TRADE SECRET

Study Title

Perfluorooctanoic Acid: Relationship Between Repeated Inhalation Exposures and Plasma PFOA Concentration in the Rat

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STUDY COMPLETED ON: November 5, 2003

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LABORATORY PROJECT ID: DuPont-12944

WORK REQUEST NUMBER: [redacted]

SERVICE CODE NUMBER: [redacted]

SPONSOR: Association of Plastics Manufacturers of Europe (APME)
Fluoropolymers Committee
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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 in 1997) published in ENV/MC/CHEM(98)17 and MAFF Japan Good Laboratory Practice Standards (59 NohSan Number 3850) except for the item documented below. The item listed does not impact the validity of the study.

The test substance is commercially available and was characterized by the supplier prior to the initiation of this study. A certificate of analysis was provided. Although the characterization was not performed under Good Laboratory Practice Standards, based on our monitoring, we have no reason to doubt the validity of the analysis.

Study Director: _____ 05-Nov-2003

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QUALITY ASSURANCE STATEMENT

Haskell Sample Number(s):

25811

Dates of Inspections:

Protocol: June 10, 2003

Conduct: June 13, 17, 20, 2003

Records, Reports: September 16-18, 25, 28, 2003

Dates Findings Reported to:

Study Director: September 29, 2003

Management: September 29, 2003; October 6, 2003

Reported by: Robert C. Rhea for J.C.H. 05-NOV-2003

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CERTIFICATION

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

Inhalation Data Evaluation by: Michael P. DeLorme — 30 OCT 03
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Issued by Study Director: Paul M. Hinderliter — 05-Nov-2003
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STUDY INFORMATION

9th Collective Nomenclature: [redacted]

Synonyms/Codes: [redacted]

- Perfluorooctanoic acid
- PFOA

[redacted]

Haskell Number: 25811

CAS Registry Number: [redacted]

Purity: [redacted]

Known Impurities: [redacted]

Physical Characteristics: White powder

Stability: The test substance appeared to be stable under the conditions of the study; no evidence of instability was observed.

Sponsor: Association of Plastics Manufacturers of Europe (APME)
Fluoropolymers Committee
Avenue E. Van Nieuwenhuyse 4
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Study Initiated/Completed: April 22, 2003 / (see report cover page)

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SUMMARY

A large pharmacokinetic database exists describing the behavior of perfluorooctanoic acid (PFOA) following oral exposure. In rat studies, whole body elimination of PFOA was found to be much more rapid in female rats compared with male rats following oral dosing. The objective of this study was to quantify plasma PFOA concentrations in rats, following single and repeated inhalation exposures at three airborne concentrations, for the purpose of bridging the oral and inhalation exposure data sets.

The study was comprised of two separate experiments: Phase I consisted of a single 6-hour nose-only exposure while Phase II consisted of repeated exposures (6 hours per day, 5 days per week for 3 weeks). In both experiments, male and female rats were exposed nose only to an aerosol of 0, 1, 10, or 25 mg/m^3 PFOA. Levels were selected to produce plasma concentrations similar to those observed in previous oral gavage studies. In Phase I, blood was drawn via the tail vein pre-exposure, during exposure at 0.5, 1, 3 and 6 hours, and post-exposure at 1, 3, 6, 12, 18 and 24 hours. Rats were not removed from the exposure chamber during the exposure period and blood was taken from the tail vein while the animals remained in the nose-only restrainers attached to the exposure chamber. For Phase II, blood was collected immediately before and after the daily inhalation exposure period three days per week. Plasma derived from the whole blood samples was analyzed by liquid chromatography-mass spectrometry (LC-MS).

PFOA appears rapidly in the blood of both male and female rats exposed via the inhalation route. PFOA elimination is sex-dependent, with female rats eliminating PFOA from the plasma much more efficiently than male rats. PFOA plasma concentrations are proportional to the inhalation exposure concentrations from 1 to 25 mg/m^3. Repeated daily inhalation exposures produce little plasma carryover in female rats, but significant carryover in male rats. Male rats reach a steady state plasma concentration by three weeks with plasma concentrations of 8, 21, and 36 μg/mL respectively for the 1, 10, and 25 mg/m^3 exposures. Female rats reached post-exposure plasma concentrations of 1, 2, and 4 μg/mL respectively for the 1, 10, and 25 mg/m^3 exposures, but returned to baseline levels for the pre-exposure time points.

INTRODUCTION

A large pharmacokinetic database exists describing the behavior of perfluorooctanoic acid (PFOA) following oral exposure. In rat studies, whole body elimination of PFOA was found to be much more rapid in female rats compared with male rats following oral dosing. The objective of this study was to quantify plasma PFOA concentrations in rats, following single and repeated inhalation exposures at three airborne concentrations, for the purpose of bridging the oral and inhalation exposure data sets.

MATERIALS AND METHODS

A. Test Substance

[redacted]PFOA was obtained from Aldrich Chemicals (Milwaukee, Wisconsin) and assigned Haskell Laboratory Number 25811 upon receipt. Available information on the purity, composition, and contaminants were provided by the vendor and documented in the study records and report.

Since this study utilized the inhalation route of exposure, no attempt was made to establish the actual dose each rat received. All results were therefore reported as a function of the group exposure concentration(s) rather than a function of dose.

Molecular Weight: 414.1
Molecular Formula:
Structure:

Purity:

B. Test System

Male and female Crl:CD®(SD)IGS BR rats were obtained from Charles River Laboratories, Inc., Raleigh, North Carolina. The Sprague-Dawley rat was chosen for this study because of the extensive experience with this strain and its suitability with respect to longevity, sensitivity, and low incidence of spontaneous diseases. Furthermore, the Sprague-Dawley rat has been used previously for toxicokinetic testing of PFOA and other fluorinated test materials.[1,2,3]

Upon arrival at Haskell Laboratory, all rats were housed singly, sexes separate, in quarantine. The rats were:

- quarantined for at least 5 days.

- identified temporarily by cage identification.
- weighed twice during the quarantine procedure.
- observed with respect to weight gain and any gross signs of disease or injury.

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

At the time of exposure, rats were approximately 6-8 weeks of age and the weight variation did not exceed ± 20% of the mean weight by exposure group. Each animal was assigned an identification number that was used throughout the study. The last 3 digits of the animal identification number was marked on the tail of each animal in indelible ink.

C. Animal Husbandry

1. Animal Housing

Except during exposure, rats were housed singly in stainless steel, wire-mesh cages suspended above cage boards. Each cage rack contained only rats of one sex.

2. Environmental Conditions

Rats were housed in proximity to the inhalation chambers. Animal room(s) were maintained at a temperature of 18-26°C (targeted to 22-24°C) and a relative humidity of 30-70% (targeted to 40-60%). Animal rooms were artificially illuminated (fluorescent light) on an approximate 12-hour light/dark cycle, except on blood collection days where lights were turned on as needed up to one hour extra per day. The relative humidity and temperature ranges in the housing rooms were recorded but were not included in this report.

3. Feed and Water

Except during exposure, PMI® Nutrition International, LLC Certified Rodent LabDiet® 5002 and tap water was available *ad libitum*.

4. 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.

D. Inhalation Exposure System
(Figure 1)

1. Atmosphere Generation

For this study, a 5% (weight/weight) solution was prepared by diluting the powdered test substance in deionized water. Concentrated ammonium hydroxide solution was added to achieve a test substance solution pH of approximately 6.0 to 8.0. Chamber atmospheres were generated by aerosolization of the 5% test substance solution in air with a Spraying Systems nebulizer. The test substance was metered into the nebulizer with a Harvard Apparatus model 22 syringe infusion pump. Filtered, high-pressure air, metered into the nebulizer by a Brooks model 5850E mass flow controller, carried the resulting atmosphere into the exposure chamber. The pump and flow controller were controlled and monitored by the Camile Inhalation Toxicology Automated Data System (CITADS). Chamber concentrations of test substance were controlled by varying the syringe infusion rate to the nebulizer except for the 1 mg/m^3 chamber where dilutional air was also used to achieve the desired atmosphere concentration. See Figure 1 for a schematic of the inhalation exposure setup.

Test atmospheres were exhausted through an MSA charcoal/HEPA filter cartridge prior to discharge into the fume hood. Air from the control chamber was exhausted directly into the fume hood.

2. Chamber Construction and Design

All exposure chambers were constructed of stainless steel and glass (NYU style) with a nominal internal volume of 150 L. A dispersion plate inside the chamber promoted uniform chamber distribution of the test atmosphere.

3. Exposure Mode

During exposure, animals were individually restrained in polycarbonate (Phase I) or perforated stainless steel cylinders (Phase II) with conical nose pieces. The restrainers were inserted into a polymethylmethacrylate faceplate which was attached to the exposure chamber so that the nose of each animal extended into the exposure chamber. Before the start of the exposure phase,

animals were placed in restrainers on 2 separate days for approximately 15 minutes each day to acclimate the animals to the restrainers. During exposure, the animals from all exposure levels were kept warm with a heat lamp placed behind the animals (see Figure 1).

E. Characterization of Chamber Atmosphere

1. Test Substance Sampling and Analysis

The atmospheric concentration of PFOA was determined by gravimetric analysis at approximately 60-minute intervals during each exposure. Known volumes of chamber atmosphere were drawn from the sampling port through a 25 mm filter cassette containing a pre-weighed Gelman glass fiber (Type A/E) filter. The filters were weighed on a Cahn model C-31 Microbalance®. The filter weights were automatically transferred to CITADS, which calculated the chamber concentrations based on the difference in pre- and post-sampling filter weights divided by the volume of chamber atmosphere sampled. Gravimetric sample start- and stop-times for each sample were controlled and recorded by CITADS.

2. Preliminary Air Sampling Studies

For this study, the test substance, PFOA, was diluted to 5% (w/w) in deionized water and subsequently aerosolized into the exposure chambers. In order to determine if the gravimetric analytical method used to quantitate the airborne test substance concentration indicated the mass of just the test substance or test substance plus water, a preliminary desiccation study was performed. In this study, air samples were taken from chamber atmospheres that ranged from 1 to 25 mg/m^3 test substance as described in Materials and Methods Section E1. Following the determination of the filter weight immediately post-sampling, the filters were placed in a desiccation chamber for 24 hours to remove any water that was on the filter. After desiccation, the filters were re-weighed, the mass recorded and compared to the values obtained immediately following air sampling. Results demonstrated that the filters lost <0.03% of their mass following 24 hours of desiccation, indicating that the material collected on the filter reflected the total mass of suspended aerosol in the exposure chambers.

3. Particle Size Determination

A sample to determine particle size distribution (mass median aerodynamic diameter and percent particles less than 1, 3, and 10 μm diameter) was taken from each test exposure chamber at least once per week during the Phase II study with a Sierra® Series 210 cyclone preseparator/Cascade impactor and Sierra® series 110 constant flow air sampler.[5]

4. Environmental Monitoring

Chamber airflow was set at the beginning of each exposure to achieve at least 10 air changes per hour and was monitored continually with a calibrated Brooks model 5850E mass flow controller. Chamber temperature was targeted at 22 ± 3°C. Chamber relative humidity was targeted at 40 to 60%. Airflow, temperature, and relative humidity were monitored continuously with a CAMILE Inhalation Toxicology Automated Data System (CITADS) and recorded at approximately 15-minute intervals during each exposure. Chamber oxygen concentration was targeted to at least

19%. Chamber oxygen concentration was measured with a Biosystems model 3100R oxygen analyzer and was recorded twice during each exposure

F. Inhalation Exposure

1. Phase I (Single Exposure)

To determine the proper exposure concentrations for Phase II, four groups of 3 male and 3 female rats each were exposed nose only for a single, 6-hour period to an aerosol of the test substance. The test groups were exposed to an atmospheric concentration of 1 mg/m^3, 10 mg/m^3, or 25 mg/m^3. A control group of rats was exposed to air only. Blood was collected via the tail vein and was drawn pre-exposure, during exposure at 0.5, 1, 3 and 6 hours, and post-exposure at 1, 3, 6, 12, 18 and 24 hours. Individual animal exposure times were staggered by five minutes to allow time for blood collection. Rats were not removed from the exposure chamber during the exposure time. Blood was taken from the tail vein while the animals remained in the nose-only restrainers in the exposure chamber. Blood was collected in heparinized tubes and stored on wet ice. Plasma was separated by centrifugation. Rats were sacrificed following the final blood collection. Plasma derived from the whole blood samples was analyzed by LC-MS as described in Section H.

The exposure concentrations selected for Phase II were levels that produced plasma concentrations similar to plasma concentrations observed in a previous study of oral gavage dosing in rats.[4]

2. Phase II (Repeated Exposure)

After the dose levels were selected, four groups of 5 male and 5 female rats each were exposed (nose only) for a 6-hour period, 5 days per week (weekends excluded), for 3 weeks to an aerosol of the test substance. The starting time of the exposure is defined as the time when the nose only restrainers containing the animals are loaded into the exposure chamber. The exposure end time is defined as the time when the nose only restrainers are removed from the chamber. After each exposure, rats were returned to their cages. The control group of rats was exposed to air only. Exposure start times were staggered by 10-30 minutes by exposure concentration group to allow time for blood collection. As in Phase I, blood was collected via the tail vein. Blood was collected before and after the daily inhalation exposure period three days per week. Rats were sacrificed following the final blood collection.

G. Analytical Methods

1. Extraction of PFOA from Plasma for LC/MS Analysis

Plasma samples were processed by protein precipitation (PPT) using Isolute Array protein precipitation columns (Argonaut Technologies, Foster City, CA). A 0.5 $\mu g/ml$ solution of [redacted] Aldrich Chemicals, Milwaukee, WI) in ACN was used as an internal standard. Plasma samples were thawed, and a 20 μL aliquot of each sample was applied to the PPT array. The plasma samples were precipitated by adding appropriate dilution rate volumes of

ACN/internal standard solution. Dilution rates, ranging from 1:4 (60 μL of internal standard solution) to 1:50 (980 μL of internal standard solution), were utilized in order to capture the sample concentrations within the range of the standard curve concentrations. The array was slowly eluted under vacuum into a 96-well receiver plate, centrifuged at ~3000 rpm for 5 minutes, and the extracts were analyzed by LC/MS.

2. Instrumentation

System:	Waters 2790 Liquid Chromatograph, equipped with quaternary pump, column heater, and autosampler	
Detector:	Quattro Micro Mass Spectrometer	
Mode:	Multiple Reaction Monitoring (MRM)	
Source:	Negative Electrospray	
LM 1 resolution:	10.0	
HM 1 resolution	10.0	
Ion energy 1:	1.0	
Entrance:	5	
Collision:	2	
Exit:	5	
LM 2 resolution:	14	
HM 2 resolution:	14	
Ion energy 2:	2.0	
Multiplier (V):	650	
Capillary (kV):	2.0	
Cone (V):	15	
Extractor (V):	0	
RF lens (V):	0	
Source temperature:	130°C	
Desolvation temperature:	350°C	
MS Method:		
Mode:	MRM, 2 transitions	
Time:	0-11.0 min	
Ch1:	413.00 → 369.00	
	Dwell:	0.25 sec
	Collision energy:	15 eV
Ch2:	469.00 → 419.00	
	Dwell:	0.25 sec
	Collision energy:	15 eV
Limit of Quantitation:	0.1 μg/mL – Phase I 0.05 μg/mL – Phase II	

3. Chromatographic Methods

Method: Plasma concentration analysis
Column: Waters Xterra MS C18, 2.1x30mm, 2.5 μm
Column temperature: Ambient
Mobile phases: A: 50 mM Ammonium Acetate
B: Acetonitrile

Gradient:

Time (min)	%B
0.0	10
0.5	10
10.0	100
10.9	100
11.0	10

Flow rate: 0.25 mL/min
Stop time: 11.0 min
Injection volume: 5 μL

H. Statistical Analysis

		Method of Statistical Analysis	
Parameter	Preliminary Test	If preliminary test is not significant	If preliminary test is significant
Exposure Concentration Data Environmental Data Plasma Concentration	None	Descriptive statistics (e.g., mean, standard deviation)	

RESULTS AND DISCUSSION

A. Phase I (Single Exposure)
(Tables 1, 3-4, and 6-7, Figures 3-6, Appendix D)

1. Chamber Concentrations of Test Substance

The mean chamber atmosphere concentrations for the three levels were all within 20% of the targeted concentrations (Table 1). Due to the logistics of performing venipunctures on the animals during the exposure, aerosol size analysis could not be performed during Phase I. However, aerosol size data obtained during the preliminary rangefinding work demonstrated aerosol sizes were 1.8-2.0 μm mass median aerodynamic diameter (MMAD) with geometric standard deviations that ranged from 1.9-2.1 μm for atmosphere concentrations that were similar to those used in the Phase I study. Aerosols were also shown to be respirable under identical generation conditions used in the Phase II studies (Table 3). Therefore, the test substance aerosols were considered to be respirable in Phase I.

2. Chamber Environmental Conditions

The mean temperature in all the exposure chambers ranged from 24-25°C except for the control chamber, where the mean temperature was 26° C, which is outside of the targeted range of 22 ± 3°C (Table 4). This temperature was out of range due to heat lamps that were utilized to keep the animals warm to facilitate the tail venipuncture procedure during the exposures. This temperature deviation (control only) is not expected to adversely affect the results of this study. The mean relative humidity in all the exposure chambers during the single 6 hour exposure ranged from 34-40%, which was within the targeted range of 50 ± 20%. The airflow into the chambers ranged from 27-70 L/min, which was adequate to achieve at least 10 air changes per hour. The mean oxygen concentration in all the exposure chambers was 21% which was within the targeted oxygen concentration of >19%.

Overall, the environmental conditions in the Phase I study were within acceptable comfort ranges for the animals and was considered adequate for the conduct of the study.

3. Blood Collection

Almost all blood collections occurred within five minutes of the described sample time; the maximum difference was seven minutes which occurred on only two samples. This difference was not judged to impact the quality of the data since the animals were not removed from the exposure chamber during blood sampling.

4. Pharmacokinetics

For both sexes, PFOA plasma concentrations rose during the 6 hour inhalation exposure (Tables 6-7). A proportional relationship was produced in both the male and female rat maximum plasma concentrations (C_{max}) between 1 and 25 mg/m^3 (Figure 3). The male C_{max} values were approximately 2-3 times higher than the female C_{max}. The female C_{max} occurred at the end of the exposure period or 1 hour post exposure while the male C_{max} occurred at the end of the exposure period up to 6 hours post exposure.

Elimination of PFOA from female rat plasma was rapid and complete at all exposure levels in Phase I. Plasma concentrations dropped below the analytical limit of quantification (0.1 μg/mL) by 12 hours post exposure (Figure 4). Plasma elimination was much slower in male rats than female rats. After 24 hours of post exposure recovery, the plasma concentrations were approximately 90% of the peak concentrations at all tested exposure levels. The male and female elimination kinetics are consistent with the previously reported elimination kinetics of PFOA following oral dosing.[4] In addition, there did not appear to be a concentration dependence of the elimination rate in either male or female rats as the plasma curves are parallel on a log scale. Figures 5 and 6 also show the Phase I plasma concentrations with standard deviation bars indicating the significant differences between exposure groups.

For the setting of exposure levels for Phase II of the study, male and female C_{max} values were compared to plasma C_{max} from an oral gavage study of PFOA.[4] This study examined single oral gavage doses from 0.1 to 25 mg PFOA/kg body weight. The C_{max} values for this study ranged from 0.598 to 160.00 μg/mL (male) and 0.67 to 132.65 (female). Because the C_{max}

values from Phase I fell within the middle of the existing range and oral gavage data, the inhalation exposure concentrations were not changed for Phase II.

B. Phase II (Repeated Exposure)

(Tables 2-3, 5, and 8-9, Figures 2 and 7-10, Appendices B-C and E)

1. Chamber Concentrations of Test Substance

The mean chamber atmosphere concentrations for the three levels were all within 10% of the targeted concentrations (Table 2, Figure 2). Aerosol size analysis of all three exposure levels indicated an aerosol size distribution of 1.3-1.9 μm MMAD with geometric standard deviations of 1.5-2.1, which is considered to be respirable to rats (Table 3). Therefore, these exposure methods were considered acceptable for the purpose of this study.

2. Chamber Environmental Conditions

The mean temperature in all the exposure chambers ranged from 24-25°C, which was within the targeted range of 22 ± 3° C (Table 5). The mean relative humidity in all the exposure chambers during the 3 week exposure period ranged from 33 –39%, which was within the targeted range of 50 ± 20%. The airflow into the chambers ranged from 28-70 L/min, which was sufficient to achieve at least 10 air changes per hour. The mean oxygen concentration in all the exposure chambers was 21% which was within the targeted oxygen concentration of >19%.

Overall, the environmental conditions in the Phase II study were within acceptable comfort ranges for the animals and considered adequate for the conduct of the study.

3. Blood Collection

No clinical signs were noted among rats during Phase II. Blood collections occurred within thirty minutes of the described sample time, samples were taken before and after the 6 hour exposure periods. Blood was collected on the first, third, and fifth exposure day for all three weeks.

4. Pharmacokinetics

Phase II plasma concentrations are shown in Tables 8-9 and in Figures 5-8. Exposures were conducted five days per week, with plasma samples taken before and after exposure on the first, third and fifth exposure day per week. The male (Figure 7) and female (Figure 9) concentration curves demonstrate the effects of the differing elimination kinetics on plasma levels following repeated exposure. In the female rats, there was little day-to-day carryover of PFOA in the plasma. There is no significant difference between the peak heights of the sampled exposure days. For the male rats, there is carryover between test days as expected from Phase I. Steady state was not achieved until week 3. This steady state value is approximately 2-3 times as high as the mean single dose C_{max}. Figures 8 and 10 show the mean plasma concentrations with standard deviation bars to demonstrate the differences by exposure level. As in Phase I, repeated exposures demonstrate a proportional relationship between exposure concentration and plasma concentrations in male and female rats. Male rats reach a steady state plasma concentration by

three weeks with plasma concentrations of 8, 21, and 36 μg/mL respectively for the 1, 10, and 25 mg/m^3 exposures. Female rats reached post-exposure plasma concentrations of 1, 2, and 4 μg/mL respectively for the 1, 10, and 25 mg/m^3 exposures, but returned to baseline levels for the pre-exposure time points.

CONCLUSIONS

PFOA appears rapidly in the blood of both male and female rats exposed via the inhalation route. PFOA elimination is sex-dependent, with female rats eliminating PFOA from the plasma much more efficiently than male rats. At the tested concentrations from 1 to 25 mg/m^3, PFOA plasma concentrations relate proportionally to the inhalation exposure concentration. Repeated daily inhalation exposures produce little plasma carryover in female rats, but significant carryover in male rats. Male rats reach a steady state plasma concentration by three weeks with plasma concentrations of 8, 21, and 36 μg/mL respectively for the 1, 10, and 25 mg/m^3 exposures. Female rats reached post-exposure plasma concentrations of 1, 2, and 4 μg/mL respectively for the 1, 10, and 25 mg/m^3 exposures, but returned to baseline levels for the pre-exposure time points.

RECORDS AND SAMPLE STORAGE

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.

REFERENCES

1. Vanden Heuvel, J.P., Kuslikis, B.I., Van Rafelghem, M.J. and Peterson, R.E. (1991) Tissue Distribution, Metabolism, and Elimination of Perfluorooctanoic Acid in Male and Female Rats. J. Biochem. Toxicol. 6(2): 83-92.

2. Biegel, L.B. (1997) Hazard Characterization for Human Health C8 Exposure. DuPont Haskell Laboratory.

3. Vanden Heuvel, J.P., Davis, J.W., Sommers, R., and Peterson, R.E. (1992). Renal Excretion of Perfluorooctanoic Acid in Male Rats: Inhibitory Effect of Testosterone. J Biochem Toxicology, 7(1): 31-36.

4. DuPont Haskell Laboratory (2003). Perfluorooctanoic Acid: Toxicokinetics in the Rat. Unpublished report [redacted]

5. Calculation described in Sierra Instruments, Inc., Bulletin 7-79-219IM, Instruction Manual: Series 210 Ambient Cascade Impactors and Cyclone Preseparators.

TABLES

TABLES

EXPLANATORY NOTES

ABBREVIATIONS:

n	number of samples
S.D.	standard deviation
S.E.M.	standard error of the mean

NOTES:

Tables 1-5: Values are reported to 2 significant figures.
Calculations were performed prior to rounding values.

TABLE 1

PHASE I (SINGLE EXPOSURE)
CHAMBER CONCENTRATIONS OF PFOA

Design Concentration (mg/m^3)	Measured Concentration (mg/m^3)			
	Mean	S.D.	Range	n
1	1.2	0.38	0.66 - 1.7	6
10	9.8	0.58	9.0 - 11	6
25	27	3.1	24 - 32	6

a Values represent the mean, standard deviation (S.D.), and range of the values obtained from 1 exposure.

TABLE 2

PHASE II (REPEATED EXPOSURE)
CHAMBER CONCENTRATIONS OF PFOA

Design Concentration (mg/m^3)	Measured Concentration (mg/m^3)			
	Mean	S.E.M.	Range	n
1	1.1	0.04	0.81 - 1.3	15
10	10	0.11	9.4 - 11	15
25	25	0.43	21 - 27	15

a Values represent the mean, standard error of the mean (S.E.M.), and range of the daily mean values obtained from n exposures.

TABLE 3

PHASE II (SINGLE EXPOSURE)
PARTICLE SIZE DISTRIBUTION OF PFOA

Design Concentration (mg/m^3)	Exposure	Mass Median Aerodynamic Diameter (μm)	Geometric Standard Deviation	% Particle by Mass		
				<1 μm	<3 μm	<10 μm
1	2	1.7	1.6	12	90	100
	4	1.7	1.6	13	90	100
	7	1.8	1.6	14	85	100
	12	1.3	1.9	33	87	100
10	3	1.3	1.9	30	92	100
	8	1.5	2.1	29	84	100
	13	1.8	1.5	10	84	100
25	5	1.7	2.0	24	80	100
	9	1.8	1.8	15	85	100
	14	1.9	1.5	6	84	100

TABLE 4

PHASE I (SINGLE EXPOSURE)
CHAMBER ENVIRONMENTAL CONDITIONS

Design Concentration	Temperature (°C)[a]				Relative Humidity (%)[a]				Airflow (L/min)[a]			
(mg/m³)	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n
0	26	0.62	24 - 27	27	37	1.1	36 - 40	27	28	0.025	28	27
1	25	1.2	22 - 27	28	34	4.5	31 - 48	16	70	0.050	70	28
10	25	1.5	22 - 26	30	40	1.7	38 - 45	30	28	0.040	28	30
25	24	0.93	21 - 25	32	34	2.5	30 - 38	32	27	0.60	26 - 28	32

a Values represent the mean, standard deviation (S.D.), and range of the values obtained from 1 exposure.

TABLE 5

PHASE II (REPEATED EXPOSURE)
CHAMBER ENVIRONMENTAL CONDITIONS

Design Concentration (mg/m^3)	Temperature (°C)[a]			Relative Humidity (%)[a]			Airflow (L/min)[a]			
	Mean	S.E.M.	Range	Mean	S.E.M.	Range	Mean	S.E.M.	Range	n
0	25	0.070	25 - 26	39	0.39	36 - 42	28	0.066	28	15
1	25	0.16	24 - 26	35	1.6	27 - 47	70	0.014	70	15
10	25	0.090	24 - 26	38	0.57	33 - 41	28	0.031	28	15
25	24	0.080	23 - 24	33	0.58	29 - 37	28	0.090	27 - 29	15

a Values represent the mean, standard error of the mean (S.E.M.), and range of the daily mean values obtained from n exposures.

TABLE 6

PHASE I (SINGLE EXPOSURE)
PLASMA CONCENTRATION DATA IN MALE RATS

	Chamber Concentration (mg/m^3)											
	0			1			10			25		
Hours	Mean	S.D.	# >LOQ	Mean	S.D.	# >LOQ	Mean	S.D.	# >LOQ	Mean	S.D.	# >LOQ
Exposure												
Predose	<LOQ	*	0	<LOQ	*	0	<LOQ	*	0	0.64	*	1
0.5	<LOQ	*	0	<LOQ	*	0	<LOQ	*	0	1.18	*	2
1	<LOQ	*	0	<LOQ	*	0	0.98	*	2	2.55	*	2
3	<LOQ	*	0	1.05	0.32	3	3.04	0.53	3	5.89	1.69	3
6	<LOQ	*	0	2.41	0.91	3	5.85	1.09	3	12.87	2.31	3
Post-Exposure												
1	<LOQ	*	0	2.16	0.42	3	7.39	1.29	3	15.31	3.95	3
3	<LOQ	*	0	2.37	*	2	7.89	0.97	3	17.78	4.79	3
6	<LOQ	*	0	1.81	0.92	3	8.57	*	2	17.58	4.72	3
12	<LOQ	*	0	2.25	1.13	3	7.43	1.32	3	16.74	4.17	3
18	<LOQ	*	0	2.03	0.77	3	6.97	1.19	3	16.1	3.56	3
24	<LOQ	*	0	2.09	0.57	3	6.63	1.33	3	15.34	3.14	3

Data expressed as μg/mL.
*Standard deviation not calculated for 2 or fewer samples >LOQ.

TABLE 7

PHASE I (SINGLE EXPOSURE)
PLASMA CONCENTRATION DATA IN FEMALE RATS

	Chamber Concentration (mg/m^3)											
	0			1			10			25		
Hours	Mean	S.D.	# >LOQ	Mean	S.D.	# >LOQ	Mean	S.D.	# >LOQ	Mean	S.D.	# >LOQ
Exposure												
Predose	<LOQ	*	0	<LOQ	*	0	<LOQ	*	0	<LOQ	*	0
0.5	<LOQ	*	0	<LOQ	*	0	0.43	*	2	1.33	*	2
1	<LOQ	*	0	<LOQ	*	0	1.2	0.18	3	2.74	0.96	3
3	<LOQ	*	0	0.83	*	2	2.62	*	2	5.91	0.53	3
6	<LOQ	*	0	0.88	0.14	3	3.68	0.53	3	6.87	2.18	3
Post-Exposure												
1	<LOQ	*	0	0.75	0.14	3	3.69	0.66	3	7.15	1.44	3
3	<LOQ	*	0	0.67	0.21	3	2.54	*	1	6.35	0.50	3
6	<LOQ	*	0	<LOQ	*	0	0.54	0.07	3	3.12	0.44	3
12	<LOQ	*	0	<LOQ	*	0	<LOQ	*	0	<LOQ	*	0
18	<LOQ	*	0	<LOQ	*	0	<LOQ	*	0	<LOQ	*	0
24	<LOQ	*	0	<LOQ	*	0	<LOQ	*	0	<LOQ	*	0

Data expressed as μg/mL.
*Standard deviation not calculated for 2 or fewer samples >LOQ.

TABLE 8

PHASE II (REPEATED EXPOSURE)
PLASMA CONCENTRATION DATA IN MALE RATS

	Chamber Concentration (mg/m^3)											
	0			1			10			25		
Hours	Mean	S.D.	# >LOQ	Mean	S.D.	# >LOQ	Mean	S.D.	# >LOQ	Mean	S.D.	# >LOQ
0	<LOQ	a	0	0.58	a	1	<LOQ	a	0	<LOQ	a	0
6	<LOQ	a	0	1.35	0.51	5	3.69	1.32	5	7.73	3.08	5
48	<LOQ	a	0	2.20	0.86	4	7.39	2.78	5	17.68	5.25	5
54	<LOQ	a	0	4.38	1.62	5	11.22	5.10	5	29.26	7.04	4
96	<LOQ	a	0	4.65	1.33	5	13.73	6.19	5	30.04	5.65	5
102	<LOQ	a	0	6.18	1.58	5	15.81	6.24	5	40.33	9.97	5
168	0.83	a	1	4.90	1.36	5	13.97	5.23	5	30.10	5.26	5
174	0.49	a	1	6.29	1.64	5	16.70	5.55	5	35.06	6.83	5
216	<LOQ	a	0	6.58	1.40	5	18.81	6.31	5	32.09	11.10	5
222	<LOQ	a	0	7.32	1.90	5	19.50	6.42	5	35.67	6.54	5
264	<LOQ	a	0	7.58	1.81	5	20.33	7.73	5	36.36	10.42	5
270	<LOQ	a	0	8.15	2.14	5	21.73	8.17	5	39.58	11.63	5
336	<LOQ	a	0	6.82	2.06	5	20.86	7.76	5	30.88	10.29	5
342	<LOQ	a	0	7.65	1.78	5	19.43	6.85	5	32.64	10.88	5
384	<LOQ	a	0	7.35	1.48	5	20.16	7.18	5	31.89	9.19	5
390	<LOQ	a	0	8.11	1.84	5	21.48	7.85	5	34.79	10.89	5
432	<LOQ	a	0	8.33	1.84	5	21.87	6.89	5	39.58	17.78	5
438	<LOQ	a	0	9.25	2.07	5	24.13	6.90	5	46.32	23.74	5
Steady State[b]	0			8			21			36		

Data expressed as μg/mL.
[a]Standard deviation not calculated for 2 or fewer samples >LOQ.
[b]Steady state values calculated as the mean of 336-438 hour samples.

TABLE 9

PHASE II (REPEATED EXPOSURE)
PLASMA CONCENTRATION DATA IN FEMALE RATS

	Chamber Concentration (mg/m^3)											
	0			1			10			25		
Hours	Mean	S.D.	# >LOQ	Mean	S.D.	# >LOQ	Mean	S.D.	# >LOQ	Mean	S.D.	# >LOQ
0	1.71	a	1	<LOQ	a	0	<LOQ	a	0	<LOQ	a	0
6	<LOQ	a	0	0.86	0.41	4	2.12	1.07	5	2.97	1.00	5
48	<LOQ	a	0	<LOQ	a	0	0.33	a	1	0.62	0.27	4
54	<LOQ	a	0	0.72	0.20	5	2.46	0.68	5	3.53	1.75	5
96	0.74	a	1	<LOQ	a	0	0.27	a	2	0.45	0.20	4
102	<LOQ	a	0	0.84	0.11	5	1.51	0.99	3	4.18	2.38	5
168	<LOQ	a	0	1.18	a	1	<LOQ	a	0	<LOQ	a	0
174	<LOQ	a	0	0.77	0.28	5	2.14	1.18	4	3.30	2.28	5
216	<LOQ	a	0	<LOQ	a	0	<LOQ	a	0	0.38	a	2
222	<LOQ	a	0	0.73	0.22	5	2.03	0.24	4	5.71	1.34	5
264	<LOQ	a	0	<LOQ	a	0	<LOQ	a	0	0.38	0.21	3
270	<LOQ	a	0	0.60	0.17	5	2.41	0.85	4	3.95	2.78	5
336	<LOQ	a	0	<LOQ	a	0	<LOQ	a	0	<LOQ	a	0
342	<LOQ	a	0	0.75	0.15	5	1.01	a	2	3.45	1.37	5
384	<LOQ	a	0	<LOQ	a	0	<LOQ	a	0	0.37	0.13	3
390	<LOQ	a	0	0.66	0.14	5	1.73	0.61	4	4.15	4.32	5
432	<LOQ	a	0	<LOQ	a	0	<LOQ	a	0	0.41	a	2
438	<LOQ	a	0	0.81	0.17	5	2.02	1.29	4	6.47	3.94	5
Steady State[b]	0			1			2			4		

Data expressed as μg/mL.
[a]Standard deviation not calculated for 2 or fewer samples >LOQ.
[b]Steady state values calculated as the mean of all post-exposure samples.

FIGURES

FIGURE 1:

SCHEMATIC OF EXPOSURE SYSTEM

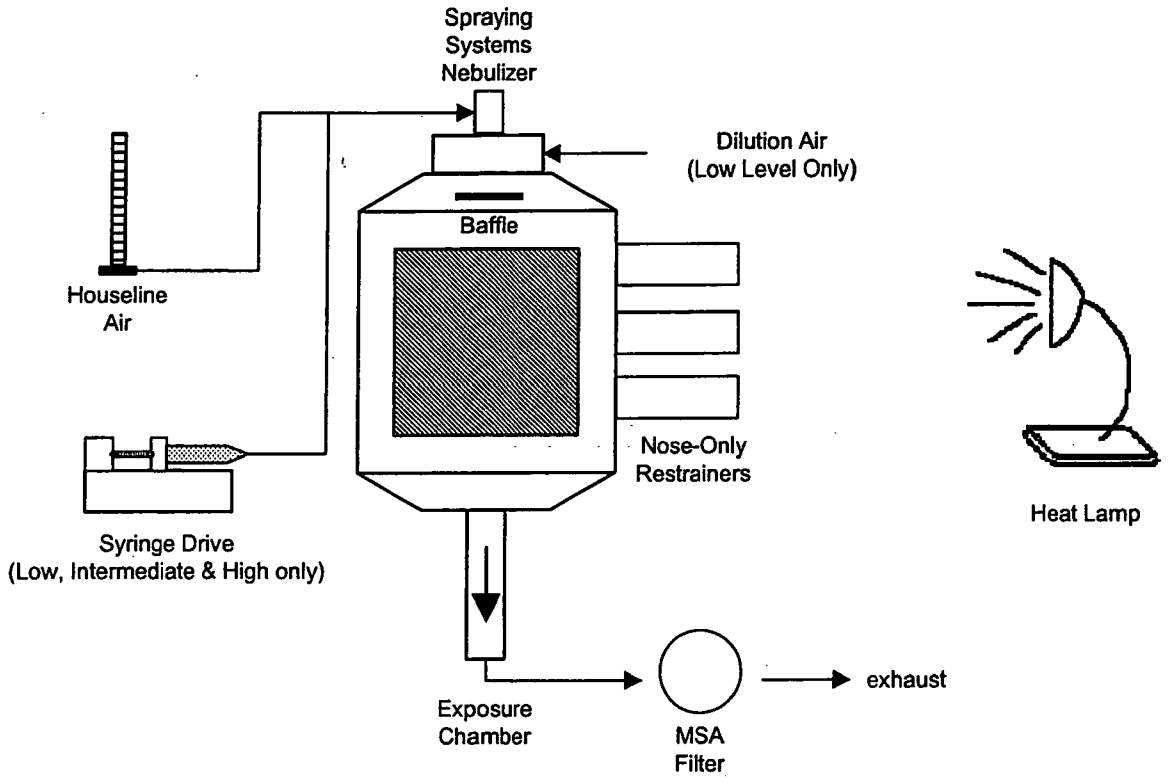


FIGURE 2:

PHASE II (SINGLE EXPOSURE)
MEAN DAILY CHAMBER CONCENTRATIONS

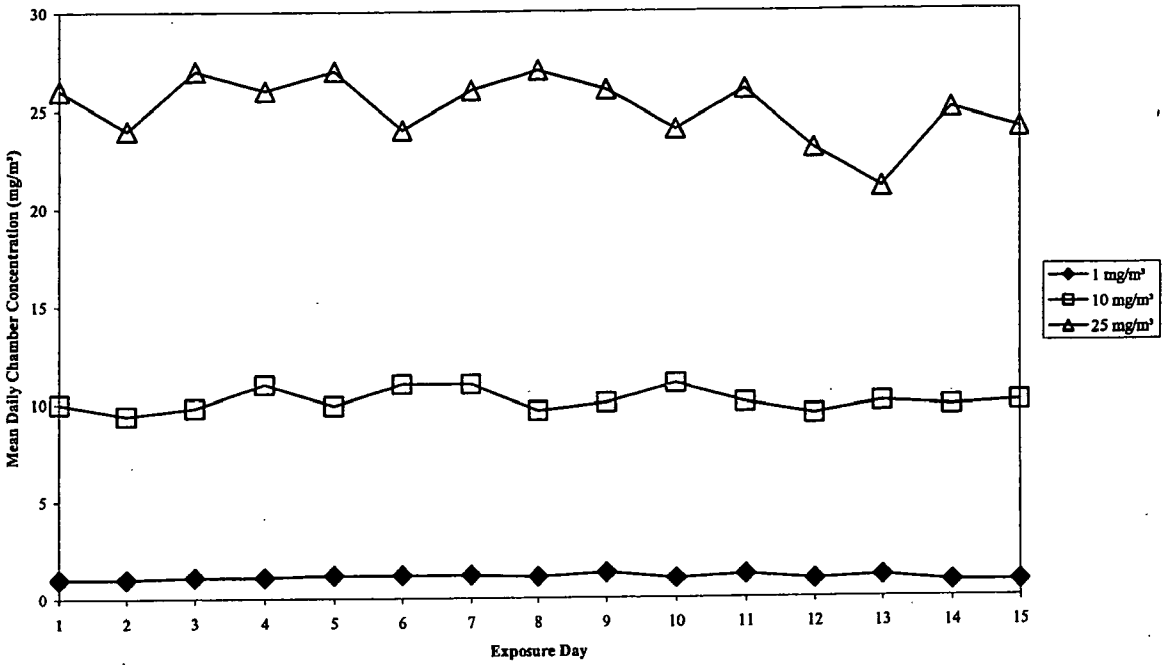


FIGURE 3:

PHASE I (SINGLE EXPOSURE)
PLASMA CONCENTRATION ON A LINEAR SCALE

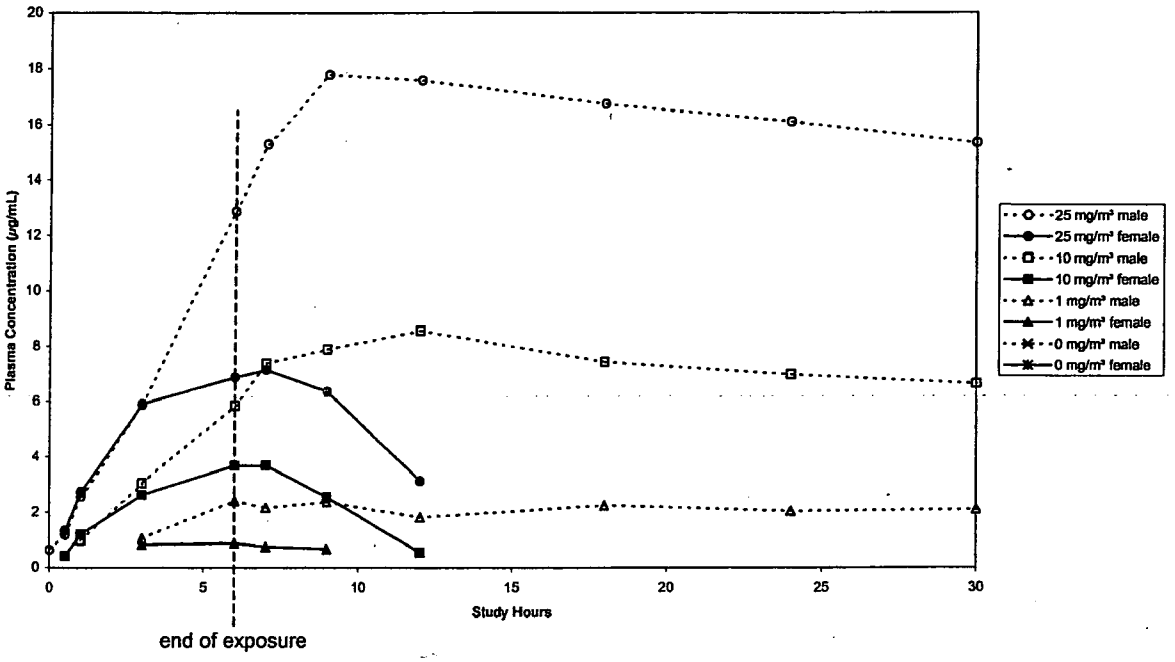


FIGURE 4:

PHASE I (SINGLE EXPOSURE)
PLASMA CONCENTRATION ON A LOGARITHMIC SCALE

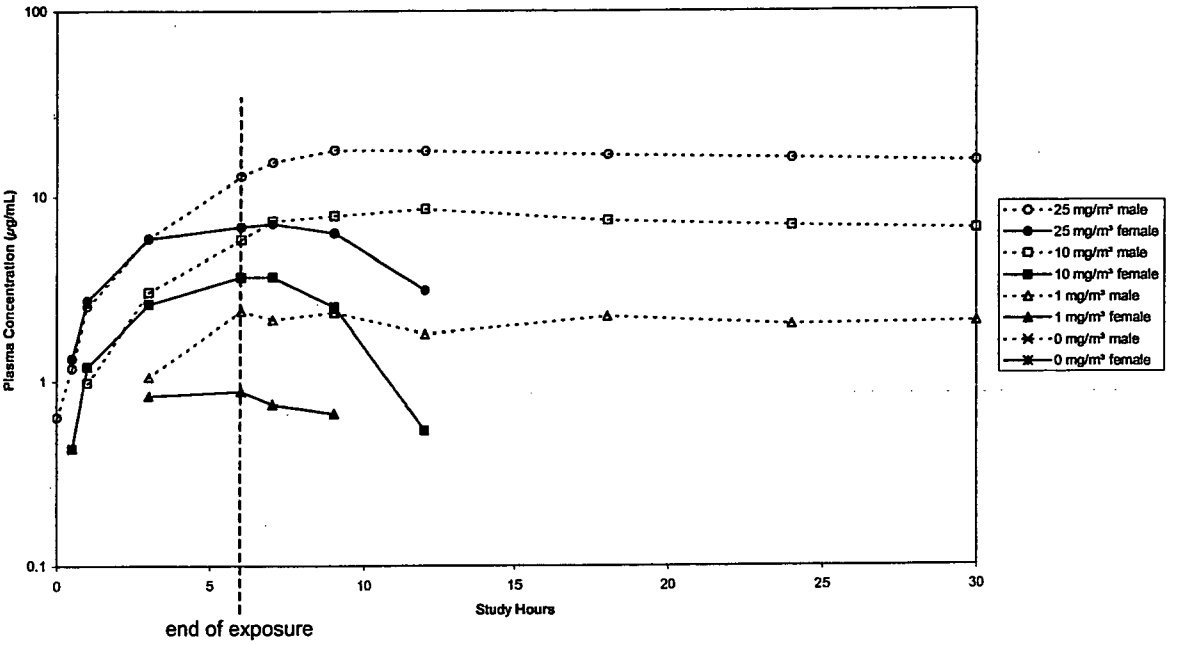


FIGURE 5:

PHASE I (SINGLE EXPOSURE)
PLASMA CONCENTRATION IN MALE RATS WITH STANDARD DEVIATION BARS

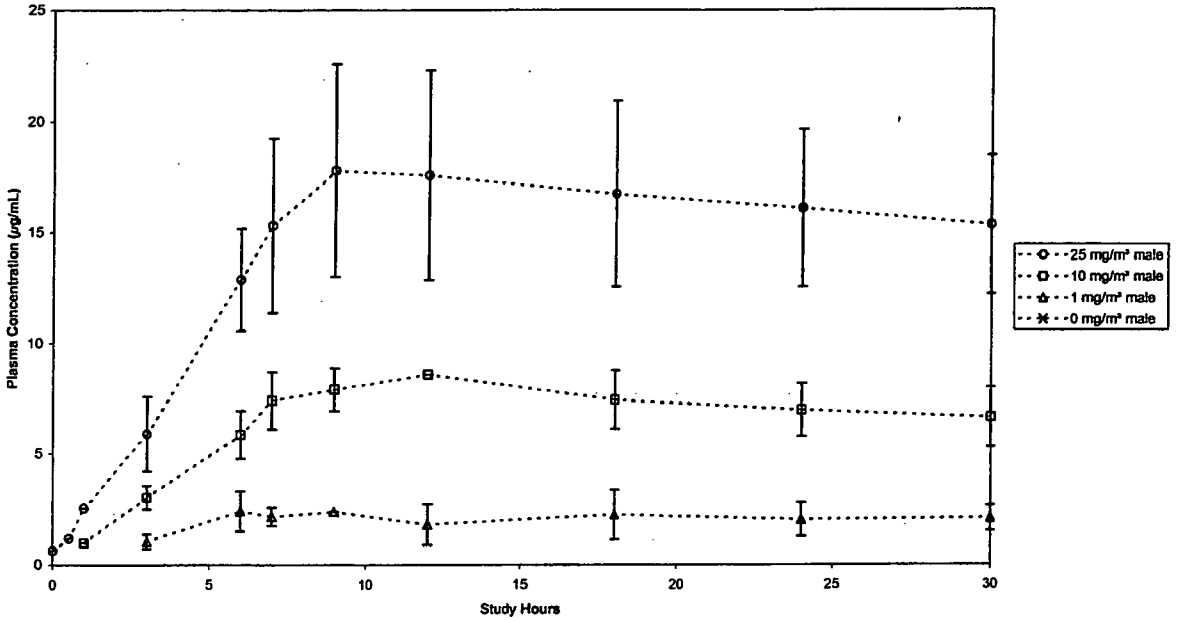


FIGURE 6:

PHASE I (SINGLE EXPOSURE)
PLASMA CONCENTRATION IN FEMALE RATS WITH STANDARD DEVIATION BARS

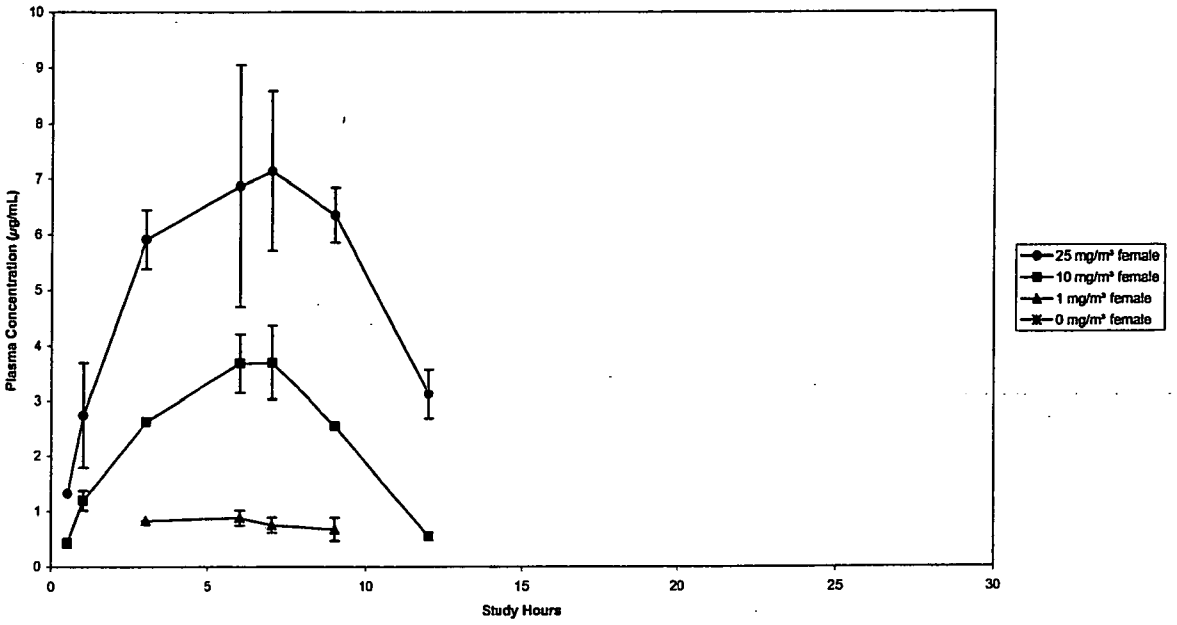


FIGURE 7:

PHASE II (REPEATED EXPOSURE)
PLASMA CONCENTRATION IN MALE RATS

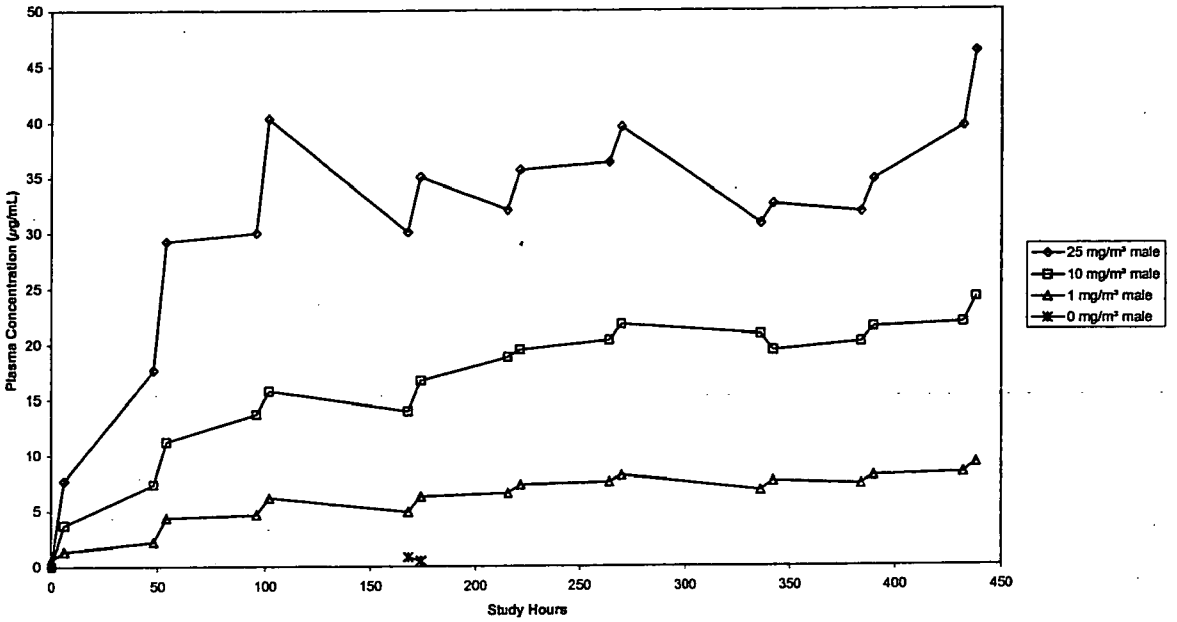


FIGURE 8:

PHASE II (REPEATED EXPOSURE)
PLASMA CONCENTRATION IN MALE RATS WITH STANDARD DEVIATION BARS

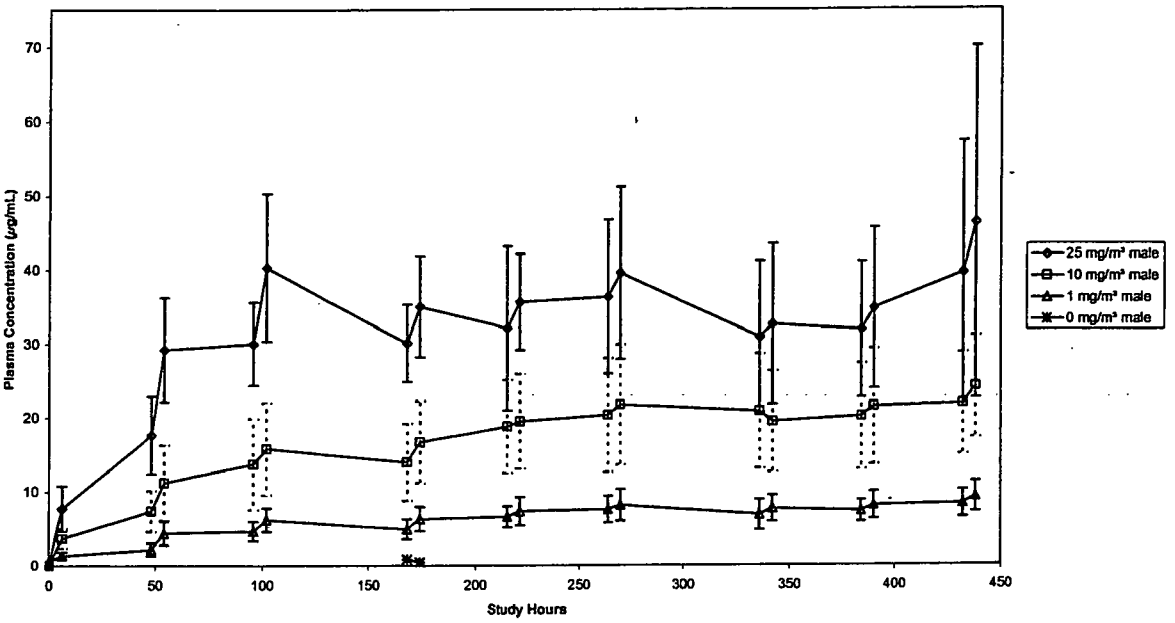


FIGURE 9:

PHASE II (REPEATED EXPOSURE)
PLASMA CONCENTRATION IN FEMALE RATS

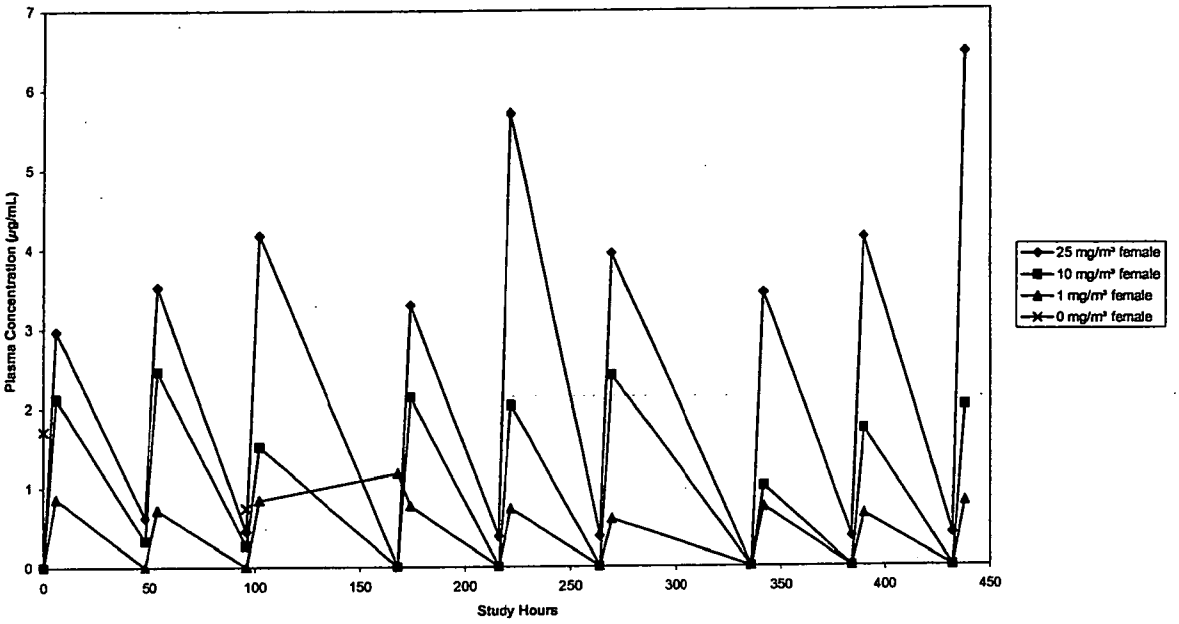
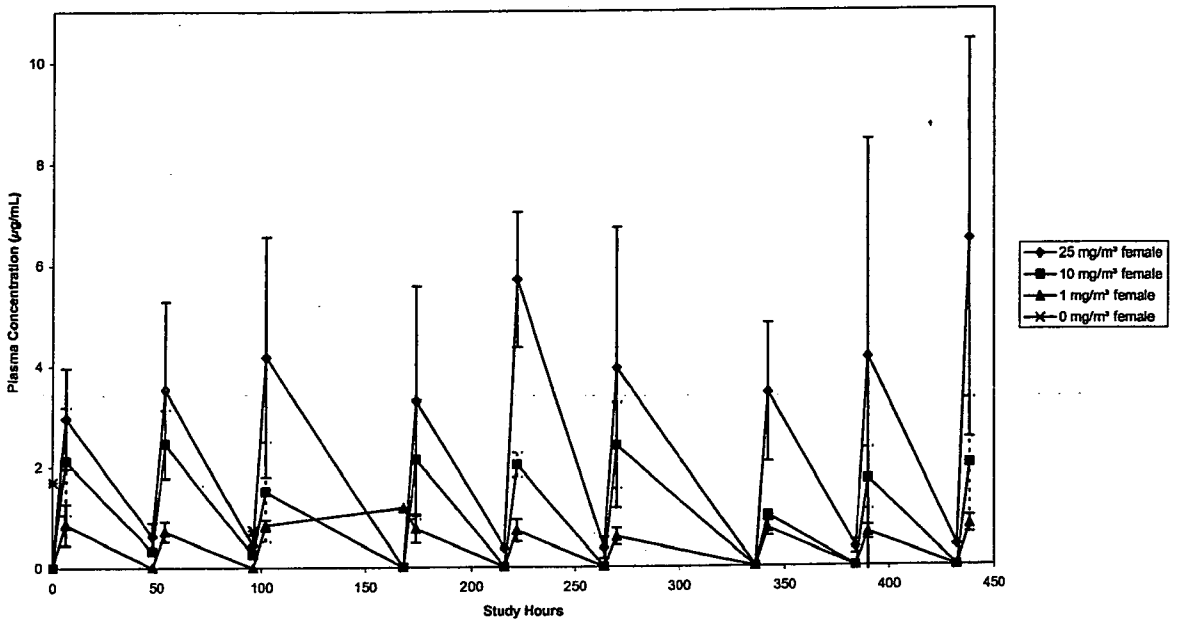


FIGURE 10:

PHASE II (REPEATED EXPOSURE)
PLASMA CONCENTRATION IN FEMALE RATS WITH STANDARD DEVIATION BARS



APPENDICES

APPENDICES

EXPLANATORY NOTES

ABBREVIATIONS:

LOQ	limit of quantitation
n	number of samples
NS	no sample
S.D.	standard deviation

NOTES:

Appendices A-B: Values are reported to 2 significant figures.
Calculations were performed prior to rounding values.

APPENDIX A

Certificate of Analysis

SIGMA-ALDRICH

3050 Spruce Street
Saint Louis, Missouri 63105 USA
Telephone (800) 521-8956 • (314) 771-5765
Fax (800) 325-5052 • (314) 77-5757
Visit Us At www.sigma-aldrich.com

Certificate of Analysis

PRODUCT NUMBER [redacted] LOT NUMBER [redacted]

PRODUCT NAME: [redacted]

FORMULA [redacted] FORMULA WEIGHT: 414.06

APPEARANCE	WHITE POWDER
INFRARED SPECTRUM	CONFORMS TO STRUCTURE AND STANDARD
TITRATION	[redacted]
GAS LIQUID CHROMATOGRAPHY	[redacted]
TITRATION	[redacted]
QUALITY CONTROL ACCEPTANCE DATE	APRIL, 2003

ALDRICH CHEMICAL COMPANY
RONNIE MARTIN
APRIL 24, 2003

We are Committed to the success of our Customers, Employees and Shareholders through leadership in Life Science, High Technology and Service.

APPENDIX B

Phase II (Repeated Exposure)
Daily Chamber Concentrations

Phase II Daily Chamber Concentrations (mg/m³)

	1 mg/m³				10 mg/m³				25 mg/m³			
Exposure	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n
1	1.0	0.44	0.39 - 1.4	6	10	1.5	9.1 - 13	6	26	2.0	23 - 29	6
2	1.0	0.31	0.51 - 1.4	6	9.4	1.2	7.2 - 10	6	24	5.0	20 - 33	6
3	1.1	0.46	0.25 - 1.5	6	9.8	0.73	8.6 - 10	6	27	3.3	21 - 31	6
4	1.1	0.29	0.67 - 1.5	6	11	1.1	8.6 - 12	6	26	18	8.9 - 68	9
5	1.2	0.35	0.60 - 1.6	6	9.9	0.58	9.1 - 11	6	27	6.1	21 - 36	6
6	1.2	0.32	0.77 - 1.7	6	11	0.98	9.2 - 12	6	24	2.9	21 - 27	6
7	1.2	0.092	1.1 - 1.3	6	11	1.7	8.3 - 13	6	26	2.5	23 - 30	6
8	1.1	0.48	0.36 - 1.7	6	9.6	0.72	8.6 - 11	6	27	1.7	24 - 29	6
9	1.3	0.22	1.1 - 1.6	6	10	0.77	8.9 - 11	6	26	7.1	22 - 42	7
10	1.0	0.24	0.65 - 1.3	6	11	0.41	10 - 11	6	24	5.4	15 - 32	6
11	1.2	0.55	0.83 - 2.2	5	10	2.2	8.7 - 14	6	26	2.4	23 - 29	6
12	0.95	0.46	0.56 - 1.7	6	9.4	0.79	8.0 - 10	6	23	5.6	18 - 34	6
13	1.1	0.60	0.38 - 2.1	6	10	0.92	9.1 - 11	6	21	3.1	18 - 26	7
14	0.81	0.34	0.25 - 1.2	6	9.8	1.3	8.4 - 12	6	25	2.5	21 - 28	6
15	0.82	0.50	0.33 - 1.6	6	10	2.07	9.0 - 15	6	24	3.2	18 - 27	6

APPENDIX C

Phase II (Repeated Exposure)
Daily Chamber Environmental Conditions

Phase II Daily Chamber Environmental Conditions - Temperature (°C)

	0 mg/m³				1 mg/m³				10 mg/m³				25 mg/m³			
Exposure	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n
1	25	0.65	23 - 26	24	24	0.49	23 - 25	24	25	0.56	23 - 25	24	24	0.38	23 - 24	24
2	25	0.52	24 - 26	24	25	0.51	23 - 26	24	25	0.91	23 - 25	24	24	0.67	22 - 25	24
3	25	0.63	23 - 26	24	24	0.46	23 - 25	24	25	1.0	22 - 26	24	24	0.52	22 - 24	24
4	25	0.34	24 - 25	24	24	0.45	23 - 25	24	25	0.87	23 - 26	24	23	0.45	22 - 24	24
5	25	0.96	22 - 26	24	24	0.48	23 - 24	24	25	0.77	23 - 26	24	23	0.36	22 - 24	24
6	25	0.79	22 - 26	24	24	0.45	22 - 24	24	25	0.88	22 - 26	24	23	0.31	22 - 24	24
7	25	0.69	23 - 26	24	25	0.48	23 - 25	24	25	0.72	23 - 26	24	23	0.37	22 - 23	24
8	25	0.69	23 - 26	24	25	0.45	23 - 25	24	25	0.66	22 - 25	24	24	0.36	23 - 24	24
9	25	0.78	24 - 26	24	25	0.55	23 - 25	24	25	0.70	23 - 26	24	23	0.53	22 - 24	24
10	25	0.48	24 - 26	24	24	0.51	23 - 25	24	25	1.0	22 - 26	24	24	0.20	23 - 24	24
11	25	0.70	23 - 26	24	25	0.76	23 - 26	24	24	0.66	23 - 25	24	24	0.54	22 - 24	24
12	26	0.56	24 - 27	24	26	0.71	24 - 27	24	26	0.88	23 - 27	24	24	0.52	22 - 24	24
13	25	0.69	23 - 26	24	26	0.40	25 - 26	24	25	0.76	22 - 26	24	24	0.39	23 - 25	24
14	25	0.35	24 - 25	24	26	0.53	24 - 26	24	25	0.73	23 - 26	24	24	0.43	22 - 24	24
15	26	0.70	23 - 27	24	25	0.39	24 - 26	24	25	0.74	23 - 26	24	24	0.32	23 - 24	24

Phase II Daily Chamber Environmental Conditions - Relative Humidity (%)

	0 mg/m³				1 mg/m³				10 mg/m³				25 mg/m³			
Exposure	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n
1	36	1.2	34 - 40	24	28	0.82	26 - 30	24	38	1.6	36 - 43	24	32	1.6	30 - 37	24
2	38	1.1	36 - 42	24	27	0.99	25 - 29	24	38	1.6	35 - 43	24	33	2.4	30 - 39	24
3	37	0.89	36 - 40	24	28	1.6	26 - 31	24	36	1.4	33 - 41	24	31	2.6	29 - 40	24
4	40	0.89	38 - 42	24	31	1.2	29 - 33	24	39	1.4	37 - 44	24	30	3.1	26 - 37	24
5	38	1.4	36 - 42	24	32	0.94	30 - 34	24	37	1.6	36 - 44	24	30	1.6	27 - 34	24
6	38	1.3	37 - 43	24	35	1.4	31 - 38	24	39	1.2	37 - 42	24	33	2.2	29 - 40	24
7	40	1.4	38 - 43	24	34	1.1	32 - 36	24	41	1.4	39 - 45	24	35	2.0	32 - 41	24
8	40	1.0	38 - 41	24	32	1.5	30 - 37	24	40	1.1	38 - 42	24	35	0.95	33 - 37	24
9	39	1.3	37 - 42	24	30	0.93	29 - 32	24	39	0.93	38 - 42	24	33	1.9	32 - 40	24
10	40	0.91	38 - 42	24	35	1.2	32 - 37	24	40	1.2	38 - 42	24	37	0.87	35 - 39	24
11	42	0.59	41 - 43	24	47	4.2	40 - 53	24	40	2.0	38 - 48	24	36	1.5	34 - 41	24
12	40	1.0	38 - 44	24	37	3.3	32 - 42	24	41	1.7	39 - 46	24	32	2.2	29 - 39	24
13	38	0.82	36 - 39	24	43	3.3	40 - 51	24	39	1.1	37 - 42	24	29	0.68	28 - 30	24
14	40	1.1	38 - 43	24	42	4.5	24 - 45	24	33	4.1	18 - 36	24	32	1.6	30 - 38	24
15	37	1.3	35 - 41	24	44	1.5	40 - 47	24	36	2.4	34 - 47	24	30	1.7	28 - 34	24

Phase II Daily Chamber Environmental Conditions - Airflow (L/min)

	0 mg/m³				1 mg/m³				10 mg/m³				25 mg/m³			
Exposure	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n
1	28	0.15	27 - 28	24	70	0.042	70	24	28	0.050	28	24	28	0.42	28 - 30	24
2	28	0.016	28	24	70	0.044	70	24	28	0.028	28	24	27	0.39	26 - 28	24
3	28	0.11	27 - 28	24	70	0.052	70	24	28	0.067	28	24	29	0.44	28 - 29	24
4	28	0.023	28	24	70	0.027	70	24	28	0.021	28	24	28	0.016	28	24
5	28	0.14	27 - 28	24	70	0.052	70	24	28	0.063	28	24	28	0.022	28	24
6	28	0.15	27 - 28	24	70	0.052	70	24	28	0.063	28	24	28	0.021	28	24
7	28	0.022	28	24	70	0.036	70	24	28	0.023	28	24	28	0.027	28	24
8	28	0.11	27 - 28	24	70	0.049	70	24	28	0.064	28	24	28	0.020	28	24
9	28	0.024	28	24	70	0.058	70	24	28	0.024	28	24	28	0.027	28	24
10	28	0.11	27 - 28	24	70	0.052	70	24	28	0.055	28	24	28	0.023	28	24
11	28	0.11	27 - 28	24	70	0.067	70	24	28	0.053	28	24	28	0.032	28	24
12	28	0.022	28	24	70	0.047	70	24	28	0.043	28	24	28	0.029	28	24
13	28	0.15	27 - 28	24	70	0.036	70	24	28	0.072	28	24	28	0.020	28	24
14	28	0.027	28	24	70	0.036	70	24	28	0.032	28	24	28	0.023	28	24
15	28	0.10	28	24	70	0.035	70	24	28	0.059	28	24	28	0.036	28	24

APPENDIX D

Phase I (Single Exposure)
Plasma Concentration Data

		Hours During Exposure				Hours Post-Exposure					
	Predose	0.5	1	3	6	1	3	6	12	18	24
Males, 0 mg/m^3											
101	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
102	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
103	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Females, 0 mg/m^3											
201	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
202	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	NS	NS	NS	NS
203	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Males, 1 mg/m^3											
301	<LOQ	<LOQ	<LOQ	0.92	2.07	2.03	1.87	1.69	1.61	1.94	1.94
302	<LOQ	<LOQ	<LOQ	1.42	3.45	2.63	2.87	2.79	3.55	2.84	2.72
303	<LOQ	<LOQ	<LOQ	0.82	1.72	1.81	NS	0.96	1.58	1.31	1.60
Females, 1 mg/m^3											
401	<LOQ	<LOQ	<LOQ	1.01	0.94	0.83	0.72	<LOQ	<LOQ	<LOQ	<LOQ
402	<LOQ	<LOQ	<LOQ	0.64	0.99	0.83	0.84	<LOQ	<LOQ	<LOQ	<LOQ
403	<LOQ	<LOQ	<LOQ	<LOQ	0.72	0.59	0.44	<LOQ	<LOQ	<LOQ	<LOQ
Males, 10 mg/m^3											
501	<LOQ	<LOQ	1.18	3.50	6.70	8.29	8.86	9.91	8.26	7.97	7.82
502	<LOQ	<LOQ	<LOQ	2.46	4.62	5.91	6.92	NS	5.91	5.65	5.20
503	<LOQ	<LOQ	0.77	3.15	6.22	7.98	7.88	7.23	8.12	7.30	6.88
Females, 10 mg/m^3											
601	<LOQ	0.46	1.16	NS	4.01	3.81	<LOQ	0.52	<LOQ	<LOQ	<LOQ
602	<LOQ	0.40	1.40	2.69	3.97	4.28	2.54	0.48	<LOQ	<LOQ	<LOQ
2001	<LOQ	<LOQ	1.05	2.55	3.07	2.97	<LOQ	0.61	<LOQ	<LOQ	<LOQ
Males, 25 mg/m^3											
701	0.64	1.51	2.86	7.36	12.84	15.26	17.68	17.24	16.25	15.75	15.42
702	<LOQ	<LOQ	NS	4.04	10.58	11.39	13.04	13.04	12.84	12.72	12.17
703	<LOQ	0.84	2.24	6.27	15.20	19.29	22.61	22.47	21.13	19.82	18.44
Females, 25 mg/m^3											
801	<LOQ	1.14	3.73	6.48	8.23	7.87	6.63	3.33	<LOQ	<LOQ	<LOQ
802	<LOQ	1.52	2.65	5.83	8.03	8.07	6.65	2.61	<LOQ	<LOQ	<LOQ
803	<LOQ	<LOQ	1.83	5.42	4.36	5.49	5.78	3.42	<LOQ	<LOQ	<LOQ

Data expressed as μg/mL.

APPENDIX E

Phase II (Repeated Exposure) Plasma Concentration Data

	Hours																	
	0	6	48	54	96	102	168	174	216	222	264	270	336	342	384	390	432	438
Males, 0 mg/m³																		
101	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
102	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0.83	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
103	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0.49	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
104	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
105	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Males, 1 mg/m³																		
301	0.58	1.87	3.25	5.52	5.16	7.67	6.18	7.27	7.59	8.53	7.58	10.06	8.73	9.60	8.74	10.07	10.00	10.77
302	<LOQ	1.39	2.24	3.49	4.44	4.94	4.10	6.73	5.59	5.95	6.84	6.71	5.40	7.36	6.99	6.95	7.99	8.45
303	<LOQ	1.05	2.15	4.06	4.27	5.83	4.89	5.84	6.82	8.00	8.64	9.41	8.42	8.58	8.11	9.69	8.88	10.57
304	<LOQ	0.64	1.15	2.37	2.87	4.48	3.08	3.69	4.76	4.77	5.02	5.10	3.97	4.84	4.94	5.69	5.31	5.95
305	<LOQ	1.79	NS	6.46	6.50	7.96	6.24	7.93	8.14	9.34	9.80	9.45	7.57	7.89	7.95	8.13	9.46	10.52
Males, 10 mg/m³																		
501	<LOQ	2.15	6.01	8.79	12.23	15.61	13.19	16.76	17.39	17.80	15.39	15.36	29.79	14.91	15.37	16.04	16.12	18.43
502	<LOQ	3.59	7.90	11.57	15.14	19.88	17.50	18.16	22.58	24.20	25.06	27.48	21.94	23.72	23.79	25.62	24.80	26.50
503	<LOQ	4.23	8.86	14.92	20.43	13.36	17.52	21.31	9.12	26.01	29.87	31.46	24.84	27.73	28.88	31.35	31.57	33.14
504	<LOQ	2.87	3.44	3.97	4.01	6.98	5.16	7.27	25.81	9.62	10.29	11.82	9.06	10.54	10.67	11.47	14.54	16.05
505	<LOQ	5.60	10.72	16.86	16.86	23.24	16.47	20.00	19.16	19.86	21.03	22.51	18.69	20.25	22.10	22.92	22.32	26.53
Males, 25 mg/m³																		
701	<LOQ	10.44	23.60	NS	37.73	51.07	38.17	45.28	47.69	45.84	40.66	49.34	42.11	45.23	43.12	47.39	54.23	68.00
702	<LOQ	5.67	12.02	27.54	31.80	49.36	30.75	37.27	37.55	38.23	52.07	54.76	40.94	43.18	40.21	45.59	62.72	75.42
703	<LOQ	10.27	22.95	39.31	30.59	38.84	29.79	35.00	18.13	30.19	24.81	29.07	19.19	21.09	22.16	23.64	22.58	22.41
704	<LOQ	3.42	14.93	27.30	27.80	35.11	28.05	29.57	28.51	30.47	31.87	31.72	23.50	25.47	26.83	28.68	27.06	31.26
705	<LOQ	8.87	14.91	22.87	22.28	27.25	23.72	28.19	28.57	33.61	32.38	33.00	28.65	28.24	27.15	28.65	31.30	34.49

Data expressed as μg/mL.

	Hours																	
	0	6	48	54	96	102	168	174	216	222	264	270	336	342	384	390	432	438
Females, 0 mg/m³																		
201	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
202	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
203	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
204	<LOQ	<LOQ	<LOQ	<LOQ	0.74	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
205	1.71	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Females, 1 mg/m³																		
401	<LOQ	0.48	<LOQ	0.77	<LOQ	0.93	<LOQ	0.95	<LOQ	0.93	<LOQ	0.77	<LOQ	0.64	<LOQ	0.59	<LOQ	0.73
402	<LOQ	0.60	<LOQ	0.81	<LOQ	0.75	1.18	0.90	<LOQ	0.51	<LOQ	0.69	<LOQ	0.59	<LOQ	0.79	<LOQ	1.03
403	<LOQ	0.96	<LOQ	0.46	<LOQ	0.89	<LOQ	0.28	<LOQ	0.74	<LOQ	0.37	<LOQ	0.82	<LOQ	0.74	<LOQ	0.90
404	<LOQ	<LOQ	<LOQ	0.59	<LOQ	0.93	<LOQ	0.94	<LOQ	0.98	<LOQ	0.69	<LOQ	0.74	<LOQ	0.75	<LOQ	0.79
405	<LOQ	1.39	<LOQ	0.98	<LOQ	0.69	<LOQ	0.80	<LOQ	0.51	<LOQ	0.46	<LOQ	0.97	<LOQ	0.45	<LOQ	0.59
Females, 10 mg/m³																		
601	<LOQ	1.99	<LOQ	1.97	0.22	2.60	<LOQ	2.84	<LOQ	2.28	<LOQ	2.24	<LOQ	0.90	<LOQ	2.01	<LOQ	2.73
602	<LOQ	1.43	<LOQ	3.11	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
603	<LOQ	2.90	0.33	2.87	<LOQ	1.25	<LOQ	1.49	<LOQ	2.19	<LOQ	3.66	<LOQ	<LOQ	<LOQ	2.38	<LOQ	3.42
604	<LOQ	0.81	<LOQ	1.53	0.32	<LOQ	<LOQ	0.83	<LOQ	1.82	<LOQ	1.91	<LOQ	<LOQ	<LOQ	1.59	<LOQ	1.29
605	<LOQ	3.46	<LOQ	2.82	<LOQ	0.67	<LOQ	3.38	<LOQ	1.83	<LOQ	1.83	<LOQ	1.11	<LOQ	0.95	<LOQ	0.62
Females, 25 mg/m³																		
801	<LOQ	2.24	<LOQ	2.98	0.74	7.07	<LOQ	7.00	0.51	7.72	0.62	8.37	<LOQ	5.42	0.52	11.33	0.58	13.03
802	<LOQ	1.59	0.32	1.44	<LOQ	1.74	<LOQ	1.67	<LOQ	6.33	0.26	2.10	<LOQ	4.31	<LOQ	2.67	<LOQ	6.42
803	<LOQ	3.84	0.74	3.72	0.29	2.54	<LOQ	4.02	<LOQ	4.34	<LOQ	2.11	<LOQ	2.26	<LOQ	0.94	<LOQ	5.34
804	<LOQ	3.58	0.93	3.24	0.38	3.19	<LOQ	1.98	<LOQ	4.98	<LOQ	2.14	<LOQ	2.34	0.27	0.96	<LOQ	2.52
805	<LOQ	3.61	0.48	6.27	0.38	6.36	<LOQ	1.81	0.24	5.16	0.25	5.04	<LOQ	2.92	0.33	4.87	0.24	5.03

Data expressed as μg/mL.