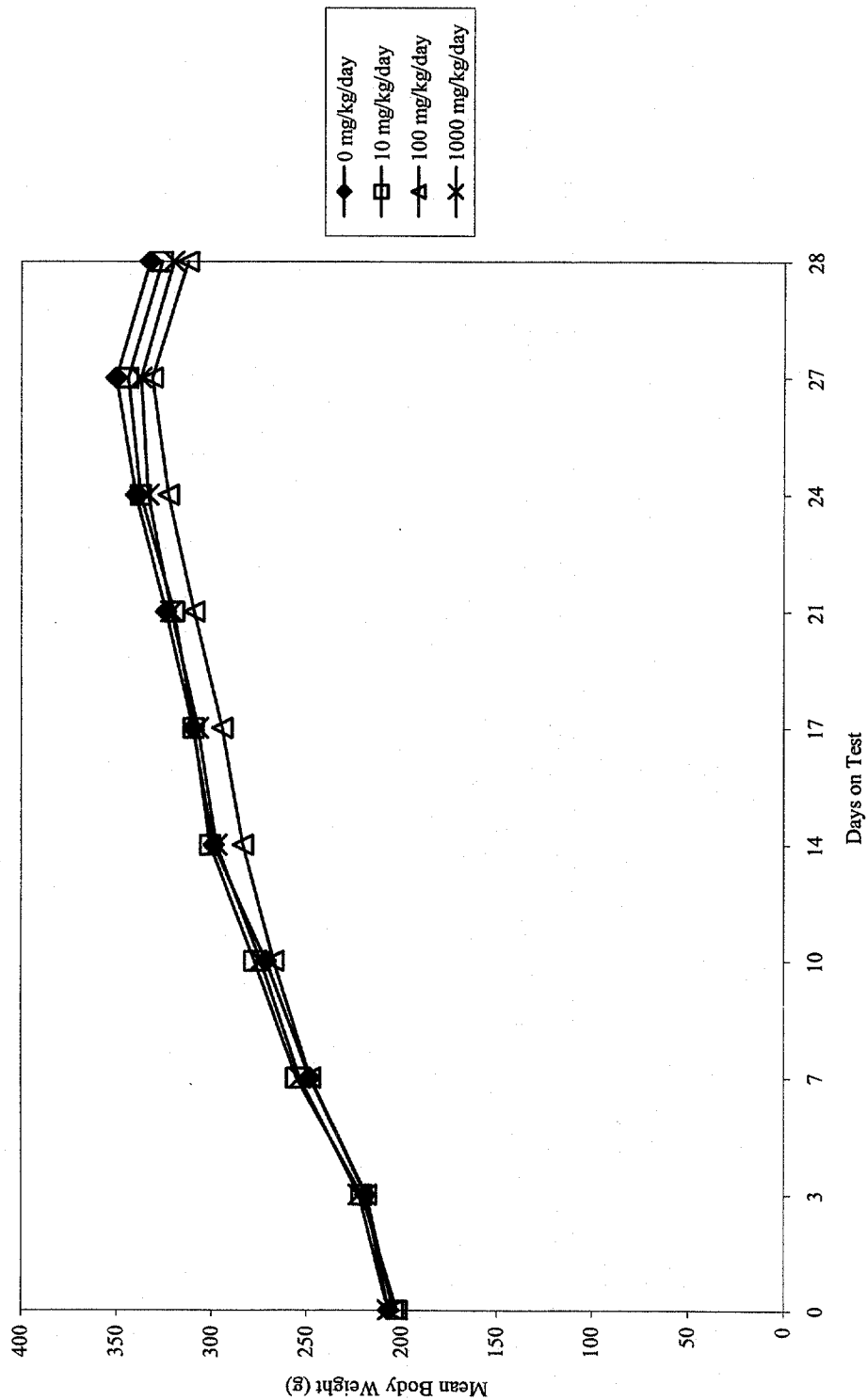
INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS

| LESIONS                                | LESION INCIDENCE (NUMERIC) |                  |                   |                      |                     |
|----------------------------------------|----------------------------|------------------|-------------------|----------------------|---------------------|
|                                        | TREATMENT                  | Males            |                   |                      |                     |
|                                        |                            | 0<br>mg/kg<br>IX | 10<br>mg/kg<br>XI | 100<br>mg/kg<br>XIII | 1000<br>mg/kg<br>XV |
| SKIN, TREATED                          |                            | (10)             |                   |                      | (10)                |
| NO ABNORMALITY DETECTED                |                            | 10               |                   |                      | 9                   |
| INFLAMMATION, FOCAL, ACUTE.            |                            |                  |                   |                      | 1                   |
| minimal                                |                            |                  |                   |                      | 1                   |
| Total observations per lesion          |                            | (10)             |                   |                      | (10)                |
| SKIN, UNTREATED                        |                            |                  |                   |                      |                     |
| NO ABNORMALITY DETECTED                |                            | 10               |                   |                      | 8                   |
| INFLAMMATION, FOCAL, SUBACUTE/CHRONIC. |                            |                  |                   |                      | 2                   |
| minimal                                |                            |                  |                   |                      | 2                   |
| Total observations per lesion          |                            |                  |                   |                      |                     |

Figures in parentheses are number of animals microscopically examined for this tissue  
The absence of a number indicates the lesion specified was not identified

**FIGURE**

FIGURE 1  
MEAN BODY WEIGHTS OF MALE RATS



## **APPENDICES**

**APPENDIX A**  
**INDIVIDUAL BODY WEIGHTS**

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Study [REDACTED]

Print Date: 14-Jan-2004  
Print Time: 15:02:40

Individual Body Weights

|                            | Body Weight |       | Body Weight |       | Body Weight |       | Body Weight |        | Body Weight |        | Body Weight |        | Body Weight |        | Body Weight |        | Body Weight |        |
|----------------------------|-------------|-------|-------------|-------|-------------|-------|-------------|--------|-------------|--------|-------------|--------|-------------|--------|-------------|--------|-------------|--------|
|                            | g           | Day 0 | g           | Day 3 | g           | Day 7 | g           | Day 10 | g           | Day 14 | g           | Day 17 | g           | Day 21 | g           | Day 24 | g           | Day 27 |
| Male, IX 0 mg/kg (Control) |             |       |             |       |             |       |             |        |             |        |             |        |             |        |             |        |             |        |
| 901                        | 214.8       | 225.3 | 259.9       | 281.5 | 310.3       | 323.7 | 337.2       | 340.9  | 357.9       |        |             |        |             |        |             |        |             |        |
| 902                        | 203.8       | 209.0 | 241.9       | 262.5 | 284.1       | 296.6 | 315.3       | 321.6  | 331.5       |        |             |        |             |        |             |        |             |        |
| 903                        | 203.9       | 220.3 | 249.9       | 266.7 | 297.0       | 312.5 | 309.6       | 338.5  | 352.6       |        |             |        |             |        |             |        |             |        |
| 904                        | 203.6       | 218.6 | 250.1       | 272.8 | 298.2       | 308.9 | 327.5       | 337.7  | 344.2       |        |             |        |             |        |             |        |             |        |
| 905                        | 195.7       | 202.8 | 230.5       | 249.3 | 276.5       | 288.5 | 308.6       | 333.2  | 344.2       |        |             |        |             |        |             |        |             |        |
| 906                        | 206.9       | 214.7 | 243.4       | 263.1 | 288.1       | 310.0 | 320.0       | 343.6  | 352.1       |        |             |        |             |        |             |        |             |        |
| 907                        | 220.9       | 243.7 | 264.1       | 295.2 | 320.2       | 326.6 | 346.8       | 359.2  | 369.9       |        |             |        |             |        |             |        |             |        |
| 908                        | 193.4       | 197.2 | 228.0       | 246.1 | 277.8       | 293.7 | 298.2       | 308.8  | 309.9       |        |             |        |             |        |             |        |             |        |
| 909                        | 218.1       | 231.7 | 249.0       | 284.1 | 315.0       | 315.0 | 342.8       | 360.0  | 371.8       |        |             |        |             |        |             |        |             |        |
| 910                        | 207.1       | 226.8 | 265.2       | 291.2 | 323.8       | 324.0 | 336.2       | 355.6  | 388.4       |        |             |        |             |        |             |        |             |        |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Print Date: 14-Jan-2004  
Print Time: 15:02:40

Study: [REDACTED]

Individual Body Weights

Body Weight  
g  
Day 28

Male, IX 0 mg/kg (Control)

|     |       |
|-----|-------|
| 901 | 340.8 |
| 902 | 309.3 |
| 903 | 337.4 |
| 904 | 321.5 |
| 905 | 323.1 |
| 906 | 331.8 |
| 907 | 340.9 |
| 908 | 296.8 |
| 909 | 357.3 |
| 910 | 366.6 |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Study: [REDACTED]

Print Date: 14-Jan-2004  
Print Time: 15:02:40

|                   | Individual Body Weights |                  |                  |                  |                  |                  |                  |                  |                  |                  |
|-------------------|-------------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
|                   | Body Weight<br>g        | Body Weight<br>g | Body Weight<br>g | Body Weight<br>g | Body Weight<br>g | Body Weight<br>g | Body Weight<br>g | Body Weight<br>g | Body Weight<br>g | Body Weight<br>g |
|                   | Day 0                   | Day 3            | Day 7            | Day 10           | Day 14           | Day 17           | Day 21           | Day 24           | Day 27           |                  |
| Male, XI 10 mg/kg |                         |                  |                  |                  |                  |                  |                  |                  |                  |                  |
| 1101              | 186.5                   | 217.5            | 256.0            | 283.8            | 309.2            | 331.4            | 341.5            | 367.9            | 367.0            |                  |
| 1102              | 203.6                   | 219.2            | 254.3            | 273.4            | 297.1            | 309.3            | 323.7            | 336.8            | 328.2            |                  |
| 1103              | 206.7                   | 228.8            | 266.3            | 286.9            | 300.9            | 306.8            | 316.4            | 328.3            | 354.2            |                  |
| 1104              | 198.7                   | 211.1            | 244.2            | 264.6            | 288.1            | 282.9            | 309.8            | 323.0            | 331.8            |                  |
| 1105              | 192.7                   | 202.6            | 236.3            | 253.1            | 274.6            | 293.0            | 305.1            | 322.7            | 324.7            |                  |
| 1106              | 202.2                   | 221.9            | 260.8            | 281.3            | 305.6            | 306.7            | 306.9            | 325.0            | 341.4            |                  |
| 1107              | 217.6                   | 237.0            | 268.1            | 295.7            | 323.0            | 329.6            | 317.8            | 342.3            | 378.1            |                  |
| 1108              | 194.7                   | 211.6            | 238.5            | 261.9            | 291.1            | 308.9            | 294.0            | 325.6            | 305.1            |                  |
| 1109              | 215.2                   | 232.6            | 267.2            | 296.6            | 321.7            | 337.3            | 365.8            | 375.1            | 377.7            |                  |
| 1110              | 205.6                   | 226.7            | 260.4            | 276.4            | 297.9            | 288.7            | 318.1            | 328.0            | 331.5            |                  |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Print Date: 14-Jan-2004  
Print Time: 15:02:40

Study [REDACTED]

Individual Body Weights

Body Weight

g

Day 28

Male, XI 10 mg/kg

|      |       |
|------|-------|
| 1101 | 349.2 |
| 1102 | 313.8 |
| 1103 | 338.7 |
| 1104 | 317.7 |
| 1105 | 301.8 |
| 1106 | 326.3 |
| 1107 | 352.1 |
| 1108 | 293.8 |
| 1109 | 359.9 |
| 1110 | 310.5 |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Study [REDACTED]

Print Date: 14-Jan-2004  
Print Time: 15:02:40

| Individual Body Weights   |                           |                           |                            |                            |                            |                            |                            |                            |       |
|---------------------------|---------------------------|---------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|-------|
| Body Weight<br>g<br>Day 0 | Body Weight<br>g<br>Day 3 | Body Weight<br>g<br>Day 7 | Body Weight<br>g<br>Day 10 | Body Weight<br>g<br>Day 14 | Body Weight<br>g<br>Day 17 | Body Weight<br>g<br>Day 21 | Body Weight<br>g<br>Day 24 | Body Weight<br>g<br>Day 27 |       |
| Male, XIII 100 mg/kg      |                           |                           |                            |                            |                            |                            |                            |                            |       |
| 1301                      | 213.5                     | 230.8                     | 261.2                      | 279.8                      | 300.1                      | 307.0                      | 325.5                      | 338.2                      | 345.3 |
| 1302                      | 205.1                     | 219.9                     | 257.2                      | 274.1                      | 301.1                      | 315.2                      | 327.6                      | 338.9                      | 348.3 |
| 1303                      | 201.9                     | 213.9                     | 234.2                      | 246.1                      | 234.7                      | 249.8                      | 279.0                      | 290.2                      | 301.2 |
| 1304                      | 195.4                     | 208.0                     | 233.0                      | 246.3                      | 260.7                      | 269.8                      | 281.4                      | 294.8                      | 297.3 |
| 1305                      | 198.2                     | 213.1                     | 241.1                      | 267.6                      | 280.9                      | 302.6                      | 302.5                      | 320.8                      | 342.5 |
| 1306                      | 200.9                     | 220.5                     | 256.4                      | 280.8                      | 306.8                      | 314.6                      | 328.0                      | 348.0                      | 366.5 |
| 1307                      | 219.5                     | 233.4                     | 266.3                      | 285.5                      | 306.7                      | 325.8                      | 339.7                      | 341.2                      | 337.4 |
| 1308                      | 192.9                     | 204.7                     | 231.8                      | 252.3                      | 269.8                      | 272.1                      | 290.5                      | 304.7                      | 303.8 |
| 1309                      | 212.1                     | 221.7                     | 255.2                      | 281.2                      | 297.4                      | 297.2                      | 317.3                      | 337.0                      | 354.6 |
| 1310                      | 205.4                     | 220.1                     | 242.6                      | 259.6                      | 278.1                      | 291.0                      | 302.8                      | 315.1                      | 317.1 |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Print Date: 14-Jan-2004  
Print Time: 15:02:40

study [REDACTED]

Individual Body Weights

Body Weight

g

Day 28

Male, XIII 100 mg/kg

|      |       |
|------|-------|
| 1301 | 329.0 |
| 1302 | 327.8 |
| 1303 | 280.7 |
| 1304 | 278.4 |
| 1305 | 319.5 |
| 1306 | 346.2 |
| 1307 | 325.2 |
| 1308 | 283.0 |
| 1309 | 340.3 |
| 1310 | 298.2 |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Study: [REDACTED]

Print Date: 14-Jan-2004  
Print Time: 15:02:40

|                     | Individual Body Weights |                  |                  |                  |                  |                  |                  |                  |                  |                  |
|---------------------|-------------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
|                     | Body Weight<br>g        | Body Weight<br>g | Body Weight<br>g | Body Weight<br>g | Body Weight<br>g | Body Weight<br>g | Body Weight<br>g | Body Weight<br>g | Body Weight<br>g | Body Weight<br>g |
|                     | Day 0                   | Day 3            | Day 7            | Day 10           | Day 14           | Day 17           | Day 21           | Day 24           | Day 27           |                  |
| Male, XV 1000 mg/kg |                         |                  |                  |                  |                  |                  |                  |                  |                  |                  |
| 1501                | 212.5                   | 226.3            | 254.3            | 277.7            | 293.1            | 305.6            | 312.4            | 329.3            | 330.6            |                  |
| 1502                | 203.6                   | 220.8            | 249.3            | 270.0            | 289.2            | 290.4            | 319.2            | 332.1            | 325.2            |                  |
| 1503                | 211.9                   | 237.9            | 272.1            | 290.7            | 315.2            | 338.4            | 340.4            | 358.8            | 384.7            |                  |
| 1504                | 201.8                   | 213.4            | 245.0            | 268.7            | 295.2            | 298.2            | 306.6            | 317.6            | 305.7            |                  |
| 1505                | 200.0                   | 215.3            | 246.4            | 264.0            | 294.6            | 307.8            | 319.8            | 336.1            | 356.0            |                  |
| 1506                | 202.3                   | 210.7            | 239.5            | 259.8            | 284.4            | 294.9            | 306.2            | 314.4            | 308.1            |                  |
| 1507                | 217.1                   | 226.2            | 259.7            | 280.2            | 300.5            | 311.4            | 331.4            | 340.8            | 347.7            |                  |
| 1508                | 198.2                   | 214.4            | 246.3            | 266.0            | 296.5            | 285.2            | 309.1            | 316.7            | 335.0            |                  |
| 1509                | 213.7                   | 231.8            | 263.9            | 285.3            | 303.5            | 323.8            | 337.5            | 337.1            | 327.8            |                  |
| 1510                | 208.8                   | 226.7            | 258.3            | 279.0            | 302.9            | 317.6            | 331.6            | 353.5            | 352.5            |                  |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Print Date: 14-Jan-2004  
Print Time: 15:02:40

Study: [REDACTED]

Individual Body Weights

Body Weight  
g  
Day 28

Male, XV 1000 mg/kg

|      |       |
|------|-------|
| 1501 | 311.7 |
| 1502 | 306.0 |
| 1503 | 362.2 |
| 1504 | 294.8 |
| 1505 | 337.9 |
| 1506 | 294.7 |
| 1507 | 332.9 |
| 1508 | 311.3 |
| 1509 | 314.4 |
| 1510 | 336.8 |

**APPENDIX B**  
**INDIVIDUAL FOOD CONSUMPTION**

## INDIVIDUAL FOOD CONSUMPTION

### EXPLANATORY NOTES

#### Abbreviation

g/anm/day = grams/animal/day

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Study [REDACTED]

Print Date: 14-Jan-2004  
Print Time: 15:02:49

Individual Food Consumption

|                            | Food Cons. g/ann/day |        | Food Cons. g/ann/day |        | Food Cons. g/ann/day |        |
|----------------------------|----------------------|--------|----------------------|--------|----------------------|--------|
|                            | Day 7                | Day 14 | Day 21               | Day 27 | Day 27               | Day 27 |
| Male, IX 0 mg/kg (Control) |                      |        |                      |        |                      |        |
| 901                        | 21.5                 | 25.9   | 25.6                 | 25.1   | 25.1                 | 25.1   |
| 902                        | 20.4                 | 23.6   | 23.4                 | 25.0   | 25.0                 | 25.0   |
| 903                        | 21.3                 | 23.8   | 23.5                 | 27.5   | 27.5                 | 27.5   |
| 904                        | 23.5                 | 27.2   | 25.9                 | 25.7   | 25.7                 | 25.7   |
| 905                        | 18.9                 | 23.6   | 24.8                 | 28.6   | 28.6                 | 28.6   |
| 906                        | 22.3                 | 24.5   | 25.5                 | 28.4   | 28.4                 | 28.4   |
| 907                        | 23.2                 | 27.1   | 24.8                 | 25.7   | 25.7                 | 25.7   |
| 908                        | 19.5                 | 24.6   | 24.8                 | 26.0   | 26.0                 | 26.0   |
| 909                        | 22.5                 | 28.4   | 26.2                 | 29.3   | 29.3                 | 29.3   |
| 910                        | 23.7                 | 28.9   | 24.6                 | 30.1   | 30.1                 | 30.1   |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Study: [REDACTED]

Print Date: 14-Jan-2004  
Print Time: 15:02:49

Individual Food Consumption

|                   | Food Cons. |       | Food Cons. |        | Food Cons. |        |
|-------------------|------------|-------|------------|--------|------------|--------|
|                   | g/ann/day  | Day 7 | g/ann/day  | Day 14 | g/ann/day  | Day 21 |
| Male, XI 10 mg/kg |            |       |            |        |            |        |
| 1101              | 21.7       | 27.7  | 26.3       | 28.5   |            |        |
| 1102              | 22.1       | 24.8  | 24.3       | 25.5   |            |        |
| 1103              | 24.3       | 28.2  | 26.0       | 28.0   |            |        |
| 1104              | 22.9       | 23.8  | 23.5       | 23.9   |            |        |
| 1105              | 24.1       | 25.7  | 25.4       | 26.2   |            |        |
| 1106              | 24.5       | 27.3  | 25.2       | 28.8   |            |        |
| 1107              | 24.5       | 27.3  | 23.2       | 30.1   |            |        |
| 1108              | 21.8       | 25.6  | 22.0       | 26.1   |            |        |
| 1109              | 24.0       | 28.2  | 28.4       | 28.3   |            |        |
| 1110              | 23.6       | 25.1  | 23.0       | 24.5   |            |        |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Print Date: 14-Jan-2004  
Print Time: 15:02:49

Study: [REDACTED]

Individual Food Consumption

|                      | Food Cons. |       | Food Cons. |        | Food Cons. |        |
|----------------------|------------|-------|------------|--------|------------|--------|
|                      | g/ann/day  | Day 7 | g/ann/day  | Day 14 | g/ann/day  | Day 27 |
| Male, XIII 100 mg/kg |            |       |            |        |            |        |
| 1301                 | 23.7       | 27.5  | 26.8       | 28.6   |            |        |
| 1302                 | 22.9       | 25.3  | 26.2       | 26.0   |            |        |
| 1303                 | 19.3       | 18.7  | 22.5       | 22.5   |            |        |
| 1304                 | 20.4       | 21.7  | 21.5       | 24.0   |            |        |
| 1305                 | 22.1       | 24.2  | 24.3       | 28.6   |            |        |
| 1306                 | 23.0       | 26.2  | 24.2       | 29.1   |            |        |
| 1307                 | 22.8       | 24.3  | 24.3       | 22.9   |            |        |
| 1308                 | 22.5       | 23.5  | 19.0       | 22.0   |            |        |
| 1309                 | 21.9       | 26.7  | 26.1       | 28.7   |            |        |
| 1310                 | 21.4       | 23.4  | 23.8       | 24.5   |            |        |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

study: [REDACTED]

Print Date: 14-Jan-2004  
Print Time: 15:02:49

Individual Food Consumption

|                     | Food Cons. |           |           | Food Cons. |           |           |
|---------------------|------------|-----------|-----------|------------|-----------|-----------|
|                     | g/ann/day  | g/ann/day | g/ann/day | g/ann/day  | g/ann/day | g/ann/day |
|                     | Day 7      | Day 14    | Day 21    | Day 27     | Day 27    | Day 27    |
| Male, XV 1000 mg/kg |            |           |           |            |           |           |
| 1501                | 22.4       | 26.2      | 25.4      | 27.3       | 27.3      | 27.3      |
| 1502                | 22.2       | 24.8      | 24.9      | 25.8       | 25.8      | 25.8      |
| 1503                | 24.6       | 27.1      | 25.7      | 29.7       | 29.7      | 29.7      |
| 1504                | 22.4       | 26.6      | 23.1      | 23.3       | 23.3      | 23.3      |
| 1505                | 23.2       | 27.3      | 27.1      | 30.0       | 30.0      | 30.0      |
| 1506                | 20.7       | 24.5      | 24.1      | 24.1       | 24.1      | 24.1      |
| 1507                | 21.7       | 25.5      | 25.1      | 25.4       | 25.4      | 25.4      |
| 1508                | 26.0       | 28.0      | 25.3      | 28.2       | 28.2      | 28.2      |
| 1509                | 23.6       | 25.5      | 24.9      | 21.6       | 21.6      | 21.6      |
| 1510                | 22.7       | 24.9      | 24.9      | 28.0       | 28.0      | 28.0      |

## **APPENDIX C**

### **INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY RECORDS**

## INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY RECORDS

### EXPLANATORY NOTES

#### Note

Clinical observations reported in this appendix were recorded during body weight collection. Clinical observations recorded post-dosing are not included but are reported in Appendix D.

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Print Date: 19-Feb-2004  
Print Time: 08:01:56

Study: [REDACTED]

|     |       | Individual Clinical Observations |                                              | Days           |
|-----|-------|----------------------------------|----------------------------------------------|----------------|
| Sex | Group | Animal                           | Observation                                  |                |
| M   | IX    | 901                              | General observation, No Abnormality Detected | 0-21           |
|     |       |                                  | Eye Observations, Dark, Right                | 24-28          |
|     |       |                                  | Discharge, Eye right, Red                    | 24             |
|     |       |                                  | Sacrificed by design                         | 28             |
| M   | IX    | 902                              | General observation, No Abnormality Detected | 0-17, 24-28    |
|     |       |                                  | Wound, Superficial, Shoulder, Left           | 21             |
|     |       |                                  | Sacrificed by design                         | 28             |
| M   | IX    | 903                              | General observation, No Abnormality Detected | 0-28           |
|     |       |                                  | Sacrificed by design                         | 28             |
| M   | IX    | 904                              | General observation, No Abnormality Detected | 0-7, 17-24     |
|     |       |                                  | Eye Observations, Dark, Right                | 10-14          |
|     |       |                                  | Eye Observations, Opaque, Right              | 28             |
|     |       |                                  | Sacrificed by design                         | 28             |
| M   | IX    | 905                              | General observation, No Abnormality Detected | 0, 7-14, 21-28 |
|     |       |                                  | Discharge, Eye bilateral, Red                | 3              |
|     |       |                                  | Wound, Superficial, Dorsal Body              | 17             |
|     |       |                                  | Sacrificed by design                         | 28             |
| M   | IX    | 906                              | General observation, No Abnormality Detected | 0-17           |
|     |       |                                  | Hair Loss, Forepaw, Bilateral                | 21-28          |
|     |       |                                  | Sacrificed by design                         | 28             |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

Study: [REDACTED]

DuPont-13830

Print Date: 19-Feb-2004  
Print Time: 08:01:56

|      |     | Individual Clinical Observations             |            |
|------|-----|----------------------------------------------|------------|
| M IX | 907 | General observation, No Abnormality Detected | 0-21       |
|      |     | Discharge, Eye bilateral, Red                | 24         |
|      |     | Discharge, Nose, Red                         | 28         |
|      |     | Sacrificed by design                         | 28         |
| M IX | 908 | General observation, No Abnormality Detected | 0-28       |
|      |     | Sacrificed by design                         | 28         |
| M IX | 909 | General observation, No Abnormality Detected | 0-7, 14-28 |
|      |     | Discharge, Eye bilateral, Red                | 10         |
|      |     | Discharge, Nose, Red                         | 10         |
|      |     | Sacrificed by design                         | 28         |
|      |     | General observation, No Abnormality Detected | 0-17       |
| M IX | 910 | Hair Loss, Forepaw, Bilateral                | 21-28      |
|      |     | Sacrificed by design                         | 28         |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Print Date: 19-Feb-2004  
Print Time: 08:01:56

|   |         | Individual Clinical Observations             |                |
|---|---------|----------------------------------------------|----------------|
| M | XI 1101 | General observation, No Abnormality Detected | 0-28           |
|   |         | Sacrificed by design                         | 28             |
| M | XI 1102 | General observation, No Abnormality Detected | 0-14           |
|   |         | Hair Loss, Forepaw, Bilateral                | 21-28          |
|   |         | Hair Loss, Forepaw, Left                     | 17             |
|   |         | Wound, Superficial, Forepaw, Left            | 21-24          |
|   |         | Sacrificed by design                         | 28             |
| M | XI 1103 | General observation, No Abnormality Detected | 0-28           |
|   |         | Sacrificed by design                         | 28             |
| M | XI 1104 | General observation, No Abnormality Detected | 0, 7-17, 24-28 |
|   |         | Discharge, Eye bilateral, Red                | 3              |
|   |         | Wound, Superficial, Neck                     | 21             |
|   |         | Sacrificed by design                         | 28             |
| M | XI 1105 | General observation, No Abnormality Detected | 0, 7-28        |
|   |         | Discharge, Eye bilateral, Red                | 3              |
|   |         | Sacrificed by design                         | 28             |
| M | XI 1106 | General observation, No Abnormality Detected | 0-28           |
|   |         | Sacrificed by design                         | 28             |
| M | XI 1107 | General observation, No Abnormality Detected | 0-14, 21-28    |
|   |         | Discharge, Nose, Red                         | 17             |
|   |         | Sacrificed by design                         | 28             |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Print Date: 19-Feb-2004  
Print Time: 08:01:56

Study: [REDACTED]

| Individual Clinical Observations |    |                                              |
|----------------------------------|----|----------------------------------------------|
| M                                | XI | 1108                                         |
|                                  |    | General observation, No Abnormality Detected |
|                                  |    | 0-17, 28                                     |
|                                  |    | Wound, Superficial, Shoulder, Left           |
|                                  |    | 21-24                                        |
|                                  |    | Sacrificed by design                         |
|                                  |    | 28                                           |
| M                                | XI | 1109                                         |
|                                  |    | General observation, No Abnormality Detected |
|                                  |    | 0-28                                         |
|                                  |    | Sacrificed by design                         |
|                                  |    | 28                                           |
| M                                | XI | 1110                                         |
|                                  |    | General observation, No Abnormality Detected |
|                                  |    | 0-28                                         |
|                                  |    | Sacrificed by design                         |
|                                  |    | 28                                           |

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|   |           | Individual Clinical Observations             |             |
|---|-----------|----------------------------------------------|-------------|
| M | XIII 1301 | General observation, No Abnormality Detected | 0-28        |
|   |           | Sacrificed by design                         | 28          |
| M | XIII 1302 | General observation, No Abnormality Detected | 0-7, 17-28  |
|   |           | Discharge, Eye bilateral, Red                | 10          |
|   |           | Discharge, Nose, Black                       | 10-14       |
|   |           | Sacrificed by design                         | 28          |
| M | XIII 1303 | General observation, No Abnormality Detected | 0-21        |
|   |           | Hair Loss, Forepaw, Bilateral                | 24-28       |
|   |           | Sacrificed by design                         | 28          |
|   |           | General observation, No Abnormality Detected | 0-3         |
| M | XIII 1304 | Eye Observations, Enophthalmus, Right        | 21-28       |
|   |           | Eye Observations, Dark, Right                | 7-28        |
|   |           | Sacrificed by design                         | 28          |
|   |           | General observation, No Abnormality Detected | 0-10, 21-28 |
| M | XIII 1305 | Wound, Superficial, Shoulder, Bilateral      | 14-17       |
|   |           | Sacrificed by design                         | 28          |
|   |           | General observation, No Abnormality Detected | 0-21        |
|   |           | Eye Observations, Dark, Right                | 24-28       |
| M | XIII 1306 | Sacrificed by design                         | 28          |
|   |           | General observation, No Abnormality Detected | 0-21        |
|   |           | Eye Observations, Dark, Right                | 24-28       |
|   |           | Sacrificed by design                         | 28          |
| M | XIII 1307 | General observation, No Abnormality Detected | 0-28        |
|   |           | Sacrificed by design                         | 28          |
|   |           |                                              |             |
|   |           |                                              |             |

H-25425: Repeated-Dose Dermal Toxicity  
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Individual Clinical Observations

|             |                                              |            |
|-------------|----------------------------------------------|------------|
| M XIII 1308 | General observation, No Abnormality Detected | 0,7-14     |
|             | Eye Observations, Corneal Opacity, Right     | 17,24-28   |
|             | Discharge, Eye bilateral, Red                | 3,17       |
|             | Discharge, Nose, Red                         | 17-21      |
|             | Comments, wound superficial right eye        | 21-28      |
|             | Sacrificed by design                         | 28         |
| M XIII 1309 | General observation, No Abnormality Detected | 0-7,14-28  |
|             | Eye Observations, Dark, Right                | 10         |
|             | Sacrificed by design                         | 28         |
| M XIII 1310 | General observation, No Abnormality Detected | 0-14,21-28 |
|             | Discharge, Nose, Red                         | 17         |
|             | Sacrificed by design                         | 28         |

H-25425: Repeated-Dose Dermal Toxicity  
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Individual Clinical Observations

|   |    |      |                                              |             |
|---|----|------|----------------------------------------------|-------------|
| M | XV | 1501 | General observation, No Abnormality Detected | 0, 7-24     |
|   |    |      | Discharge, Eye bilateral, Red                | 3           |
|   |    |      | Discharge, Nose, Red                         | 28          |
|   |    |      | Sacrificed by design                         | 28          |
| M | XV | 1502 | General observation, No Abnormality Detected | 0-28        |
|   |    |      | Sacrificed by design                         | 28          |
| M | XV | 1503 | General observation, No Abnormality Detected | 0-17, 24-28 |
|   |    |      | Discharge, Nose, Red                         | 21          |
|   |    |      | Sacrificed by design                         | 28          |
| M | XV | 1504 | General observation, No Abnormality Detected | 0-10, 21-28 |
|   |    |      | Wound, Superficial, Dorsal Body              | 14-17       |
|   |    |      | Sacrificed by design                         | 28          |
| M | XV | 1505 | General observation, No Abnormality Detected | 0-7, 14-28  |
|   |    |      | Discharge, Eye bilateral, Red                | 10          |
|   |    |      | Sacrificed by design                         | 28          |
| M | XV | 1506 | General observation, No Abnormality Detected | 0-28        |
|   |    |      | Sacrificed by design                         | 28          |
| M | XV | 1507 | General observation, No Abnormality Detected | 0-14, 21-28 |
|   |    |      | Discharge, Nose, Red                         | 17          |
|   |    |      | Sacrificed by design                         | 28          |
| M | XV | 1508 | General observation, No Abnormality Detected | 0-28        |
|   |    |      | Sacrificed by design                         | 28          |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

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Study: [REDACTED]

Individual Clinical Observations

|   |    |      |                                              |      |
|---|----|------|----------------------------------------------|------|
| M | XV | 1509 | General observation, No Abnormality Detected | 0-24 |
|   |    |      | Eye Observations, Dark, Right                | 28   |
|   |    |      | Sacrificed by design                         | 28   |
| M | XV | 1510 | General observation, No Abnormality Detected | 0-28 |
|   |    |      | Sacrificed by design                         | 28   |

**APPENDIX D**  
**INDIVIDUAL CLINICAL OBSERVATIONS - POSTDOSING**

## INDIVIDUAL CLINICAL OBSERVATIONS- POSTDOSING

### EXPLANATORY NOTES

Clinical observations reported in this appendix were recorded daily after removal of the test substance. Clinical observations recorded during body weight collection are not included but are reported in Appendix C.

HI-25425: Repeated-Dose Dermal Toxicity  
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Study [REDACTED]

| Individual Clinical Observations - Post Dosing |       |        |                                              |
|------------------------------------------------|-------|--------|----------------------------------------------|
| Sex                                            | Group | Animal | Observation                                  |
| M                                              | IX    | 901    | General observation, No Abnormality Detected |
|                                                |       |        | Eye Observations, Dark, Right                |
|                                                |       |        | Discharge, Eye bilateral, Red                |
|                                                |       |        | Discharge, Nose, Red                         |
|                                                |       |        | Discharge, Eye right, Red                    |
|                                                |       |        | Stain Fur/Skin, Thoracic, Red                |
| M                                              | IX    | 902    | General observation, No Abnormality Detected |
|                                                |       |        | Discharge, Eye bilateral, Red                |
|                                                |       |        | Discharge, Nose, Red                         |
|                                                |       |        | Wound, Superficial, Shoulder, Left           |
| M                                              | IX    | 903    | General observation, No Abnormality Detected |
|                                                |       |        | Discharge, Eye bilateral, Red                |
|                                                |       |        | Discharge, Nose, Red                         |
|                                                |       |        | Swollen Observations, Face                   |
| M                                              | IX    | 904    | General observation, No Abnormality Detected |
|                                                |       |        | Eye Observations, Opaque, Right              |
|                                                |       |        | Eye Observations, Dark, Right                |
|                                                |       |        | Discharge, Eye bilateral, Red                |
|                                                |       |        | Discharge, Nose, Red                         |

Days  
3, 8, 10-11, 20  
22-27  
0-2, 4-7, 9,  
14-16, 21-23  
12-15, 17-19,  
21-23  
24-27  
19  
13, 26  
0-12, 14-16,  
23-25, 27  
11-12, 21-23  
17-23  
20-21, 25  
0-19, 22-24,  
27  
11-19, 23, 26-27  
2  
20, 24-26  
27  
8-13  
0-12, 14-19,  
21-23, 27  
11-12, 14-19

H-25425: Repeated-Dose Dermal Toxicity  
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Study: [REDACTED]

|     |       |        | Individual Clinical Observations - Post Dosing |                         |
|-----|-------|--------|------------------------------------------------|-------------------------|
| Sex | Group | Animal | Observation                                    | Days                    |
| M   | IX    | 904    | Swollen Observations, Face                     | 0                       |
| M   | IX    | 905    | General observation, No Abnormality Detected   | 11,13,18-27             |
|     |       |        | Discharge, Eye bilateral, Red                  | 0-10,15-16              |
|     |       |        | Discharge, Nose, Red                           | 12,14-16                |
|     |       |        | Wound, Superficial, Dorsal Body                | 16-17                   |
| M   | IX    | 906    | General observation, No Abnormality Detected   | 0-1,4,10-14,17-20       |
|     |       |        | Discharge, Eye bilateral, Red                  | 2-3,5-9,15-16,21-23     |
|     |       |        | Discharge, Nose, Red                           | 15-16                   |
|     |       |        | Hair Loss, Forepaw, Bilateral                  | 21-27                   |
| M   | IX    | 907    | General observation, No Abnormality Detected   | 13,16,21,25-26          |
|     |       |        | Eye Observations, Dark, Right                  | 22-23                   |
|     |       |        | Discharge, Eye bilateral, Red                  | 0-12,14-15,22-24,27     |
|     |       |        | Discharge, Nose, Red                           | 11-12,14-15,17-20,23,27 |
| M   | IX    | 908    | General observation, No Abnormality Detected   | 0,11-14,20,24-26        |
|     |       |        | Discharge, Eye bilateral, Red                  | 1-10,15-19,22-23,27     |
|     |       |        | Discharge, Nose, Red                           | 15-19,21                |
|     |       |        | Stain Fur/Skin, Thoracic, Red                  | 19                      |
| M   | IX    | 909    | General observation, No Abnormality Detected   | 13,20,25-26             |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

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Study: [REDACTED]

Individual Clinical Observations - Post Dosing

| Sex | Group | Animal | Observation                                  | Days                       |
|-----|-------|--------|----------------------------------------------|----------------------------|
| M   | IX    | 909    | Discharge, Eye bilateral, Red                | 0-12,14-16,<br>19,21-24,27 |
|     |       |        | Discharge, Nose, Red                         | 9-12,15-19,<br>21-23       |
| M   | IX    | 910    | General observation, No Abnormality Detected | 13,20                      |
|     |       |        | Discharge, Eye bilateral, Red                | 0-12,14-16,<br>22-23       |
|     |       |        | Discharge, Nose, Red                         | 7,11-12,15-19,<br>23       |
|     |       |        | Hair Loss, Forepaw, Bilateral                | 21-27                      |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

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Study: [REDACTED]

Individual Clinical Observations - Post Dosing

| Sex | Group | Animal | Observation                                  | Days                                    |
|-----|-------|--------|----------------------------------------------|-----------------------------------------|
| M   | XI    | 1101   | General observation, No Abnormality Detected | 3, 10, 14, 20, 24-27                    |
|     |       |        | Discharge, Eye bilateral, Red                | 0-2, 4-9,<br>11-12, 16, 23              |
|     |       |        | Discharge, Nose, Red                         | 11-13, 15-19,<br>21-23                  |
|     |       |        | Swollen Observations, Face                   | 1                                       |
| M   | XI    | 1102   | General observation, No Abnormality Detected | 13                                      |
|     |       |        | Discharge, Eye bilateral, Red                | 0-12, 14-19,<br>23                      |
|     |       |        | Discharge, Nose, Red                         | 11-12, 14-23                            |
|     |       |        | Hair Loss, Forepaw, Bilateral                | 21-27                                   |
|     |       |        | Hair Loss, Forepaw, Left                     | 17-20                                   |
|     |       |        | Wound, Superficial, Forepaw, Left            | 18-24                                   |
|     |       |        | Swollen Observations, Face                   | 2                                       |
| M   | XI    | 1103   | General observation, No Abnormality Detected | 5, 8, 13, 15, 20, 24-27                 |
|     |       |        | Discharge, Eye bilateral, Red                | 0-4, 6-7,<br>10-12, 14, 16-19,<br>21-23 |
|     |       |        | Discharge, Nose, Red                         | 9, 11-12, 14                            |
| M   | XI    | 1104   | General observation, No Abnormality Detected | 13, 24-26                               |
|     |       |        | Discharge, Eye bilateral, Red                | 0-10, 12, 14-19,<br>22-23, 27           |
|     |       |        | Discharge, Nose, Red                         | 11-12, 14-19,<br>21-23, 27              |
|     |       |        | Wound, Superficial, Neck                     | 18-23                                   |

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28-Day Study in Male Rats

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Study: [REDACTED]

Individual Clinical Observations - Post Dosing

| Sex | Group | Animal | Observation                                  | Days                            |
|-----|-------|--------|----------------------------------------------|---------------------------------|
| M   | XI    | 1105   | General observation, No Abnormality Detected | 11, 13, 20, 25-26               |
|     |       |        | Discharge, Eye bilateral, Red                | 0-10, 12, 14-16, 21-24, 27      |
|     |       |        | Discharge, Nose, Rec                         | 8-9, 12, 14-19, 21-24, 27       |
| M   | XI    | 1106   | General observation, No Abnormality Detected | 0-1, 3, 13, 20, 24-27           |
|     |       |        | Discharge, Eye bilateral, Red                | 2, 4-12, 14-16, 21-23           |
|     |       |        | Discharge, Nose, Rec                         | 11-12, 17-19, 21-23             |
| M   | XI    | 1107   | General observation, No Abnormality Detected | 6, 8, 10-13, 24-26              |
|     |       |        | Discharge, Eye bilateral, Red                | 0-5, 7, 9, 14-20, 22-23         |
|     |       |        | Discharge, Nose, Rec                         | 15-23, 27                       |
| M   | XI    | 1108   | General observation, No Abnormality Detected | 3, 11-14, 25-27                 |
|     |       |        | Eye Observations, Dark, Right                | 8                               |
|     |       |        | Discharge, Eye bilateral, Red                | 0-2, 4-10, 15-19, 22-23         |
|     |       |        | Discharge, Nose, Rec                         | 16, 18-19                       |
|     |       |        | Wound, Superficial, Shoulder, Left           | 19-24                           |
| M   | XI    | 1109   | General observation, No Abnormality Detected | 5, 11, 13, 20, 24-26            |
|     |       |        | Discharge, Eye bilateral, Red                | 0-4, 6-10, 12, 14-16, 21-23, 27 |
|     |       |        | Discharge, Nose, Rec                         | 12, 15-19, 21-23                |

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Study: [REDACTED]

| Individual Clinical Observations - Post Dosing |       |        |
|------------------------------------------------|-------|--------|
| Sex                                            | Group | Animal |
| Observation                                    |       |        |
| M                                              | XI    | 1110   |
| General observation, No Abnormality Detected   |       |        |
| Discharge, Eye bilateral, Red                  |       |        |
| Discharge, Nose, Red                           |       |        |
| Stain Fur/Skin, Neck, Red                      |       |        |
| Days                                           |       |        |
| 13,17-27                                       |       |        |
| 0-12,15-16                                     |       |        |
| 14                                             |       |        |
| 11-12                                          |       |        |

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Study: [REDACTED]

Individual Clinical Observations - Post Dosing

| Sex | Group | Animal | Observation                                  | Days                          |
|-----|-------|--------|----------------------------------------------|-------------------------------|
| M   | XIII  | 1301   | General observation, No Abnormality Detected | 6, 11-14, 17-21, 24-27        |
|     |       |        | Discharge, Eye bilateral, Red                | 0-5, 7-10, 15-16, 22-23       |
|     |       |        | Discharge, Nose, Red                         | 23                            |
| M   | XIII  | 1302   | Discharge, Eye bilateral, Red                | 0-12, 15-16, 18-19, 21-25, 27 |
|     |       |        | Discharge, Nose, Black                       | 9-16                          |
|     |       |        | Discharge, Nose, Red                         | 8, 17-23, 25-27               |
| M   | XIII  | 1303   | General observation, No Abnormality Detected | 13, 15, 20                    |
|     |       |        | Eye Observations, Dark, Right                | 14                            |
|     |       |        | Discharge, Eye bilateral, Red                | 0-12, 22-23                   |
|     |       |        | Discharge, Nose, Red                         | 16-19, 21-23                  |
|     |       |        | Hair Loss, Forepaw, Bilateral                | 24-27                         |
|     |       |        | Stain Fur/Skin, Forelimb, Bilateral, Red     | 11                            |
|     |       |        | Stain Fur/Skin, Shoulder, Bilateral, Red     | 11                            |
|     |       |        | Stain Fur/Skin, Neck, Red                    | 11                            |
| M   | XIII  | 1304   | General observation, No Abnormality Detected | 3, 6                          |
|     |       |        | Eye Observations, Enophthalmus, Right        | 18-27                         |
|     |       |        | Eye Observations, Dark, Right                | 7-27                          |
|     |       |        | Discharge, Eye bilateral, Red                | 0-2, 4-5, 8-10, 16            |

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Study: [REDACTED]

Individual Clinical Observations - Post Dosing

| Sex | Group | Animal | Observation                                  | Days                      |
|-----|-------|--------|----------------------------------------------|---------------------------|
| M   | XIII  | 1304   | Discharge, Nose, Red                         | 14-16, 21-23, 27          |
| M   | XIII  | 1305   | General observation, No Abnormality Detected | 4, 10, 21-22, 24-26       |
|     |       |        | Discharge, Eye bilateral, Red                | 0-3, 5-9, 15-16           |
|     |       |        | Discharge, Nose, Red                         | 3, 15-16, 23, 27          |
|     |       |        | Wound, Superficial, Shoulder, Bilateral      | 11-20                     |
| M   | XIII  | 1306   | General observation, No Abnormality Detected | 3, 8, 11-13, 17-21        |
|     |       |        | Eye Observations, Dark, Right                | 22-27                     |
|     |       |        | Discharge, Eye bilateral, Red                | 0-2, 4-7, 9-10, 22-23, 27 |
|     |       |        | Discharge, Nose, Red                         | 14-16                     |
| M   | XIII  | 1307   | General observation, No Abnormality Detected | 13, 20, 22, 24-26         |
|     |       |        | Discharge, Eye bilateral, Red                | 0-12, 14-19, 21, 23       |
|     |       |        | Discharge, Nose, Red                         | 11-12, 14-19, 21, 23, 27  |
|     |       |        | Swollen Observations, Face                   | 0-1                       |
| M   | XIII  | 1308   | General observation, No Abnormality Detected | 10                        |
|     |       |        | Eye Observations, Corneal Opacity, Right     | 15-27                     |
|     |       |        | Discharge, Eye bilateral, Red                | 0-9, 11-20                |
|     |       |        | Discharge, Nose, Red                         | 9, 11-23, 27              |
|     |       |        | Comments, wound superficial right eye        | 18-27                     |
| M   | XIII  | 1309   | General observation, No Abnormality Detected | 20-21, 24-26              |

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Study: [REDACTED]

Individual Clinical Observations - Post Dosing

| Sex | Group | Animal | Observation                                  | Days                     |
|-----|-------|--------|----------------------------------------------|--------------------------|
| M   | XIII  | 1309   | Eye Observations, Dark, Right                | 9-13                     |
|     |       |        | Discharge, Eye bilateral, Red                | 0-9, 15-16,<br>22-23, 27 |
|     |       |        | Discharge, Nose, Red                         | 11-12, 14-19,<br>23, 27  |
| M   | XIII  | 1310   | General observation, No Abnormality Detected | 5, 10, 13, 21, 24-27     |
|     |       |        | Discharge, Eye bilateral, Red                | 0-4, 6-9, 16,<br>22-23   |
|     |       |        | Discharge, Nose, Red                         | 8, 11-12, 14-20,<br>23   |

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Study: [REDACTED]

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| Individual Clinical Observations - Post Dosing |       |        | Days                                         |
|------------------------------------------------|-------|--------|----------------------------------------------|
| Sex                                            | Group | Animal | Observation                                  |
| M                                              | XV    | 1501   | General observation, No Abnormality Detected |
|                                                |       |        | Discharge, Eye bilateral, Red                |
|                                                |       |        | Discharge, Nose, Red                         |
|                                                |       |        | 10-13, 20, 24-26                             |
|                                                |       |        | 0-9, 14-16                                   |
|                                                |       |        | 15-19, 21-23, 27                             |
| M                                              | XV    | 1502   | General observation, No Abnormality Detected |
|                                                |       |        | Discharge, Eye bilateral, Red                |
|                                                |       |        | Discharge, Nose, Red                         |
|                                                |       |        | 2, 13, 20, 24-27                             |
|                                                |       |        | 0-1, 3-12, 15-19, 22-23                      |
|                                                |       |        | 11-12, 14-19, 21-23                          |
| M                                              | XV    | 1503   | General observation, No Abnormality Detected |
|                                                |       |        | Discharge, Eye bilateral, Red                |
|                                                |       |        | Discharge, Nose, Red                         |
|                                                |       |        | 5-6, 10, 22, 24-26                           |
|                                                |       |        | 0-4, 7-9                                     |
|                                                |       |        | 11-21, 23, 27                                |
| M                                              | XV    | 1504   | General observation, No Abnormality Detected |
|                                                |       |        | Discharge, Eye bilateral, Red                |
|                                                |       |        | Discharge, Nose, Red                         |
|                                                |       |        | 2-4, 6-7, 10, 24, 26                         |
|                                                |       |        | 0-1, 5, 8-9, 15-16                           |
|                                                |       |        | 14-23, 27                                    |
|                                                |       |        | 11-16                                        |
|                                                |       |        | 25                                           |
|                                                |       |        | 19-20                                        |
| M                                              | XV    | 1505   | General observation, No Abnormality Detected |
|                                                |       |        | Discharge, Eye bilateral, Red                |
|                                                |       |        | Discharge, Nose, Red                         |
|                                                |       |        | 13, 17, 20, 24-26                            |
|                                                |       |        | 0-10, 15-16                                  |
|                                                |       |        | 11-12, 14-16, 18-19, 21-23, 27               |

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Study: [REDACTED]

Individual Clinical Observations - Post Dosing

| Sex | Group | Animal | Observation                                  | Days                       |
|-----|-------|--------|----------------------------------------------|----------------------------|
| M   | XV    | 1506   | General observation, No Abnormality Detected | 6,11,13-14,20,25-27        |
|     |       |        | Discharge, Eye bilateral, Red                | 0-5,7-10,12,15-19,23-24    |
|     |       |        | Discharge, Nose, Red                         | 12,15-19,21-23             |
| M   | XV    | 1507   | General observation, No Abnormality Detected | 2-6,22,24-25               |
|     |       |        | Discharge, Eye bilateral, Red                | 0-1,7-21,23,26-27          |
|     |       |        | Discharge, Nose, Red                         | 11-12,16-21,23,27          |
| M   | XV    | 1508   | General observation, No Abnormality Detected | 3,5,8,13,22,24,26-27       |
|     |       |        | Discharge, Eye bilateral, Red                | 0-2,4,6-7,9-12,15-16       |
|     |       |        | Discharge, Nose, Red                         | 11-12,14-21,23,25          |
|     |       |        | Stain Fur/Skin, Thoracic, Red                | 19                         |
| M   | XV    | 1509   | General observation, No Abnormality Detected | 2,5,9-10,13,16,20,22,24-26 |
|     |       |        | Discharge, Eye bilateral, Red                | 0-1,3-4,6-8                |
|     |       |        | Discharge, Nose, Red                         | 11-12,14-15,17-19,21,23,27 |
| M   | XV    | 1510   | General observation, No Abnormality Detected | 10,13,24-26                |
|     |       |        | Discharge, Eye bilateral, Red                | 0-9,11-12,14-20,27         |
|     |       |        | Discharge, Nose, Red                         | 9,11-12,15-16,18-23        |

**APPENDIX E**  
**INDIVIDUAL EDEMA AND ERYTHEMA SCORES**

## INDIVIDUAL EDEMA AND ERYTHEMA SCORES

### EXPLANATORY NOTES

#### DRAIZE<sup>a</sup> SCALE FOR SCORING SKIN IRRITATION

| Evaluation of Skin Reactions                                                        | Score |
|-------------------------------------------------------------------------------------|-------|
| <b>Erythema and eschar formation:</b>                                               |       |
| No erythema .....                                                                   | 0     |
| Very slight erythema (barely perceptible) .....                                     | 1     |
| Well-defined erythema .....                                                         | 2     |
| Moderate to severe erythema .....                                                   | 3     |
| Severe erythema (beet redness) to slight eschar formation (injuries in depth) ..... | 4     |
| <b>Edema formation:</b>                                                             |       |
| No edema .....                                                                      | 0     |
| Very slight edema (barely perceptible) .....                                        | 1     |
| Slight edema (edges of area well defined by definite raising) .....                 | 2     |
| Moderate edema (raised approximately 1.0 mm) .....                                  | 3     |
| Severe edema (raised more than 1.0 mm extending beyond the area of exposure) ..     | 4     |

- a Draize, J. H., "Dermal Toxicity." Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics. The Editorial Committee of the Association of Food and Drug Officials of the United States, Austin, Texas, 1959, pp. 46-59.

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

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Study: [REDACTED]

Individual Edema and Erythema Scores

| Edema                      | Edema | Edema | Edema | Edema | Edema | Edema | Edema | Edema | Edema | Edema  | Edema  | Edema  | Edema  | Edema  |
|----------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|--------|--------|--------|--------|--------|
| Day 0                      | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Day 10 | Day 11 | Day 11 | Day 11 | Day 11 |
| Male, IX 0 mg/kg (Control) |       |       |       |       |       |       |       |       |       |        |        |        |        |        |
| 901                        | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0      | 0      | 0      | 0      | 0      |
| 902                        | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0      | 0      | 0      | 0      | 0      |
| 903                        | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0      | 0      | 0      | 0      | 0      |
| 904                        | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0      | 0      | 0      | 0      | 0      |
| 905                        | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0      | 0      | 0      | 0      | 0      |
| 906                        | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0      | 0      | 0      | 0      | 0      |
| 907                        | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0      | 0      | 0      | 0      | 0      |
| 908                        | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0      | 0      | 0      | 0      | 0      |
| 909                        | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0      | 0      | 0      | 0      | 0      |
| 910                        | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0      | 0      | 0      | 0      | 0      |

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Study:

### Individual Edema and Erythema Scores

[illegible]

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28-Day Study in Male Rats

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Print Time: 12:04:21

Individual Edema and Erythema Scores

|                            | Edema  |        |        |        |
|----------------------------|--------|--------|--------|--------|
|                            | Day 24 | Day 25 | Day 26 | Day 27 |
| Male, IX 0 mg/kg (Control) |        |        |        |        |
| 901                        | 0      | 0      | 0      | 0      |
| 902                        | 0      | 0      | 0      | 0      |
| 903                        | 0      | 0      | 0      | 0      |
| 904                        | 0      | 0      | 0      | 0      |
| 905                        | 0      | 0      | 0      | 0      |
| 906                        | 0      | 0      | 0      | 0      |
| 907                        | 0      | 0      | 0      | 0      |
| 908                        | 0      | 0      | 0      | 0      |
| 909                        | 0      | 0      | 0      | 0      |
| 910                        | 0      | 0      | 0      | 0      |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

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Print Time: 12:04:21

Individual Edema and Erythema Scores

| Edema             | Edema | Edema | Edema | Edema | Edema | Edema | Edema | Edema | Edema | Edema  | Edema  | Edema  | Edema  |
|-------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|--------|--------|--------|--------|
| Day 0             | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Day 10 | Day 11 | Day 11 | Day 11 |
| Male, XI 10 mg/kg |       |       |       |       |       |       |       |       |       |        |        |        |        |
| 1101              | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0      | 0      | 0      | 0      |
| 1102              | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0      | 0      | 0      | 0      |
| 1103              | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0      | 0      | 0      | 0      |
| 1104              | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0      | 0      | 0      | 0      |
| 1105              | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0      | 0      | 0      | 0      |
| 1106              | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0      | 0      | 0      | 0      |
| 1107              | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0      | 0      | 0      | 0      |
| 1108              | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0      | 0      | 0      | 0      |
| 1109              | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0      | 0      | 0      | 0      |
| 1110              | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0      | 0      | 0      | 0      |

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## Individual Edema and Erythema Scores

[illegible]

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28-Day Study in Male Rats

DuPont-13830

Study: [REDACTED]

Print Date: 15-Jan-2004  
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Individual Edema and Erythema Scores

|                   | Edema  |        | Edema  |        | Edema  |        |
|-------------------|--------|--------|--------|--------|--------|--------|
|                   | Day 24 | Day 25 | Day 26 | Day 27 | Day 28 | Day 29 |
| Male, XI 10 mg/kg |        |        |        |        |        |        |
| 1101              | 0      | 0      | 0      | 0      | 0      | 0      |
| 1102              | 0      | 0      | 0      | 0      | 0      | 0      |
| 1103              | 0      | 0      | 0      | 0      | 0      | 0      |
| 1104              | 0      | 0      | 0      | 0      | 0      | 0      |
| 1105              | 0      | 0      | 0      | 0      | 0      | 0      |
| 1106              | 0      | 0      | 0      | 0      | 0      | 0      |
| 1107              | 0      | 0      | 0      | 0      | 0      | 0      |
| 1108              | 0      | 0      | 0      | 0      | 0      | 0      |
| 1109              | 0      | 0      | 0      | 0      | 0      | 0      |
| 1110              | 0      | 0      | 0      | 0      | 0      | 0      |

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Print Date: 15-Jan-2004  
Print Time: 12:04:21

Study: [REDACTED]

### Individual Edema and Erythema Scores

[illegible]

## DuPont-13830

Print Date: 15-Jan-2004  
Print Time: 12:04:21

### Individual Edema and Erythema Scores

[illegible]

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Print Date: 15-Jan-2004  
Print Time: 12:04:21

Study: [REDACTED]

Individual Edema and Erythema Scores

|                      | Edema  |        | Edema  |        | Edema  |        |
|----------------------|--------|--------|--------|--------|--------|--------|
|                      | Day 24 | Day 25 | Day 26 | Day 27 | Day 28 | Day 29 |
| Male, XIII 100 mg/kg |        |        |        |        |        |        |
| 1301                 | 0      | 0      | 0      | 0      | 0      | 0      |
| 1302                 | 0      | 0      | 0      | 0      | 0      | 0      |
| 1303                 | 0      | 0      | 0      | 0      | 0      | 0      |
| 1304                 | 0      | 0      | 0      | 0      | 0      | 0      |
| 1305                 | 0      | 0      | 0      | 0      | 0      | 0      |
| 1306                 | 0      | 0      | 0      | 0      | 0      | 0      |
| 1307                 | 0      | 0      | 0      | 0      | 0      | 0      |
| 1308                 | 0      | 0      | 0      | 0      | 0      | 0      |
| 1309                 | 0      | 0      | 0      | 0      | 0      | 0      |
| 1310                 | 0      | 0      | 0      | 0      | 0      | 0      |

**Study:**

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### Individual Edema and Erythema Scores

[illegible]

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Print Date: 15-Jan-2004  
Print Time: 12:04:21

Study: [REDACTED]

Individual Edema and Erythema Scores

|                     | Edema<br>Day 12 | Edema<br>Day 13 | Edema<br>Day 14 | Edema<br>Day 15 | Edema<br>Day 16 | Edema<br>Day 17 | Edema<br>Day 18 | Edema<br>Day 19 | Edema<br>Day 20 | Edema<br>Day 21 | Edema<br>Day 22 | Edema<br>Day 23 |
|---------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Male, XV 1000 mg/kg |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| 1501                | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               |
| 1502                | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               |
| 1503                | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               |
| 1504                | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               |
| 1505                | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               |
| 1506                | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               |
| 1507                | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               |
| 1508                | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               |
| 1509                | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               |
| 1510                | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               | 0               |

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28-Day Study in Male Rats

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Study: [REDACTED]

Individual Edema and Erythema Scores

|                     | Edema  | Edema  | Edema  | Edema  |
|---------------------|--------|--------|--------|--------|
|                     | Day 24 | Day 25 | Day 26 | Day 27 |
| Male, XV 1000 mg/kg |        |        |        |        |
| 1501                | 0      | 0      | 0      | 0      |
| 1502                | 0      | 0      | 0      | 0      |
| 1503                | 0      | 0      | 0      | 0      |
| 1504                | 0      | 0      | 0      | 0      |
| 1505                | 0      | 0      | 0      | 0      |
| 1506                | 0      | 0      | 0      | 0      |
| 1507                | 0      | 0      | 0      | 0      |
| 1508                | 0      | 0      | 0      | 0      |
| 1509                | 0      | 0      | 0      | 0      |
| 1510                | 0      | 0      | 0      | 0      |

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### Individual Edema and Erythema Scores

[illegible]

**DuPont-13830**

Print Date: 15-Jan-2004  
Print Time: 12:04:45

Study { [REDACTED] }

### Individual Edema and Erythema Scores

Erythema Erythema Erythema Erythema Erythema Erythema Erythema Erythema

[illegible]

Male, IX 0 mg/kg (Control)

[illegible]

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

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Print Time: 12:04:45

Study: [REDACTED]

Individual Edema and Erythema Scores

|                            | Erythema |        |        |        | Erythema |        |        |        |
|----------------------------|----------|--------|--------|--------|----------|--------|--------|--------|
|                            | Day 24   | Day 25 | Day 26 | Day 27 | Day 24   | Day 25 | Day 26 | Day 27 |
| Male, IX 0 mg/kg (Control) |          |        |        |        |          |        |        |        |
| 901                        | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 902                        | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 903                        | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 904                        | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 905                        | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 906                        | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 907                        | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 908                        | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 909                        | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 910                        | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |

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**Study:** [REDACTED]

### Individual Edema and Erythema Scores

Erythema Erythema Erythema Erythema Erythema Erythema Erythema

[illegible]

Male, XI 10 mg/kg

[illegible]

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Study: [REDACTED]

### Individual Edema and Erythema Scores

[illegible]

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28-Day Study in Male Rats

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Print Time: 12:04:45

Study: [REDACTED]

Individual Edema and Erythema Scores

|                   | Erythema |        |        |        | Erythema |        |        |        |
|-------------------|----------|--------|--------|--------|----------|--------|--------|--------|
|                   | Day 24   | Day 25 | Day 26 | Day 27 | Day 24   | Day 25 | Day 26 | Day 27 |
| Male, XI 10 mg/kg |          |        |        |        |          |        |        |        |
| 1101              | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 1102              | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 1103              | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 1104              | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 1105              | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 1106              | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 1107              | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 1108              | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 1109              | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 1110              | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |

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Study

### Individual Eczema and Erythema Scores

[illegible]

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### Individual Edema and Erythema Scores

[illegible]

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Print Date: 15-Jan-2004  
Print Time: 12:04:45

Individual Edema and Erythema Scores

|                      | Erythema |        |        |        | Erythema |        |        |        | Erythema |        |        |        |
|----------------------|----------|--------|--------|--------|----------|--------|--------|--------|----------|--------|--------|--------|
|                      | Day 24   | Day 25 | Day 26 | Day 27 | Day 24   | Day 25 | Day 26 | Day 27 | Day 24   | Day 25 | Day 26 | Day 27 |
| Male, XIII 100 mg/kg |          |        |        |        |          |        |        |        |          |        |        |        |
| 1301                 | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 1302                 | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 1303                 | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 1304                 | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 1305                 | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 1306                 | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 1307                 | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 1308                 | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 1309                 | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |
| 1310                 | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      | 0        | 0      | 0      | 0      |

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Print Time: 12:04:45

### Individual Edema and Erythema Scores

[illegible]

## DuPont-13830

Print Date: 15-Jan-2004  
Print Time: 12:04:45

Study/

### Individual Edema and Erythema Scores

[illegible]

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Print Date: 15-Jan-2004  
Print Time: 12:04:45

Study: [REDACTED]

Individual Edema and Erythema Scores

| Male, XV 1000 mg/kg | Erythema |        |        |        |
|---------------------|----------|--------|--------|--------|
|                     | Day 24   | Day 25 | Day 26 | Day 27 |
| 1501                | 0        | 0      | 0      | 0      |
| 1502                | 0        | 0      | 0      | 0      |
| 1503                | 2        | 0      | 0      | 0      |
| 1504                | 0        | 0      | 0      | 0      |
| 1505                | 0        | 0      | 0      | 0      |
| 1506                | 0        | 0      | 0      | 0      |
| 1507                | 0        | 0      | 0      | 0      |
| 1508                | 0        | 0      | 0      | 0      |
| 1509                | 0        | 0      | 0      | 0      |
| 1510                | 0        | 0      | 0      | 0      |

**APPENDIX F**  
**PFOA ANALYTICAL REPORT**

**STUDY TITLE**

H-25425: Repeated-Dose Dermal Toxicity 28-Day Study in Male Rats

**DATA REQUIREMENTS**

Analytical Method Requirements

**STUDY DIRECTOR**

Carol Finlay

**ANALYTICAL PHASE COMPLETED ON**

March 10, 2004

**PERFORMING LABORATORY**

Exygen Research  
3058 Research Drive  
State College, PA 16801  
Phone: 814-272-1039

**STUDY SPONSOR**

E. I. du Pont de Nemours and Company (DuPont)  
P.O. Box 50  
Newark, DE 19714-0050 USA

**PROJECT**

Exygen Study Number: 008-406  
Sponsor Study No.: DuPont-13830

Total Pages: 65

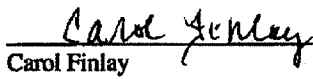
Exygen Study No.: 008-406

**GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT**

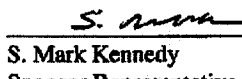
Exygen Study Number 008-406, entitled "H-25425: Repeated-Dose Dermal Toxicity 28-Day Study in Male Rats," was conducted for DuPont in compliance with US EPA TSCA (40 CFR part 792) Good Laboratory Practice Standards, which are consistent with OECD Principles of Good Laboratory Practice (as revised in 1997), published in ENV/MS/CHEM(98)17.

  
\_\_\_\_\_  
Emily R. Decker  
Principal Investigator  
Exygen Research

3/10/04  
\_\_\_\_\_  
Date

  
\_\_\_\_\_  
Carol Finlay  
Study Director  
DuPont

16-March-2004  
\_\_\_\_\_  
Date

  
\_\_\_\_\_  
S. Mark Kennedy  
Sponsor Representative  
DuPont

16-MAR-2004  
\_\_\_\_\_  
Date

Exygen Research

Page 2 of 65

Exygen Study No.: 008-406

**QUALITY ASSURANCE STATEMENT**

Exygen Research's Quality Assurance Unit reviewed Exygen Study Number 008-406, entitled, "H-25425: Repeated-Dose Dermal Toxicity 28-Day Study in Male Rats". All phases were reviewed for conduct according to Exygen Research's Standard Operating Procedures, the Study Protocol, and all applicable Good Laboratory Practice Standards. All findings were reported to the Study Director and to management.

| <u>Phase</u>                                 | <u>Date Inspected</u> | <u>Date Reported to Principal Investigator</u> | <u>Date Reported to Exygen Management</u> | <u>Date Reported to Study Director and Sponsor Management</u> |
|----------------------------------------------|-----------------------|------------------------------------------------|-------------------------------------------|---------------------------------------------------------------|
| 1. Fortification, and Extraction             | 01/13/04              | 01/15/04                                       | 01/19/04                                  | 02/23/04                                                      |
| 2. Raw Data & Draft Analytical Report Review | 01/26/04              | 01/29/04                                       | 02/02/04                                  | 02/23/04                                                      |
| 3. Final Analytical Report Review            | 02/23/04              | 02/23/04                                       | 02/23/04                                  | 02/23/04                                                      |

Miwa Nabetani  
Miwa Nabetani  
Quality Assurance Auditor

2/10/04  
Date

Exygen Study No.: 008-406

**CERTIFICATION OF AUTHENTICITY**

This report, for Exygen Study Number 008-406, is a true and complete representation of the raw data for the study.

Submitted by: Exygen Research  
3058 Research Drive  
State College, PA 16801  
(814) 272-1039

Principal Investigator, Exygen:

Emily R. Decker  
Emily R. Decker  
Scientist/Principal Investigator  
Exygen Research

3/10/04  
Date

Exygen Research Facility Management:

John M. Flaherty  
John M. Flaherty  
Vice President  
Exygen Research

3/10/04  
Date

Study Director, DuPont:

Carol Finlay  
Carol Finlay  
DuPont

16-Mar-2004  
Date

Sponsor Representative, DuPont:

S. Mark Kennedy  
S. Mark Kennedy  
DuPont

16-MAR-2004  
Date

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Exygen Study No.: 008-406

**EXYGEN STUDY IDENTIFICATION**

H-25425: Repeated-Dose Dermal Toxicity 28-Day Study in Male Rats

SPONSOR STUDY NUMBER: DuPont-13830

EXYGEN STUDY NUMBER: 008-406

TYPE OF ANALYTICAL PHASE: Residue

SAMPLE MATRIX: Rat Plasma

TEST SUBSTANCE: Pentadecafluorooctanoic acid (PFOA)

SPONSOR: E. I. du Pont de Nemours and Company  
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STUDY DIRECTOR: Carol Finlay  
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PERFORMING LABORATORY: Exygen Research  
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ANALYTICAL PHASE  
TIMETABLE: Study Initiation Date: 11/18/03  
Analytical Start Date: 01/13/04  
Analytical Termination Date: 01/15/04  
Analytical Report Completion Date: 03/10/04

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**PROJECT PERSONNEL**

The Study Director for this project at DuPont was Carol Finlay. The following personnel from Exygen Research were associated with various phases of the study:

| <u>Name</u>   | <u>Title</u>         |
|---------------|----------------------|
| Paul Connolly | Technical Lead-LC/MS |
| Emily Decker  | Scientist            |
| Karen Risha   | Scientist            |
| Mark Ammerman | Sample Custodian     |
| Shawn Robb    | Sample Custodian     |

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## **1.0 SUMMARY**

Exygen Research (Exygen) analyzed samples of rat plasma for residues of PFOA in according to protocol DuPont-13830 (Appendix A) using the analytical method ExM-008-276 Revision 2 (Appendix B).

The limit of quantitation for this method is 10 ppb, which was established at Exygen in the method validation study [REDACTED]

Residues of PFOA in the rat plasma samples ranged from < 10.0 ppb to 134 ppb.

The average recovery  $\pm$  standard deviation for PFOA in fortified rat plasma samples was  $97\% \pm 13.3\%$ .

## **2.0 OBJECTIVE**

The objective of this analytical phase was to analyze rat plasma samples received at Exygen using the method ExM-008-276 Revision 2 entitled "Method of Analysis for the Determination of Pentadecafluorooctanoic Acid (PFOA) in Serum by LC/MS/MS".

## **3.0 INTRODUCTION**

This report details the results of the analysis of rat plasma samples for PFOA using the analytical method ExM-008-276 Revision 2.

The study was initiated on November 18, 2003, when the study director signed protocol number DuPont-13830. The analytical start date was January 13, 2004, and the analytical termination date was January 15, 2004.

## **4.0 TEST SYSTEM**

The control rat plasma used for control samples and laboratory control fortified samples was received from DuPont on 10/01/03. Forty rat plasma samples were received at Exygen on January 06, 2004. All samples were logged in by Exygen personnel upon receipt and placed in frozen storage ( $\leq -20^{\circ}\text{C}$ ).

Sample login and chain of custody information can be found in the raw data package associated with this study. Storage records will be kept at Exygen Research and a true copy of the storage records will be furnished upon request.

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## 5.0 REFERENCE MATERIAL

The analytical standard pentadecafluorooctanoic acid (PFOA) was received at Exygen on March 05, 2003 from Critical Path Services. The control article (internal standard) n-perfluorooctanoic acid (1,2 di-<sup>13</sup>C) was received at Exygen on February 20, 2003 from DuPont.

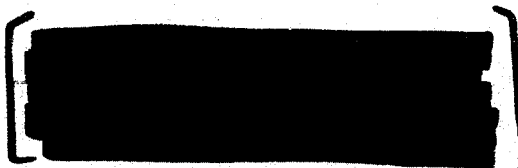
The available information for the reference material is listed below. The analytical standard was stored in a refrigerator and the control article was stored at room temperature.

| <u>Compound</u>      | <u>Exygen</u><br><u>Inventory No.</u> | <u>Lot No.</u> | <u>Purity (%)</u> | <u>Expiration Date</u> |
|----------------------|---------------------------------------|----------------|-------------------|------------------------|
| PFOA                 | SP2516                                | [REDACTED]     | [REDACTED]        | 03/05/04               |
| <sup>13</sup> C-PFOA | SP2492                                | [REDACTED]     | [REDACTED]        | 01/31/05               |

The structure of perfluorooctanoic acid (PFOA) and the internal standard are given below.

### PFOA

Chemical Name = perfluorooctanoic acid  
Molecular weight = 414



### <sup>13</sup>C - PFOA

Chemical Name = perfluorooctanoic acid, [1,2-di-<sup>13</sup>C]  
Molecular weight = 416



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## 6.0 DESCRIPTION OF ANALYTICAL METHOD

### 6.1 Extraction Procedure

1. Measure 0.1 mL of sample into 1 mL eppendorf centrifuge tubes (fortify with analyte as needed, close lid, and vortex ~ 10 seconds).
2. Add enough acetonitrile containing internal standard at 0.005 µg/mL (accounting for fortification volume) to make extraction volume 500 µL and vortex for ~ 10 seconds.
3. Centrifuge for ~ 10 minutes at ~ 14,000 rpm.
4. Analyze samples using electrospray LC/MS/MS.

### 6.2 Preparation of Standards and Fortification Solutions

The stock standard solution of PFOA was prepared on September 17, 2003, at a concentration of 100 µg/mL by dissolving approximately 10 mg of the standard (corrected for purity) in methanol. The stock standard solution of <sup>13</sup>C-PFOA was prepared on September 17, 2003, at a concentration of 100 µg/mL by dissolving approximately 10 mg of the standard (corrected for purity) in methanol. A fortification solution of PFOA at 10 µg/mL was prepared by taking 10 mL of the stock standard solution and bringing the volume up to 100 in acetonitrile. A 1.0 µg/mL fortification solution of <sup>13</sup>C-PFOA was prepared by taking 1.0 mL of the stock and bringing the volume up to 100 mL with acetonitrile.

A set of standards containing PFOA with internal standards was prepared by dilution of the 10.0 µg/mL PFOA solution and the 1.0 µg/mL <sup>13</sup>C-PFOA solution in the following manner. These solutions were used to fortify the samples and the extracted calibration standards.

| Initial Conc.<br>(µg/mL) <sup>1</sup> | Volume (mL) | Diluted to (mL)  | Final Conc.<br>(µg/mL) <sup>1</sup> |
|---------------------------------------|-------------|------------------|-------------------------------------|
| 10.0                                  | 10.0        | 100 <sup>2</sup> | 1.0                                 |
| 10.0                                  | 1.0         | 100 <sup>2</sup> | 0.1                                 |
| 10.0                                  | 0.1         | 100 <sup>2</sup> | 0.01                                |

<sup>1</sup> of PFOA only

<sup>2</sup> 0.5 mL of the 1.0 µg/mL <sup>13</sup>C-PFOA solution was added prior to making final volume to give a concentration of 0.005 µg/mL of <sup>13</sup>C-PFOA in each solution.

The calibration standards are processed through the extraction procedure, identical to the samples. The extracted standards are assigned a two-week expiration date from the date of extraction based on refrigerator stability data obtained during the method validation study (Exygen study: 008-277). The fortification of the standards before extraction is done according to the following table:

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| Conc. Of<br>PFOA<br>Fortification<br>Solution<br>( $\mu\text{g/mL}$ ) | Fortification<br>Volume ( $\mu\text{L}$ ) | Volume of<br>Control<br>Sample (mL) | Conc. of<br>Extracted<br>Calibration<br>Standard<br>(ppb) |
|-----------------------------------------------------------------------|-------------------------------------------|-------------------------------------|-----------------------------------------------------------|
| 0.01                                                                  | 100                                       | 0.1                                 | 10                                                        |
| 0.01                                                                  | 200                                       | 0.1                                 | 20                                                        |
| 0.1                                                                   | 50                                        | 0.1                                 | 50                                                        |
| 0.1                                                                   | 100                                       | 0.1                                 | 100                                                       |
| 0.1                                                                   | 200                                       | 0.1                                 | 200                                                       |

The extraction solution was prepared by taking 0.5 mL of the 1.0  $\mu\text{g/mL}$   $^{13}\text{C}$ -PFOA solution and bringing the volume up to 100 mL with acetonitrile. The dilution solution was prepared by taking 0.5 mL of the 1.0  $\mu\text{g/mL}$   $^{13}\text{C}$ -PFOA solution and bringing the volume up to 100 mL with 50:50 methanol:water.

The stock standard solution and all fortification/calibration standard solutions were stored in a refrigerator ( $4^\circ \pm 2^\circ\text{C}$ ) when not in use. Documentation of standard preparation can be found in the raw data associated with this report.

### 6.3 Chromatography

Quantification of PFOA was accomplished by analysis using electrospray LC-MS/MS. The retention time of PFOA was ~ 2.0 min., with no significant interfering peaks (< 20% of the LOQ standard) in the control samples corresponding to the analyte retention times.

### 6.4 Instrument Sensitivity

The smallest amount of PFOA injected during the chromatographic run was equivalent to 10 ppb.

### 6.5 Description of Instrument and Operating Conditions

A PE Sciex LC-MS/MS coupled to a Hewlett Packard HPLC system was used. Data acquisition and processing were performed using Analyst 1.2 software. Detailed operating conditions are listed below:

|            |                                                                                 |
|------------|---------------------------------------------------------------------------------|
| Mass Spec: | PE SCIEX API 4000 Biomolecular Mass Analyzer                                    |
| Interface: | SCIEX Turbo Ion Spray Liquid Introduction Interface                             |
|            | Turbo Ion Spray temperature = $350^\circ\text{C}$ with $\text{N}_2$ at ~7 L/min |
| Computer:  | Dell Optiplex GX110                                                             |
| Software:  | PE Sciex Analyst: Version 1.2                                                   |
| HPLC:      | Hewlett Packard (HP) Series 1100                                                |

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HP Quat Pump  
HP Vacuum Degasser  
HP Autoinjector  
HP Column Compartment

Filter Cartridge(s): 2 Keystone Hypercarbs in tandem, exiting pump  
HPLC Column: Genesis C<sub>8</sub> (Jones Chromatography), 2.1 mm x 50 mm, 4μ  
Column Temp.: 30° C  
Mobile Phase (A): 2 mM Ammonium Acetate in water  
Mobile Phase (B): Methanol

| <u>Time</u> | <u>% A</u> | <u>% B</u> | <u>Flow (mL/min)</u> |
|-------------|------------|------------|----------------------|
| 0           | 40         | 60         | 0.3                  |
| 3.0         | 40         | 60         | 0.3                  |
| 3.5         | 0          | 100        | 0.3                  |
| 3.7         | 0          | 100        | 0.5                  |
| 7.0         | 0          | 100        | 0.5                  |
| 7.5         | 40         | 60         | 0.5                  |
| 9.0         | 40         | 60         | 0.5                  |
| 9.5         | 40         | 60         | 0.3                  |
| 12.0        | 40         | 60         | 0.3                  |

Injection Vol.: 5 μL

Ions monitored:

| <u>Analyte</u>       | <u>Mode</u> | <u>Transition Monitored</u> |
|----------------------|-------------|-----------------------------|
| PFOA                 | Negative    | 413 → 369                   |
| <sup>13</sup> C-PFOA | Negative    | 415 → 370                   |

#### 6.6 Quantitation and Example Calculation

Five microliters of sample or calibration standard were injected into the LC-MS/MS. The peak area was measured and the standard curve was generated by linear regression using 1/x weighting of the ratio analyte peak area/internal standard peak area versus the ratio of the concentration of analyte/concentration of internal standard using Analyst 1.2 (or equivalent) software system. The residue concentration for PFOA was determined from the following equations:

Equation 1 was used to calculate the amount of analyte found (in ppb or ng/mL, based on ratio of analyte peak area to internal standard peak area) using the standard curve (linear regression parameters) generated by the Analyst software program.

Equation 1:

$$\text{Analyte found (ppb)} = \frac{((\text{Analyte Peak area} / \text{IS peak area}) - \text{intercept})}{\text{slope}} \times \text{IS conc. (ng/mL)} \times \text{DF}$$

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For samples fortified with known amounts of analyte prior to extraction, Equation 2 was used to calculate the percent recovery.

Equation 2:

Recovery (%) =

$$\frac{\text{Analyte found (ppb)} - \text{avg. Analyte found in control (ppb)}}{\text{Amount Analyte added (ppb)}} \times 100$$

For plasma samples fortified with known amounts of analyte prior to extraction, Equation 3 was used to calculate the percent recovery.

Equation 3:

Recovery (%) =

$$\frac{\text{Analyte found (ppb)} - \text{avg. Analyte found in sample (ppb)}}{\text{Amount Analyte added (ppb)}} \times 100$$

An example of a calculation using an actual sample follows: Rat plasma sample Exygen ID 0302238 Spk A (Set: 011404A), fortified at 10 ppb with PFOA.

Where:

|                        |   |             |
|------------------------|---|-------------|
| analyte peak area      | = | 216030      |
| IS peak area           | = | 535991      |
| IS conc. (ng/mL)       | = | 4.167 ng/mL |
| intercept              | = | 0.000435159 |
| slope                  | = | 0.173906    |
| dilution factor (DF)   | = | 1           |
| ppb added (fort level) | = | 10          |
| amt found in control   | = | ND          |

**From equation 1:**

$$\begin{aligned} \text{Analyte found (ppb)} &= \frac{[(216030/535991) - 0.000435159]}{0.173906} \times 4.167 \times 1 \\ &= 9.65 \text{ ppb} \end{aligned}$$

**From equation 2:**

$$\begin{aligned} \% \text{ Recovery} &= \frac{(9.65 \text{ ppb} - 0)}{10 \text{ ppb}} \times 100 \\ &= 97\% \end{aligned}$$

Note: This example calculation was done using rounded numbers, and therefore may be slightly different from the values shown in the RAW DATA.

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## **7.0 EXPERIMENTAL DESIGN**

Each analytical set was extracted according to method ExM-008-276 Revision 2 and consisted of a reagent blank, one matrix control, two laboratory matrix controls fortified at known concentrations, one field sample fortified at a known concentration, 20 plasma samples, and one field sample extracted in duplicate.

## **8.0 RESULTS**

The PFOA found in the control rat plasma samples are listed in Table I.

Individual recoveries for PFOA in the laboratory fortified rat plasma samples are detailed in Table II. The average percent recoveries  $\pm$  standard deviation for PFOA in the rat plasma samples was  $97\% \pm 13.3\%$ .

Individual results for the PFOA in the rat plasma samples are given in Table III. Residues of PFOA in the rat plasma samples ranged from  $< 10.0$  ppb to 134 ppb.

A typical calibration curve for PFOA and representative chromatograms are given in Figures 1-5.

## **9.0 CIRCUMSTANCES THAT MAY HAVE AFFECTED THE QUALITY OR INTEGRITY OF THE DATA**

There are no known circumstances that have affected the quality or integrity of the data.

## **10.0 CONCLUSIONS**

The rat plasma samples were successfully analyzed according to method ExM-008-276 Revision 2.

## **11.0 RETENTION OF DATA AND SAMPLES**

When the final report is complete, all original paper data generated by Exygen Research will be shipped to the sponsor. This does not include facility-specific raw data such as instrument logs. Exact copies of all raw data, as well as a signed copy of the final analytical report and all original facility-specific raw data, will be retained in the Exygen Research's archives for the period of time specified in 40 CFR Part 792. Retained samples of reference substances are archived by the sponsor.

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# TABLES

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**Table I. Summary of PFOA (ppb) in Rat Plasma Control Samples**

| <b>Sponsor<br/>ID</b>            | <b>PFOA<br/>(ng/mL)</b> |
|----------------------------------|-------------------------|
| <b>669160 Control A 01/13/04</b> | <b>ND</b>               |
| <b>669119 Control A 01/14/04</b> | <b>ND</b>               |

ND = Not Detected (less than 10.0 ppb)

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**Table II. Summary of Recoveries of PFOA (%) in Rat Plasma Samples**

| Sponsor ID                 | PFOA (ppb) | Amount Fortified (ppb) | Recovery (%) |
|----------------------------|------------|------------------------|--------------|
| 669160 (LCS A) 01/13/04    | 10.4       | 10.0                   | 104          |
| 669160 (LCS B) 01/13/04    | 881        | 1000                   | 88           |
| 1301 (Matrix Spk) 01/13/04 | 776        | 1000                   | 78           |
| 669119 (LCS A) 01/14/04    | 9.65       | 10.0                   | 96           |
| 669119 (LCS B) 01/14/04    | 1090       | 1000                   | 109          |
| 901 (Matrix Spk) 01/14/04  | 1100       | 1000                   | 110          |
| AVERAGE:                   |            |                        | 97           |
| STD DEV:                   |            |                        | 13.3         |
| % RSD:                     |            |                        | 13.7         |

LCS = Laboratory Control Spike

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**Table III. Summary of Residue Found for PFOA (ppb) in Rat Plasma Samples**

| <b>Sponsor<br/>ID</b> | <b>PFOA<br/>(ppb)</b> |
|-----------------------|-----------------------|
| 901                   | < 10.0                |
| 901 Dup               | < 10.0                |
| 902                   | < 10.0                |
| 903                   | < 10.0                |
| 904                   | < 10.0                |
| 905                   | < 10.0                |
| 906                   | < 10.0                |
| 907                   | < 10.0                |
| 908                   | < 10.0                |
| 909                   | < 10.0                |
| 910                   | < 10.0                |
| 1101                  | < 10.0                |
| 1102                  | < 10.0                |
| 1103                  | < 10.0                |
| 1104                  | < 10.0                |
| 1105                  | < 10.0                |
| 1106                  | < 10.0                |
| 1107                  | < 10.0                |
| 1108                  | < 10.0                |
| 1109                  | < 10.0                |
| 1110                  | < 10.0                |
| 1301                  | 11.6                  |
| 1301 Dup              | 11.4                  |
| 1302                  | 13.6                  |
| 1303                  | 14.0                  |
| 1304                  | 16.2                  |
| 1305                  | 11.0                  |
| 1306                  | < 10.0                |
| 1307                  | 14.5                  |
| 1308                  | 13.2                  |
| 1309                  | 13.1                  |
| 1310                  | 13.1                  |
| 1501                  | 92.9                  |
| 1502                  | 124                   |
| 1503                  | 75.4                  |
| 1504                  | 134                   |
| 1505                  | 72.1                  |
| 1506                  | 119                   |
| 1507                  | 133                   |
| 1508                  | 75.2                  |
| 1509                  | 114                   |
| 1510                  | 115                   |

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# FIGURES

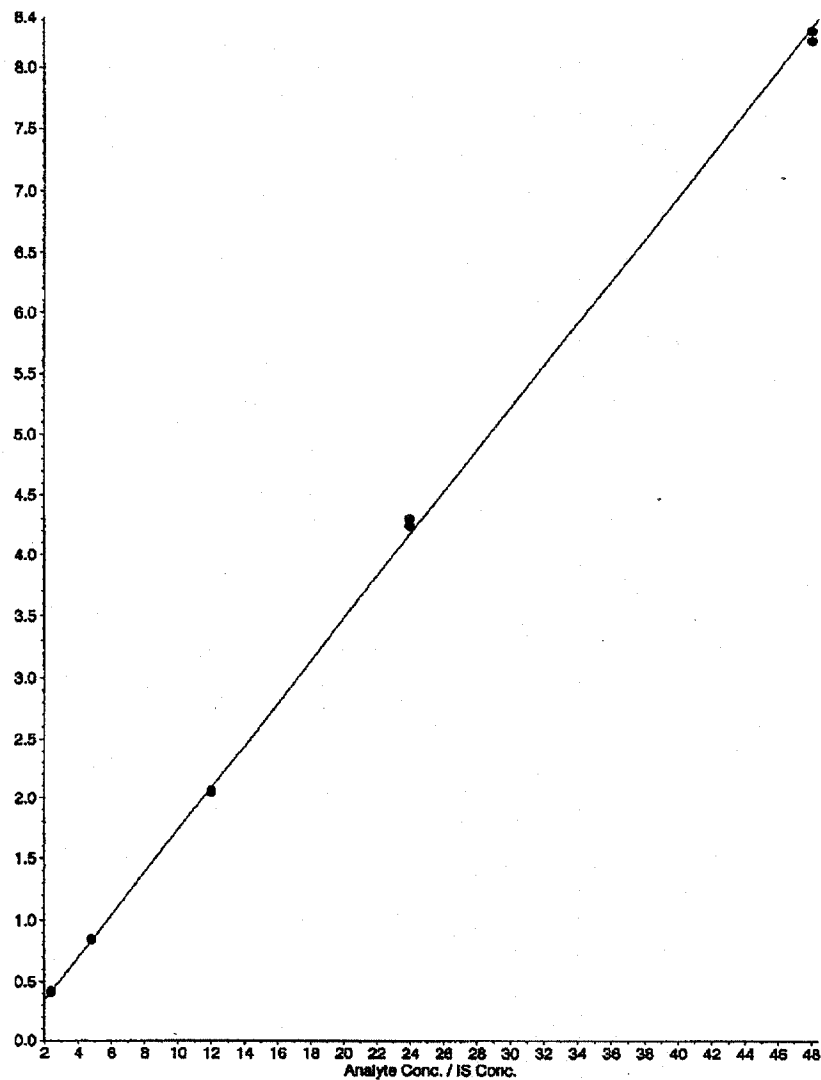
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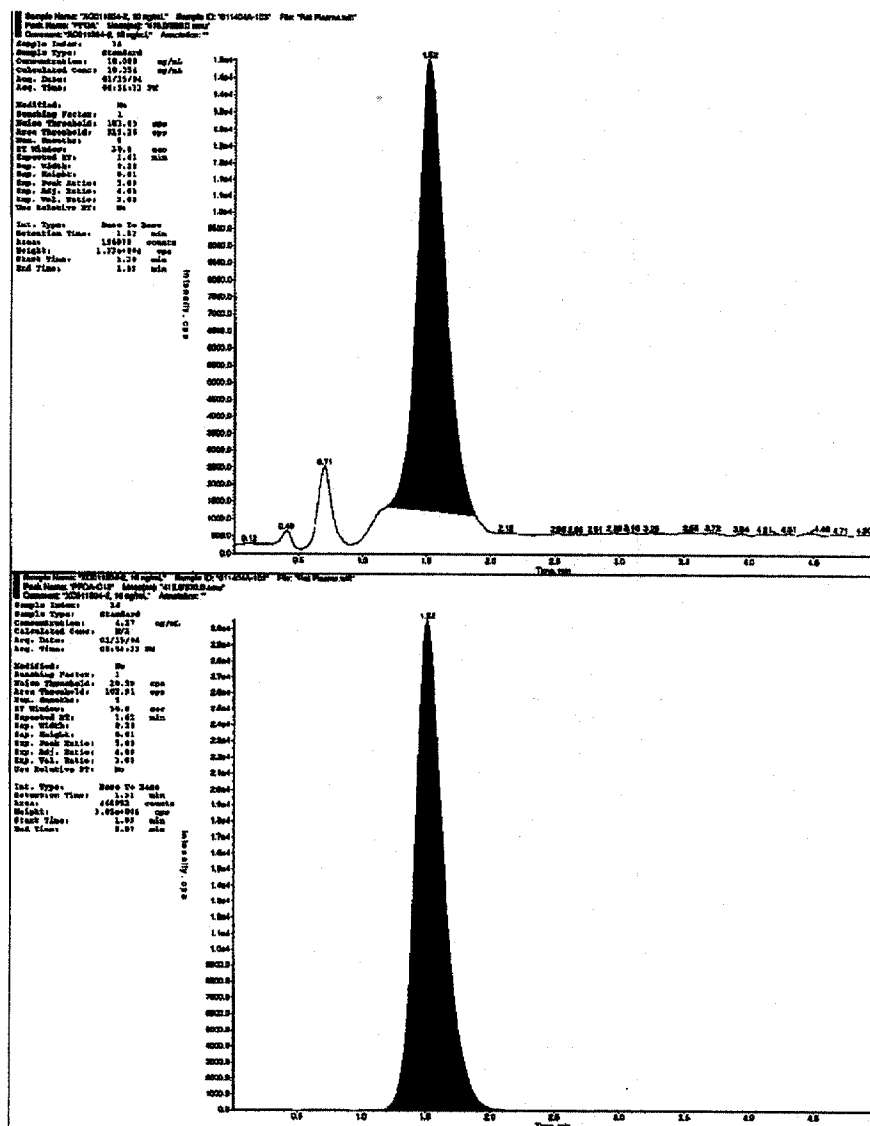
**Figure 1. Typical Calibration Curve for PFOA**

■ 011404A.rdb (PFOA): "Linear" Regression ("1/x" weighting):  $y = 0.173906x + 0.000435159$  ( $r = 0.9997871$ )

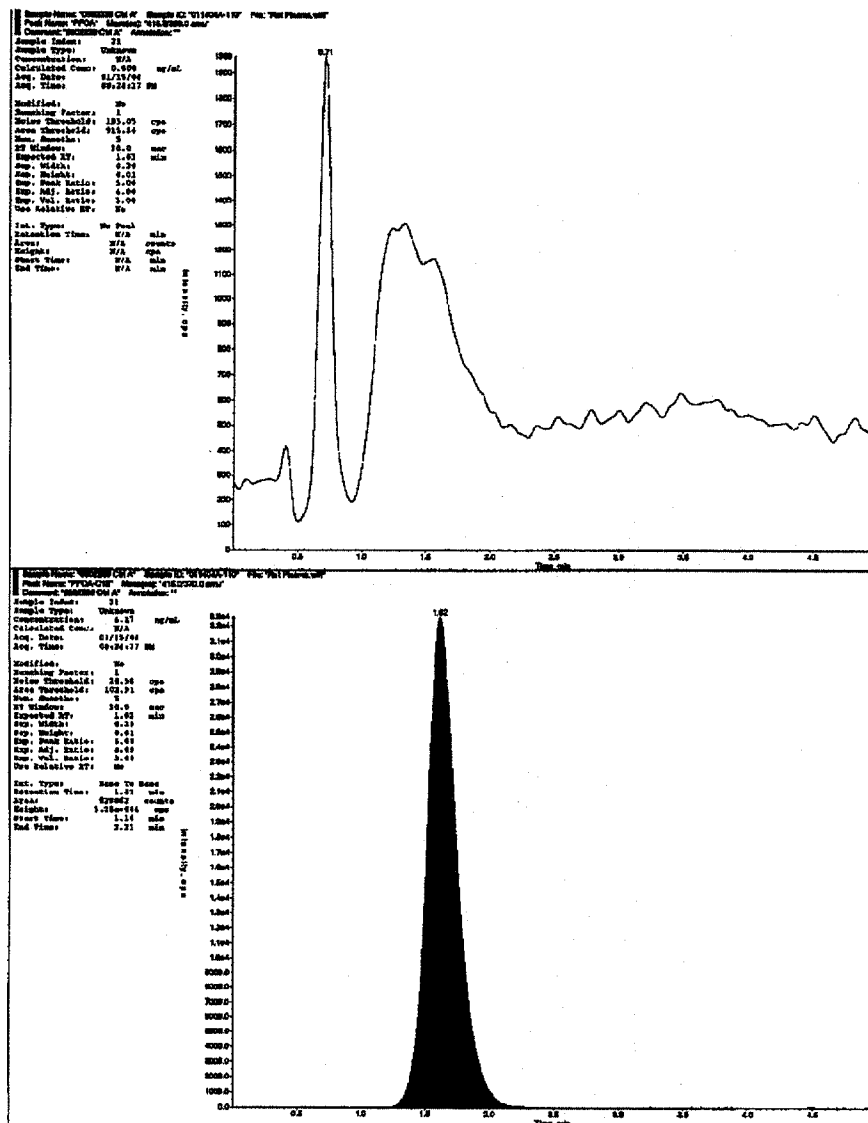


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**Figure 2. Chromatogram Representing a Calibration Standard for PFOA at 10 ppb with ~ 5 ng/mL of <sup>13</sup>C-PFOA**

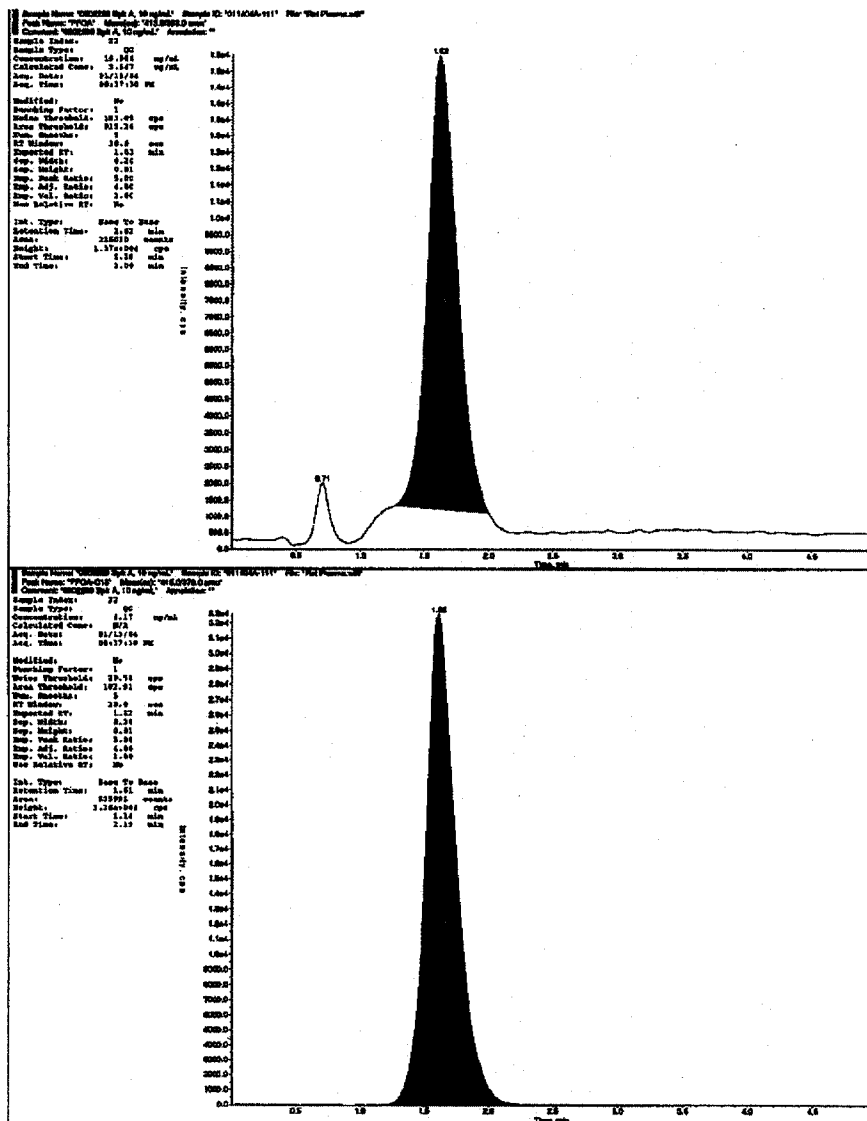


**Figure 3. Chromatogram Representing Control Rat Plasma for PFOA with ~ 5 ng/mL of <sup>13</sup>C-PFOA (Oxygen ID: 0302238 Control A, Sponsor ID: 669160, Set: 011404A)**



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**Figure 4. Chromatogram Representing Control Rat Plasma Fortified at 10 ppb with PFOA and ~ 5 ng/mL of <sup>13</sup>C-PFOA (Exygen ID: 0302238 Spk A, Sponsor ID: 669160, Set: 011404A)**

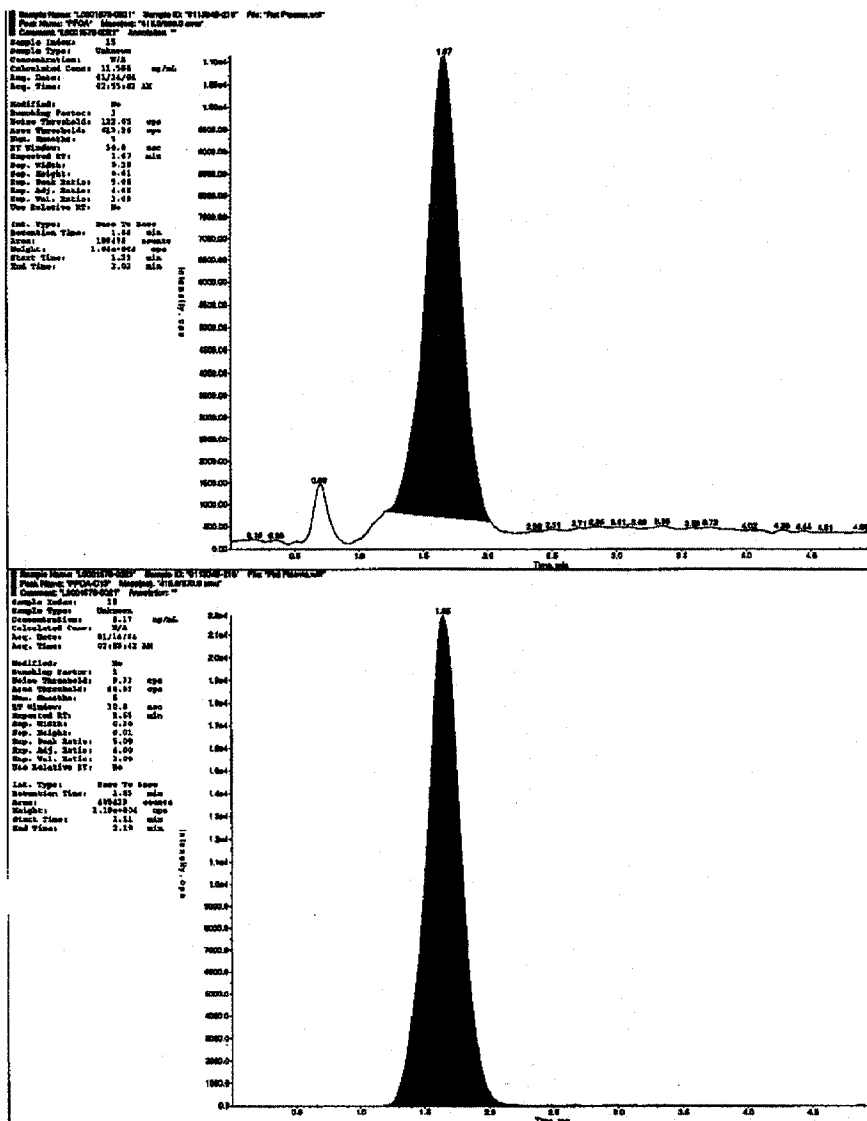


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**Figure 5. Chromatogram Representing Rat Plasma Sample for PFOA with ~ 5 ng/mL of  $^{13}\text{C}$ -PFOA (Oxygen ID: L0001573-0021, Sponsor ID: 1301, Set: 011304B)**



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# **APPENDIX A**

## **Study Protocol DuPont-13830 (Exygen Study No. 008-406) and Amendments and Deviation**

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H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

[REDACTED]  
[REDACTED]

Protocol

Haskell Animal Welfare Committee Number [REDACTED]

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H-25425: Repeated-Dose Dermal Toxicity  
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Exygen Study No.: 008-406

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

#### INTRODUCTION

The test substance, H-25425, is a [REDACTED]. In a previously conducted 90-day oral gavage study with the test substance, male and female rats were dosed at 0 (control), 10, 100, or 1000 mg/kg for 90 consecutive days.<sup>(1)</sup> No adverse test substance-related effects on body weight, body weight gain, food consumption, food efficiency, or clinical pathology parameters were observed in any male or female dose group. Reversible, minimal to mild thyroid follicular hypertrophy was observed in the 1000 mg/kg/day male and female groups. The no-observed-effect level (NOEL) for subchronic toxicity endpoints in male and female rats was 100 mg/kg/day.

Dose levels for the present study were selected to duplicate the dose levels of the oral gavage study.

#### OBJECTIVE

The objective of this study is to evaluate the potential toxicity of H-25425 when administered dermally to male rats for 28 days. The dermal route of administration was selected because it is a potential route of human exposure.

#### SPONSOR AND TEST FACILITY

This study is sponsored by E.I. du Pont de Nemours and Company, Wilmington, Delaware. The sponsor's approval was effective the date the sponsor authorized the work on the Work Authorization Form.

The study will be conducted at Haskell Laboratory for Health and Environmental Sciences, E.I. du Pont de Nemours and Company, Newark, Delaware.

#### REGULATORY COMPLIANCE

This study will be conducted in compliance with U.S. EPA TSCA (40 CFR part 792) Good Laboratory Practice Standards, which are consistent with the OECD Principles of Good Laboratory Practice (as revised in 1997) published in ENV/MC/CHEM(98)17.<sup>(2,3)</sup> The study design is based on U.S. Environmental Protection Agency (EPA) Office of Prevention, Pesticides, and Toxic Substances (OPPTS),<sup>(4)</sup> Organization for Economic Cooperation and Development (OECD),<sup>(5)</sup> test guidelines. Areas of noncompliance will be documented in the final report.

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Oxygen Study No.: 008-406

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

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#### STUDY DESIGN

The study design is as follows:

| Group | Number/Group | Dosage (mg/kg) |
|-------|--------------|----------------|
| I     | 10           | 0 (Control)    |
| III   | 10           | 10             |
| V     | 10           | 100            |
| VII   | 10           | 1000           |

| Study Parameters                             | Frequency                                      |
|----------------------------------------------|------------------------------------------------|
| Body Weight                                  | Test day 0 and at 3-4 day intervals thereafter |
| Food Consumption                             | Test day 0 and weekly thereafter               |
| Clinical Observations                        | Daily                                          |
| Observations for Dermal Effects              | Daily                                          |
| Mortality/Morbidity Checks                   | Twice daily                                    |
| Blood Collection for Total Fluorine Analysis | Test days 0, 7, 14, 21, 28                     |
| Clinical Pathology                           | Week 4                                         |
| PFOA Blood Analysis                          | Week 4                                         |
| Necropsy                                     | Week 4                                         |

#### MATERIALS AND METHODS

##### A. Test Substance

The test substance was supplied by the sponsor and was assigned the unique Haskell Laboratory Number 25425.

##### B. Test Species

Male Crl:CD<sup>®</sup>(SD)IGS BR rats will be obtained from Charles River Laboratories, Inc. The location of the supplier (city/state) will be documented in the study records and final report. The Crl:CD<sup>®</sup>(SD)IGS BR rat has been selected on the bases of extensive experience with this strain at Haskell Laboratory and its suitability with respect to hardiness, longevity, sensitivity, and low incidence of spontaneous diseases.

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#### C. Animal Husbandry

All rats will be housed in stainless steel, wire-mesh cages suspended above cage boards. Animal rooms will be maintained at a temperature of  $22 \pm 3^\circ\text{C}$  and a relative humidity of  $50 \pm 20\%$ . Animal rooms will be artificially illuminated (fluorescent light) on an approximate 12-hour light/dark cycle.

All rats will be provided tap water *ad libitum*. All rats will be fed PMI® Nutrition International, LLC Certified Rodent LabDiet® 5002 *ad libitum*.

As specified in the Haskell Laboratory animal health and environmental monitoring program, the following procedures are performed periodically to ensure that contaminant levels are below those that would be expected to impact the scientific integrity of the study:

- Water samples are analyzed for total bacterial counts, and the presence of coliforms, lead, and other contaminants.
- Feed samples are analyzed for total bacterial, spore, and fungal counts.
- Samples from freshly washed cages and cage racks are analyzed to ensure adequate sanitation by the cagewashers.

Certified animal feed is used, guaranteed by the manufacturer to meet specified nutritional requirements and not to exceed stated maximum concentrations of key contaminants, including specified heavy metals, aflatoxin, chlorinated hydrocarbons, and organophosphates. The presence of these contaminants below the maximum concentration stated by the manufacturer would not be expected to impact the integrity of the study.

The animal health and environmental monitoring program is administered by the attending laboratory animal veterinarian. Data are maintained separately from study records and may be included in the final report at the discretion of the study director.

#### D. Pretest Period

Upon arrival at Haskell Laboratory, all rats will be housed one per cage in quarantine. The rats will be:

- quarantined for a minimum of 5 days.
- identified temporarily by cage identification.
- weighed at least 3 times during quarantine.
- observed with respect to weight gain and any gross signs of disease or injury.

The rats will be released from quarantine by the laboratory animal veterinarian or designee on the bases of body weights and clinical signs.

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Rats that are accidentally killed or removed from study during the pretest period will be discarded without necropsy. Rats that are found dead or sacrificed *in extremis* during the pretest period will be sent to Pathology and given a gross examination to check for the presence of disease. Dependent upon these findings, further diagnostic procedures may be employed at the discretion of the study director, a pathologist, or the laboratory animal veterinarian. The results will not be reported in the final report unless considered significant to the evaluation of the study.

#### E. Assignment to Groups

The rats, selected on the bases of adequate body weight gain and freedom from any clinical signs of disease or injury, will be distributed by computerized, stratified randomization into study groups as designated in the Study Design, so that there are no statistically significant differences among group body weight means. The weight variation of selected rats will not exceed  $\pm 20\%$  of the mean weight.

Each rat will be housed individually and assigned an animal number. Prior to assignment to groups, each rat will be temporarily identified by cage identification. After assignment to groups, the animal number will be tattooed on the tail of each rat and included on the cage label.

At study start (test day 0) the rats will be 8 weeks old. On test day 0, when possible, rats with body weights that are not within  $\pm 20\%$  of the mean will be removed from study and replaced with rats having body weights within that range (subject to the same selection criteria as the original rats).

Rats that have not been assigned to a test group or which have been removed from study on test day 0, for out-of-range body weight, will be released for other laboratory purposes, or be sacrificed by carbon dioxide asphyxiation and discarded without pathological evaluation, at the discretion of the study director.

#### F. Administration of Test Substance

Approximately 24 hours prior to the first treatment, the fur of each rat will be closely shaved to expose the skin from the back and trunk. The target area to be treated is  $5\text{ cm} \times 7.4\text{ cm} = 37\text{ cm}^2$ . The  $37\text{ cm}^2$  treatment area is approximately equal to 10% of the total body surface area for rats in the 200 to 300 g range of body weights. The test substance will be moistened with deionized water to form a thick paste and applied in a thin and uniform layer to cover as much surface of the target area as possible. For some doses, the volume of test substance may be too small to cover the entire target area. The approximate area to be covered will be marked on the back of each rat with a water insoluble marker and the percentage of the marked area covered will be documented in the study records. The test substance will be covered with a 2-ply gauze pad followed by successive layers of stretch gauze and self-adhesive bandage. The control rats will receive deionized water at the same volume as the high-dose rats. The rats may be fitted with plastic collars during the exposure period to prevent ingestion of the test substance and disruption of the wrappings.

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The rats will be treated for 28 consecutive days. The amount of test substance needed to treat each rat will be based on the most recently determined body weight measurement.

The exposure period will be approximately 6 hours. After the exposure period, the wrappings and collar if used will be removed and excess test substance will be washed off with warm tap water. Soap will be used if necessary. The test site of each rat will then gently be patted dry and the rat returned to its cage. Control animals will receive the same washing technique as the treated animals.

The animals will be reshaved during the study to facilitate the evaluation of dermal effects. The entire area that was originally shaved (including the untreated control skin) will be reshaved. The animals will be reshaved only after an evaluation.

#### G. Body Weights

The rats will be weighed at 3-4 day intervals during the study.

#### H. Food Consumption and Food Efficiency

The amount of food consumed by each rat will be determined weekly by weighing each feeder at the beginning and end of the week and subtracting the final weight and the amount of spillage from the feeder during the week from the initial weight. From these measurements, mean daily food consumption over the week will be determined. From the food consumption and body weight data, the mean daily food efficiency will be calculated.

#### I. Clinical Observations and Mortality

The rats will be observed for clinical signs and dermal effects after removal of the test substance. The rats will also be observed for clinical signs at each weighing. The Draize Scale will be used to score skin irritation. Adjacent areas of untreated skin will be used for comparison. Rats will be checked twice daily for mortality and for signs of illness, injury, or abnormal behavior.

#### J. Total Fluorine and Perfluorooctanoic Acid Level Evaluations

Blood (approximately 1 mL) will be collected into EDTA tubes from the orbital sinus of all rats on test days 0, 7, 14, 21, and 28. The blood will be collected from the animals approximately one hour after removal of the test substance. The blood will be refrigerated. The total fluorine content of the blood samples from the first five animals in each group will be determined by using a Wickbold torch combustion method followed by analysis with a fluoride ion selective electrode. The analysis will be done at Jackson Laboratory, Deepwater, NJ 08023. Initially, only the day 21 samples will be analyzed. Additional analyses will be requested by the study director based on the results of the day 21 analysis.

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Additional blood (approximately 2 mL) will be collected from the vena cava of all rats at necropsy into a tube containing EDTA. Plasma will be prepared and stored frozen at -80°C to -20°C until analyzed for concentration of perfluorooctanoic acid (PFOA). Plasma will be evaluated from all rats. Plasma samples will be extracted by organic solvent protein precipitation and then analyzed for PFOA by an appropriate method at Exygen Research (3058 Research Drive, State College, PA 16801).

#### K. Clinical Pathology Evaluation

A clinical pathology evaluation will be conducted on all rats the day after the last dose. The day before collection of blood samples for the clinical pathology evaluation, the animals will be placed in metabolism cages. These animals will be fasted overnight (approximately 16 hours) and urine will be collected from each animal. Blood samples for hematology and clinical chemistry measurements will be collected from the orbital sinus of each animal while the animal is under light carbon dioxide anesthesia. Blood samples for plasma fluoride, PFOA, and coagulation measurements will be collected at sacrifice from the abdominal vena cava of each animal while the animal is under carbon dioxide anesthesia. Additional blood collected from the vena cava will be placed in a serum tube, processed to serum, and frozen at -80°C to -20°C. Bone marrow smears will be prepared at the final sacrifice from all surviving animals and will be evaluated if warranted by experimental findings.

At the discretion of the study director or clinical pathologist, additional samples for selected clinical pathology tests will be collected from animals showing clinical evidence of toxicity or sacrificed *in extremis*.

##### 1. Hematology

Blood samples will be evaluated for quality by visual examination prior to analysis.

The following hematology parameters will be determined:

|                                           |                                     |
|-------------------------------------------|-------------------------------------|
| red blood cell count                      | red cell distribution width         |
| hemoglobin                                | absolute reticulocyte count         |
| hematocrit                                | platelet count                      |
| mean corpuscular volume                   | white blood cell count              |
| mean corpuscular hemoglobin               | differential white blood cell count |
| mean corpuscular hemoglobin concentration | microscopic blood smear examination |
| prothrombin time                          |                                     |
| activated partial thromboplastin time     |                                     |

In addition, blood smears, stained with new methylene-blue, will be prepared from all hematology samples and will be evaluated, if required, to substantiate or clarify the results of hematology findings.

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## 2. Clinical Chemistry

The following serum chemistry parameters will be determined:

|                            |                       |
|----------------------------|-----------------------|
| aspartate aminotransferase | glucose               |
| alanine aminotransferase   | total protein         |
| sorbitol dehydrogenase     | albumin               |
| alkaline phosphatase       | globulin              |
| total bilirubin            | calcium               |
| urea nitrogen              | inorganic phosphorus  |
| creatinine                 | sodium                |
| cholesterol                | potassium             |
| triglycerides              | chloride              |
|                            | fluoride <sup>a</sup> |

## 3. Urinalysis

The following urinalysis parameters will be determined:

|            |                                        |
|------------|----------------------------------------|
| quality    | ketone                                 |
| color      | bilirubin                              |
| clarity    | blood                                  |
| volume     | urobilinogen                           |
| osmolality | fluoride                               |
| pH         | protein                                |
| glucose    | microscopic urine sediment examination |

## L. Anatomical Pathology

### 1. Pretest

See Materials and Methods, Section D. Pretest Period.

### 2. Dosing Phase

All rats found dead, accidentally killed, sacrificed *in extremis*, or sacrificed by design will undergo a gross and microscopic evaluation. All rats removed from study (except for out-of-range body weight on test day 0) will be sent to Pathology for gross evaluation and collection of tissues. Rats will be euthanatized by carbon dioxide anesthesia and exsanguination. Rats sacrificed by design will be fasted after 3 p.m. on the afternoon before their scheduled sacrifice. A final sacrifice will be performed on surviving rats following the final clinical pathology evaluation. The order of sacrifice for scheduled deaths will be random among all treatment groups.

<sup>a</sup> Fluoride-determination will be analyzed from EDTA plasma.

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The following tissues will be collected from rats which are found dead or accidentally killed (tissue integrity permitting), sacrificed *in extremis*, removed from study (except out-of-range body weight on test day 0), or sacrificed by design:

liver<sup>a</sup>  
kidneys<sup>a</sup>  
thyroid gland (after fixation)<sup>a</sup>  
skin (treated and untreated)  
gross observations<sup>b</sup>

- a. Organs to be weighed.  
b. Gross observations made at necropsy for which histopathology is not appropriate (e.g., fluid, ruffled fur, and missing anatomic parts) will generally not be collected.

All tissues will be placed in the appropriate fixative.

Rats sacrificed by design will have the following organs weighed: liver, kidneys, and thyroid. Relative organ weights (percent of final body weight) will be calculated. Final body weights determined just prior to necropsy will be used in the assessment of organ weight changes. Organs from rats found dead, sacrificed *in extremis*, or accidentally killed may be weighed at the discretion of the pathologist or study director.

Tissues collected from rats sacrificed by design in the high-dose and control group, and from rats that are found dead or accidentally killed (tissue integrity permitting), or are sacrificed *in extremis*, will be further processed to slides, stained with hematoxylin and eosin, and examined microscopically. Most gross lesions and any additional target organs from rats in the low- and intermediate-dosage groups will be evaluated microscopically. Selected gross observations for which a microscopic diagnosis would not be additive (e.g., osteoarthritis, pododermatitis, chronic tail dermatitis, calculus, and deformities of the teeth, toe, tail, or ear pinna) will be saved, but will generally not be processed for microscopic evaluation. Tissues from rats removed from study (for other than out-of-range body weight on test day 0), will not be processed for microscopic evaluation unless considered necessary by the study director or pathologist.

Additional procedures to identify and/or clarify histologic features of lesions may be performed at the discretion of the pathologist and will be documented in the final report.

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# STATISTICAL ANALYSES

Significance will be judged at  $p < 0.05$ .

| Parameter                                                                              | Preliminary Test                                                                                              | Method of Statistical Analysis                                                            |                                                                               |
|----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
|                                                                                        |                                                                                                               | If preliminary test is not significant                                                    | If preliminary test is significant                                            |
| Body Weight<br>Body Weight Gain<br>Food Consumption<br>Food Efficiency<br>Organ Weight | Test for lack of trend <sup>(6)</sup>                                                                         | Sequential application of the Jonckheere-Terpstra trend test <sup>(7)</sup>               | Preliminary tests for pairwise comparison                                     |
| OR <sup>a</sup>                                                                        |                                                                                                               |                                                                                           |                                                                               |
|                                                                                        | Levene's test for homogeneity <sup>(9)</sup> and Shapiro-Wilk test <sup>(10)</sup> for normality <sup>b</sup> | One-way analysis of variance <sup>(11)</sup> followed with Dunnett's test <sup>(12)</sup> | Kruskal-Wallis test <sup>(13)</sup> followed with Dunn's test <sup>(14)</sup> |
| Clinical Pathology <sup>c</sup>                                                        | Levene's test for homogeneity <sup>(9)</sup> and Shapiro-Wilk test <sup>(10)</sup> for normality <sup>b</sup> | One-way analysis of variance <sup>(11)</sup> followed with Dunnett's test <sup>(12)</sup> | Kruskal-Wallis test <sup>(13)</sup> followed with Dunn's test <sup>(14)</sup> |
| Survival<br>Incidence of Clinical Observations<br>Incidence of Dermal Effects          | None                                                                                                          | Cochran-Armitage test for trend <sup>(15)</sup>                                           |                                                                               |

- Pairwise comparisons and associated preliminary tests are only conducted if the test for lack of trend is significant.
- If the Shapiro-Wilk test is not significant but Levene's test is significant, a robust version of Dunnett's test will be used.
- When an individual observation is recorded as being less than a certain value, calculations are performed on half the recorded value. For example, if bilirubin is reported as  $<0.1$ , 0.05 is used for any calculations performed with that bilirubin data.
- If the incidence is not significant, but a significant lack of fit occurs, then Fisher's Exact test<sup>(15)</sup> with a Bonferroni correction is used.

Other methods will be used, if appropriate, at the time of analysis. The statistical methods used will be described in the final report.

## SAFETY AND HOUSEKEEPING

Good housekeeping procedures will be practiced to avoid contamination of the test substance and to avoid potential health hazards. To avoid skin contact, gloves will be worn when handling the test substance. Animal carcasses and feces will be incinerated.

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#### RECORDS AND SAMPLE STORAGE

All data and records for analytical characterizations conducted by the sponsor will be archived by the sponsor. Laboratory-specific or site-specific raw data such as personnel files, instrument, equipment, refrigerator and/or freezer raw data will be retained at the facility where the work was done.

A sample of the test substance will be collected for archive purposes and retained at Haskell Laboratory, Newark, Delaware. Specimens (if applicable), raw data, and the final report will be retained at Haskell Laboratory, Newark, Delaware, or at Iron Mountain Records Management, Wilmington, Delaware.

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#### REFERENCES

1. DuPont Haskell Laboratory (2003). H-25425: Subchronic Toxicity, 90-Day Gavage Study in Rats with One-Generation Reproduction Evaluations. Unpublished report.
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28-Day Study in Male Rats

DuPont-13830

PROTOCOL APPENDIX

Study Function

Study Personnel

Study Director

Carol Finlay  
Staff Toxicologist

Clinical Pathology Evaluation:

Nancy E. Everds  
Principal Research Clinical Pathologist  
and Manager

Anatomic Pathology Evaluation

Greg P. Sykes  
Veterinary Pathologist

Study Dates

Initiation of Test Substance Administration November 25, 2003

Collection of Blood for Fluorine Analysis  
November 25, 2003  
December 2, 2003  
December 9, 2003  
December 16, 2003  
December 23, 2003

Clinical Pathology Evaluations December 23, 2003

Anatomic Pathology Evaluation December 23, 2003

Scheduled Sacrifice December 23, 2003

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SIGNATURE

Approved by:

Carol Finlay  
Carol Finlay  
Study Director

18-Nov-2003  
Date

cc: Haskell

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Exygen Research

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Exygen Study No.: 008-406

H-25425: Repeated-Dose Dermal Toxicity  
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Work Request Number [REDACTED]  
Service Code [REDACTED]

Protocol Amendment 1

The protocol is amended as follows:

Page 4, Study Design, change group numbers to IX, XI, XIII, and XV.

Rationale: To avoid duplicating animal numbers with another study housed in the same animal room.

Approved by:

Carol Finley  
Carol Finley  
Study Director

24-Nov-2003  
Date

cc: Haskell

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Exygen Study No.: 008-406

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Work Request Number [REDACTED]

Service Code [REDACTED]

Protocol Amendment 2

The protocol is amended as follows:

1. Page 4, Study Design, and Page 7, section J. Total Fluorine and Perfluorooctanoic Acid Level Evaluations, change the last blood collection for fluorine analysis from test day 28 to test day 27.

Rationale: The day was incorrect.

2. Page 14, Study Dates, change the last date of blood collection for fluorine analysis from December 23, 2003 to December 22, 2003.

Rationale: The day was incorrect.

Approved by:

Carol Fusley  
Carol Fusley  
Study Director

10-Dec-2003  
Date

- 1 -

Exygen Study No.: 008-406



|                                                                                                                                 |                                      |
|---------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| Page <u>1</u> of <u>1</u>                                                                                                       |                                      |
| <b>PROTOCOL DEVIATION</b>                                                                                                       |                                      |
| Deviation Number: <u>1</u>                                                                                                      |                                      |
| Date of Occurrence: <u>01/14/04</u>                                                                                             |                                      |
| Exygen Study Number: <u>008-406</u>                                                                                             | Protocol Number: <u>DuPont-13830</u> |
| <b>DESCRIPTION OF DEVIATION</b>                                                                                                 |                                      |
| 1. Section J. Analytical Method Section 4.5.4.e--accepted recovery of 76% for Exygen sample ID L0001573-0001 Spk C at 1000 ppb. |                                      |
| <b>ACTIONS TAKEN</b><br><small>for example - deviation issued, SOP revision, etc.</small>                                       |                                      |
| 1. Protocol Deviation Issued.                                                                                                   |                                      |
| Recorded By: <u>Paul R. Decker</u>                                                                                              | Date: <u>1/14/04</u>                 |
| <b>IMPACT ON STUDY</b>                                                                                                          |                                      |
| 1. No negative impact because the LCS at the LLOQ and 1000 ppb levels were within the acceptable range for this analytical set. |                                      |
| <u>Paul R. Decker</u><br>Principal Investigator Signature                                                                       | <u>2/19/04</u><br>Date               |
| <u>Carol Kentley</u><br>Study Director Signature                                                                                | <u>17-Feb-2004</u><br>Date           |
| <u>S. [Signature]</u><br>Management Signature                                                                                   | <u>17-Feb-2004</u><br>Date           |
| (Sponsor)                                                                                                                       | Date                                 |
| Exygen QAU Review <u>Ph. W. 1/26/04</u>                                                                                         |                                      |

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9/25/2002/6

**X**  
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State College, PA 16801, USA  
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F: 814.272.1019  
exygen.com

Exygen Study No.: 008-406

# **APPENDIX B**

## **Analytical Method ExM-008-276, Revision 2 "Method of Analysis for the Determination of Pentadecafluorooctanoic Acid (PFOA) in Serum by LC/MS/MS"**

Exygen Research

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Exygen Study No.: 008-406



**TITLE**

Method of Analysis for the Determination of Perfluorooctanoic Acid (PFOA) in Serum  
by LC/MS/MS - Revision 2

**AUTHOR**

Emily Decker

**DATE ISSUED**

January 8, 2004

**SPONSOR**

DuPont  
Haskell Laboratory for Health & Environmental Sciences  
P.O. Box 50  
Newark, DE 19714-0050 USA  
DuPont Study Number: DuPont-13090

**PERFORMING LABORATORY**

Exygen Research  
3058 Research Drive  
State College, PA 16801

**METHOD NUMBER**

ExM-008-276 Revision 2

**TOTAL NUMBER OF PAGES**

20

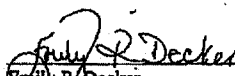
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Exygen Research

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Oxygen Study No.: 008-406

MANAGEMENT APPROVAL

  
Emily R. Decker  
Scientist  
Oxygen Research  
1/8/04  
Date

  
John Flaherty  
Vice President  
Oxygen Research  
1/8/04  
Date

  
S. Mark Kennedy  
Sponsor Representative  
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9-Jan-2004  
Date

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## 1. SUMMARY

This report details a method of analysis for perfluorooctanoic acid (PFOA) in serum.

PFOA is extracted from serum by protein precipitation in acetonitrile. Quantification of PFOA is accomplished by liquid chromatography/tandem mass spectrometry (LC/MS/MS) analysis using selected reaction monitoring (SRM). The chemical formula of PFOA is given in section 2 of this method.

The lower limit of quantitation (LLOQ) for this method is 10 ppb for PFOA in serum.

Quantification is performed using extracted calibration standards containing an internal standard.

This method was developed using monkey serum. The overall percent recovery  $\pm$  standard deviation for PFOA in monkey serum at 10, 100, and 1000 ppb was 94%  $\pm$  6.9% (Table I).

A representative calibration curve for PFOA in monkey serum is shown in Figure 1. Representative chromatograms for PFOA in monkey serum are shown in Figures 2 to 4.

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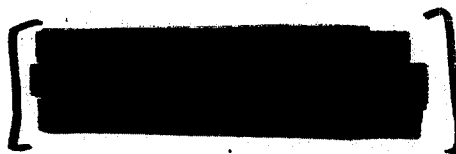
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## 2. EXPERIMENTAL COMPOUNDS

The structure of perfluorooctanoic acid (PFOA) and the internal standard are given below.

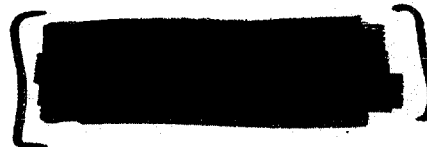
### PFOA

Chemical Name = perfluorooctanoic acid  
Molecular weight = 414



### <sup>13</sup>C - PFOA

Chemical Name = perfluorooctanoic acid, [1,2-di-<sup>13</sup>C]  
Molecular weight = 416



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### 3. CHEMICALS AND SUPPLIES

#### 3.1. CHEMICALS

| Chemical           | Grade   | Source        | Catalog No. |
|--------------------|---------|---------------|-------------|
| Methanol (MeOH)    | HPLC    | EM Science    | JT9093-2    |
| Acetonitrile (ACN) | HPLC    | EM Science    | AX0145-1    |
| Ammonium Acetate   | Reagent | Sigma-Aldrich | A-7330      |
| OmniSolv Water     | HPLC    | EM Science    | WX0004-1    |

#### 3.2. STANDARDS

| Standard                                       | Lot Number | Purity (%) | Source           |
|------------------------------------------------|------------|------------|------------------|
| perfluorooctanoic acid (PFOA)                  | [REDACTED] | [REDACTED] | Oakwood Products |
| perfluorooctanoic acid, [1,2- <sup>13</sup> C] |            |            | DuPont           |

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### 3.3. EQUIPMENT AND SUPPLIES

| Equipment                                                              | Supplier                        |
|------------------------------------------------------------------------|---------------------------------|
| Balance, analytical (display at least 0.0001 g)                        | Mettler                         |
| Centrifuge                                                             | Eppendorf                       |
| 2 mL eppendorf centrifuge tubes                                        | VWR                             |
| Disposable micropipets (50-100uL, 100-200uL)                           | Drummond (VWR)                  |
| Class A pipets and volumetric flasks                                   | various suppliers               |
| Hypercarb drop-in guard column (4 mm)<br>(part # 844017-400)           | Keystone                        |
| Stand-alone drop-in guard cartridge holder                             | Keystone                        |
| 125-mL LDPE narrow-mouth bottles                                       | Nalgene                         |
| 2 mL clear HPLC vial kit (cat # 5181-3400)                             | HP                              |
| Standard lab equipment (graduated cylinders,<br>disposable tubes etc.) | various suppliers               |
| LC/MS/MS and HPLC systems                                              | As described in<br>section 4.5. |

Note: Equivalent materials may be substituted for those specified in this method if they can be shown to produce satisfactory results.

#### Notes:

1. In order to avoid contamination, the use of disposable labware is highly recommended (tubes, pipets, etc.).
2. PTFE or PTFE lined containers or equipment, including PTFE-lined HPLC vials for the HPLC autosampler must not be used.
3. It is necessary to check the solvents (methanol) for the presence of contaminants by LC/MS/MS before use. Certain lot numbers have been found to be unsuitable for use.
4. Use disposable micropipets or pipets to aliquot standard solutions to make calibration standards and sample fortifications.
5. The hypercarb cartridges should be changed when the system contaminants (elevated baseline) move to within 1 minute from the elution of PFOA.

### 3.4. SOLUTIONS

- (1) 2 mM ammonium acetate solution is prepared by weighing 0.15 g of ammonium acetate and dissolving in 1 L of OmniSolv Water.

Note: The aforementioned example is provided for guidance, alternative volumes may be prepared as long as the ratios of the solvent to solute are maintained.

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### 3.5. PREPARATION OF STANDARDS AND FORTIFICATION SOLUTIONS

Analytical standards are used for three purposes:

1. Calibration Standards – These standards are prepared in control monkey serum and are used to calibrate the response of the detector used in the analysis.
2. Laboratory Control Spikes – These fortifications are usually prepared at concentrations corresponding to the LLOQ and 10x LLOQ and are used to determine analytical recovery. Laboratory control spikes are prepared in control monkey serum.
3. Matrix Spikes – These fortifications are prepared by spiking into the field samples at known concentrations. Matrix spikes are used to evaluate the effect of the sample matrix on analytical recovery.

The absolute volumes of the standards may be varied by the analyst as long as the correct proportions of solute to solvent are maintained. Alternate concentrations may be prepared as long as the preparation and concentration are accurately recorded in the raw data. Note also that additional concentrations may be prepared if necessary.

#### 3.5.1. Stock solution

Prepare individual stock solutions of ~ 100 µg/mL of PFOA and <sup>13</sup>C-PFOA by weighing out ~ 10 mg of analytical standard (corrected for purity) and dilute to 100 mL with methanol in a 100-mL volumetric flask. Each stock solution (in 125-mL LDPE bottles) is to be stored in a refrigerator at 2°C to 6°C and is stable for a maximum period of 1 year from the date of preparation.

#### 3.5.2. Fortification Solutions

- a. Prepare a fortification standard of 10.0 µg/mL for PFOA by diluting 10.0 mL of the PFOA solution described in 3.5.1 to 100 mL with acetonitrile in a volumetric flask.
- b. Prepare a fortification standard of 1.0 µg/mL for <sup>13</sup>C-PFOA by diluting 1.0 mL of the <sup>13</sup>C-PFOA solution described in 3.5.1 to 100 mL with acetonitrile in a volumetric flask.
- c. Prepare a fortification standard of 1.0 µg/mL for PFOA containing 0.005 µg/mL of <sup>13</sup>C-PFOA by diluting 10.0 mL of the PFOA solution described in 3.5.2.a and 0.5 mL of the <sup>13</sup>C-PFOA solution described in 3.5.2.b to 100 mL with acetonitrile in a volumetric flask.
- d. Prepare a fortification standard of 0.1 µg/mL for PFOA containing 0.005 µg/mL of <sup>13</sup>C-PFOA by diluting 1.0 mL of the PFOA solution described in 3.5.2.a and 0.5 mL of the <sup>13</sup>C-PFOA solution described in 3.5.2.b to 100 mL with acetonitrile in a volumetric flask.
- e. Prepare a fortification standard of 0.01 µg/mL for PFOA containing 0.005 µg/mL of <sup>13</sup>C-PFOA by diluting 0.1 mL of the PFOA solution

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described in 3.5.2.a and 0.5 mL of the  $^{13}\text{C}$ -PFOA solution described in 3.5.2.b to 100 mL with acetonitrile in a volumetric flask.

Store all fortification standard solutions in a refrigerator (in 125-mL LDPE bottles) at 2°C to 6°C for a maximum period of 1 year from the date of preparation, after which time it is necessary to make new standards using the stock solution.

#### 3.5.3. Calibration Standards

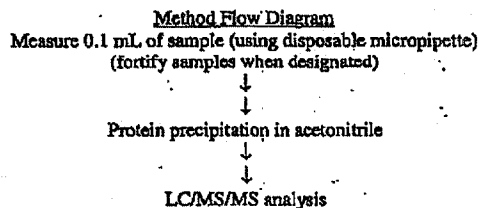
The calibration standards are processed through the extraction procedure, identical to the samples. The fortification of the standards before extraction is done according to the following table:

| Conc. Of<br>Mixed<br>Fortification<br>Solution<br>( $\mu\text{g/mL}$ ) | Fortification<br>Volume ( $\mu\text{L}$ ) | Volume of<br>Control<br>Sample (mL) | Conc. of<br>Extracted<br>Calibration<br>Standard<br>(ppb) |
|------------------------------------------------------------------------|-------------------------------------------|-------------------------------------|-----------------------------------------------------------|
| 0.01                                                                   | 100                                       | 0.1                                 | 10                                                        |
| 0.01                                                                   | 200                                       | 0.1                                 | 20                                                        |
| 0.1                                                                    | 50                                        | 0.1                                 | 50                                                        |
| 0.1                                                                    | 100                                       | 0.1                                 | 100                                                       |
| 0.1                                                                    | 200                                       | 0.1                                 | 200                                                       |

## 4. METHOD

### 4.1. FLOW DIAGRAM

The flow diagram of the method is given below, followed by a detailed description of each step.



### 4.2. SAMPLE PROCESSING

No sample processing is needed for serum samples. However, frozen samples must be allowed to completely thaw, un-aided, at room temperature. Samples

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stored, refrigerated should also be allowed to equilibrate to room temperature. All samples must be thoroughly mixed before being sampled for extraction.

#### 4.3. SAMPLE PREPARATION

- a. Each batch of samples extracted (typically 30 or less) must include at least one reagent control (acetonitrile blank), one matrix control (method blank), and two matrix controls fortified at known concentrations to verify procedural recovery for the batch.
- b. At least one sample per batch should be extracted in duplicate.
- c. At least one sample extracted should be separately fortified at a known concentration and carried through the procedure to verify recovery. Additional matrix spikes may be performed at the sponsor's request.

#### 4.4. EXTRACTION

1. Measure 0.1 mL of sample into 2 mL eppendorf centrifuge tubes (fortify with analyte as needed, close lid, and vortex ~ 10 seconds).
2. Add enough acetonitrile containing internal standard at 0.005 µg/mL (accounting for fortification volume) to make extraction volume 500 µL and vortex for ~ 10 seconds.
3. Centrifuge for ~ 10 minutes at ~ 14,000 rpm.
4. Analyze samples using electrospray LC/MS/MS.

#### 4.5. QUANTITATION

##### 4.5.1. LC/MS/MS System and Operating Conditions

Instrument: PE SCIEX API 4000 Biomolecular Mass Analyzer  
SCIEX Turbo Ion Spray Liquid Introduction Interface

Computer: Dell OptiPlex GX 110

Software: PE Sciex Analyst 1.2

HPLC Equipment: Hewlett Packard (HP) Series 1100  
Quatpump G1311A  
Vacuum Degasser G1322A  
Autoinjector G1313A  
Column Compartment G1316A

Note: Two 4 × 10 mm hypercarb drop-in guard cartridges (Keystone, part # 844017-400) are attached in-line after the purge valve and before the sample injector port to trap any residue contaminants that may be in the mobile phase and/or HPLC system.

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HPLC Column: Genesis C<sub>8</sub> (Jones Chromatography), 2.1 mm x 50 mm, 4μ  
Column Temperature: 30° C  
Injection Volume: 5 μL  
Mobile Phase (A): 2 mM Ammonium Acetate in OmniSolv Water  
Mobile Phase (B): Methanol

| Time | % A | % B | Flow (mL/min) |
|------|-----|-----|---------------|
| 0.0  | 40  | 60  | 0.3           |
| 3    | 40  | 60  | 0.3           |
| 3.5  | 0   | 100 | 0.3           |
| 3.7  | 0   | 100 | 0.5           |
| 7    | 0   | 100 | 0.5           |
| 7.5  | 40  | 60  | 0.5           |
| 9    | 40  | 60  | 0.5           |
| 9.5  | 40  | 60  | 0.3           |
| 12   | 40  | 60  | 0.3           |

It may be necessary to adjust the HPLC gradient in order to optimize instrument performance.

Ions monitored:

| Analyte              | Mode     | Transition Monitored | Approximate Retention Time |
|----------------------|----------|----------------------|----------------------------|
| PFOA                 | Negative | 413 → 369            | ~2.8 min.                  |
| <sup>13</sup> C-PFOA | Negative | 415 → 370            | ~2.8 min.                  |

The retention times may vary, on a day-to-day basis, depending on the batch of mobile phase etc. Drift in retention times is acceptable within an analytical run, as long as the drift continues through the entire analysis and the standards are interspersed throughout the analytical run.

Note: An alternative LC/MS/MS system may be used once demonstrated to be equivalent.

4.5.2. Tune File Parameters

The mass spectrometer is tuned for the analyte by infusing a ~ 1 μg/mL standard solution of PFOA (at 10 μL/min, using an infusion pump) via a "T" into a stream of mobile phase containing 60% methanol and 40% 2mM ammonium acetate at 0.3 mL/min flow rate. The analyte is initially tuned for the parent ion and then tuned for the product ion. Once the instrument is tuned, the optimized parameters are saved as a tune file. This tune file is then used during routine analysis.

4.5.3. Calibration Procedures

- Inject the same aliquot (5 μL) of each calibration standard into the LC/MS/MS.

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- b. Use linear standard curves for quantitation. Linear standard curves are generated for each analyte by linear regression using  $1/x$  weighting of the ratio analyte peak area/internal standard peak area versus the ratio of the concentration of analyte/concentration of internal standard using Analyst 1.2 (or equivalent) software system. Any calibration standard found to be a statistical outlier by using the appropriate outlier test (e.g. Huge Outlier Test) may be excluded from the calibration curve. However, the total number of calibration standards that could be excluded must not exceed 20% of the total number of standards injected and at least one calibration standard at the LLOQ must be retained.
- c. The correlation coefficient ( $r$ ) for calibration curves generated must be  $\geq 0.9925$  ( $r^2 \geq 0.985$ ). If calibration results fall outside these limits, then appropriate steps must be taken to adjust instrument operation, and the standards or the relevant set of samples should be reanalyzed.

#### 4.5.4. Sample Analysis

- a. Inject the same aliquot (5  $\mu$ L) of each standard, sample, recovery, control, etc. into the LC/MS/MS system.
- b. Standards corresponding to at least five or more concentration levels must be included in an analytical set.
- c. An entire set of calibration standards should be injected at the beginning of a set followed by calibration standards interspersed every 5-10 samples (to account for a second set of standards). As an alternative, an entire set of calibration standards may be included at the beginning and at the end of a sample set. In either case, calibration standards must be the first and last injection in a sample set.
- d. The concentration of each sample/fortification/control is determined from the standard curve, based on the peak area of each analyte. The standard responses should bracket responses of the residue found in each sample set. If necessary, dilute the samples in 50:50 methanol:water to give a response within the standard curve range.
- e. Fortification recoveries falling within 85 to 115% (80 to 120% for levels at the LLOQ) are considered acceptable.
- f. Extracted samples must be stored refrigerated between 2°C to 6°C until analysis.
- g. Samples in which no peaks are detected (i.e. signal : noise ratio < 3:1) at the corresponding analyte retention times will be reported as ND (not detected). Samples in which peaks are detected at the corresponding analyte retention

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times but are less than the lowest concentration of the calibration standards (10 ppb where LLOQ = 10 ppb) will be reported as <10 ppb.

#### 4.6. ACCEPTANCE CRITERIA

The following criteria must be met to ensure the presence of PFOA and  $^{13}\text{C}$ -PFOA:

1. The chromatograms must show the following peaks:  
PFOA: a daughter ion at 369 amu from a parent of 413 amu  
 $^{13}\text{C}$ -PFOA: a daughter ion at 370 amu from a parent of 415 amu
2. Any analyte present in method blanks must be at least 5-fold lower than the LLOQ. Any analyte present in the reagent blank must be at least 5-fold lower than the LLOQ.
3. Recoveries of lab control spikes and matrix spikes must be between 85-115% (80-120% for levels at the LLOQ) of their known values. Any method fortification (lab control spike) falling outside the acceptable limits warrants re-extraction of the entire analytical set. Any matrix spike outside the acceptable range should be evaluated by the analyst to determine if re-extraction is warranted.
4. Any calibration standard found to be a statistical outlier by using an appropriate outlier test, may be excluded from the curve. However, the total number of calibration standards that could be excluded must not exceed 20% of the total number of standards injected and at least one calibration standard at the LLOQ must be retained.
5. The correlation coefficient ( $r$ ) for calibration curves generated must be  $\geq 0.9925$  ( $r^2 \geq 0.985$ ). If calibration results fall outside these limits, then appropriate steps must be taken to adjust instrument operation, and the standards or the relevant set of samples should be reanalyzed.

#### 4.7. PERFORMANCE CRITERIA

The following two criteria must be performed as a system suitability test, before the commencement of analysis when using an instrumentation set-up that has not been used for this method.

##### First Criterion:

Run a standard solution on LC/MS/MS corresponding to the estimated LLOQ and obtain a signal-to-noise ratio of at least 2:1, compared to a reagent blank. If this criterion cannot be met, optimize and change instrument operating parameters.

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Second Criterion:

Run a set of standards of five or more concentration levels, spanning a range starting at or below the LLOQ up to the highest concentration level to be included in the analysis. Generate a calibration curve for each analyte and obtain a linear regression with a coefficient of determination ( $r^2$ ) of at least 0.985. Once this criterion is met, samples may be analyzed with standards interspersed.

**4.8. TIME REQUIRED FOR ANALYSIS**

A set of 35 samples (1 reagent control, 1 matrix control, 1 laboratory spike, 2 laboratory control spikes, and 30 samples) can be taken through the extraction procedure in approximately 8 hours by one person. The LC/MS/MS analysis (standards and 35 samples) will take approximately 9 hours.

**5. CALCULATIONS**

- a. Use Equation 1 to calculate the amount of analyte found (in ng/mL, based on peak area) using the standard curve (linear regression parameters) generated by the Analyst software program.

Equation 1:

$$\text{Analyte found (ppb)} = \frac{(\text{Analyte Peak area} / \text{IS peak area}) - \text{intercept}}{\text{slope}} \times \text{IS conc. (ng/mL)}$$

- b. For samples fortified with known amounts of analyte prior to extraction, use Equation 2 to calculate the percent recovery.

Equation 2:

Recovery (%) =

$$\frac{\text{Analyte found (ppb)} - \text{avg. Analyte found in control (ppb)}}{\text{Amount Analyte added (ppb)}} \times 100\%$$

**6. SAFETY**

The analyst should read the material safety data sheets for all standards and reagents before performing this method. Use universal precautions when handling standards and reagents, including working in fume hoods and wearing laboratory coats, safety glasses, and gloves. Use blood-borne pathogen handling precautions when handling serum.

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**Table I. Recovery of PFOA from Fortifications in Monkey Serum**

**Summary of PFOA Recoveries for 10 ppb Fortification in Monkey Serum**

| Exygen ID                    | Sponsor ID  | Extraction Date | Analysis Date | Fort. Level (ppb) | % Recovery |
|------------------------------|-------------|-----------------|---------------|-------------------|------------|
| 0300808 Spk A                | Lot 40K7400 | 05/30/03        | 05/30/03      | 10                | 95         |
| 0300808 Spk B                | Lot 40K7400 | 05/30/03        | 05/30/03      | 10                | 94         |
| 0300808 Spk C                | Lot 40K7400 | 05/30/03        | 05/30/03      | 10                | 98         |
| AVERAGE:                     |             |                 |               |                   | 96         |
| STANDARD DEVIATION:          |             |                 |               |                   | 2.1        |
| RELATIVE STANDARD DEVIATION: |             |                 |               |                   | 2.2        |

**Summary of PFOA Recoveries for 100 ppb Fortification in Monkey Serum**

| Exygen ID                    | Sponsor ID  | Extraction Date | Analysis Date | Fort. Level (ppb) | % Recovery |
|------------------------------|-------------|-----------------|---------------|-------------------|------------|
| 0300808 Spk D                | Lot 40K7400 | 05/30/03        | 05/30/03      | 100               | 92         |
| 0300808 Spk E                | Lot 40K7400 | 05/30/03        | 05/30/03      | 100               | 90         |
| 0300808 Spk F                | Lot 40K7400 | 05/30/03        | 05/30/03      | 100               | 93         |
| AVERAGE:                     |             |                 |               |                   | 92         |
| STANDARD DEVIATION:          |             |                 |               |                   | 1.5        |
| RELATIVE STANDARD DEVIATION: |             |                 |               |                   | 1.7        |

**Summary of PFOA Recoveries for 1000 ppb Fortification in Monkey Serum**

| Exygen ID                            | Sponsor ID  | Extraction Date | Analysis Date | Fort. Level (ppb) | % Recovery |
|--------------------------------------|-------------|-----------------|---------------|-------------------|------------|
| 0300808 Spk G                        | Lot 40K7400 | 05/30/03        | 05/30/03      | 1000              | 107        |
| 0300808 Spk H                        | Lot 40K7400 | 05/30/03        | 05/30/03      | 1000              | 95         |
| 0300808 Spk I                        | Lot 40K7400 | 05/30/03        | 05/30/03      | 1000              | 81         |
| AVERAGE:                             |             |                 |               |                   | 94         |
| STANDARD DEVIATION:                  |             |                 |               |                   | 13.8       |
| RELATIVE STANDARD DEVIATION:         |             |                 |               |                   | 13.8       |
| OVERALL AVERAGE:                     |             |                 |               |                   | 94         |
| OVERALL STANDARD DEVIATION:          |             |                 |               |                   | 6.9        |
| OVERALL RELATIVE STANDARD DEVIATION: |             |                 |               |                   | 7.3        |

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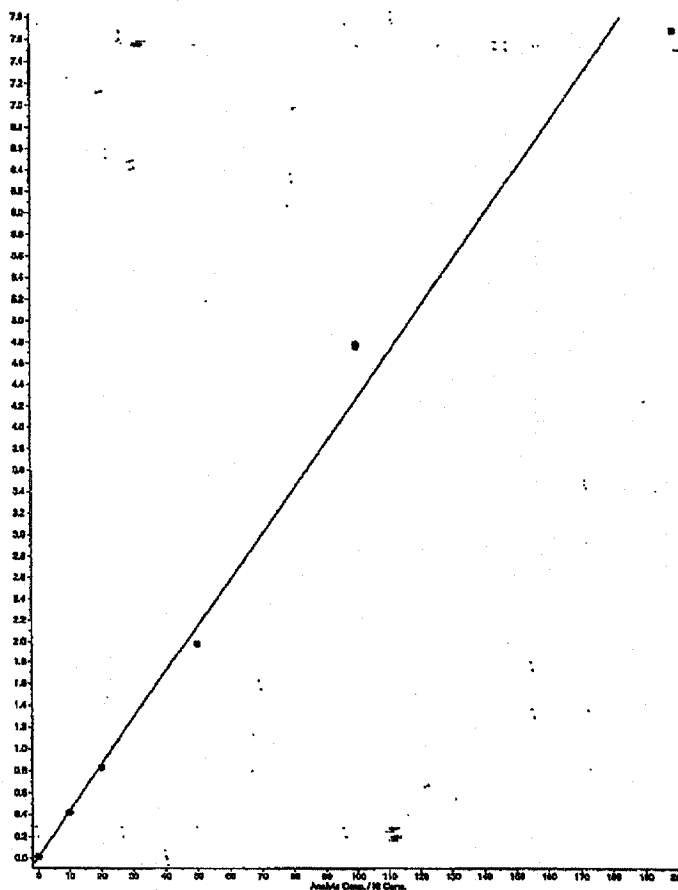
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Figure 1. Calibration curve for PFOA in Control Monkey Serum

■ 053005A.Dlt (PFOA): "Linear" Regression ("1/x" weighting):  $y = 0.0425214x + 0.8150303$  ( $r = 0.9848548$ )



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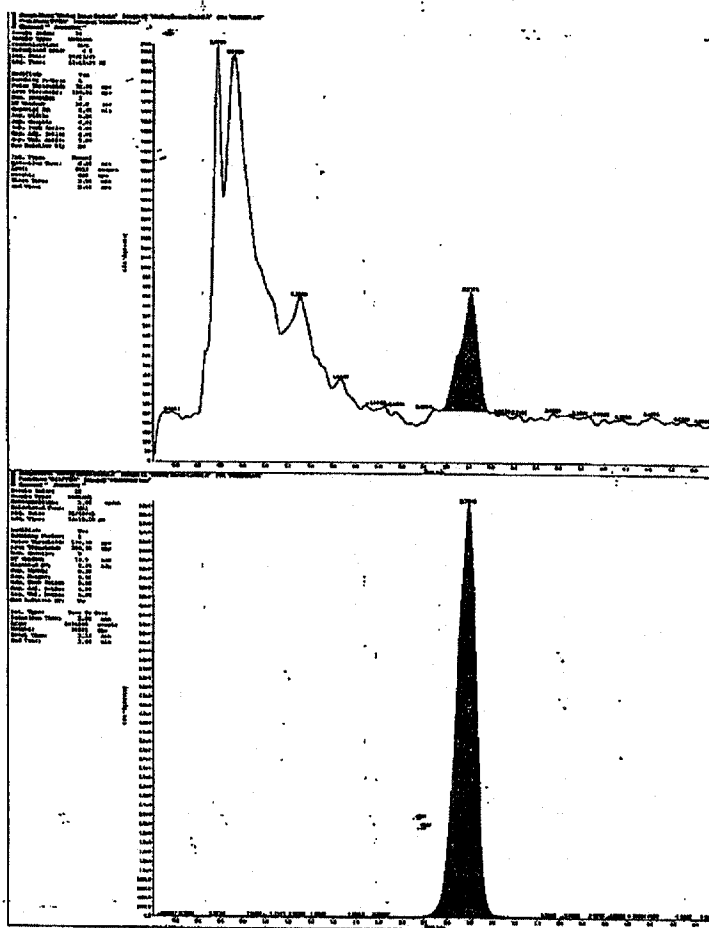
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Figure 2. Representative Chromatogram of a Control Monkey Serum  
Sample for PFOA with ~ 5 ng/mL of  $^{13}\text{C}$ -PFOA



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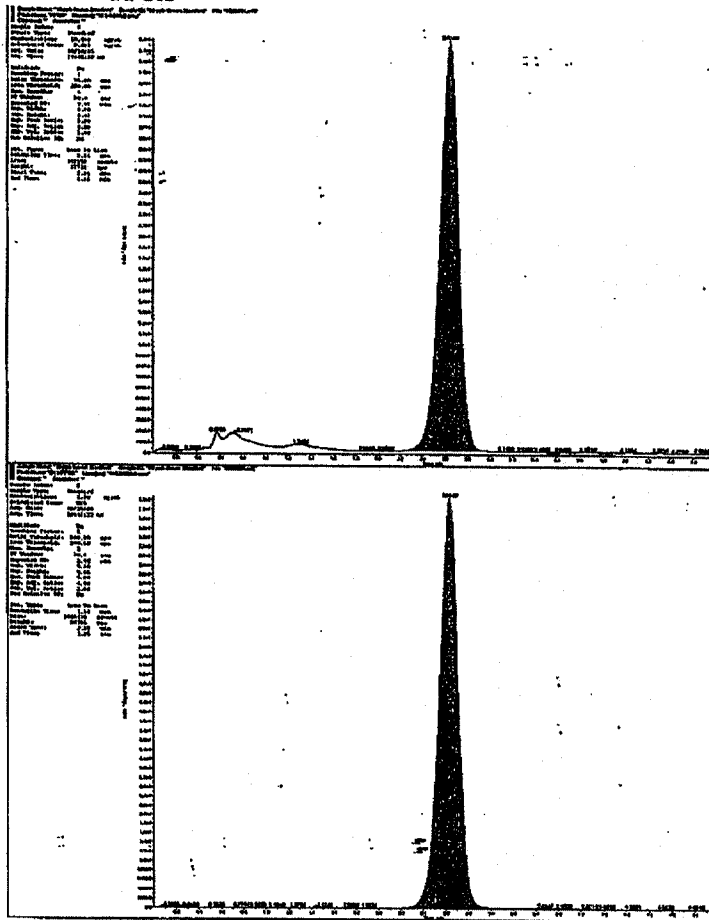
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Figure 3. Representative Chromatogram of a 10 ppb Standard for PFOA in Control Monkey Serum with ~ 5 ng/mL of  $^{13}\text{C}$ -PFOA



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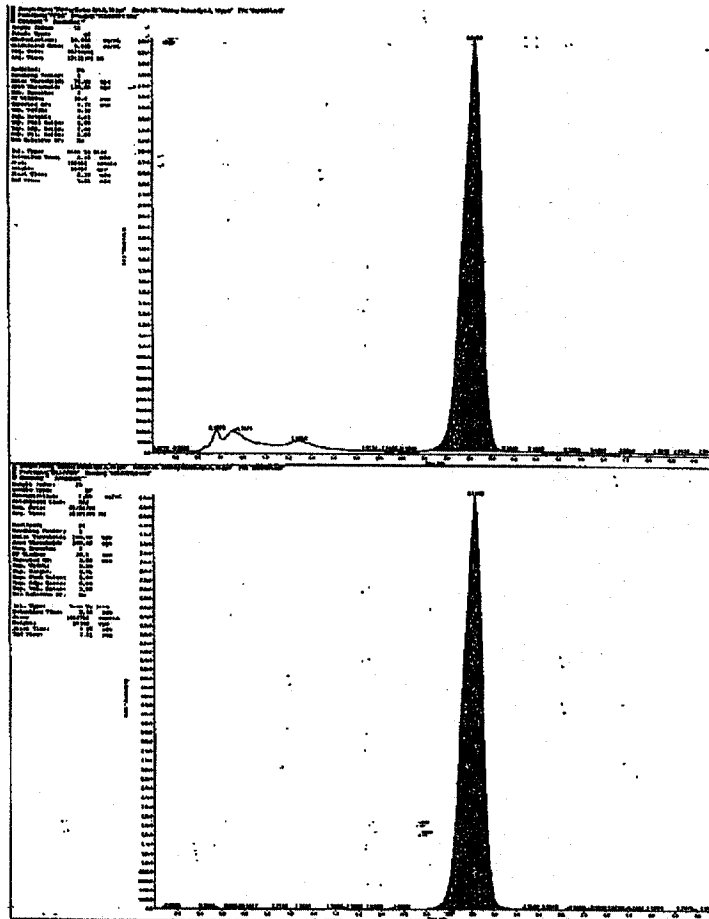
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Figure 4. Representative Chromatogram of Control Monkey Serum  
Fortified at 10 ppb with PFOA and with ~ 5 ng/mL of  $^{13}\text{C}$ -  
PFOA



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**APPENDIX G**  
**INDIVIDUAL BLOOD FLUORINE LEVELS**

INDIVIDUAL BLOOD FLUORINE LEVELS

| Group | Dosage<br>(mg/kg/day) | Animal<br>Number | ppb Fluorine  |
|-------|-----------------------|------------------|---------------|
| IX    | 0                     | 906              | less than 500 |
| IX    | 0                     | 907              | ND            |
| IX    | 0                     | 908              | ND            |
| IX    | 0                     | 909              | ND            |
| IX    | 0                     | 910              | ND            |
| XI    | 10                    | 1106             | ND            |
| XI    | 10                    | 1107             | ND            |
| XI    | 10                    | 1108             | ND            |
| XI    | 10                    | 1109             | ND            |
| XI    | 10                    | 1110             | ND            |
| XIII  | 100                   | 1306             | less than 500 |
| XIII  | 100                   | 1307             | ND            |
| XIII  | 100                   | 1308             | ND            |
| XIII  | 100                   | 1309             | ND            |
| XIII  | 100                   | 1310             | ND            |
| XV    | 1000                  | 1506             | less than 500 |
| XV    | 1000                  | 1507             | less than 500 |
| XV    | 1000                  | 1508             | less than 500 |
| XV    | 1000                  | 1509             | ND            |
| XV    | 1000                  | 1510             | less than 500 |

ND = not detectable = values < 200 ppb

Values "less than 500 ppb" are  $\geq 200$  ppb and < 500 ppb. 500 ppb = limit of quantification (LOQ).

**APPENDIX H**  
**INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA**

## INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA

### EXPLANATORY NOTES

#### ABBREVIATIONS:

##### **General:**

Adeq - adequate  
CLOT - sample clotted  
NP - not taken or not performed  
OK - sample condition OK for testing  
QNS - quantity not sufficient for testing  
UTD - unable to determine

##### **Individual Hematology Values:**

COND - sample condition  
RBC - red blood cell count  
HGB - hemoglobin  
HCT - hematocrit  
MCV - mean corpuscular volume  
MCH - mean corpuscular hemoglobin  
MCHC - mean corpuscular hemoglobin concentration  
RDW - red cell distribution width  
ARET - absolute reticulocyte count  
PLT - platelet count  
WBC - white blood cell count  
ANEU - absolute neutrophil (all forms)  
ALYM - absolute lymphocyte  
AMON - absolute monocyte  
AEOS - absolute eosinophil  
ABAS - absolute basophil  
ALUC - absolute large unstained cell

##### **Individual Red Blood Cell Morphology Values:**

ANIS - anisocytosis  
MIC - microcytes  
MAC - macrocytes  
POLY - polychromasia  
HYPO - hypochromasia  
ECHI - echinocytes  
ACAN - acanthocytes  
TARG - Target cells  
RX - rouleaux  
HJB - Howell-Jolly body  
Mod - moderate  
- - not observed or not examined; see whole blood sample condition

##### **Individual White Blood Cell / Platelet Morphology Values:**

SM - Smudge white blood cells  
TOX - toxic neutrophils  
DB - Döhle bodies  
VC - vacuolated cytoplasm  
BC - basophilic cytoplasm  
PCE - platelet clumps / estimate  
GP - giant platelets  
BP - bizarre platelets  
Mod - moderate  
- - not observed or not examined; see whole blood sample condition

##### **Individual Coagulation Values:**

PHEM - plasma hemolysis  
PLIP - plasma lipemia  
PICT - plasma icterus  
PT - prothrombin time  
APTT - activated partial thromboplastin time

## INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA

### EXPLANATORY NOTES (Continued)

#### ABBREVIATIONS: (Continued)

##### **Individual Clinical Chemistry Values:**

SHEM - serum hemolysis  
SLIP - serum lipemia  
SICT - serum icterus  
AST - aspartate aminotransferase  
ALT - alanine aminotransferase  
SDH - sorbitol dehydrogenase  
ALKP - alkaline phosphatase  
BILI - total bilirubin  
BUN - urea nitrogen  
CREA - creatinine  
CHOL - cholesterol  
TRIG - triglycerides  
GLUC - glucose  
TP - total protein  
ALB - albumin  
GLOB - globulin  
CALC - calcium  
IPHS - inorganic phosphorous  
NA - sodium  
K - potassium  
CL - chloride  
FHEM - plasma hemolysis from blood sample for fluoride determination  
FLIP - plasma lipemia from blood sample for fluoride determination  
FICT - plasma icterus from blood sample for fluoride determination  
PFLU - plasma fluoride

##### **Individual Urinalysis Values:**

QUAL - quality (modifies color)  
COL - color  
CLAR - clarity  
VOL - volume  
UOSM - urine osmolality  
pH - the logarithm of the reciprocal of the hydrogen ion concentration  
UGLU - urine glucose  
KET - ketone  
UBIL - urine bilirubin  
BLD - blood  
URO - urobilinogen  
UMTP - urine protein  
UFLU - urine fluoride

##### **Individual Urine Microscopic Examination Values:**

EPIT - epithelial cells  
UWBC - urine white blood cells  
URBC - urine red blood cells  
NCRY - normal crystals  
MICR - microorganisms  
SPER - sperm

## INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA

### EXPLANATORY NOTES (Continued)

NOTES:

When individual animal data are not reported, it may be due to one of the following reasons or other reasons, all of which are explained in the study records:

the sample was clotted (CLOT)  
there was insufficient sample for testing (QNS)  
a valid result could not be obtained (RNV)  
the sample was not suitable for testing  
the animal died prior to sample collection  
no sample was available for testing (NSR)

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Individual Animal Clinical Pathology Data

| Male,  | Group | IX                   | - 0 mg/kg -  | Day  | 28   | MCV                                                                    | MCH  | MCHC | RDW                  | ARET                 | PLT |
|--------|-------|----------------------|--------------|------|------|------------------------------------------------------------------------|------|------|----------------------|----------------------|-----|
| Animal | COND  | RBC                  | HGB          | HCT  | MCV  | MCH                                                                    | MCHC | RDW  | ARET                 | PLT                  |     |
|        |       | x10 <sup>6</sup> /μL | g/dL         | %    | fL   | pg                                                                     | g/dL | %    | x10 <sup>3</sup> /μL | x10 <sup>3</sup> /μL |     |
| 901    | OK    | 7.50                 | 14.3         | 47.2 | 63.0 | 19.1                                                                   | 30.4 | 12.5 | 496.9                | 1447                 |     |
| 902    | OK    | 7.49                 | 15.0         | 49.3 | 65.8 | 20.0                                                                   | 30.4 | 11.8 | 404.3                | NP                   |     |
| 903    | CLOT  | NP                   | NP           | NP   | NP   | NP                                                                     | NP   | NP   | NP                   | NP                   |     |
| 904    | CLOT  | NP                   | NP           | NP   | NP   | NP                                                                     | NP   | NP   | NP                   | NP                   |     |
| 905    | OK    | 7.30                 | 15.0         | 47.4 | 64.9 | 20.5                                                                   | 31.6 | 11.0 | 314.3                | NP                   |     |
| 906    | OK    | 7.12                 | 14.3         | 45.0 | 63.2 | 20.1                                                                   | 31.8 | 11.5 | 280.8                | NP                   |     |
| 907    | OK    | 7.32                 | 14.1         | 45.7 | 62.4 | 19.2                                                                   | 30.8 | 12.0 | 269.9                | 1080                 |     |
| 908    | OK    | 7.32                 | 14.6         | 48.3 | 66.0 | 19.9                                                                   | 30.2 | 10.8 | 230.8                | NP                   |     |
| 909    | CLOT  | NP                   | NP           | NP   | NP   | NP                                                                     | NP   | NP   | NP                   | NP                   |     |
| 910    | OK    | 7.13                 | 15.0         | 48.5 | 68.1 | 21.1                                                                   | 30.9 | 11.2 | 256.3                | NP                   |     |
| Male,  | Group | XI                   | - 10 mg/kg - | Day  | 28   | MCV <th>MCH</th> <th>MCHC</th> <th>RDW</th> <th>ARET</th> <th>PLT</th> | MCH  | MCHC | RDW                  | ARET                 | PLT |
| Animal | COND  | RBC                  | HGB          | HCT  | MCV  | MCH                                                                    | MCHC | RDW  | ARET                 | PLT                  |     |
|        |       | x10 <sup>6</sup> /μL | g/dL         | %    | fL   | pg                                                                     | g/dL | %    | x10 <sup>3</sup> /μL | x10 <sup>3</sup> /μL |     |
| 1101   | CLOT  | NP                   | NP           | NP   | NP   | NP                                                                     | NP   | NP   | NP                   | NP                   |     |
| 1102   | OK    | 6.80                 | 14.5         | 46.0 | 67.7 | 21.4                                                                   | 31.5 | 11.6 | 261.4                | 1103                 |     |
| 1103   | OK    | 7.27                 | 14.9         | 47.3 | 65.1 | 20.5                                                                   | 31.4 | 11.8 | 258.1                | 1193                 |     |
| 1104   | OK    | 7.27                 | 14.5         | 45.7 | 62.8 | 19.9                                                                   | 31.8 | 11.7 | 379.7                | NP                   |     |
| 1105   | OK    | 7.02                 | 14.8         | 46.8 | 66.7 | 21.1                                                                   | 31.6 | 11.3 | 246.7                | 1036                 |     |
| 1106   | OK    | 7.36                 | 15.1         | 47.9 | 65.0 | 20.5                                                                   | 31.5 | 10.8 | 208.9                | 1143                 |     |
| 1107   | OK    | 7.11                 | 14.0         | 45.5 | 64.0 | 19.7                                                                   | 30.8 | 12.4 | 238.9                | 1377                 |     |
| 1108   | OK    | 6.81                 | 14.4         | 45.2 | 66.4 | 21.1                                                                   | 31.8 | 11.8 | 340.5                | 1094                 |     |
| 1109   | OK    | 7.06                 | 14.9         | 46.4 | 65.8 | 21.1                                                                   | 32.1 | 11.9 | 241.4                | NP                   |     |
| 1110   | OK    | 7.70                 | 15.5         | 49.8 | 64.6 | 20.1                                                                   | 31.1 | 11.4 | 204.4                | 1048                 |     |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Individual Animal Clinical Pathology Data

| Male,  | Group | XIII | mg/kg | Day  | 28   | MCH | MCV                                                                                                                        | HCT | HGB  | RBC                  | COND | OK | MCHC | RDW  | ARET                 | PLT                  |
|--------|-------|------|-------|------|------|-----|----------------------------------------------------------------------------------------------------------------------------|-----|------|----------------------|------|----|------|------|----------------------|----------------------|
|        |       |      |       |      |      | pg  | fL                                                                                                                         | %   | g/dL | x10 <sup>6</sup> /μL |      |    | g/dL | %    | x10 <sup>3</sup> /μL | x10 <sup>3</sup> /μL |
| Animal |       |      |       |      |      |     |                                                                                                                            |     |      |                      |      |    |      |      |                      |                      |
| 1301   | OK    | 7.02 | 44.6  | 63.5 | 19.9 | NP  | NP                                                                                                                         | NP  | 14.0 | 7.02                 | OK   |    | 31.5 | 11.4 | 123.4                | 1092                 |
| 1302   | OK    | 7.25 | 47.0  | 64.8 | 20.4 | NP  | NP                                                                                                                         | NP  | 14.8 | 7.25                 | OK   |    | 31.4 | 11.3 | 291.2                | 1144                 |
| 1303   | CLOT  | 6.97 | 45.1  | 64.7 | 20.5 | NP  | NP                                                                                                                         | NP  | 14.3 | 6.97                 | CLOT |    | NP   | NP   | NP                   | NP                   |
| 1304   | OK    | 7.15 | 47.0  | 65.7 | 20.7 | NP  | NP                                                                                                                         | NP  | 14.8 | 7.15                 | OK   |    | 31.7 | 11.5 | 307.5                | 1148                 |
| 1305   | OK    | 6.96 | 44.0  | 63.3 | 19.5 | NP  | NP                                                                                                                         | NP  | 13.6 | 6.96                 | OK   |    | 31.4 | 11.2 | 277.5                | 1292                 |
| 1306   | OK    | 6.88 | 44.0  | 64.0 | 20.5 | NP  | NP                                                                                                                         | NP  | 13.6 | 6.88                 | OK   |    | 30.8 | 11.8 | 363.0                | 1261                 |
| 1307   | OK    | 6.65 | 44.0  | 66.7 | 21.0 | NP  | NP                                                                                                                         | NP  | 14.1 | 6.65                 | OK   |    | 32.0 | 11.0 | 246.7                | 1250                 |
| 1308   | OK    | 7.21 | 46.0  | 63.7 | 20.0 | NP  | NP                                                                                                                         | NP  | 14.0 | 7.21                 | OK   |    | 31.5 | 13.9 | 632.6                | NP                   |
| 1309   | OK    | 7.56 | 49.1  | 64.9 | 20.0 | NP  | NP                                                                                                                         | NP  | 14.4 | 7.56                 | OK   |    | 31.3 | 11.9 | 265.1                | 1175                 |
| 1310   | OK    |      |       |      |      |     |                                                                                                                            |     | 15.1 |                      | OK   |    | 30.8 | 11.3 | 211.3                | 1317                 |
| Male,  | Group | XV   | mg/kg | Day  | 28   | MCH | MCV <th>HCT</th> <th>HGB</th> <th>RBC</th> <th>COND</th> <th>OK</th> <th>MCHC</th> <th>RDW</th> <th>ARET</th> <th>PLT</th> | HCT | HGB  | RBC                  | COND | OK | MCHC | RDW  | ARET                 | PLT                  |
|        |       |      |       |      |      | pg  | fL                                                                                                                         | %   | g/dL | x10 <sup>6</sup> /μL |      |    | g/dL | %    | x10 <sup>3</sup> /μL | x10 <sup>3</sup> /μL |
| Animal |       |      |       |      |      |     |                                                                                                                            |     |      |                      |      |    |      |      |                      |                      |
| 1501   | CLOT  | 7.34 | 45.7  | 62.3 | 19.6 | NP  | NP                                                                                                                         | NP  | 14.4 | 7.34                 | CLOT |    | NP   | NP   | NP                   | NP                   |
| 1502   | OK    | 7.68 | 47.8  | 62.3 | 19.7 | NP  | NP                                                                                                                         | NP  | 15.2 | 7.68                 | OK   |    | 31.5 | 11.4 | 264.8                | 1344                 |
| 1503   | OK    | 6.78 | 44.4  | 65.5 | 20.9 | NP  | NP                                                                                                                         | NP  | 14.2 | 6.78                 | OK   |    | 31.7 | 11.3 | 117.0                | 1286                 |
| 1504   | OK    | 6.95 | 44.7  | 64.3 | 20.2 | NP  | NP                                                                                                                         | NP  | 14.2 | 6.95                 | OK   |    | 31.9 | 11.5 | 301.7                | 1219                 |
| 1505   | OK    | 7.74 | 47.3  | 61.1 | 19.1 | NP  | NP                                                                                                                         | NP  | 14.1 | 7.74                 | OK   |    | 31.4 | 11.0 | 261.7                | 1160                 |
| 1506   | OK    | 7.23 | 46.1  | 63.8 | 20.3 | NP  | NP                                                                                                                         | NP  | 14.8 | 7.23                 | OK   |    | 31.3 | 10.9 | 245.1                | 1231                 |
| 1507   | OK    | 7.20 | 46.4  | 64.5 | 20.4 | NP  | NP                                                                                                                         | NP  | 14.7 | 7.20                 | OK   |    | 31.8 | 11.0 | 307.6                | 1420                 |
| 1508   | OK    | 6.79 | 43.3  | 63.7 | 20.3 | NP  | NP                                                                                                                         | NP  | 14.7 | 6.79                 | OK   |    | 31.6 | 11.3 | 241.5                | NP                   |
| 1509   | OK    | 6.89 | 45.5  | 66.0 | 20.6 | NP  | NP                                                                                                                         | NP  | 13.8 | 6.79                 | OK   |    | 31.9 | 11.7 | 269.4                | 1053                 |
| 1510   | OK    |      |       |      |      |     |                                                                                                                            |     | 14.2 | 6.89                 | OK   |    | 31.2 | 11.0 | 249.9                | 1219                 |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Individual Animal Clinical Pathology Data

| Male,  | Group                       | IX                           | -                            | 0                            | mg/kg                        | -                            | Day                          | 28 |  |
|--------|-----------------------------|------------------------------|------------------------------|------------------------------|------------------------------|------------------------------|------------------------------|----|--|
| Animal | WBC<br>x10 <sup>3</sup> /μL | ANEU<br>x10 <sup>3</sup> /μL | ALYM<br>x10 <sup>3</sup> /μL | AMON<br>x10 <sup>3</sup> /μL | AEOS<br>x10 <sup>3</sup> /μL | ABAS<br>x10 <sup>3</sup> /μL | ALUC<br>x10 <sup>3</sup> /μL |    |  |
| 901    | 21.31                       | 2.23                         | 17.84                        | 0.52                         | 0.22                         | 0.09                         | 0.42                         |    |  |
| 902    | 13.98                       | 2.67                         | 10.46                        | 0.37                         | 0.29                         | 0.04                         | 0.16                         |    |  |
| 903    | NP                          | NP                           | NP                           | NP                           | NP                           | NP                           | NP                           |    |  |
| 904    | NP                          | NP                           | NP                           | NP                           | NP                           | NP                           | NP                           |    |  |
| 905    | 11.55                       | 1.68                         | 8.97                         | 0.37                         | 0.31                         | 0.09                         | 0.13                         |    |  |
| 906    | 14.77                       | 4.43                         | 9.90                         | 0.44                         | 0.00                         | 0.00                         | 0.00                         |    |  |
| 907    | 13.96                       | 1.85                         | 11.12                        | 0.39                         | 0.15                         | 0.13                         | 0.31                         |    |  |
| 908    | 13.00                       | 1.83                         | 10.54                        | 0.28                         | 0.18                         | 0.08                         | 0.10                         |    |  |
| 909    | NP                          | NP                           | NP                           | NP                           | NP                           | NP                           | NP                           |    |  |
| 910    | 15.40                       | 2.77                         | 11.69                        | 0.34                         | 0.24                         | 0.10                         | 0.26                         |    |  |

| Male,  | Group                       | XI                           | - | 10                           | mg/kg                        | - | Day                          | 28                           |                              |
|--------|-----------------------------|------------------------------|---|------------------------------|------------------------------|---|------------------------------|------------------------------|------------------------------|
| Animal | WBC<br>x10 <sup>3</sup> /μL | ANEU<br>x10 <sup>3</sup> /μL |   | ALYM<br>x10 <sup>3</sup> /μL | AMON<br>x10 <sup>3</sup> /μL |   | AEOS<br>x10 <sup>3</sup> /μL | ABAS<br>x10 <sup>3</sup> /μL | ALUC<br>x10 <sup>3</sup> /μL |
| 1101   | NP                          | NP                           |   | NP                           | NP                           |   | NP                           | NP                           | NP                           |
| 1102   | 14.12                       | 2.00                         |   | 11.15                        | 0.45                         |   | 0.12                         | 0.09                         | 0.31                         |
| 1103   | 17.03                       | 2.41                         |   | 13.70                        | 0.32                         |   | 0.25                         | 0.10                         | 0.25                         |
| 1104   | 12.38                       | 1.73                         |   | 10.53                        | 0.00                         |   | 0.12                         | 0.00                         | 0.00                         |
| 1105   | 13.18                       | 1.67                         |   | 10.79                        | 0.32                         |   | 0.14                         | 0.07                         | 0.19                         |
| 1106   | 14.21                       | 2.12                         |   | 11.01                        | 0.39                         |   | 0.17                         | 0.16                         | 0.36                         |
| 1107   | 18.00                       | 2.96                         |   | 14.03                        | 0.33                         |   | 0.21                         | 0.11                         | 0.36                         |
| 1108   | 13.54                       | 2.64                         |   | 10.12                        | 0.29                         |   | 0.05                         | 0.14                         | 0.30                         |
| 1109   | 9.82                        | 1.62                         |   | 7.55                         | 0.38                         |   | 0.16                         | 0.03                         | 0.09                         |
| 1110   | 11.94                       | 2.18                         |   | 8.86                         | 0.44                         |   | 0.14                         | 0.08                         | 0.23                         |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Individual Animal Clinical Pathology Data

| Male,  | Group                       | XIII-                        | 100                          | mg/kg-                       | Day                          | 28                           |                              |  |
|--------|-----------------------------|------------------------------|------------------------------|------------------------------|------------------------------|------------------------------|------------------------------|--|
| Animal | WBC<br>x10 <sup>3</sup> /μL | ANEU<br>x10 <sup>3</sup> /μL | ALYM<br>x10 <sup>3</sup> /μL | AMON<br>x10 <sup>3</sup> /μL | AEOS<br>x10 <sup>3</sup> /μL | ABAS<br>x10 <sup>3</sup> /μL | ALUC<br>x10 <sup>3</sup> /μL |  |
| 1301   | 17.08                       | 4.06                         | 12.30                        | 0.34                         | 0.22                         | 0.06                         | 0.12                         |  |
| 1302   | 12.72                       | 1.47                         | 10.11                        | 0.56                         | 0.13                         | 0.08                         | 0.37                         |  |
| 1303   | NP                          | NP                           | NP                           | NP                           | NP                           | NP                           | NP                           |  |
| 1304   | 13.14                       | 1.32                         | 11.17                        | 0.29                         | 0.13                         | 0.10                         | 0.12                         |  |
| 1305   | 10.84                       | 1.17                         | 9.20                         | 0.19                         | 0.04                         | 0.18                         | 0.18                         |  |
| 1306   | 14.19                       | 2.11                         | 11.31                        | 0.37                         | 0.15                         | 0.08                         | 0.16                         |  |
| 1307   | 14.19                       | 1.87                         | 11.53                        | 0.34                         | 0.13                         | 0.11                         | 0.20                         |  |
| 1308   | 15.15                       | 1.97                         | 12.88                        | 0.30                         | 0.00                         | 0.00                         | 0.00                         |  |
| 1309   | 18.74                       | 3.70                         | 14.14                        | 0.38                         | 0.17                         | 0.11                         | 0.23                         |  |
| 1310   | 12.71                       | 2.59                         | 9.27                         | 0.46                         | 0.21                         | 0.05                         | 0.13                         |  |

| Male,  | Group                       | XV                           | - | 1000                         | mg/kg                        | - | Day                          | 28                           |                              |
|--------|-----------------------------|------------------------------|---|------------------------------|------------------------------|---|------------------------------|------------------------------|------------------------------|
| Animal | WBC<br>x10 <sup>3</sup> /μL | ANEU<br>x10 <sup>3</sup> /μL |   | ALYM<br>x10 <sup>3</sup> /μL | AMON<br>x10 <sup>3</sup> /μL |   | AEOS<br>x10 <sup>3</sup> /μL | ABAS<br>x10 <sup>3</sup> /μL | ALUC<br>x10 <sup>3</sup> /μL |
| 1501   | NP                          | NP                           |   | NP                           | NP                           |   | NP                           | NP                           |                              |
| 1502   | 12.76                       | 1.97                         |   | 9.96                         | 0.45                         |   | 0.19                         | 0.05                         | 0.14                         |
| 1503   | 19.14                       | 2.34                         |   | 15.88                        | 0.44                         |   | 0.20                         | 0.04                         | 0.24                         |
| 1504   | 13.30                       | 1.98                         |   | 10.30                        | 0.58                         |   | 0.11                         | 0.05                         | 0.28                         |
| 1505   | 14.92                       | 2.02                         |   | 11.98                        | 0.47                         |   | 0.13                         | 0.09                         | 0.24                         |
| 1506   | 12.65                       | 2.14                         |   | 9.85                         | 0.30                         |   | 0.16                         | 0.05                         | 0.14                         |
| 1507   | 13.68                       | 2.47                         |   | 10.36                        | 0.52                         |   | 0.14                         | 0.06                         | 0.12                         |
| 1508   | 12.38                       | 1.12                         |   | 10.62                        | 0.23                         |   | 0.15                         | 0.08                         | 0.19                         |
| 1509   | 14.19                       | 2.01                         |   | 11.36                        | 0.48                         |   | 0.07                         | 0.05                         | 0.21                         |
| 1510   | 11.55                       | 1.64                         |   | 9.14                         | 0.35                         |   | 0.17                         | 0.06                         | 0.19                         |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Individual Animal Clinical Pathology Data

| Male,<br>Animal | Group    | IX  | 0        | mg/kg | Day   | 28    |       |      |    |     |  |  |
|-----------------|----------|-----|----------|-------|-------|-------|-------|------|----|-----|--|--|
|                 | ANIS     | MIC | MAC      | POLY  | HYPO  | ECHI  | ACAN  | TARG | RX | HJB |  |  |
| 901             | -        | -   | -        | Few   | -     | Trace | -     | -    | -  | -   |  |  |
| 902             | -        | -   | -        | Trace | -     | Trace | -     | -    | -  | -   |  |  |
| 903             | NP       | NP  | NP       | NP    | NP    | NP    | NP    | NP   | NP | NP  |  |  |
| 904             | NP       | NP  | NP       | NP    | NP    | NP    | NP    | NP   | NP | NP  |  |  |
| 905             | -        | -   | -        | Few   | -     | -     | -     | -    | -  | -   |  |  |
| 906             | -        | -   | -        | Trace | -     | Trace | Trace | -    | -  | -   |  |  |
| 907             | -        | -   | -        | Trace | -     | -     | Trace | -    | -  | -   |  |  |
| 908             | -        | -   | -        | Trace | -     | -     | -     | -    | -  | -   |  |  |
| 909             | NP       | NP  | NP       | NP    | NP    | NP    | NP    | NP   | NP | NP  |  |  |
| 910             | -        | -   | -        | Trace | -     | -     | -     | -    | -  | -   |  |  |
| Male,<br>Animal | Group XI | -   | 10 mg/kg | -     | Day28 |       |       |      |    |     |  |  |
|                 | ANIS     | MIC | MAC      | POLY  | HYPO  | ECHI  | ACAN  | TARG | RX | HJB |  |  |
| 1101            | NP       | NP  | NP       | NP    | NP    | NP    | NP    | NP   | NP | NP  |  |  |
| 1102            | -        | -   | -        | Few   | -     | Trace | -     | -    | -  | -   |  |  |
| 1103            | -        | -   | -        | Trace | -     | -     | -     | -    | -  | -   |  |  |
| 1104            | -        | -   | -        | Few   | -     | Trace | -     | -    | -  | -   |  |  |
| 1105            | -        | -   | -        | Trace | -     | Trace | -     | -    | -  | -   |  |  |
| 1106            | -        | -   | -        | Trace | -     | -     | -     | -    | -  | -   |  |  |
| 1107            | -        | -   | -        | Trace | -     | Trace | Trace | -    | -  | -   |  |  |
| 1108            | -        | -   | -        | Few   | -     | Trace | Trace | -    | -  | -   |  |  |
| 1109            | -        | -   | -        | Trace | -     | Mod   | -     | -    | -  | -   |  |  |
| 1110            | -        | -   | -        | Trace | -     | -     | -     | -    | -  | -   |  |  |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Individual Animal Clinical Pathology Data

| Male, Animal | Group | XIII - | 100 | mg/kg | Day | 28    | HYPO | ECHI  | ACAN | TARG | RX | HJB |
|--------------|-------|--------|-----|-------|-----|-------|------|-------|------|------|----|-----|
| 1301         | -     | -      | -   | Trace | -   | -     | -    | -     | -    | -    | -  | -   |
| 1302         | -     | -      | -   | Trace | -   | -     | -    | -     | -    | -    | -  | -   |
| 1303         | NP    | NP     | NP  | NP    | NP  | Trace | NP   | NP    | NP   | NP   | NP | NP  |
| 1304         | -     | -      | -   | Few   | -   | Trace | -    | Trace | -    | -    | -  | -   |
| 1305         | -     | -      | -   | Trace | -   | -     | -    | -     | -    | -    | -  | -   |
| 1306         | -     | -      | -   | Few   | -   | Trace | -    | -     | -    | -    | -  | -   |
| 1307         | -     | -      | -   | Trace | -   | Mod   | -    | Few   | -    | -    | -  | -   |
| 1308         | -     | -      | -   | Mod   | -   | Trace | -    | Trace | -    | -    | -  | -   |
| 1309         | -     | -      | -   | Trace | -   | Trace | -    | Trace | -    | -    | -  | -   |
| 1310         | -     | -      | -   | Trace | -   | -     | -    | -     | -    | -    | -  | -   |

| Male, Animal | Group | XV - | 1000 | mg/kg | Day | 28    | HYPO | ECHI  | ACAN  | TARG | RX | HJB |
|--------------|-------|------|------|-------|-----|-------|------|-------|-------|------|----|-----|
| 1501         | NP    | NP   | NP   | NP    | NP  | Trace | NP   | NP    | NP    | NP   | NP | NP  |
| 1502         | -     | -    | -    | Trace | -   | -     | -    | -     | -     | -    | -  | -   |
| 1503         | -     | -    | -    | Trace | -   | -     | -    | -     | -     | -    | -  | -   |
| 1504         | -     | -    | -    | Few   | -   | -     | -    | -     | -     | -    | -  | -   |
| 1505         | -     | -    | -    | Trace | -   | -     | -    | -     | -     | -    | -  | -   |
| 1506         | -     | -    | -    | Trace | -   | -     | -    | -     | -     | -    | -  | -   |
| 1507         | -     | -    | -    | Trace | -   | -     | -    | -     | -     | -    | -  | -   |
| 1508         | -     | -    | -    | Trace | -   | -     | -    | -     | -     | -    | -  | -   |
| 1509         | -     | -    | -    | Few   | -   | -     | -    | Few   | Trace | -    | -  | -   |
| 1510         | -     | -    | -    | Few   | -   | Trace | -    | Trace | Trace | -    | -  | -   |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Individual Animal Clinical Pathology Data

| Male,<br>Animal | Group | IX  | 0  | mg/kg | Day | 28   | BP |
|-----------------|-------|-----|----|-------|-----|------|----|
|                 | SM    | TOX | DB | VC    | BC  | PCE  | GP |
| 901             | -     | -   | -  | -     | -   | -    | -  |
| 902             | -     | -   | -  | -     | -   | UTD  | -  |
| 903             | NP    | NP  | NP | NP    | NP  | NP   | NP |
| 904             | NP    | NP  | NP | NP    | NP  | NP   | NP |
| 905             | -     | -   | -  | -     | -   | UTD  | -  |
| 906             | -     | -   | -  | -     | -   | UTD  | -  |
| 907             | -     | -   | -  | -     | -   | -    | -  |
| 908             | -     | -   | -  | -     | -   | Adeq | -  |
| 909             | NP    | NP  | NP | NP    | NP  | NP   | NP |
| 910             | -     | -   | -  | -     | -   | Adeq | -  |

| Male,<br>Animal | Group | XI  | 10 | mg/kg | Day | 28  | BP |
|-----------------|-------|-----|----|-------|-----|-----|----|
|                 | SM    | TOX | DB | VC    | BC  | PCE | GP |
| 1101            | NP    | NP  | NP | NP    | NP  | NP  | NP |
| 1102            | -     | -   | -  | -     | -   | -   | -  |
| 1103            | -     | -   | -  | -     | -   | -   | -  |
| 1104            | -     | -   | -  | -     | -   | UTD | -  |
| 1105            | -     | -   | -  | -     | -   | -   | -  |
| 1106            | -     | -   | -  | -     | -   | -   | -  |
| 1107            | -     | -   | -  | -     | -   | -   | -  |
| 1108            | -     | -   | -  | -     | -   | -   | -  |
| 1109            | -     | -   | -  | -     | -   | UTD | -  |
| 1110            | -     | -   | -  | -     | -   | -   | -  |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Individual Animal Clinical Pathology Data

| Male,<br>Animal | Group | SM | XIII | TOX | DB | 100 | mg/kg | VC | BC | Day | 28 | PCE | GP | BP |
|-----------------|-------|----|------|-----|----|-----|-------|----|----|-----|----|-----|----|----|
| 1301            | -     | -  | -    | -   | -  | -   | -     | -  | -  | -   | -  | -   | -  | -  |
| 1302            | -     | -  | -    | -   | -  | -   | -     | -  | -  | -   | -  | -   | -  | -  |
| 1303            | NP    | NP | NP   | NP  | NP | NP  | NP    | NP | NP | NP  | NP | NP  | NP | NP |
| 1304            | -     | -  | -    | -   | -  | -   | -     | -  | -  | -   | -  | -   | -  | -  |
| 1305            | -     | -  | -    | -   | -  | -   | -     | -  | -  | -   | -  | -   | -  | -  |
| 1306            | -     | -  | -    | -   | -  | -   | -     | -  | -  | -   | -  | -   | -  | -  |
| 1307            | -     | -  | -    | -   | -  | -   | -     | -  | -  | -   | -  | -   | -  | -  |
| 1308            | -     | -  | -    | -   | -  | -   | -     | -  | -  | -   | -  | -   | -  | -  |
| 1309            | -     | -  | -    | -   | -  | -   | -     | -  | -  | -   | -  | -   | -  | -  |
| 1310            | -     | -  | -    | -   | -  | -   | -     | -  | -  | -   | -  | -   | -  | -  |

| Male,<br>Animal | Group | SM | XV | TOX | DB | 1000 | mg/kg | VC | BC | Day | 28 | PCE | GP | BP |
|-----------------|-------|----|----|-----|----|------|-------|----|----|-----|----|-----|----|----|
| 1501            | NP    | NP | NP | NP  | NP | NP   | NP    | NP | NP | NP  | NP | NP  | NP | NP |
| 1502            | -     | -  | -  | -   | -  | -    | -     | -  | -  | -   | -  | -   | -  | -  |
| 1503            | -     | -  | -  | -   | -  | -    | -     | -  | -  | -   | -  | -   | -  | -  |
| 1504            | -     | -  | -  | -   | -  | -    | -     | -  | -  | -   | -  | -   | -  | -  |
| 1505            | -     | -  | -  | -   | -  | -    | -     | -  | -  | -   | -  | -   | -  | -  |
| 1506            | -     | -  | -  | -   | -  | -    | -     | -  | -  | -   | -  | -   | -  | -  |
| 1507            | -     | -  | -  | -   | -  | -    | -     | -  | -  | -   | -  | -   | -  | -  |
| 1508            | -     | -  | -  | -   | -  | -    | -     | -  | -  | -   | -  | -   | -  | -  |
| 1509            | -     | -  | -  | -   | -  | -    | -     | -  | -  | -   | -  | -   | -  | -  |
| 1510            | -     | -  | -  | -   | -  | -    | -     | -  | -  | -   | -  | -   | -  | -  |

## DuPont-13830

## 28

28

| APTT | Sec |
|------|-----|
| 4.2  |     |
| 21.3 |     |
| 21.8 |     |
| 7.0  |     |
| 8.3  |     |
| 8.3  |     |
| 9.4  |     |
| 10.3 |     |
| 7.2  |     |
| 8.7  |     |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Individual Animal Clinical Pathology Data

| Male,  | Group | XIII | -    | 100  | mg/kg | -    | Day | 28 |
|--------|-------|------|------|------|-------|------|-----|----|
| Animal | PHEM  | PLIP | PICT | PT   | Sec   | APTT | Sec |    |
| 1301   | None  | None | None | 15.0 |       | 17.1 |     |    |
| 1302   | None  | None | None | 15.7 |       | 15.8 |     |    |
| 1303   | None  | None | None | 15.4 |       | 17.1 |     |    |
| 1304   | None  | None | None | 15.7 |       | 16.6 |     |    |
| 1305   | None  | None | None | 15.2 |       | 18.3 |     |    |
| 1306   | None  | None | None | 16.0 |       | 19.5 |     |    |
| 1307   | None  | None | None | 15.8 |       | 19.6 |     |    |
| 1308   | None  | None | None | 16.5 |       | 16.9 |     |    |
| 1309   | None  | None | None | 15.1 |       | 16.9 |     |    |
| 1310   | None  | None | None | 15.5 |       | 17.4 |     |    |

| Male,  | Group | XV   | -    | 1000 | mg/kg | -    | Day | 28 |
|--------|-------|------|------|------|-------|------|-----|----|
| Animal | PHEM  | PLIP | PICT | PT   | Sec   | APTT | Sec |    |
| 1501   | None  | None | None | 15.2 |       | 19.3 |     |    |
| 1502   | None  | None | None | 17.1 |       | 20.4 |     |    |
| 1503   | None  | None | None | 16.1 |       | 18.5 |     |    |
| 1504   | None  | None | None | 17.1 |       | 16.1 |     |    |
| 1505   | None  | None | None | 16.0 |       | 22.2 |     |    |
| 1506   | None  | None | None | 14.9 |       | 19.3 |     |    |
| 1507   | None  | None | None | 15.5 |       | 19.3 |     |    |
| 1508   | None  | None | None | 15.5 |       | 15.9 |     |    |
| 1509   | None  | None | None | 16.7 |       | 18.5 |     |    |
| 1510   | None  | None | None | 16.7 |       | 18.1 |     |    |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Individual Animal Clinical Pathology Data

| Male,<br>Animal | Group | IX   | -    | 0   | mg/kg | -    | Day  | 28    |       |       |       |       |  |  |  |  |  |  |  |  |
|-----------------|-------|------|------|-----|-------|------|------|-------|-------|-------|-------|-------|--|--|--|--|--|--|--|--|
|                 |       |      |      | AST | ALT   | SDH  | ALKP | BILI  | BUN   | CREA  | CHOL  | TRIG  |  |  |  |  |  |  |  |  |
|                 |       |      | SICT | U/L | U/L   | U/L  | U/L  | mg/dL | mg/dL | mg/dL | mg/dL | mg/dL |  |  |  |  |  |  |  |  |
| 901             | None  | None | None | 165 | 44    | 9.2  | 144  | 0.05  | 16    | 0.34  | 48    | 16    |  |  |  |  |  |  |  |  |
| 902             | None  | None | None | 115 | 51    | 20.2 | 257  | 0.05  | 20    | 0.35  | 51    | 46    |  |  |  |  |  |  |  |  |
| 903             | None  | None | None | 139 | 54    | 24.7 | 192  | 0.05  | 15    | 0.23  | 41    | 33    |  |  |  |  |  |  |  |  |
| 904             | None  | None | None | 114 | 59    | 20.2 | 281  | 0.05  | 21    | 0.32  | 39    | 42    |  |  |  |  |  |  |  |  |
| 905             | None  | None | None | 105 | 51    | 16.0 | 232  | 0.05  | 20    | 0.29  | 51    | 85    |  |  |  |  |  |  |  |  |
| 906             | None  | None | None | 144 | 49    | 9.9  | 246  | 0.05  | 18    | 0.27  | 61    | 40    |  |  |  |  |  |  |  |  |
| 907             | None  | None | None | 53  | 40    | 17.0 | 145  | 0.05  | 18    | 0.21  | 38    | 49    |  |  |  |  |  |  |  |  |
| 908             | None  | None | None | 142 | 49    | 10.1 | 203  | 0.05  | 17    | 0.25  | 34    | 29    |  |  |  |  |  |  |  |  |
| 909             | None  | None | None | 125 | 60    | 27.7 | 223  | 0.05  | 17    | 0.36  | 68    | 51    |  |  |  |  |  |  |  |  |
| 910             | Trace | None | None | 118 | 64    | 30.6 | 195  | 0.05  | 15    | 0.30  | 47    | 37    |  |  |  |  |  |  |  |  |
| Male,<br>Animal | Group | XI   | -    | 10  | mg/kg | -    | Day  | 28    |       |       |       |       |  |  |  |  |  |  |  |  |
|                 |       |      |      | AST | ALT   | SDH  | ALKP | BILI  | BUN   | CREA  | CHOL  | TRIG  |  |  |  |  |  |  |  |  |
|                 |       |      | SICT | U/L | U/L   | U/L  | U/L  | mg/dL | mg/dL | mg/dL | mg/dL | mg/dL |  |  |  |  |  |  |  |  |
| 1101            | None  | None | None | 115 | 52    | 17.6 | 244  | 0.05  | 17    | 0.30  | 47    | 86    |  |  |  |  |  |  |  |  |
| 1102            | None  | None | None | 107 | 42    | 14.5 | 163  | 0.05  | 20    | 0.27  | 51    | 28    |  |  |  |  |  |  |  |  |
| 1103            | None  | None | None | 109 | 53    | 17.7 | 286  | 0.05  | 16    | 0.22  | 52    | 61    |  |  |  |  |  |  |  |  |
| 1104            | Trace | None | None | 148 | 45    | 6.4  | 264  | 0.10  | 19    | 0.38  | 54    | 64    |  |  |  |  |  |  |  |  |
| 1105            | None  | None | None | 120 | 38    | 13.3 | 214  | 0.05  | 17    | 0.24  | 43    | 38    |  |  |  |  |  |  |  |  |
| 1106            | None  | None | None | 132 | 71    | 31.5 | 190  | 0.05  | 15    | 0.26  | 37    | 28    |  |  |  |  |  |  |  |  |
| 1107            | None  | None | None | 98  | 57    | 16.4 | 266  | 0.05  | 16    | 0.25  | 50    | 80    |  |  |  |  |  |  |  |  |
| 1108            | None  | None | None | 104 | 53    | 11.0 | 152  | 0.05  | 18    | 0.26  | 39    | 21    |  |  |  |  |  |  |  |  |
| 1109            | Trace | None | None | 169 | 46    | 7.5  | 246  | 0.05  | 16    | 0.25  | 55    | 48    |  |  |  |  |  |  |  |  |
| 1110            | None  | None | None | 117 | 51    | 14.0 | 179  | 0.05  | 16    | 0.20  | 60    | 21    |  |  |  |  |  |  |  |  |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Individual Animal Clinical Pathology Data

| Male,  | Group | XIII | -    | 100        | mg/kg      | -          | Day         | 28            |              |               |               |               |  |  |  |  |
|--------|-------|------|------|------------|------------|------------|-------------|---------------|--------------|---------------|---------------|---------------|--|--|--|--|
| Animal | SHEM  | SLIP | SICT | AST<br>U/L | ALT<br>U/L | SDH<br>U/L | ALKP<br>U/L | BILI<br>mg/dL | BUN<br>mg/dL | CREA<br>mg/dL | CHOL<br>mg/dL | TRIG<br>mg/dL |  |  |  |  |
| 1301   | None  | None | None | 89         | 37         | 12.7       | 227         | 0.05          | 14           | 0.24          | 41            | 28            |  |  |  |  |
| 1302   | None  | None | None | 110        | 58         | 16.4       | 241         | 0.05          | 15           | 0.23          | 52            | 37            |  |  |  |  |
| 1303   | None  | None | None | 124        | 43         | 12.3       | 157         | 0.05          | 15           | 0.27          | 46            | 23            |  |  |  |  |
| 1304   | None  | None | None | 96         | 40         | 11.0       | 171         | 0.05          | 16           | 0.23          | 48            | 26            |  |  |  |  |
| 1305   | None  | None | None | 93         | 35         | 11.1       | 223         | 0.05          | 15           | 0.22          | 55            | 36            |  |  |  |  |
| 1306   | None  | None | None | 86         | 33         | 9.3        | 266         | 0.05          | 17           | 0.23          | 45            | 37            |  |  |  |  |
| 1307   | None  | None | None | 105        | 54         | 12.2       | 200         | 0.05          | 13           | 0.20          | 49            | 60            |  |  |  |  |
| 1308   | Trace | None | None | 151        | 51         | 7.4        | 244         | 0.05          | 14           | 0.24          | 42            | 16            |  |  |  |  |
| 1309   | None  | None | None | 88         | 37         | 12.8       | 133         | 0.05          | 15           | 0.23          | 43            | 49            |  |  |  |  |
| 1310   | None  | None | None | 116        | 47         | 13.3       | 184         | 0.05          | 19           | 0.28          | 55            | 45            |  |  |  |  |
| Male,  | Group | XV   | -    | 1000       | mg/kg      | -          | Day         | 28            |              |               |               |               |  |  |  |  |
| Animal | SHEM  | SLIP | SICT | AST<br>U/L | ALT<br>U/L | SDH<br>U/L | ALKP<br>U/L | BILI<br>mg/dL | BUN<br>mg/dL | CREA<br>mg/dL | CHOL<br>mg/dL | TRIG<br>mg/dL |  |  |  |  |
| 1501   | None  | None | None | 83         | 30         | 10.9       | 220         | 0.05          | 15           | 0.19          | 34            | 30            |  |  |  |  |
| 1502   | Trace | None | None | 151        | 50         | 23.1       | 234         | 0.05          | 17           | 0.28          | 35            | 15            |  |  |  |  |
| 1503   | None  | None | None | 100        | 47         | 12.1       | 208         | 0.05          | 14           | 0.19          | 43            | 35            |  |  |  |  |
| 1504   | None  | None | None | 84         | 29         | 9.3        | 184         | 0.12          | 20           | 0.22          | 53            | 25            |  |  |  |  |
| 1505   | None  | None | None | 90         | 48         | 9.0        | 235         | 0.05          | 12           | 0.18          | 40            | 31            |  |  |  |  |
| 1506   | None  | None | None | 135        | 68         | 17.7       | 329         | 0.05          | 15           | 0.20          | 34            | 14            |  |  |  |  |
| 1507   | None  | None | None | 91         | 43         | 11.1       | 182         | 0.05          | 15           | 0.21          | 40            | 58            |  |  |  |  |
| 1508   | None  | None | None | 124        | 48         | 13.2       | 296         | 0.05          | 14           | 0.24          | 32            | 38            |  |  |  |  |
| 1509   | None  | None | None | 100        | 48         | 7.9        | 244         | 0.05          | 17           | 0.23          | 42            | 40            |  |  |  |  |
| 1510   | None  | None | None | 121        | 56         | 14.3       | 310         | 0.05          | 15           | 0.24          | 39            | 26            |  |  |  |  |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Individual Animal Clinical Pathology Data

| Male,<br>Animal | Group | IX       | TP    | ALB   | GLOB | CALC  | IPHS  | NA     | K      | CL     | FHEM | FLIP | FICT | PFLU  |
|-----------------|-------|----------|-------|-------|------|-------|-------|--------|--------|--------|------|------|------|-------|
|                 |       | 0 mg/kg  | -     | Day28 |      |       |       |        |        |        |      |      |      |       |
|                 |       | GLUC     | mg/dL | g/dL  | g/dL | mg/dL | mg/dL | mmol/L | mmol/L | mmol/L |      |      |      | μg/mL |
| 901             | 159   | 6.2      | 4.2   | 2.0   | 11.5 | 11.6  | 143.9 | 6.01   | 102.5  | None   | None | None | None | 0.2   |
| 902             | 108   | 6.7      | 4.3   | 2.4   | 12.5 | 13.7  | 146.4 | 7.72   | 103.6  | None   | None | None | None | 0.1   |
| 903             | 89    | 5.6      | 3.9   | 1.7   | 10.5 | 9.6   | 146.5 | 5.69   | 100.5  | None   | None | None | None | 0.1   |
| 904             | 149   | 6.1      | 4.1   | 2.0   | 11.9 | 13.0  | 146.7 | 5.55   | 101.2  | None   | None | None | None | 0.1   |
| 905             | 92    | 6.2      | 4.3   | 1.9   | 11.4 | 10.9  | 147.1 | 6.51   | 99.3   | None   | None | None | None | 0.1   |
| 906             | 90    | 6.0      | 4.2   | 1.8   | 10.9 | 11.2  | 147.7 | 6.54   | 105.2  | None   | None | None | None | 0.1   |
| 907             | 86    | 5.9      | 4.0   | 1.9   | 11.1 | 10.0  | 148.3 | 6.34   | 99.6   | None   | None | None | None | 0.1   |
| 908             | 92    | 6.0      | 4.4   | 1.6   | 11.0 | 10.9  | 145.9 | 6.35   | 102.4  | None   | None | None | None | 0.1   |
| 909             | 134   | 6.1      | 4.1   | 2.0   | 12.5 | 16.9  | 148.9 | 7.16   | 103.6  | None   | None | None | None | 0.1   |
| 910             | 128   | 6.3      | 3.9   | 2.4   | 11.0 | 11.0  | 150.2 | 6.23   | 104.8  | None   | None | None | None | 0.1   |
| Male,<br>Animal | Group | XI       | TP    | ALB   | GLOB | CALC  | IPHS  | NA     | K      | CL     | FHEM | FLIP | FICT | PFLU  |
|                 |       | 10 mg/kg | -     | Day   |      |       |       |        |        |        |      |      |      |       |
|                 |       | GLUC     | mg/dL | g/dL  | g/dL | mg/dL | mg/dL | mmol/L | mmol/L | mmol/L |      |      |      | μg/mL |
| 1101            | 107   | 6.6      | 4.4   | 2.2   | 12.6 | 13.8  | 149.3 | 6.59   | 104.4  | None   | None | None | None | 0.1   |
| 1102            | 93    | 5.5      | 3.7   | 1.8   | 11.0 | 11.0  | 147.5 | 5.88   | 102.1  | None   | None | None | None | 0.1   |
| 1103            | 111   | 6.1      | 4.2   | 1.9   | 10.6 | 9.6   | 144.8 | 6.18   | 99.5   | None   | None | None | None | 0.1   |
| 1104            | 126   | 6.2      | 4.1   | 2.1   | 11.1 | 12.8  | 144.3 | 7.21   | 101.9  | None   | None | None | None | 0.1   |
| 1105            | 103   | 6.1      | 4.1   | 2.0   | 11.6 | 11.4  | 146.8 | 5.89   | 103.9  | None   | None | None | None | 0.1   |
| 1106            | 106   | 6.6      | 4.2   | 2.4   | 11.1 | 9.6   | 147.9 | 6.12   | 102.9  | None   | None | None | None | 0.1   |
| 1107            | 118   | 6.3      | 4.1   | 2.2   | 10.7 | 10.1  | 145.0 | 6.22   | 101.5  | None   | None | None | None | 0.1   |
| 1108            | 95    | 5.5      | 3.6   | 1.9   | 10.8 | 10.2  | 150.2 | 5.75   | 101.4  | None   | None | None | None | 0.1   |
| 1109            | 93    | 6.2      | 4.1   | 2.1   | 11.2 | 13.0  | 149.1 | 6.47   | 105.4  | None   | None | None | None | 0.1   |
| 1110            | 89    | 6.3      | 4.4   | 1.9   | 11.2 | 10.3  | 151.0 | 6.23   | 103.3  | None   | None | None | None | 0.1   |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Individual Animal Clinical Pathology Data

| Male,  | Group | XIII | -    | 100  | mg/kg | -     | Day    | 28     |        |      |      |      |       |  |  |  |  |
|--------|-------|------|------|------|-------|-------|--------|--------|--------|------|------|------|-------|--|--|--|--|
| Animal | GLUC  | TP   | ALB  | GLOB | CALC  | IPHS  | NA     | K      | CL     | FHEM | FLIP | FICT | PFLU  |  |  |  |  |
|        | mg/dL | g/dL | g/dL | g/dL | mg/dL | mg/dL | mmol/L | mmol/L | mmol/L |      |      |      | μg/mL |  |  |  |  |
| 1301   | 112   | 6.1  | 4.1  | 2.0  | 11.2  | 9.2   | 148.0  | 5.89   | 102.3  | None | None | None | 0.1   |  |  |  |  |
| 1302   | 95    | 5.7  | 4.0  | 1.7  | 11.6  | 10.7  | 149.2  | 6.26   | 102.1  | None | None | None | 0.1   |  |  |  |  |
| 1303   | 118   | 5.9  | 4.0  | 1.9  | 11.0  | 11.0  | 146.5  | 5.26   | 103.9  | None | None | None | 0.1   |  |  |  |  |
| 1304   | 81    | 5.9  | 4.1  | 1.8  | 11.2  | 11.2  | 146.7  | 6.23   | 100.9  | None | None | None | 0.1   |  |  |  |  |
| 1305   | 93    | 6.3  | 4.0  | 2.3  | 10.9  | 10.1  | 146.1  | 6.55   | 103.2  | None | None | None | 0.1   |  |  |  |  |
| 1306   | 99    | 6.1  | 4.1  | 2.0  | 11.2  | 10.5  | 149.4  | 6.04   | 104.1  | None | None | None | 0.1   |  |  |  |  |
| 1307   | 97    | 5.9  | 3.9  | 2.0  | 11.1  | 10.1  | 147.2  | 5.53   | 101.8  | None | None | None | 0.1   |  |  |  |  |
| 1308   | 103   | 6.0  | 4.0  | 2.0  | 10.6  | 11.0  | 145.6  | 6.11   | 104.7  | None | None | None | 0.1   |  |  |  |  |
| 1309   | 106   | 5.9  | 4.0  | 1.9  | 10.6  | 9.3   | 147.8  | 5.89   | 104.6  | None | None | None | 0.1   |  |  |  |  |
| 1310   | 102   | 6.6  | 4.4  | 2.2  | 11.5  | 10.9  | 150.7  | 6.77   | 103.9  | None | None | None | 0.1   |  |  |  |  |

| Male,  | Group | XV   | - | 1000 | mg/kg | - | Day   | 28    |        |        |        |      |      |      |       |  |  |
|--------|-------|------|---|------|-------|---|-------|-------|--------|--------|--------|------|------|------|-------|--|--|
|        | GLUC  | TP   |   | ALB  | GLOB  |   | CALC  | IPHS  | NA     | K      | CL     | FHEM | FLIP | FICT | PFLJ  |  |  |
| Animal | mg/dL | g/dL |   | g/dL | g/dL  |   | mg/dL | mg/dL | mmol/L | mmol/L | mmol/L |      |      |      | μg/mL |  |  |
| 1501   | 91    | 6.0  |   | 4.2  | 1.8   |   | 11.2  | 11.0  | 148.3  | 5.90   | 106.8  | None | None | None | 0.1   |  |  |
| 1502   | 155   | 6.0  |   | 4.4  | 1.6   |   | 11.4  | 11.8  | 148.9  | 5.78   | 106.0  | None | None | None | 0.1   |  |  |
| 1503   | 105   | 5.7  |   | 3.9  | 1.8   |   | 10.9  | 10.0  | 145.0  | 6.21   | 102.1  | None | None | None | 0.1   |  |  |
| 1504   | 99    | 5.6  |   | 3.7  | 1.9   |   | 11.0  | 11.1  | 145.5  | 5.78   | 101.0  | None | None | None | 0.1   |  |  |
| 1505   | 115   | 6.1  |   | 4.1  | 2.0   |   | 11.1  | 10.1  | 147.6  | 5.45   | 102.3  | None | None | None | 0.1   |  |  |
| 1506   | 109   | 6.7  |   | 4.3  | 2.4   |   | 11.3  | 10.9  | 149.7  | 5.71   | 105.1  | None | None | None | 0.1   |  |  |
| 1507   | 101   | 5.8  |   | 4.0  | 1.8   |   | 11.2  | 10.8  | 148.4  | 5.85   | 104.5  | None | None | None | 0.1   |  |  |
| 1508   | 101   | 5.9  |   | 4.1  | 1.8   |   | 11.2  | 10.2  | 148.3  | 5.94   | 104.4  | None | None | None | 0.1   |  |  |
| 1509   | 104   | 5.9  |   | 4.0  | 1.9   |   | 11.2  | 10.2  | 149.5  | 5.23   | 101.4  | None | None | None | 0.1   |  |  |
| 1510   | 93    | 6.0  |   | 4.2  | 1.8   |   | 11.6  | 11.2  | 150.8  | 6.17   | 108.5  | None | None | None | 0.1   |  |  |

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| Individual Animal Clinical Pathology Data |        |        |        |      |         |     |          |          |          |          |       |       |      |
|-------------------------------------------|--------|--------|--------|------|---------|-----|----------|----------|----------|----------|-------|-------|------|
| Male,                                     | Group  | IX     | -      | 0    | mg/kg   | -   | Day      | 28       |          |          |       |       |      |
| Animal                                    | QUAL   | COL    | CLAR   | VOL  | UOSM    | pH  | UGLU     | KET      | UBIL     | BLD      | URO   | UMTP  |      |
|                                           |        |        |        | mL   | mOsm/kg |     | mg/dL    | mg/dL    |          |          | EU/dL | mg/dL |      |
|                                           |        |        |        |      |         |     |          |          |          |          |       | UFLU  |      |
|                                           |        |        |        |      |         |     |          |          |          |          |       | μg    |      |
| 901                                       | Medium | Yellow | Hazy   | 6.4  | 1547    | 7.5 | NEGATIVE | TRACE    | NEGATIVE | NEGATIVE | 0.2   | 74    | 10.4 |
| 902                                       | Light  | Yellow | Clear  | 12.2 | 695     | 8.0 | NEGATIVE | TRACE    | NEGATIVE | SMALL    | 0.2   | 29    | 8.8  |
| 903                                       | Light  | Yellow | Hazy   | 5.3  | 1362    | 7.0 | NEGATIVE | 15       | NEGATIVE | MODERATE | 0.2   | 99    | 6.6  |
| 904                                       | Medium | Yellow | Hazy   | 1.3  | 2767    | NP  | NP       | NP       | NP       | NP       | NP    | 124   | 2.8  |
| 905                                       | Light  | Brown  | Cloudy | 10.8 | 938     | 7.5 | NEGATIVE | 15       | NEGATIVE | MODERATE | 0.2   | 75    | 7.8  |
| 906                                       | Light  | Yellow | Hazy   | 5.0  | 1032    | 7.0 | NEGATIVE | 15       | NEGATIVE | TRACE    | 0.2   | 90    | 7.2  |
| 907                                       | Light  | Yellow | Hazy   | 11.0 | 664     | 7.5 | NEGATIVE | TRACE    | NEGATIVE | TRACE    | 0.2   | 34    | 8.6  |
| 908                                       | Light  | Yellow | Hazy   | 12.8 | 531     | 7.0 | NEGATIVE | TRACE    | NEGATIVE | MODERATE | 0.2   | 21    | 8.6  |
| 909                                       | Light  | Yellow | Hazy   | 18.4 | 526     | 8.0 | NEGATIVE | TRACE    | NEGATIVE | SMALL    | 0.2   | 33    | 13.5 |
| 910                                       | Light  | Yellow | Hazy   | 6.5  | 627     | 8.0 | NEGATIVE | 15       | NEGATIVE | NEGATIVE | 0.2   | 40    | 5.2  |
| Male,                                     | Group  | XI     | -      | 10   | mg/kg   | -   | Day      | 28       |          |          |       |       |      |
| Animal                                    | QUAL   | COL    | CLAR   | VOL  | UOSM    | pH  | UGLU     | KET      | UBIL     | BLD      | URO   | UMTP  | UFLU |
|                                           |        |        |        | mL   | mOsm/kg |     | mg/dL    | mg/dL    |          |          | EU/dL | mg/dL | μg   |
| 1101                                      | Medium | Yellow | Hazy   | 10.0 | 860     | 7.5 | NEGATIVE | 15       | NEGATIVE | MODERATE | 0.2   | 98    | 7.1  |
| 1102                                      | Medium | Yellow | Hazy   | 3.5  | 1859    | 6.5 | NEGATIVE | 15       | NEGATIVE | SMALL    | 0.2   | 140   | 5.2  |
| 1103                                      | Medium | Yellow | Hazy   | 3.9  | 2215    | 8.5 | NEGATIVE | 15       | NEGATIVE | NEGATIVE | 0.2   | 180   | 8.7  |
| 1104                                      | Light  | Yellow | Cloudy | 5.8  | 975     | 8.0 | NEGATIVE | 15       | NEGATIVE | MODERATE | 0.2   | 106   | 7.5  |
| 1105                                      | Light  | Yellow | Hazy   | 13.2 | 512     | 7.5 | NEGATIVE | TRACE    | NEGATIVE | TRACE    | 0.2   | 22    | 9.5  |
| 1106                                      | Medium | Yellow | Hazy   | 2.6  | 2126    | 7.0 | NEGATIVE | TRACE    | NEGATIVE | NEGATIVE | 0.2   | 180   | 5.2  |
| 1107                                      | Light  | Yellow | Hazy   | 5.4  | 1936    | 8.0 | NEGATIVE | TRACE    | NEGATIVE | NEGATIVE | 0.2   | 148   | 8.5  |
| 1108                                      | Medium | Yellow | Hazy   | 2.0  | 1901    | 6.0 | NEGATIVE | TRACE    | NEGATIVE | SMALL    | 0.2   | NP    | 3.1  |
| 1109                                      | Light  | Yellow | Hazy   | 13.0 | 1668    | 7.0 | NEGATIVE | TRACE    | NEGATIVE | TRACE    | 0.2   | 97    | 8.9  |
| 1110                                      | Light  | Yellow | Hazy   | 12.2 | 556     | 8.0 | NEGATIVE | NEGATIVE | NEGATIVE | NEGATIVE | 0.2   | 25    | 6.8  |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Individual Animal Clinical Pathology Data

| Male, Animal | Group  | QUAL   | COL    | CLAR   | VOL<br>mL | UOSM<br>mOsm/kg | pH  | UGLU<br>mg/dL | KET<br>mg/dL | UBIL     | BLD      | URO<br>EU/dL | UMTP<br>mg/dL | UFLU<br>μg |
|--------------|--------|--------|--------|--------|-----------|-----------------|-----|---------------|--------------|----------|----------|--------------|---------------|------------|
|              |        |        | XIII   | 100    | mg/kg     | Day             | 28  |               |              |          |          |              |               |            |
| 1301         | Light  | Yellow | Yellow | Hazy   | 5.0       | 1581            | 7.0 | NEGATIVE      | TRACE        | NEGATIVE | LARGE    | 0.2          | 101           | 7.3        |
| 1302         | Light  | Yellow | Yellow | Clear  | 18.0      | 478             | 7.5 | NEGATIVE      | TRACE        | NEGATIVE | LARGE    | 0.2          | 26            | 10.5       |
| 1303         | Light  | Yellow | Yellow | Hazy   | 14.6      | 476             | 7.5 | NEGATIVE      | NEGATIVE     | NEGATIVE | LARGE    | 0.2          | 25            | 8.5        |
| 1304         | Light  | Yellow | Yellow | Hazy   | 13.0      | 522             | 8.0 | NEGATIVE      | TRACE        | NEGATIVE | MODERATE | 0.2          | 25            | 8.5        |
| 1305         | Light  | Yellow | Yellow | Hazy   | 12.4      | 565             | 8.0 | NEGATIVE      | NEGATIVE     | NEGATIVE | TRACE    | 0.2          | 23            | 8.7        |
| 1306         | Light  | Yellow | Yellow | Hazy   | 8.9       | 879             | 7.0 | NEGATIVE      | 15           | NEGATIVE | MODERATE | 0.2          | 53            | 7.7        |
| 1307         | Light  | Yellow | Yellow | Hazy   | 5.5       | 970             | 7.0 | NEGATIVE      | TRACE        | NEGATIVE | NEGATIVE | 0.2          | 76            | 6.1        |
| 1308         | Light  | Yellow | Yellow | Hazy   | 15.8      | 470             | 8.0 | NEGATIVE      | NEGATIVE     | NEGATIVE | SMALL    | 0.2          | 22            | 9.1        |
| 1309         | Light  | Yellow | Yellow | Hazy   | 15.0      | 486             | 8.0 | NEGATIVE      | NEGATIVE     | NEGATIVE | TRACE    | 0.2          | 23            | 9.3        |
| 1310         | Light  | Yellow | Yellow | Hazy   | 4.0       | 1351            | 8.0 | NEGATIVE      | TRACE        | NEGATIVE | NEGATIVE | 0.2          | 101           | 5.2        |
| Male, Animal | Group  | QUAL   | COL    | CLAR   | VOL<br>mL | UOSM<br>mOsm/kg | pH  | UGLU<br>mg/dL | KET<br>mg/dL | UBIL     | BLD      | URO<br>EU/dL | UMTP<br>mg/dL | UFLU<br>μg |
|              |        |        | XV     | 1000   | mg/kg     | Day             | 28  |               |              |          |          |              |               |            |
| 1501         | Light  | Yellow | Yellow | Hazy   | 12.4      | 652             | 7.5 | NEGATIVE      | TRACE        | NEGATIVE | TRACE    | 0.2          | 29            | 9.8        |
| 1502         | Light  | Yellow | Yellow | Hazy   | 11.0      | 692             | 8.0 | NEGATIVE      | TRACE        | NEGATIVE | TRACE    | 0.2          | 42            | 9.4        |
| 1503         | Light  | Yellow | Yellow | Cloudy | 10.8      | 823             | 8.0 | NEGATIVE      | TRACE        | NEGATIVE | MODERATE | 0.2          | 60            | 7.1        |
| 1504         | Light  | Yellow | Yellow | Hazy   | 4.5       | 987             | 7.0 | NEGATIVE      | TRACE        | NEGATIVE | SMALL    | 0.2          | 45            | 6.9        |
| 1505         | Light  | Yellow | Yellow | Hazy   | 8.4       | 1022            | 7.5 | NEGATIVE      | TRACE        | NEGATIVE | SMALL    | 0.2          | 61            | 9.8        |
| 1506         | Light  | Yellow | Yellow | Clear  | 8.0       | 726             | 6.5 | NEGATIVE      | TRACE        | NEGATIVE | TRACE    | 0.2          | 56            | 8.3        |
| 1507         | Light  | Yellow | Yellow | Hazy   | 9.0       | 803             | 7.5 | NEGATIVE      | TRACE        | NEGATIVE | TRACE    | 0.2          | 56            | 9.3        |
| 1508         | Light  | Yellow | Yellow | Hazy   | 5.0       | 1382            | 7.5 | NEGATIVE      | TRACE        | NEGATIVE | NEGATIVE | 0.2          | 61            | 6.5        |
| 1509         | Medium | Yellow | Yellow | Hazy   | 3.1       | 1632            | 6.5 | NEGATIVE      | TRACE        | NEGATIVE | LARGE    | 0.2          | 145           | 5.3        |
| 1510         | Light  | Yellow | Yellow | Hazy   | 12.8      | 520             | 7.5 | NEGATIVE      | TRACE        | NEGATIVE | MODERATE | 0.2          | 32            | 7.5        |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Individual Animal Clinical Pathology Data

| Male,<br>Animal | Group | IX   | 0    | mg/kg | Day  | 28   |
|-----------------|-------|------|------|-------|------|------|
|                 | EPIT  | UWBC | URBC | NCRY  | MICR | SPER |
| 901             | None  | None | None | Few   | Few  | Few  |
| 902             | None  | None | None | Few   | Few  | None |
| 903             | None  | Few  | None | Few   | Few  | None |
| 904             | QNS   | NP   | NP   | NP    | NP   | NP   |
| 905             | Few   | Few  | None | Few   | Many | Few  |
| 906             | None  | None | None | Few   | Few  | Mod  |
| 907             | None  | None | None | Few   | Few  | Mod  |
| 908             | None  | None | None | Few   | Few  | Few  |
| 909             | None  | None | None | Few   | Few  | None |
| 910             | None  | None | None | Few   | None | None |

| Male,<br>Animal | Group | XI   | 10   | mg/kg | Day  | 28   |
|-----------------|-------|------|------|-------|------|------|
|                 | EPIT  | UWBC | URBC | NCRY  | MICR | SPER |
| 1101            | Few   | Few  | None | Few   | Few  | Few  |
| 1102            | Few   | None | None | Few   | Few  | None |
| 1103            | None  | Few  | None | Few   | Few  | Few  |
| 1104            | Few   | Few  | None | Few   | Mod  | Mod  |
| 1105            | None  | None | None | Few   | Few  | None |
| 1106            | QNS   | NP   | NP   | NP    | NP   | NP   |
| 1107            | None  | None | None | None  | Few  | None |
| 1108            | QNS   | NP   | NP   | NP    | NP   | NP   |
| 1109            | None  | None | None | Few   | Few  | None |
| 1110            | None  | None | None | Few   | Few  | Few  |

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Individual Animal Clinical Pathology Data

| Male,<br>Animal | Group | XIII | UWBC | URBC | mg/kg | Day  | 28   |
|-----------------|-------|------|------|------|-------|------|------|
|                 | EPIT  |      |      |      | NCRY  | MICR | SPER |
| 1301            | None  | None | None | Few  | Few   | Few  | None |
| 1302            | None  | None | None | None | Few   | Few  | Few  |
| 1303            | None  | None | None | None | Few   | Few  | Few  |
| 1304            | None  | Few  | None | None | Few   | Mod  | Few  |
| 1305            | None  | Few  | None | None | Few   | Few  | Mod  |
| 1306            | Few   | None | None | None | None  | Few  | Few  |
| 1307            | None  | None | None | None | Few   | Few  | Mod  |
| 1308            | None  | None | None | None | Few   | Few  | Few  |
| 1309            | None  | None | None | None | Few   | Few  | None |
| 1310            | Few   | None | None | None | Few   | Few  | None |
| Male,<br>Animal | Group | XV   | UWBC | URBC | mg/kg | Day  | 28   |
|                 | EPIT  |      |      |      | NCRY  | MICR | SPER |
| 1501            | None  | Few  | Few  | None | Few   | Mod  | None |
| 1502            | None  | Few  | Few  | None | Few   | Few  | Mod  |
| 1503            | Few   | Few  | Few  | Few  | Mod   | Mod  | None |
| 1504            | None  | None | None | None | Few   | Few  | None |
| 1505            | None  | Few  | None | None | None  | Few  | Few  |
| 1506            | None  | None | None | None | None  | Few  | None |
| 1507            | None  | None | None | None | None  | None | None |
| 1508            | None  | Few  | None | None | None  | None | Few  |
| 1509            | None  | None | None | None | Few   | Few  | None |
| 1510            | Few   | Few  | None | None | Mod   | Mod  | None |

**APPENDIX I**  
**INDIVIDUAL ANIMAL BODY AND ORGAN WEIGHTS**

INDIVIDUAL ANIMAL BODY AND ORGAN WEIGHTS

EXPLANATORY NOTES

Note

mg/kg = mg/kg/day

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Organ Weight Listing  
Study: [REDACTED]  
Individual Animal & Summary Stats Report  
PLACES 2000 v1.400

Group : IX 0 mg/kg (Control) Treatment : 0 mg/kg IX Sex : MALES

| ANIMAL | FBW<br>(Gms) | KIDNEYS<br>(Gms) | %FBW   | LIVER<br>(Gms) | %FBW   | THYROID GLAND<br>(Gms) | %FBW   |
|--------|--------------|------------------|--------|----------------|--------|------------------------|--------|
| 901    | 340.80       | 2.842            | 0.8339 | 10.916         | 3.2031 | 0.016                  | 0.0047 |
| 902    | 309.30       | 2.484            | 0.8031 | 9.819          | 3.1746 | 0.015                  | 0.0048 |
| 903    | 337.40       | 2.641            | 0.7828 | 9.813          | 2.9084 | 0.012                  | 0.0036 |
| 904    | 321.50       | 2.939            | 0.9142 | 9.571          | 2.9770 | 0.018                  | 0.0056 |
| 905    | 323.10       | 2.834            | 0.8771 | 9.716          | 3.0071 | 0.014                  | 0.0043 |
| 906    | 331.80       | 2.652            | 0.7993 | 10.253         | 3.0901 | 0.012                  | 0.0036 |
| 907    | 340.90       | 3.175            | 0.9314 | 11.271         | 3.3062 | 0.018                  | 0.0053 |
| 908    | 296.80       | 2.587            | 0.8716 | 8.367          | 2.8191 | 0.015                  | 0.0051 |
| 909    | 357.30       | 2.962            | 0.8290 | 11.252         | 3.1492 | 0.019                  | 0.0053 |
| 910    | 366.60       | 3.314            | 0.9040 | 13.076         | 3.5668 | 0.018                  | 0.0049 |
| Mean   | 332.55       | 2.843            | 0.8546 | 10.405         | 3.1202 | 0.016                  | 0.0047 |
| S.D.   | 20.986       | 0.264            | 0.0523 | 1.287          | 0.2146 | 0.003                  | 0.0007 |

Group : XI 10 mg/kg Treatment : 10 mg/kg XI Sex : MALES

| ANIMAL | FBW<br>(Gms) | KIDNEYS<br>(Gms) | %FBW   | LIVER<br>(Gms) | %FBW   | THYROID GLAND<br>(Gms) | %FBW   |
|--------|--------------|------------------|--------|----------------|--------|------------------------|--------|
| 1101   | 349.20       | 2.861            | 0.8193 | 10.871         | 3.1131 | 0.016                  | 0.0046 |
| 1102   | 313.80       | 2.666            | 0.8496 | 8.825          | 2.8123 | 0.016                  | 0.0051 |
| 1103   | 338.70       | 2.842            | 0.8391 | 11.477         | 3.3885 | 0.012                  | 0.0035 |
| 1104   | 317.70       | 2.503            | 0.7879 | 10.116         | 3.1841 | 0.013                  | 0.0041 |
| 1105   | 301.80       | 2.907            | 0.9632 | 9.635          | 3.1925 | 0.014                  | 0.0046 |
| 1106   | 326.30       | 3.044            | 0.9329 | 10.793         | 3.3077 | 0.020                  | 0.0061 |
| 1107   | 352.10       | 2.868            | 0.8145 | 12.537         | 3.5606 | 0.019                  | 0.0054 |
| 1108   | 293.80       | 2.739            | 0.9323 | 9.933          | 3.3809 | 0.018                  | 0.0061 |
| 1109   | 359.90       | 3.616            | 1.0047 | 11.533         | 3.2045 | 0.023                  | 0.0064 |
| 1110   | 310.50       | 2.849            | 0.9176 | 9.989          | 3.2171 | 0.022                  | 0.0071 |
| Mean   | 326.38       | 2.890            | 0.8861 | 10.571         | 3.2361 | 0.017                  | 0.0053 |
| S.D.   | 22.630       | 0.294            | 0.0731 | 1.087          | 0.1987 | 0.004                  | 0.0011 |

FBW - Final Body Weight

H-25425: Repeated-Dose Dermal Toxicity  
28-Day Study in Male Rats

DuPont-13830

Organ Weight Listing  
Study: [REDACTED]  
Individual Animal & Summary Stats Report  
PLACES 2000 v1.400

Group : XIII 100 mg/kg Treatment : 100 mg/kg XIII Sex : MALES

| ANIMAL | FBW<br>(Gms) | KIDNEYS<br>(Gms) | %FBW   | LIVER<br>(Gms) | %FBW   | THYROID GLAND<br>(Gms) | %FBW   |
|--------|--------------|------------------|--------|----------------|--------|------------------------|--------|
| 1301   | 329.00       | 3.100            | 0.9422 | 10.853         | 3.2988 | 0.016                  | 0.0049 |
| 1302   | 327.80       | 2.843            | 0.8673 | 9.868          | 3.0104 | 0.014                  | 0.0043 |
| 1303   | 280.70       | 2.629            | 0.9366 | 8.880          | 3.1635 | 0.013                  | 0.0046 |
| 1304   | 278.40       | 2.711            | 0.9738 | 9.022          | 3.2407 | 0.019                  | 0.0068 |
| 1305   | 319.50       | 2.840            | 0.8889 | 10.094         | 3.1593 | 0.018                  | 0.0056 |
| 1306   | 346.20       | 3.193            | 0.9223 | 11.686         | 3.3755 | 0.020                  | 0.0058 |
| 1307   | 325.20       | 2.852            | 0.8770 | 10.697         | 3.2894 | 0.021                  | 0.0065 |
| 1308   | 283.00       | 2.357            | 0.8329 | 7.852          | 2.7746 | 0.014                  | 0.0049 |
| 1309   | 340.30       | 3.004            | 0.8828 | 10.795         | 3.1722 | 0.017                  | 0.0050 |
| 1310   | 298.20       | 2.652            | 0.8893 | 9.483          | 3.1801 | 0.015                  | 0.0050 |
| Mean   | 312.83       | 2.818            | 0.9013 | 9.923          | 3.1664 | 0.017                  | 0.0053 |
| S.D.   | 25.545       | 0.246            | 0.0418 | 1.142          | 0.1700 | 0.003                  | 0.0008 |

Group : XV 1000 mg/kg Treatment : 1000 mg/kg XV Sex : MALES

| ANIMAL | FBW<br>(Gms) | KIDNEYS<br>(Gms) | %FBW   | LIVER<br>(Gms) | %FBW   | THYROID GLAND<br>(Gms) | %FBW   |
|--------|--------------|------------------|--------|----------------|--------|------------------------|--------|
| 1501   | 311.70       | 2.675            | 0.8582 | 10.061         | 3.2278 | 0.017                  | 0.0055 |
| 1502   | 306.00       | 2.879            | 0.9408 | 10.345         | 3.3807 | 0.014                  | 0.0046 |
| 1503   | 362.20       | 2.881            | 0.7954 | 10.946         | 3.0221 | 0.016                  | 0.0044 |
| 1504   | 294.80       | 2.677            | 0.9081 | 9.789          | 3.3206 | 0.018                  | 0.0061 |
| 1505   | 337.90       | 3.049            | 0.9023 | 11.708         | 3.4649 | 0.019                  | 0.0056 |
| 1506   | 294.70       | 2.777            | 0.9423 | 10.338         | 3.5080 | 0.013                  | 0.0044 |
| 1507   | 332.90       | 3.007            | 0.9033 | 10.772         | 3.2358 | 0.017                  | 0.0051 |
| 1508   | 311.30       | 2.725            | 0.8754 | 9.414          | 3.0241 | 0.016                  | 0.0051 |
| 1509   | 314.40       | 2.612            | 0.8308 | 9.182          | 2.9205 | 0.012                  | 0.0038 |
| 1510   | 336.80       | 2.869            | 0.8518 | 10.367         | 3.0781 | 0.026                  | 0.0077 |
| Mean   | 320.27       | 2.815            | 0.8808 | 10.292         | 3.2183 | 0.017                  | 0.0052 |
| S.D.   | 21.593       | 0.146            | 0.0475 | 0.744          | 0.2018 | 0.004                  | 0.0011 |

\*\*\* Listing Complete \*\*\*

FBW - Final Body Weight

## **APPENDIX J**

### **INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC OBSERVATIONS**

## INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC OBSERVATIONS

### EXPLANATORY NOTES

#### Note

mg/kg = mg/kg/day

#### Lesion Grading

Histopathological changes are described according to their morphologic character, distribution and severity. The distribution (extent of tissue involvement) is indicated, where appropriate, by modifiers such as focal, multifocal, diffuse, unilateral, bilateral, etc.; A severity score, if appropriate, is also assigned as follows:

- Minimal: the amount of change present barely exceeds that which is considered to be within normal limits.
- Mild: in general, the lesion is easily identified but of limited severity. The lesion probably does not produce any functional impairment.
- Moderate: the lesion is prominent but there is significant potential for increased severity. Limited tissue or organ dysfunction is possible.
- Severe: the degree of change is either as complete as considered possible or great enough in intensity or extent to expect significant tissue or organ dysfunction.

Comment: grades minimal through severe represent progressive involvement/severity along a continuum with minimal lesions being the least severe and severe lesions being the most severe. While the grades refer to the morphological characteristics of lesions, they also indicate their relative biological significance.

Gross observations listing multiple masses for a tissue are distinguished with letters (i.e., a, b, c, d, etc.)

1  
Date: 20-FEB-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : [REDACTED] \* APPROVED PROTOCOL \*)

Dose Group : IX 0 mg/kg (Control) Treatment: 0 mg/kg IX Sex: Males

| Animal Ref | Microscopic & Macroscopic Findings                                             |
|------------|--------------------------------------------------------------------------------|
| 901        | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

Histopathology :

LIVER :  
INFLAMMATION, SUBACUTE/CHRONIC, mild.  
KIDNEYS :  
CHRONIC PROGRESSIVE NEPHROPATHY, minimal.

No Microscopic Abnormality Observed :  
THYROID GLAND, SKIN, TREATED, SKIN, UNTREATED

|     |                                                                                |
|-----|--------------------------------------------------------------------------------|
| 902 | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |
|-----|--------------------------------------------------------------------------------|

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

Histopathology :

LIVER :  
INFLAMMATION, SUBACUTE/CHRONIC, mild.  
KIDNEYS :  
AGGREGATES, LYMPHOID, minimal.  
THYROID GLAND :  
ECTOPIC THYMUS TISSUE.

No Microscopic Abnormality Observed :  
THYROID GLAND, SKIN, TREATED, SKIN, UNTREATED

2  
Date: 20-FEB-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : [REDACTED] (\* APPROVED PROTOCOL \*)  
Dose Group : IX 0 mg/kg (Control) Treatment: 0 mg/kg IX Sex: Males

| Animal Ref | Microscopic & Macroscopic Findings                                             |
|------------|--------------------------------------------------------------------------------|
| 903        | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

Histopathology :

LIVER :  
INFLAMMATION, SUBACUTE/CHRONIC, minimal.  
KIDNEYS :  
CHRONIC PROGRESSIVE NEPHROPATHY, minimal.

No Microscopic Abnormality Observed :  
THYROID GLAND, SKIN, TREATED, SKIN, UNTREATED

|     |                                                                                |
|-----|--------------------------------------------------------------------------------|
| 904 | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |
|-----|--------------------------------------------------------------------------------|

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

Histopathology :

LIVER :  
INFLAMMATION, SUBACUTE/CHRONIC, minimal.  
KIDNEYS :  
CHRONIC PROGRESSIVE NEPHROPATHY, minimal.

No Microscopic Abnormality Observed :  
THYROID GLAND, SKIN, TREATED, SKIN, UNTREATED

3  
Date:20-FEB-04

Individual Animal Listing  
Showing animal data for individual animals  
STUDY : [REDACTED] \* APPROVED PROTOCOL \*)  
Dose Group : IX 0 mg/kg (Control) Treatment: 0 mg/kg IX Sex: Males

| Animal Ref | Microscopic & Macroscopic Findings                                             |
|------------|--------------------------------------------------------------------------------|
| 905        | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

Histopathology :

LIVER :  
INFLAMMATION, SUBACUTE/CHRONIC, minimal.  
KIDNEYS :  
AGGREGATES, LYMPHOID, minimal.

No Microscopic Abnormality Observed :  
THYROID GLAND, SKIN, TREATED, SKIN, UNTREATED

|     |                                                                                |
|-----|--------------------------------------------------------------------------------|
| 906 | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |
|-----|--------------------------------------------------------------------------------|

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

Histopathology :

LIVER :  
HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED, minimal.  
INFLAMMATION, SUBACUTE/CHRONIC, minimal.  
KIDNEYS :  
AGGREGATES, LYMPHOID, minimal.

No Microscopic Abnormality Observed :  
THYROID GLAND, SKIN, TREATED, SKIN, UNTREATED

4  
Date: 20-FEB-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : [REDACTED] (\* APPROVED PROTOCOL \*)

Dose Group : IX 0 mg/kg (Control) Treatment: 0 mg/kg IX Sex: Males

| Animal Ref | Microscopic & Macroscopic Findings                                             |
|------------|--------------------------------------------------------------------------------|
| 907        | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

Histopathology :

LIVER :  
INFLAMMATION, SUBACUTE/CHRONIC, minimal.  
THYROID GLAND :  
HYPERTROPHY, FOLLICULAR CELL, minimal.

No Microscopic Abnormality Observed :  
KIDNEYS, SKIN, TREATED, SKIN, UNTREATED

908  
Terminal Sacrifice  
Killed on Day : 28  
Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

Histopathology :

LIVER :  
INFLAMMATION, SUBACUTE/CHRONIC, minimal.  
NECROSIS, FOCAL, minimal.  
KIDNEYS :  
AGGREGATES, LYMPHOID, minimal.  
THYROID GLAND :  
HYPERTROPHY, FOLLICULAR CELL, minimal.

No Microscopic Abnormality Observed :  
SKIN, TREATED, SKIN, UNTREATED

5  
Date:20-FEB-04

Individual Animal Listing  
Showing animal data for individual animals  
STUDY : [REDACTED] (\* APPROVED PROTOCOL \*)  
Dose Group : IX 0 mg/kg (Control) Treatment: 0 mg/kg IX Sex: Males

| Animal Ref | Microscopic & Macroscopic Findings                                             |
|------------|--------------------------------------------------------------------------------|
| 909        | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |

Gross Pathology :

KIDNEYS :  
DILATATION, RIGHT, PELVIS.

No Macroscopic Abnormality Observed :  
LIVER, THYROID GLAND, SKIN, TREATED, SKIN, UNTREATED

Histopathology :

LIVER :  
INFLAMMATION, SUBACUTE/CHRONIC, minimal.  
HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED, minimal.  
KIDNEYS :  
CHRONIC PROGRESSIVE NEPHROPATHY, minimal.  
HYDRONEPHROSIS, UNILATERAL, minimal.

No Microscopic Abnormality Observed :  
THYROID GLAND, SKIN, TREATED, SKIN, UNTREATED

|     |                                                                                |
|-----|--------------------------------------------------------------------------------|
| 910 | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |
|-----|--------------------------------------------------------------------------------|

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

Histopathology :

LIVER :  
INFLAMMATION, SUBACUTE/CHRONIC, mild.  
KIDNEYS :  
AGGREGATES, LYMPHOID, minimal.  
CHRONIC PROGRESSIVE NEPHROPATHY, minimal.

910 Continued on the next page ....

6  
Date: 20-FEB-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : [REDACTED] (\* APPROVED PROTOCOL \*)

Dose Group : IX 0 mg/kg (Control) Treatment: 0 mg/kg IX Sex: Males

-----  
Animal Ref                      Microscopic & Macroscopic Findings  
-----

910                      Continued from previous page

Histopathology :

No Microscopic Abnormality Observed :  
THYROID GLAND, SKIN, TREATED, SKIN, UNTREATED

7  
Date: 20-FEB-04

Individual Animal Listing

Showing animal data for individual animals  
STUDY : [REDACTED] (\* APPROVED PROTOCOL \*)  
Dose Group : XI 10 mg/kg Treatment: 10 mg/kg XI Sex: Males

| Animal Ref | Microscopic & Macroscopic Findings                                             |
|------------|--------------------------------------------------------------------------------|
| 1101       | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

|      |                                                                                |
|------|--------------------------------------------------------------------------------|
| 1102 | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |
|------|--------------------------------------------------------------------------------|

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

|      |                                                                                |
|------|--------------------------------------------------------------------------------|
| 1103 | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |
|------|--------------------------------------------------------------------------------|

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

|      |                                                                                |
|------|--------------------------------------------------------------------------------|
| 1104 | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |
|------|--------------------------------------------------------------------------------|

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

8  
Date: 20-FEB-04

Individual Animal Listing  
Showing animal data for individual animals  
STUDY : [REDACTED] \* APPROVED PROTOCOL \*)  
Dose Group : XI 10 mg/kg Treatment: 10 mg/kg XI Sex: Males

| Animal Ref | Microscopic & Macroscopic Findings                                             |
|------------|--------------------------------------------------------------------------------|
| 1105       | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

|      |                                                                                  |
|------|----------------------------------------------------------------------------------|
| 1106 | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy . |
|------|----------------------------------------------------------------------------------|

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

|      |                                                                                |
|------|--------------------------------------------------------------------------------|
| 1107 | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |
|------|--------------------------------------------------------------------------------|

Gross Pathology :

LIVER :  
DISCOLORATION, BROWN, RIGHT DORSAL LOBE.

No Macroscopic Abnormality Observed :  
KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN, UNTREATED

Histopathology :

LIVER :  
FIBROSIS, FOCAL, CENTRIOLOBULAR, mild, with inflammation.

9  
Date: 20-FEB-04

Individual Animal Listing  
Showing animal data for individual animals  
STUDY : [REDACTED] (\* APPROVED PROTOCOL \*)  
Dose Group : XI 10 mg/kg Treatment: 10 mg/kg XI Sex: Males

| Animal Ref | Microscopic & Macroscopic Findings                                             |
|------------|--------------------------------------------------------------------------------|
| 1108       | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

|      |                                                                                |
|------|--------------------------------------------------------------------------------|
| 1109 | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |
|------|--------------------------------------------------------------------------------|

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

|      |                                                                                |
|------|--------------------------------------------------------------------------------|
| 1110 | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |
|------|--------------------------------------------------------------------------------|

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

10  
Date: 20-FEB-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : [REDACTED] (\* APPROVED PROTOCOL \*)

Dose Group : XIII 100 mg/kg Treatment: 100 mg/kg XIII Sex: Males

| Animal Ref | Microscopic & Macroscopic Findings                                             |
|------------|--------------------------------------------------------------------------------|
| 1301       | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |

Gross Pathology :

ORAL CAVITY :

ULCER/EROSION, BETWEEN UPPER INCISORS <2MM DIA.

No Macroscopic Abnormality Observed :

LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

|      |                                                                                |
|------|--------------------------------------------------------------------------------|
| 1302 | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |
|------|--------------------------------------------------------------------------------|

Gross Pathology :

No Macroscopic Abnormality Observed :

LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

|      |                                                                                |
|------|--------------------------------------------------------------------------------|
| 1303 | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |
|------|--------------------------------------------------------------------------------|

Gross Pathology :

No Macroscopic Abnormality Observed :

LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

|      |                                                                                |
|------|--------------------------------------------------------------------------------|
| 1304 | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |
|------|--------------------------------------------------------------------------------|

Gross Pathology :

No Macroscopic Abnormality Observed :

LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

11  
Date: 20-FEB-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : [REDACTED] (\* APPROVED PROTOCOL \*)

Dose Group : XIII 100 mg/kg Treatment: 100 mg/kg XIII Sex: Males

-----  
Animal Ref                      Microscopic & Macroscopic Findings  
-----

1305                      Terminal Sacrifice  
                         Killed on Day : 28  
                         Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

1306                      Terminal Sacrifice  
                         Killed on Day : 28  
                         Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

1307                      Terminal Sacrifice  
                         Killed on Day : 28  
                         Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

1308                      Terminal Sacrifice  
                         Killed on Day : 28  
                         Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

12  
Date: 20-FEB-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : [REDACTED] (\* APPROVED PROTOCOL \*)  
Dose Group : XIII 100 mg/kg Treatment: 100 mg/kg XIII Sex: Males

| Animal Ref | Microscopic & Macroscopic Findings                                             |
|------------|--------------------------------------------------------------------------------|
| 1309       | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

|      |                                                                                |
|------|--------------------------------------------------------------------------------|
| 1310 | Terminal Sacrifice<br>Killed on Day : 28<br>Animal is signed off from necropsy |
|------|--------------------------------------------------------------------------------|

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

13  
Date:20-FEB-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : [REDACTED] (\* APPROVED PROTOCOL \*)  
Dose Group : XV 1000 mg/kg Treatment: 1000 mg/kg XV Sex: Males

-----  
Animal Ref                      Microscopic & Macroscopic Findings  
-----

1501                      Terminal Sacrifice  
                         Killed on Day : 28  
                         Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

Histopathology :

LIVER :  
INFLAMMATION, SUBACUTE/CHRONIC, mild.

No Microscopic Abnormality Observed :  
KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN, UNTREATED

1502                      Terminal Sacrifice  
                         Killed on Day : 28  
                         Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

Histopathology :

LIVER :  
INFLAMMATION, SUBACUTE/CHRONIC, minimal.

No Microscopic Abnormality Observed :  
KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN, UNTREATED

1503                      Terminal Sacrifice  
                         Killed on Day : 28  
                         Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

14  
Date:20-FEB-04

Individual Animal Listing  
Showing animal data for individual animals  
STUDY : [REDACTED] (\* APPROVED PROTOCOL \*)  
Dose Group : XV 1000 mg/kg Treatment: 1000 mg/kg XV Sex: Males

-----  
Animal Ref                      Microscopic & Macroscopic Findings  
-----

1503                      Continued from previous page

Histopathology :

LIVER :  
    INFLAMMATION, SUBACUTE/CHRONIC, minimal.  
KIDNEYS :  
    CHRONIC PROGRESSIVE NEPHROPATHY, minimal.  
    AGGREGATES, LYMPHOID, minimal.  
THYROID GLAND :  
    HYPERTROPHY, FOLLICULAR CELL, minimal.

No Microscopic Abnormality Observed :  
    SKIN, TREATED, SKIN, UNTREATED

1504                      Terminal Sacrifice  
                         Killed on Day : 28  
                         Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :  
    LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
    UNTREATED

Histopathology :

LIVER :  
    INFLAMMATION, SUBACUTE/CHRONIC, mild.  
No Microscopic Abnormality Observed :  
    KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN, UNTREATED

1505                      Terminal Sacrifice  
                         Killed on Day : 28  
                         Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :  
    LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
    UNTREATED

1505 Continued on the next page ....

15  
Date:20-FEB-04

Individual Animal Listing

Showing animal data for individual animals  
STUDY : [REDACTED] (\* APPROVED PROTOCOL \*)  
Dose Group : XV 1000 mg/kg Treatment: 1000 mg/kg XV Sex: Males

-----  
Animal Ref                      Microscopic & Macroscopic Findings  
-----

1505                      Continued from previous page

Histopathology :

LIVER :  
INFLAMMATION, SUBACUTE/CHRONIC, minimal.

No Microscopic Abnormality Observed :  
KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN, UNTREATED

1506                      Terminal Sacrifice  
Killed on Day : 28  
Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

Histopathology :

LIVER :  
INFLAMMATION, SUBACUTE/CHRONIC, minimal.

No Microscopic Abnormality Observed :  
KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN, UNTREATED

1507                      Terminal Sacrifice  
Killed on Day : 28  
Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :  
LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

Histopathology :

LIVER :  
INFLAMMATION, SUBACUTE/CHRONIC, minimal.

1507 Continued on the next page ....

16  
Date: 20-FEB-04

Individual Animal Listing  
Showing animal data for individual animals  
STUDY : [REDACTED] (\* APPROVED PROTOCOL \*)  
Dose Group : XV 1000 mg/kg Treatment: 1000 mg/kg XV Sex: Males

-----  
Animal Ref                      Microscopic & Macroscopic Findings  
-----

1507                      Continued from previous page

Histopathology :

THYROID GLAND :  
    HYPERTROPHY, FOLLICULAR CELL, minimal.  
SKIN, UNTREATED :  
    INFLAMMATION, FOCAL, SUBACUTE/CHRONIC, minimal, dermal.

No Microscopic Abnormality Observed :  
    KIDNEYS, SKIN, TREATED

1508                      Terminal Sacrifice  
                         Killed on Day : 28  
                         Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :  
    LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
    UNTREATED

Histopathology :

LIVER :  
    INFLAMMATION, SUBACUTE/CHRONIC, mild.  
KIDNEYS :  
    CHRONIC PROGRESSIVE NEPHROPATHY, minimal.

No Microscopic Abnormality Observed :  
    THYROID GLAND, SKIN, TREATED, SKIN, UNTREATED

1509                      Terminal Sacrifice  
                         Killed on Day : 28  
                         Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :  
    LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
    UNTREATED

1509 Continued on the next page ....

17  
Date:20-FEB-04

Individual Animal Listing  
Showing animal data for individual animals  
STUDY : [REDACTED] (\* APPROVED PROTOCOL \*)  
Dose Group : XV 1000 mg/kg Treatment: 1000 mg/kg XV Sex: Males

-----  
Animal Ref                      Microscopic & Macroscopic Findings  
-----

1509                      Continued from previous page

Histopathology :

LIVER :

INFLAMMATION, SUBACUTE/CHRONIC, minimal.  
NECROSIS, FOCAL, minimal.

SKIN, UNTREATED :

INFLAMMATION, FOCAL, SUBACUTE/CHRONIC, minimal, muscular.

No Microscopic Abnormality Observed :

KIDNEYS, THYROID GLAND, SKIN, TREATED

1510

Terminal Sacrifice

Killed on Day : 28

Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :

LIVER, KIDNEYS, THYROID GLAND, SKIN, TREATED, SKIN,  
UNTREATED

Histopathology :

LIVER :

INFLAMMATION, SUBACUTE/CHRONIC, mild.

KIDNEYS :

CHRONIC PROGRESSIVE NEPHROPATHY, minimal.

SKIN, TREATED :

INFLAMMATION, FOCAL, ACUTE, minimal, epidermal.

No Microscopic Abnormality Observed :

THYROID GLAND, SKIN, UNTREATED

\*\*\* Listing Complete \*\*\*