

TRADE SECRET*Study Title*

Perfluorooctanoic Acid: Toxicokinetics in the Rat

Laboratory Project ID: DuPont-7473

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TEST GUIDELINES: U.S. EPA Health Effects Test Guidelines
OPPTS 870.7485, Metabolism and Pharmacokinetics
(1998)

OECD Guidelines for the Testing of Chemicals
Section 4: Toxicokinetics, No. 417 (1984)

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STUDY COMPLETED ON: April 2, 2003

SPONSOR: Association of Plastics Manufacturers of Europe (APME)
Fluoropolymers Committee
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PERFORMING LABORATORY: E.I. du Pont de Nemours and Company
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WORK REQUEST NUMBER: 13697

SERVICE CODE NUMBER: 1389

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 No. 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: _____

Raymond A. Kemper
Raymond A. Kemper, Ph.D.
Research Toxicologist

02-Apr-2003
Date

QUALITY ASSURANCE STATEMENT

Haskell Sample Number(s):

25028, 22705-48, 22705-49, 22705-50, 22705-51, 22705-52, 22705-53, 22705-54,
22705-55

Dates of Inspections:

Protocol: August 31, 2001

Conduct: September 28, 2001; October 1, 5, 2001; November 5, 2001;
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2002; August 2, 2002

Records, Reports: February 4-6, 10-14, 19, 20, 24, 25, 2003

Dates Findings Reported to:

Study Director: February 25, 2003

Management: April 1, 2003

Reported by:

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Staff Quality Assurance Auditor

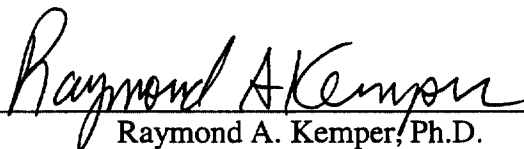
02-APR-2003

Date

CERTIFICATION

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

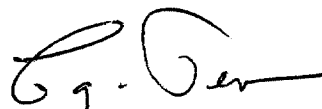
Issued by Study
Director:


Raymond A. Kemper, Ph.D.

Research Toxicologist

02-Apr-2003
Date

Approved by:

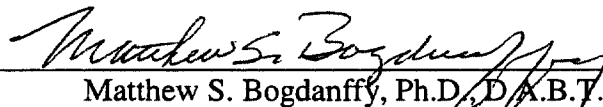


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Date

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Research Manager and Director

02-Apr-2003
Date

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STUDY INFORMATION

9th Collective Nomenclature: Pentadecafluorooctanoic acid

Synonyms/Codes:

- Pentadecafluoro-n-octanoic acid
- Perfluorocaprylic acid
- Perfluoroheptanecarboxylic acid
- Perfluorooctanoic acid
- PFOA
- 08316DO (Aldrich Chemical Co., Inc) (Lot No.)

Haskell Number: 25028

CAS Registry Number: 335-67-1

Purity: 100.4% (titration with NaOH)
99.9% (gas liquid chromatography)

Known Impurities: None identified

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
Box 3, B-1160 Brussels
Belgium

Study Initiated/Completed: August 3, 2001 / (see report cover page)

STUDY PERSONNEL

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Analytical Associate: Julia N. Wang, Ph.D.

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William Singleton, D.V.M., A.C.L.A.M.

SUMMARY

Perfluorooctanoic acid (PFOA) is a fluorinated fatty acid analogue used as a surfactant in industrial applications. The purpose of the current study was to characterize the absorption, distribution, elimination and pharmacokinetic behavior of PFOA in male and female rats.

Male and female CD rats were administered ^{14}C -PFOA (carbonyl label) by oral gavage at dose levels of 1, 5, and 25 mg/kg. Urine and feces were collected for 28 days in males and 7 days in females, and tissues were analyzed for residual radioactivity at sacrifice. Urine was the primary route of elimination for ^{14}C in both sexes. In males, urinary excretion accounted for approximately 43-62% of the administered dose. In females, the extent of urinary elimination was greater, accounting for approximately 76-84% of the administered dose. In males, fecal excretion of ^{14}C accounted for approximately 6-14% of the administered dose, while in females, approximately 2-6% of the dose was recovered in feces. Pilot experiments demonstrated that ^{14}C was not eliminated as either $^{14}\text{CO}_2$ or volatile organic compounds in ^{14}C -PFOA-treated rats. At sacrifice, approximately 13-24% of the dose remained in the tissues of male rats, while females retained less than 0.25% of the dose at any dose level. The highest concentrations of residual ^{14}C were found in the blood, liver and kidney. Overall mean recovery of radioactivity ranged from 83.8 to 91.6% in males and 81.3 to 93.3% in females. Pretreatment of rats with 1 mg/kg PFOA for 14 days had little or no effect on excretion or terminal tissue distribution of a challenge dose of 1 mg/kg ^{14}C .

The pharmacokinetic behavior of PFOA was investigated following oral administration of PFOA at dose rates of 0.1, 1, 5, and 25 mg/kg PFOA, and after intravenous administration of 1 mg/kg PFOA. Plasma was collected for 22 days after dosing in males and 5 days in females. Concentration vs. time data were analyzed by non-compartmental pharmacokinetic methods. Comparison of AUC for the oral and intravenous 1 mg/kg doses indicated that oral bioavailability of PFOA was approximately 100%. Plasma elimination curves were linear with respect to time in male rats at all dose levels, while elimination kinetics were biphasic in females at the 5 mg/kg and 25 mg/kg dose levels. In males, plasma elimination half-lives were independent of dose level and ranged from approximately 138 hours to 202 hours. In females, terminal elimination half-lives ranged from approximately 2.8 hours at the lowest dose to approximately 16 hours at the high dose. To further characterize plasma elimination kinetics, particularly in male rats, animals were given oral PFOA at a rate of 0.1 mg/kg, and plasma samples were collected until PFOA concentrations fell below quantitation limits (24 hours and 2016 hours in females and males, respectively). Estimated plasma elimination half-lives in this experiment were approximately 277 hours in males and 3.4 hours in females.

The tissue distribution of ^{14}C at the time corresponding to maximum plasma concentrations (T_{max}) and at the time corresponding to a return to 50% of maximum plasma concentration following attainment of maximum concentrations ($T_{\text{max}/2}$) was investigated following administration of 1, 5, and 25 mg/kg ^{14}C -PFOA. Tissues were collected at 10.5 and 171 hours after dosing in male rats and at 1.25 and 4 hours after dosing in female rats. For both sexes and at both sampling times, the major tissues for distribution of ^{14}C were liver, kidney and blood. In

males, the fraction of the dose found in liver increased from $T_{\max}$ to $T_{\max/2}$, but remained constant or decreased in other tissues. In females, the fraction of the dose present in all tissues remained constant or decreased between $T_{\max}$ and $T_{\max/2}$. Liver: blood concentration ratios for ^{14}C at $T_{\max}$ in males were greater than 1, and increased between $T_{\max}$ and $T_{\max/2}$. Kidney: blood concentration ratios at $T_{\max}$ in females were approximately 2 at all dose levels and remained relatively constant between $T_{\max}$ and $T_{\max/2}$.

Overall, the results of this study demonstrated significant sex differences in excretion, pharmacokinetics, and tissue distribution of PFOA in rats.

INTRODUCTION

Perfluorooctanoic acid (PFOA) is a synthetic perfluorinated fatty acid analogue, used as a surfactant in industrial applications. In rat metabolism studies with PFOA, elimination following oral administration was found to be much more rapid in females compared to males.⁽¹⁻²⁾ The dramatic gender differences elimination rate observed for PFOA may be unique to rats. For example, in rabbits and mice treated with ¹⁴C-ammonium perfluorooctanoate, no sex differences in elimination rates of ¹⁴C were observed, while in hamsters, elimination was more rapid in males compared to females⁽³⁾. In dogs, a relatively minor (2-fold) sex difference in urinary elimination of PFOA was reported⁽⁴⁾. A comprehensive comparison of PFOA elimination rates and tissue distribution between male and female rats will provide a foundation for conducting mechanistic studies to elucidate the basis for the observed sex differences in PFOA elimination kinetics.

The objectives of this study were determine the absorption, distribution, excretion and metabolism of PFOA in male and female rats following oral dosing.

MATERIALS AND METHODS

A. Regulatory Test Guidelines

This study was designed to meet the testing requirements of OECD Guidelines for Testing of Chemicals, Toxicokinetics, 417 (April 1984), and U.S. EPA Health Effects Test Guidelines, OPPTS 870.7485, Metabolism and Pharmacokinetics.

B. Test Substance

Industrial grade PFOA contains various proportions of branched chain isomers in addition to the linear form. For consistency, the current study was conducted using only the linear isomer.

Unlabeled PFOA was obtained from Aldrich Chemicals (Milwaukee, Wisconsin).

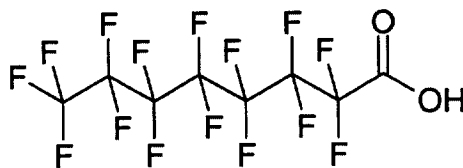
CAS Registry Number: 335-67-1

Molecular Weight: 414.1

Molecular Formula: C₈F₁₅O₂H

Haskell Number H-25028

Structure:



Purity:

100.4% Titration
99.9% Gas Liquid Chromatography

C. Radiolabeled Test Substances

[Carbonyl- ^{14}C]Ammonium Perfluorooctanoate (^{14}C -PFOA) was synthesized and characterized by Amersham Pharmacia Biotech (Piscataway, NJ). ^{14}C -PFOA, and supplied as an aqueous solution with a radiochemical concentration of approximately 506 $\mu\text{Ci/g}$ and chemical concentration of approximately 4.0 mg/g.

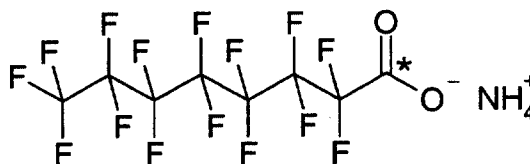
Specific Activity: 125.4 $\mu\text{Ci/mg}$

Molecular Weight 432.9

Haskell Numbers 22705-48, 22705-49, 22705-50, 22705-51, 22705-52, 22705-53, 22705-54, 22705-55

Radiochemical Purity: >95%

[C^{14}] Ammonium
Perfluorooctanoate



[*] denotes the position of the radiolabel

D. Test Species

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 pharmacokinetic and toxicity testing of PFOA and other fluorinated test materials.⁽¹⁻²⁾

At the time of dosing, male rats weighed 193.3-280.0 g and female rats weighed 155.1-231.5 g. At the time of dosing, rats were sexually mature and the weight variation did not exceed $\pm 20\%$ of the mean weight by dose group. Each animal was assigned a unique identification number

that was used throughout the study. The last 3 digits of the animal identification number were marked on the tail of each animal in indelible ink.

E. Animal Husbandry

Upon arrival at Haskell Laboratory, rats were removed from shipping cartons and housed in appropriate cages, according to Standard Operating Procedures LA003-P-006 unless specified in the study records. Animals were maintained under quarantine for at least six days unless approved otherwise by the site veterinarian, had three recorded weight gains and no abnormalities detected. After the quarantine period, rats were selected for study.

Animal rooms were targeted at a temperature of $23 \pm 1^\circ\text{C}$ and a relative humidity of 40-60%. Animal rooms are artificially illuminated (fluorescent light) on an approximate 12-hour light/dark cycle.

Throughout the dosing period with test compound, the rats were housed individually in appropriate cages according to the SOP.

All animals were provided tap water and fed PMI[®] Nutrition International, LLC Certified Rodent LabDiet[®] 5002 *ad libitum*. Animals were fasted overnight prior to dosing and were allowed access to food approximately 24 hours after dosing. The actual duration of fasting is documented in the study records.

F. Animal Health Monitoring

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.

G. Dose Preparation, Analysis and Rates

The primary route of test substance administration was oral gavage. This route was chosen at the request of the sponsor. For one experiment, PFOA was administered by intravenous injection to allow estimation of oral bioavailability. PFOA and/or ^{14}C -PFOA was mixed with water as required to achieve the target dose concentrations. The pH of the dose solutions was adjusted to approximately 6.0 with ammonium hydroxide to ensure complete dissolution of the test material. ^{14}C -PFOA was diluted with PFOA to the appropriate specific activity for each dose level. For excretion material balance and tissue distribution experiments, dose solutions were targeted to deliver approximately 20-30 μCi ^{14}C per animal. For oral dosing, a dose volume of approximately 4 mL/kg body weight was used. For intravenous dosing, a dose volume of approximately 2 mL/kg was used. Dose solutions were prepared as follows:

Absorption/Plasma Pharmacokinetic Experiments		
Dose level (mg/kg)	Dose Volume (mL/kg)	Chemical Concentration (mg/mL)
0.1	4	0.025
1.0	4	0.250
1.0 (iv)	2	0.500
5.0	4	1.250
25.0	4	6.250

Material Balance/Tissue Distribution Experiments					
Dose Level (mg/kg)	Dose Volume (mL/kg)	Radiochemical Dose ($\mu\text{Ci/kg}$)	Specific Activity ($\mu\text{Ci/mg}$)	Chemical Concentration (mg/mL)	Radiochemical Concentration ($\mu\text{Ci/mL}$)
1.0	4	120	120.0	0.25	30
5.0	4	120	24.0	1.25	30
25.0	4	120	4.8	6.25	30

Dose levels were determined based on previous toxicokinetic and toxicity studies with PFOA.⁽¹⁾ Preparation and data management for radioactive dose solutions was carried out using the DEBRA5 laboratory information management system (Lablogic LTD., Sheffield, UK). Dose preparations for the single dose experiments were prepared prior to the day of use and stored at approximately 4°C until used. Dose solution for the repeat dose experiments was prepared in bulk, stored at approximately 4°C, and used as needed.

HPLC-MS was used to analyze dose solutions for chemical concentration. Dose solutions containing ^{14}C -PFOA were assayed in triplicate for radioactive concentration by liquid scintillation counting (LSC), and radiochemical purity was determined by HPLC using radiometric detection.

H. Sacrifice

Rats were sacrificed by CO_2 asphyxiation and exsanguinated by cardiac puncture.

I. Pilot Studies

The following pilot studies were conducted to determine the plasma kinetics of PFOA and to characterize PFOA elimination rates following oral administration. The data from these experiments were used in setting the whole blood serial collection time-points and determining the principal routes and rates of elimination.

1. Plasma kinetics following Oral Dosing with Non-Radiolabeled PFOA

Two male and two female rats with surgically implanted jugular vein cannulas were obtained from the vendor and allowed to recover for at least one day after surgery before dosing. Rats were administered PFOA at a dose level of 1 mg/kg by the oral route and housed in metabolism cages.

Following dosing, serial blood samples were removed from the jugular vein cannula and placed into tubes containing EDTA. In cases where patency of the cannulas became compromised, whole blood was collected from the tail vein. Samples were collected predose, and at 0.5, 2, 4, 8, 12, 16, and 24 hours post dose, and at 24-hour intervals thereafter up to 168 hours.

Whole blood samples were maintained on wet ice. Plasma was separated from red cells by centrifugation. Plasma was stored frozen at $< -10^\circ\text{C}$ until processed for analysis.

2. Excretion and Material Balance following Oral Dosing with Radiolabeled PFOA

Two male and two female rats were administered the test material formulated with ^{14}C -PFOA at the 25 mg/kg dose level by oral gavage. Following dosing, rats were housed individually in glass metabolism units suitable for the collection of urine, feces, expired air and volatile organics.

Urine and feces were collected on dry ice at approximately 4, 8, 12, and 24 hours post-dose, and every 24 hours thereafter until sacrifice.

Expired air was passed through two scrubbing towers, one containing 2 N NaOH to trap expired $^{14}\text{CO}_2$ and the second containing ethylene glycol to trap volatile organic compounds. Scrubbing towers were replaced every 24 hours post-dose until sacrifice.

Animals were sacrificed after 168 hours post-dosing.

At the conclusion of the radiolabeled dose experiments, cages were rinsed with detergent and water (50:50 v/v), followed by water, and finally with acetone.

The following tissues were collected at sacrifice:

Blood	Fat	Liver
Kidney	Muscle	Heart
Lung	Testes	Ovaries
Uterus	Bone	Brain
Spleen	Adrenals	Skin sample
G.I. tract and contents	Prostate	Thymus

After collection, tissue samples were stored at $<-10^{\circ}\text{C}$ until processing and analysis. The remaining carcass was homogenized and assayed so that total material balance could be determined.

J. Main Study

1. Excretion/Material Balance Experiments (Experiments 1-4)

The objectives of the excretion/material balance experiments were to:

- determine the rates and routes for elimination of PFOA.
- determine the material balance for total radioactivity administered.
- determine if repeated (daily) low oral dose exposure alters the excretion kinetics of PFOA.

Dose Routes and Frequency

The excretion/material balance experiments were comprised of four dose groups.

Experiment	Dose Group
1	1 mg/kg, single oral dose
2	5 mg/kg, single oral dose
3	25 mg/kg, single oral dose
4	1 mg/kg, 14-day repeated dose (unlabeled)
	1 mg/kg ^{14}C -PFOA challenge dose (day 15)

Each dose group (single dose) was composed of 4 male rats and 4 female rats. Each dose group received dose formulated with ^{14}C -PFOA.

For the daily (repeat) low-dose oral gavage experiment, four male and four female rats were administered non-radiolabeled test compound at the low dose rate once per day for

14 consecutive days. Rats were administered a challenge dose of the test material formulated with ^{14}C -PFOA on day 15.

Experimental Design

Following administration of the radiolabeled dose, urine and feces of male rats were collected on dry ice at approximately 4, 8, 12, and 24 hours following dosing, and at 24-hour intervals thereafter through 336 hours (14 days). Excreta were collected at 48-hour intervals from 336 hours until sacrifice at 672 hours (28 days). For female rats, excreta was collected on dry ice at 4, 8, 12 and 24 hours following dosing and at 24-hour intervals thereafter until sacrifice at 168 hours (7 days). As specified in OECD and OPPTS guidelines, since less than 1% of the administered dose was eliminated as expired CO_2 and volatile organic compounds in the pilot study, CO_2 and volatile organics were not collected in the main study experiments. Moreover, since less than 20% of the administered dose was recovered in the feces in the pilot experiment, bile was not collected in the main study experiments.

The following tissues were collected at sacrifice:

Blood	Muscle	Heart
Kidney	Testes	Ovaries
Lung	Bone	Brain
Uterus	Adrenals	Skin sample
Spleen	Prostate	Thymus
G.I. tract and contents	Liver	Thyroid
Fat		

After collection, tissue samples were stored at $<-10^\circ\text{C}$ until processing and analysis. The remaining carcass was homogenized and assayed so that total material balance could be determined.

At the conclusion of the radiolabeled dose experiments, cages were rinsed with detergent and water (50:50 v/v), followed by water, and finally with acetone. Cage wash was stored at room temperature.

2. Pharmacokinetic Experiments (Experiments 5-9)

The principal objective of the pharmacokinetic experiments was to determine the extent of absorption of PFOA following oral dosing and to characterize rates of elimination of PFOA from plasma using plasma pharmacokinetic methods.

Dose Routes and Frequency

The pharmacokinetic experiments were comprised of five dose groups.

Experiment	Dose Group
5	0.1 mg/kg, oral
6	1 mg/kg, oral
	1 mg/kg, intravenous
7	5 mg/kg, oral
8	25 mg/kg, oral
9	0.1 mg/kg, oral, extended time course

Each dose group was composed of 4 male and 4 female rats. Each dose group received non-radiolabeled test compound. The intravenous dose provided a reference for estimating bioavailability of PFOA by the oral exposure routes.

Experimental Design

Rats with surgically implanted jugular vein cannulas were obtained from the vendor and allowed to recover for at least additional one day after arrival before dosing. Following dosing, serial whole blood samples were drawn from the cannula and placed into Microtainer® tubes containing EDTA. In some cases, whole blood was collected from the tail vein. For male rats, blood samples were collected pre-dose, and at 0.25, 0.5, 1, 2, 4, 8, 12, 16, and 24 hours post-dose, at 24-hour intervals through 192 hours, then at 48-hour intervals from 192 hours through 528 hours. For female rats, blood samples were collected pre-dose, and at 0.25, 0.5, 1, 2, 4, 8, 12, 16, 24, 36, 48, 72, and 96 hours post-dose. In some cases, whole blood from donor animals of the same age and sex was infused into test animals via the jugular vein cannula following sample removal to prevent volume depletion, as per Haskell Animal Welfare Committee guidelines. Rats were sacrificed after the final sampling time. Whole blood was placed on wet ice, and plasma was separated by centrifugation and frozen at <-10°C until analyzed.

To further characterize the potential persistence of PFOA in rat plasma, a satellite group of four rats per sex was administered PFOA at a rate of approximately 0.1 mg/kg by oral gavage, and plasma samples were obtained over a more extended sampling period than used in previous toxicokinetics experiments. In female rats, plasma samples were obtained through 312 hours post dose, while in males, samples were obtained through 2016 hours (84 days). Samples were analyzed by LC-MS using multiple reaction monitoring (MRM, Section N).

3. Distribution Experiments (Experiments 10-12)

The principal objective of the distribution experiments was to determine the concentration and clearance of PFOA in selected tissues and organs at the time corresponding to maximum plasma concentrations (T_{max}) and at the time corresponding to a return to 50% of maximum plasma concentration following attainment of maximum concentrations ($T_{max/2}$) for PFOA. Tissues were selected based upon previous toxicology data and the results of the pilot excretion/material

balance experiment. Sampling times were determined based on the results of the plasma pharmacokinetic experiments.

Dose Routes and Frequency

The distribution experiments were comprised of the following six dose groups.

Experiment	Dose Level	Sacrifice Time
10	1 mg/kg	T _{max}
	1 mg/kg	T _{max/2}
11	5 mg/kg	T _{max}
	5 mg/kg	T _{max/2}
12	25 mg/kg	T _{max}
	25 mg/kg	T _{max/2}

Each dose group was composed of 4 male and 4 female rats. Each dose group received dose formulated with ¹⁴C-PFOA.

Experimental Design

Male and female rats were administered ¹⁴C-PFOA by oral gavage at the nominal dose rates indicated (Section G). Male rats were sacrificed approximately 10.5 hours (T_{max}) and 171 hours (T_{max/2}) after dosing. Females rats were sacrificed approximately 1.25 hours (T_{max}) and 4 hours (T_{max/2}) after dosing

The following tissues were collected at sacrifice:

Blood	Fat	Liver
Kidney	Muscle	Heart
Lung	Testes	Ovaries
Uterus	Bone	Brain
Spleen	Adrenals	Skin sample
G.I. tract and contents	Prostate	Thymus
Thyroid	Carcass	

After collection, tissue samples were stored at <-10°C until processing and analysis. Total radioactivity in tissues will be determined by oxidation/LSC.

K. Sample Processing and Quantitation of Radioactive Residues

Solid samples were oxidized using a Packard Model 307 Oxidizer (Perkin-Elmer Life Sciences, Boston, MA). LSC was carried out using a Packard Tricarb liquid scintillation analyzer (Perkin-Elmer Life Sciences, Boston, MA).

1. Whole Blood

Whole blood samples were maintained on wet ice and stored at approximately 4°C until analysis. Aliquots of whole blood were applied to combustion cones and allowed to dry at room temperature. Dried samples were combusted and analyzed by LSC. Analyses were carried out in triplicate.

2. Urine

Urine samples from each analysis were thawed at room temperature and mixed prior to analysis by vortexing briefly. Aliquots of each urine sample were analyzed in triplicate by LSC.

3. Feces

Feces from each collection interval were thawed at room temperature prior to processing. Thawed feces were mixed with an appropriate volume of distilled water and homogenized using a hand held homogenizer. Aliquots of the homogenate were applied to combustion cones and allowed to dry at room temperature. Dried homogenates were combusted, and analyzed by LSC.

4. Tissues

Tissues were thawed at room temperature prior to processing. For smaller tissues, the entire tissue was divided into two or three aliquots and applied to combustion cones. Tissue aliquots were combusted and analyzed by LSC.

5. CO₂

Aliquots of CO₂ trap solution were analyzed in triplicate by LSC.

6. Volatile Organics

Aliquots of volatile organics trap solution were analyzed in triplicate by LSC.

7. Cage Rinse

Aliquots of cage rinse were analyzed in triplicate by LSC.

8. Residual Feed

Residual feed was separated from feces, stored at <-10 °C and thawed at room temperature prior to processing. Samples of residual feed were mixed with an appropriate volume of distilled water and homogenized using a hand held homogenizer. Aliquots of the homogenate were applied to combustion cones and allowed to dry at room temperature. Dried homogenates were combusted and analyzed by LSC.

9. Carcass

Frozen carcasses were chopped into smaller pieces, mixed with an appropriate volume of distilled water, and homogenized using an electric blender. Aliquots of the homogenate were applied to combustion cones and allowed to dry at room temperature. Dried homogenates were combusted, and analyzed by LSC.

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

Plasma samples were processed by solid phase extraction (SPE) using 96-well Isolute array protein precipitation columns (Jones Chromatography, Lakewood, CO). In the pilot experiment, perfluoroheptanoic acid (Aldrich Chemicals, Milwaukee, WI) was used as an internal standard for quantitation of PFOA. In all main study experiments, perfluorononanoic acid (Aldrich Chemicals, Milwaukee, WI) was used as the internal standard. Plasma samples were thawed, and a 75 μ L aliquot was applied to the SPE array. Internal standard was added (10 μ L of a 3 μ g/mL solution in water), followed by 0.215 mL of ACN. The SPE array was eluted slowly under vacuum into a 96-well receiver plate, and the extracts were analyzed by LC/MS. All samples were extracted and analyzed in duplicate.

M. Material Balance

Total recovery for rats receiving ^{14} C-PFOA was expected to be $100 \pm 10\%$ of the amount administered.

N. Analytical Methods

1. Instrumentation

System 1: Hewlett-Packard Series 1100 Liquid Chromatograph, equipped with quaternary pump, column heater, and autosampler

Detector: Packard 500TR Flow Scintillation Analyzer, with CaF_2 solid flow cell

System 2: Waters 2790 Liquid Chromatograph, equipped with quaternary pump, column heater, and autosampler

Detector: Quattro Ultima Mass Spectrometer

Mode: SIR and Full Scan

Analyzer Conditions:

Source:	Negative Electrospray
LM 1 Resolution:	10.0
HM 1 Resolution:	10.0
Ion energy 1:	1.0
Entrance:	50
Collision:	0

Exit: 50
LM 2 resolution: 12.0
HM 2 resolution: 12.0
Ion energy 2: 2.0
Multiplier (V): 650
SIR dwell time(s): 0.25

Mode: MRM**Analyzer Conditions:**

Source: Negative Electrospray
LM 1 Resolution: 14.0
HM 1 Resolution: 14.0
Ion energy 1: 0.5 – 1.0
Entrance: -2 – 50
Collision: 10 – 13
Exit: 5 – 50
LM 2 resolution: 15.0
HM 2 resolution: 15.0
Ion energy 2: 1.0
Multiplier (V): 650

MS Method 1: Mode: SIR, 2 masses
Time: 0-10.0 min
Ch1: 413.00
Ch2: 463.00

MS Method 2: Mode: SIR, 1 mass
Time: 0-10.0 min
Ch1: 413.00

MS Method 3: Mode: SIR, 2 masses
Time: 0-7.0 min
Ch1: 413.00
Ch2: 363.00

MS Method 4: Mode: Full Scan
Time: 0-10.0 min
Mass Range: 300-700 Da
Scan Time: 0.8 s

MS Method 5: Mode: MRM, 2 mass pairs
Time: 0-12.0 min
Ch1: (413.00 – 368.60)
Ch2: (462.90 – 418.90)
Dwell Time: 0.25 s

System 3: Hewlett-Packard Series 1100 Liquid Chromatograph, equipped with quaternary pump, column heater, and autosampler

Detector: Quattro LC Mass Spectrometer

Mode: Full Scan

Analyzer Conditions:

	Source:	Negative Electrospray
	LM 1 Resolution:	15.0
	HM 1 Resolution:	15.0
	Ion energy 1:	0
	Entrance:	50
	Exit:	50
	LM 2 resolution:	12.0
	HM 2 resolution:	12.0
	Ion energy 2:	1.0
	Multiplier (V):	650
MS Method 6:	Mode:	Full Scan
	Time:	0-10.0 min
	Mass Range:	170-500 Da
	Scan Time:	1.0 s
System 4:	Hewlett-Packard Series 1100 Liquid Chromatograph, equipped with quaternary pump, column heater, and autosampler	
Detector:	Finnigan LCQ Mass Spectrometer	
	Mode: MRM	
	Analyzer Conditions:	
MS Method 7:	Source:	Negative Electrospray
	Scan Events	1
	Scan 1:	412.8 – (368-370) [^{12}C -PFOA only] 414.8 – (368-370) [^{14}C -PFOA only] (413.5-413.8) – (368-370) [$^{12}\text{C}/^{14}\text{C}$ Mixture]
MS Method 8:	Source:	Negative Electrospray
	Scan Events	2
	Scan 1:	412.8 – (368-370)
	Scan 2:	463.0 – (418-420)
	Mode: SIR	
MS Method 9:	Source:	Negative Electrospray
	Scan Events	1
	Scan 1:	SIR (411.9 – 415.9)

2. Chromatographic Methods

Method 1: Dose radiochemical purity analysis (all ^{14}C experiments)

Instrument: System 1
 Column: Waters Symmetry C18, 2.1 x 30 mm, 3.5 μm
 Column temperature: Ambient
 Mobile phases: A: 50 mM Ammonium Acetate
 B: Acetonitrile

Timetable:

Time (min)	%B
0.00	20.0

2.50	20.0
7.00	90.0
10.0	90.0

Flow rate: 0.25 mL/min

Stop time: 15.00 min

Injection volume: 10 μ L

Method 2: Dose concentration and plasma concentration analysis (pilot pharmacokinetics experiment)

Instrument System 2
MS: MS Method 3
Column: Waters x Terra MS C18, 2.1 x 30 mm, 3.5 μ m
Column temperature: Ambient
Mobile phases: A: 50 mM Ammonium Acetate
B: Acetonitrile

Timetable:

Time (min)	%B
0.00	20.0
5.00	100.0
5.10	20.0
7.00	20.0

Flow rate: 0.30 mL/min

Stop time: 7.00 min

Injection volume: 5 μ L

Method 3: Dose concentration analysis (pilot material balance experiment)

Instrument System 3
MS: MS Method 6
Column: Phenomenex Synergi Max-RP, 2.0 x 20 mm, 2 μ m
Column temperature: Ambient
Mobile phases: A: 50 mM Ammonium Acetate
B: Acetonitrile

Timetable:

Time (min)	%B
0.00	20.0
0.50	20.0
2.00	100.0
3.00	100.0
3.10	20.0
10.0	20.0

Flow rate: 0.30 mL/min

Stop time: 10.00 min

Injection volume: 5 μ L

Method 4: Dose concentration analysis (main study experiments 1, 4, 6, 9, and 10)

Instrument System 4
MS: MS Method 7
Column: Zorbax SB-C18 Rapid Resolution, 4.6 x 75 mm, 3.5 μ m

Column temperature: Ambient
Mobile phases: A: 50 mM Ammonium Acetate
B: Acetonitrile

Timetable:

Time (min)	%B
0.00	5.0
2.00	5.0
4.00	100.0
4.01	5.00
7.00	5.0

Flow rate: 1.0 mL/min
Stop time: 7.00 min
Injection volume: 5 µL

Method 5: Dose concentration analysis (main study experiment 8)

Instrument System 4
MS: MS Method 7
Column: Zorbax SB-C18 Rapid Resolution, 4.6 x 75 mm, 3.5 µm
Column temperature: Ambient
Mobile phases: A: 50 mM Ammonium Acetate
B: Acetonitrile

Timetable:

Time (min)	%B
0.00	5.0
2.00	5.0
8.00	100.0
8.01	5.00
10.0	5.0

Flow rate: 1.0 mL/min
Stop time: 10.00 min
Injection volume: 5 µL

Method 6: Plasma concentration analysis (main study experiment 5 [females])

Instrument System 4
MS: MS Method 8
Column: Zorbax SB-C18 Rapid Resolution, 4.6 x 75 mm, 3.5 µm
Column temperature: Ambient
Mobile phases: A: 50 mM Ammonium Acetate
B: Acetonitrile

Timetable:

Time (min)	%B
0.00	5.0
2.00	5.0
8.00	90.0
8.01	5.00
10.0	5.0

Flow rate: 1.0 mL/min
Stop time: 10.00 min
Injection volume: 5 µL

Method 7: Dose concentration analysis (main study experiment 12)

Instrument System 4
MS: MS Method 9
Column: Zorbax SB-C18 Rapid Resolution, 4.6 x 75 mm, 3.5 μ m
Column temperature: Ambient
Mobile phases: A: 50 mM Ammonium Acetate
B: Acetonitrile

Timetable:

Time (min)	%B
0.00	5.0
2.00	5.0
8.00	95.0
10.0	95.0

Flow rate: 1.0 mL/min
Stop time: 10.00 min
Injection volume: 5 μ L

Method 8: Dose concentration analysis (main study experiment 5)

Instrument System 4
MS: MS Method 7
Column: Waters x Terra MS C18 2.0 x 30 mm, 2.5 μ m
Column temperature: Ambient
Mobile phases: A: 50 mM Ammonium Acetate
B: Acetonitrile

Timetable:

Time (min)	%B
0.00	25.0
9.00	100.0

Flow rate: 0.3 mL/min
Stop time: 10.00 min
Injection volume: 5 μ L

Method 9: Dose concentration analysis (main study experiment 7) and plasma concentration analysis (main study experiments 5 [males], and 6-8)

Instrument System 2
MS: MS Method 1 (plasma analysis)
MS Method 2 (dose analysis)
Column: Phenomenex Synergi Max-RP, 2.0 x 20 mm, 2 μ m
Column temperature: Ambient
Mobile phases: A: 50 mM Ammonium Acetate
B: Acetonitrile

Timetable:

Time (min)	%B
0.00	10.0
0.50	10.0
10.0	80.0

Flow rate: 1.0 mL/min (0.0-0.5 min)
0.25 mL/min (0.5-10.0 min)
Stop time: 10.00 min
Injection volume: 5 µL

Method 10: Dose concentration analysis (main study experiments 2 and 11)

Instrument System 2
MS: MS Method 4
Column: Phenomenex Synergi Max-RP, 2.0 x 20 mm, 2 µm
Column temperature: Ambient
Mobile phases: A: 50 mM Ammonium Acetate
B: Acetonitrile

Timetable:

Time (min)	%B
0.00	10.0
0.50	10.0
10.0	80.0

Flow rate: 1.0 mL/min (0.0-0.5 min)
0.25 mL/min (0.5-10.0 min)
Stop time: 10.00 min
Injection volume: 5 µL

Method 11: Plasma concentration analysis (main study experiment 9)

Instrument System 2
MS: MS Method 5
Column: Phenomenex Synergi Max-RP, 2.0 x 20 mm, 2 µm
Column temperature: Ambient
Mobile phases: A: 50 mM Ammonium Acetate
B: Acetonitrile

Timetable:

Time (min)	%B
0.00	10.0
0.50	10.0
10.0	80.0
10.01	100.0
11.00	100.0
11.01	10

Flow rate: 1.0 mL/min (0.0-0.5 min)
0.25 mL/min (0.5-12.0 min)
Stop time: 12.00 min
Injection volume: 5 µL

Method 12: Dose concentration analysis (main study experiment 3)

Instrument System 4
MS: MS Method 9
Column: Zorbax SB-C18 Rapid Resolution, 4.6 x 75 mm, 3.5 µm
Column temperature: Ambient
Mobile phases: A: 50 mM Ammonium Acetate
B: Acetonitrile

Timetable:

Time (min)	%B
0.00	5.0
2.00	5.0
4.00	100.0
5.00	100.0
5.01	5.0
8.00	5.0

Flow rate: 1.0 mL/min
Stop time: 10.00 min
Injection volume: 5 μ L

O. Clinical Observations and Mortality

Cage-site examinations to detect moribund or dead rats and abnormal behavior and/or appearance among rats was conducted at least once daily throughout the study. Moribund rats were sacrificed.

P. Measurement of Radioactivity

Radioactivity in selected liquid samples was assayed by LSC. Total radioactive residues in solid samples were determined by combustion, trapping liberated $^{14}\text{CO}_2$ followed by LSC.

Samples for LSC were analyzed for 10 minutes, or until 160,000 disintegrations (0.5% 2σ) was accumulated, whichever came first.

Q. Data Analyses

Group data is represented as a mean $\pm$ SD. Non-compartmental pharmacokinetic analysis of plasma PFOA time course data was accomplished using WinNonlin (Pharsight, Mountain View, CA) using models 200 (single oral bolus) and 201 (single IV bolus). Values for $T_{\max}$ and $T_{\max/2}$ across dose levels were analyzed by one-way ANOVA using Microsoft Excel.

RESULTS AND DISCUSSION

A. Pilot Experiments

1. Pharmacokinetics in Male and Female Rats following Oral Gavage with 1 mg/kg PFOA (Appendix B, Tables 1-2, Figure 1).

Analysis of the dose solution indicated an actual concentration of 0.206 mg/mL, compared to a target concentration of 0.25 mg/mL. Thus, the actual dose rates for male and female rats were 0.78 ± 0.05 mg/kg and 0.80 ± 0.01 mg/kg, respectively.

In male rats, mean plasma concentrations reached a peak of approximately 26 μ g/mL after approximately 7 hours ($T_{\max}$), and declined slowly thereafter throughout the observation period (168 hours). The plasma half-life for male rats observed in this experiment was approximately 103 hours. The peak plasma concentrations of PFOA observed in female rats (~25 μ g/mL) was similar to that seen in male rats. However, peak plasma concentrations of PFOA were achieved within 0.5 hours of dosing in female rats, and plasma concentrations dropped rapidly thereafter. In female rats, PFOA was no longer detectable by 96 hours post-dose. The apparent half-life of PFOA in female rats in this experiment was approximately 3 hours. Furthermore, plasma clearance of PFOA was approximately 32 times greater in female rats compared to male rats. Based on these data, the observation periods for toxicokinetic experiments in the main study were set at 528 hours and 96 hours in male and female rats, respectively. Furthermore, an additional time point was added at 0.25 hours to more accurately define $T_{\max}$ for PFOA in female rats.

2. Excretion and Material Balance in Male and Female Rats following Oral Gavage with 25 mg/kg ^{14}C -PFOA (Appendix C, Tables 1, 3-8, Figure 2)

Upon analysis, the concentration of test substance in the dose solution was determined to be approximately 6.37 mg/g, compared with a target value of 6.25 mg/g. Based on the volume of dose solution administered, male and female rats received PFOA doses of approximately 18.1 and 18.3 mg/kg, respectively. The radiochemical dose rate was approximately 77 μ Ci/kg for both males and females.

For both sexes, urinary excretion was the primary route for elimination of ^{14}C -PFOA, with males and females eliminating approximately 30 and 92% of the administered dose by this route, respectively. Urinary excretion of ^{14}C -PFOA in females was rapid, and virtually complete within 24 hours. In contrast, urinary elimination of radioactivity in males was gradual and essentially linear throughout the observation period. The other significant route of elimination for ^{14}C -PFOA was in the feces. Males excreted approximately 8.5% of the administered radioactivity by this route, while females only eliminated approximately 0.5% of the dose in the feces. No radioactivity was detected in either the CO_2 trap or the volatile organics trap at any timepoint, confirming that exhalation is not a significant route of elimination for PFOA (Table 8).

At sacrifice (168 hours) approximately 54% of the administered radioactivity remained in the body of male rats, while less than 0.2% of the dose remained in females (Table 5). For both sexes, the highest amounts of residual radioactivity were found in the liver, followed by the kidney. In males, significant amounts of radioactivity were also found in the carcass and whole blood. Mean terminal tissue concentration of PFOA in males ranged from 0.57 $\mu\text{g equiv/g}$ in brain to 57.38 $\mu\text{g equiv/g}$ in liver (Table 6). In female rats, mean terminal liver and kidney concentrations of PFOA were 0.030 $\mu\text{g equiv/g}$ and 0.023 $\mu\text{g equiv/g}$, respectively. Overall, mean recovery of radioactivity in male and female rats was 93.93% and 93.90%, respectively (Table 8).

Since no radioactivity was recovered in either the CO_2 or the volatile organic fraction, these fractions were not collected in the main study experiments. Furthermore, since less than 20% of the administered dose was recovered in the feces of either sex, bile was not collected in main study experiments.

B. Main Study

1. Excretion/Material Balance of ^{14}C -PFOA in Male and Female Rats (Tables 9-33, Figures 3-10, Appendices D-G)

The objective of the excretion/material balance experiments was to characterize the rates and dose dependence of fecal and urinary excretion of ^{14}C -PFOA, and to determine the terminal tissue distribution of residual ^{14}C -PFOA in male and female rats. In addition, experiments were performed to determine potential effects of repeated exposure to PFOA on the excretion and disposition of ^{14}C -PFOA.

Dosing (Table 9, Appendices D-G)

Excretion and material balance of ^{14}C -PFOA following oral administration were investigated in male and female rats at nominal dose rates of 1, 5 and 25 mg/kg body weight. Actual dose rates were calculated based on analysis of the dose solutions and are presented in Table 9. For all experiments, actual dose rates fell within $\pm 15\%$ of target dose rates. Animals received approximately 21-28 μCi of ^{14}C -PFOA in the single dose experiments and approximately 29-40 μCi of ^{14}C -PFOA for the repeated dose experiment (Table 9). The actual dose rate of unlabeled PFOA used for the 14 day repeated dosing was approximately 0.93 mg/kg, based on analysis of the dose solution and the volume administered.

Experiment 1: Excretion and terminal disposition of ^{14}C following administration of 1 mg/kg ^{14}C -PFOA by oral gavage (Tables 10-15, Figures 3-4, Appendix D).

Urinary excretion was the primary route of elimination for ^{14}C in both males and females (Table 10). Within 28 days, male rats excreted approximately 43% of the administered dose in the urine. Urinary excretion of ^{14}C was gradual in males throughout the observation period, and cumulative recovery of ^{14}C in the urine was still increasing at 28 days (Figure 3). Female rats excreted approximately 76% of the administered dose of ^{14}C in the urine over 7 days. In female rats, urinary excretion of ^{14}C was rapid, and nearly complete within 72 hours after dosing.

Significant amounts of ^{14}C were also detected in feces of both male and female rats over their respective observation periods (Table 11). The extent of fecal excretion of ^{14}C was greater in males than in females. In both sexes, the majority of fecal elimination of ^{14}C occurred within the first 72 hours after dosing (Figure 3).

At the termination of the experiment, approximately 24% of the dose remained in the tissues in male rats, compared to only 0.23% in females (Table 12). In both sexes, liver contained the highest concentrations of ^{14}C (Table 13). In males, ^{14}C was detected in all tissues examined, and ranged from 0.008 $\mu\text{g equiv/g}$ in brain to approximately 2 $\mu\text{g equiv/g}$ in liver. In females, ^{14}C was detected in liver, kidney, whole blood, and skin, and mean concentrations of ^{14}C were less than 0.003 $\mu\text{g equiv/g}$ for all tissues. For male rats, the terminal tissue blood concentration ratio for ^{14}C in liver was nearly 6 (Figure 4). Tissue:blood concentration ratios were approximately 1 or less in all other tissues in males. In females, tissue:blood concentration ratios greater than 1 were observed in liver and kidney.

Approximately 3% of the dose was recovered in the cage wash and residual feed fractions (Table 14). Total radioactivity recovered from excreta, tissues, cage wash and residual feed amounted to approximately 84% and 81% of the administered dose in male and female rats, respectively (Table 15).

Experiment 2: Excretion and terminal disposition of ^{14}C following administration of 5 mg/kg ^{14}C -PFOA by oral gavage (Tables 9, 16-21, Figures 5-6, Appendix E).

Over the course of the experiment, urinary excretion accounted for approximately 62% and 78% of the administered dose of PFOA in male and female rats, respectively (Table 16). Cumulative recovery of ^{14}C in the urine increased gradually throughout the experiment in male rats, but was essentially complete in females within the first 72 hours after dosing (Figure 5).

In this experiment, fecal excretion of ^{14}C accounted for approximately 5-6% of the administered dose in both male and female rats (Table 17). Cumulative fecal excretion of radioactivity was more gradual at this dose level compared to the 1 mg/kg dose level, and continued to increase throughout the observation period in both sexes (Figure 5).

At the conclusion of the experiment, approximately 20% and 0.1% of the administered dose was recovered from the tissues of male and female rats, respectively (Table 18). In male rats, highest concentrations of ^{14}C were found in liver, kidney and whole blood (Table 19). In males, tissue concentrations of ^{14}C ranged from 0.027 $\mu\text{g equiv/g}$ in brain to 5.33 $\mu\text{g equiv/g}$ in liver. Tissue:blood concentration ratios were 1 or less in all tissues of male rats except liver, for which a tissue:blood ratio of approximately 5 was observed (Figure 6). In females, only liver, kidney and carcass contained detectable concentrations of ^{14}C . Tissue concentrations of ^{14}C in female rats were less than 0.02 $\mu\text{g equiv/g}$ in all tissues. Since ^{14}C was not detected in whole blood of female rats, tissue:blood concentration ratios could not be calculated.

Approximately 3-4% of the dose was recovered in the cage wash and residual feed for both sexes (Table 20). The overall material balance for ^{14}C -PFOA was 91.6% and 86.8% in male and female rats respectively (Table 21).

Experiment 3: Excretion and terminal disposition of ^{14}C following administration of 25 mg/kg ^{14}C -PFOA by oral gavage (Tables 9, 22-27, Figures 7-8, Appendix F).

As seen for the 1 and 5 mg/kg dose levels, urinary excretion was the primary route of elimination of ^{14}C following oral administration of ^{14}C -PFOA at the 25 mg/kg dose rate (Table 22). Male rats eliminated approximately 53% of the administered dose in the urine. Cumulative urinary elimination in males was more rapid over the first 96 hours following dose administration, but slowed thereafter and appeared to be approaching a plateau after 10-11 days (Figure 7). Female rats eliminated approximately 84% of the dose in the urine, primarily in the first 72 hours after dosing.

Fecal excretion accounted for elimination of approximately 12.5 and 1.9% of the administered dose in male and female rats respectively (Table 23). In females, cumulative fecal excretion of ^{14}C was essentially complete within 48 hours after dose administration (Figure 7). In males, fecal excretion of ^{14}C continued throughout the observation period.

At sacrifice, approximately 13% of the administered dose was recovered from tissues of male rats (Table 24). In females, approximately 0.2% of the dose was recovered from the tissues. As seen for the two lower dose groups, the highest concentrations of ^{14}C were found in the liver, kidney and whole blood of male rats, and in the liver and kidney of female rats (Table 25). For both sexes, the highest tissue concentrations were observed in the liver. In males, a tissue:blood ratio of approximately 3 was observed in the liver, while this ratio was close to or less than 1 in all other tissues (Figure 8). Radioactivity was not detected in the whole blood of female rats in this experiment, so tissue:blood ratios could not be calculated.

In this experiment, the cage wash and residual feed contained approximately 5-7% of the administered radioactivity (Table 26). The overall material balance of ^{14}C in this experiment was 83.9% for male rats and 93.3% for female rats (Table 27).

Experiment 4: Excretion and terminal disposition of ^{14}C following administration of 1 mg/kg ^{14}C -PFOA by oral gavage following 14-day repeated dosing with 1 mg/kg PFOA (Tables 9, 28-33, Figures 9-10, Appendix G).

Overall, approximately 52% and 68% of the administered radioactivity was recovered in the urine of male and female rats, respectively (Table 28). Similar to the single gavage dose experiments, urinary excretion of ^{14}C continued gradually throughout the observation period in male rats, but was nearly complete within 72 hours for female rats (Figure 9). Thus, repeated administration of PFOA for 14 days prior to challenge with ^{14}C -PFOA did not have significant effects on either the rate or extent of urinary ^{14}C excretion in male or female rats.

Fecal excretion accounted for approximately 20% and 12% of the administered dose in male and female rats respectively (Table 29). However, the variability associated with the female feces is very high, possibly due to contamination of the fecal samples with urine. Thus, the high mean value for recovery of ^{14}C in female feces may be artifactual. Apparent rates of fecal ^{14}C excretion in male and female rats were similar in this experiment (Figure 9).

Approximately 13% and 0.31% of the dose was recovered in the tissues of male and female rats respectively (Table 30). For both males and females, the highest concentrations of ^{14}C were detected in liver and kidney (Table 31). In males, the concentration of ^{14}C retained in liver after repeated exposure is lower than after single exposure ($0.94 \mu\text{g equiv/g}$ vs. $1.99 \mu\text{g equiv/g}$). In other tissues in males, ^{14}C concentrations were similar. In female tissues, ^{14}C concentrations were less than $0.01 \mu\text{g equiv/g}$ for both single and repeated exposures (Tables 12 and 31). Tissue:blood concentration ratios were greater than 1 in the liver of male rats (~ 3.5), and in both liver (~ 7.5) and kidney (~ 6) of female rats (Figure 10).

Combined, the cage wash and residual feed accounted for approximately 2.5% and 8.4% of the administered radioactivity in male and female rats respectively (Table 32). In this experiment, the mean overall recovery of radioactivity was approximately 88.0% in males and 89.6% in females (Table 33).

2. Plasma Pharmacokinetics of PFOA in Male and Female Rats (Tables 34-40, Figures 11-16, Appendices H-M)

The objectives of the pharmacokinetic experiments were to characterize the plasma pharmacokinetic parameters of PFOA in male and female rats following single oral and intravenous administration and to estimate oral bioavailability of PFOA.

Dosing (Table 34, Appendices H-M)

Non-compartmental pharmacokinetic parameters were estimated after oral dosing at four nominal dose rates (0.1, 1.0, 5.0 and 25.0 mg/kg) and after intravenous administration at a nominal dose rate of 1 mg/kg. Dose solutions were prepared and analyzed by LC/MS as described under Materials and Methods. Actual dose rates for all pharmacokinetic experiments are summarized in Table 34. Actual dose rates fell within $\pm 15\%$ of target dose rates for all experiments.

Experiment 5: Plasma pharmacokinetics of PFOA in male and female rats following administration of 0.1 mg/kg PFOA by oral gavage (Table 35, Figure 11, Appendix H).

Non-compartmental pharmacokinetic parameters for 0.1 mg/kg PFOA are presented in Table 35. While similar peak plasma concentrations were observed in males and females, the time required to achieve the plasma peak was much longer in males than in female rats. In both sexes, elimination of PFOA was essentially linear with respect to time following achievement of peak plasma levels (Figure 11). However, the elimination half life ($T_{1/2}$) was nearly 63 times longer in male rats compared to females. Similarly, plasma clearance was much more rapid ($\sim 34\text{X}$) in female rats compared to males.

Experiment 6: Plasma pharmacokinetics of PFOA in male and female rats following administration of 1 mg/kg PFOA by oral gavage and by intravenous injection (Tables 36-37, Figures 12-13, Appendix I-J).

Non-compartmental pharmacokinetic parameters for 1 mg/kg PFOA following oral administration are presented in Table 36. Peak plasma concentrations of PFOA in male and

female rats were comparable, though somewhat higher in males. Significant sex differences in other pharmacokinetic parameters are evident, and are similar in magnitude to those observed at the 0.1 mg/kg dose rate. Plasma elimination curves were still essentially linear in both sexes, though some there is some evidence for biphasic behavior in females at later time points (Figure 12). One male rat was found dead on day 9 of this experiment. This event does not appear to be compound-related in that no signs of morbidity were observed in other animals in this experiment or in the other pharmacokinetic experiments.

Pharmacokinetic parameters for intravenous administration of PFOA are summarized in Table 37, and plasma elimination curves are presented in Figure 13. Values for common pharmacokinetic parameters were similar between oral and intravenous routes of administration within each sex, and similar sex differences in plasma elimination rates were observed for both routes. Oral bioavailability can be estimated as the ratio of the AUC for oral administration to the AUC for intravenous administration. Comparison of values for oral and intravenous AUC suggests that oral bioavailability of PFOA was essentially 100% (95.5-114.9%). The origin of the spike in plasma PFOA levels in female rats at 12 hours is unknown, and may be artifactual, since it was not observed in either sex dosed orally or in males dosed intravenously.

Experiment 7: Plasma pharmacokinetics of PFOA in male and female rats following administration of 5 mg/kg PFOA by oral gavage (Table 38, Figure 14, Appendix K).

Non-compartmental pharmacokinetic parameters for 5 mg/kg PFOA are presented in Table 38. At the 5 mg/kg dose level, significant sex differences were observed for all pharmacokinetic parameters calculated. Males exhibited higher peak plasma PFOA concentrations than females, and as with lower dose levels, elimination of PFOA from plasma is much more rapid in females compared to males. In males, the plasma elimination curve is linear at this dose level (Figure 14) and kinetic parameters are similar to those observed at lower doses. However, the plasma elimination curve is biphasic in females, resulting in an increased elimination half-life compared to lower doses.

Experiment 8: Plasma pharmacokinetics of PFOA in male and female rats following administration of 25 mg/kg PFOA by oral gavage (Table 39, Figure 15, Appendix L).

Non-compartmental pharmacokinetic parameters for 25 mg/kg PFOA are presented in Table 39. With the exception of the peak plasma concentration, the marked sex differences in pharmacokinetic parameters observed at lower doses are also seen at the highest dose level. While plasma elimination was linear with respect to time in male rats at 25 mg/kg, plasma elimination of PFOA in female rats was clearly biphasic (Figure 15), with a consequent increase in terminal plasma elimination half-life compared to lower dose levels.

Experiment 9: Plasma pharmacokinetics of PFOA in male and female rats following administration of 0.1 mg/kg PFOA by oral gavage with extended observation interval (Table 40, Figure 16, Appendix M).

To further characterize plasma elimination kinetics of PFOA in male and female rats, a second experiment was carried out at the 0.1 mg/kg dose levels using a more sensitive analytical method.

Plasma samples were collected and analyzed until the PFOA concentration dropped below quantifiable levels.

In this experiment, PFOA was detected in female rat plasma through 24 hours after dosing, while male rat plasma contained quantifiable levels of PFOA through 2016 hours (84 days). Analysis of the plasma elimination data from this experiment yielded results similar to those obtained in the initial 0.1 mg/kg pharmacokinetic experiment (Table 40). The primary differences between experiments were seen with males, for which the estimates for elimination half-life were somewhat greater, and the values for plasma clearance consequently lower. As in the first 0.1 mg/kg experiment, plasma elimination curves were linear with respect to time for both sexes (Figure 16).

3. Tissue Distribution of ^{14}C -PFOA at Plasma $T_{\max}$ and $T_{\max/2}$ in Male and Female Rats (Tables 41-53, Figures 17-22, Appendices N-P)

The tissue distribution experiments were carried out to characterize the tissue burden of ^{14}C -PFOA and to investigate the kinetics of elimination and accumulation of PFOA in various tissues of male and female rats.

Dosing and Sampling Times (Table 41, Appendices N-P)

Tissue distribution of ^{14}C at $T_{\max}$ and $T_{\max/2}$ following oral administration was investigated in male and female rats at nominal dose rates of 1, 5 and 25 mg/kg body weight. Actual dose rates were calculated based on analysis of the dose solutions and are presented in Table 41. For all experiments, actual dose rates fell within $\pm 15\%$ of target dose rates. Animals received approximately 21-28 μCi of ^{14}C -PFOA in these experiments (Table 41).

Values for $T_{\max}$ and $T_{\max/2}$ for male and female rats were determined from pharmacokinetic experiments. $T_{\max/2}$ was calculated as $T_{\max} + T_{1/2}$. For cases in which biphasic elimination was evident, the rapid phase $T_{1/2}$ was used for calculation of $T_{\max/2}$. Values for $T_{\max}$ and $T_{\max/2}$ were analyzed by one-way ANOVA to establish whether different sampling times were required for each dose level. ANOVA analysis indicated that there were no significant differences in $T_{\max}$ or $T_{\max/2}$ across dose levels within each sex. For this reason, mean values for $T_{\max}$ and $T_{\max/2}$ were calculated across all dose levels to establish sampling times for tissue distribution. The resultant sampling times for male rats were 10.5 hours and 171 hours. Sampling times for female rats were 1.25 hours and 4 hours.

Experiment 10: Tissue distribution of ^{14}C at plasma $T_{\max}$ and $T_{\max/2}$ in male and female rats following oral administration of 1 mg/kg ^{14}C -PFOA (Tables 42-45, Figures 17-18, Appendix N)

The overall body burden of ^{14}C following administration of 1 mg/kg ^{14}C -PFOA was approximately 85% and 51% of the administered dose in male and female rats, respectively (Table 42). In male rats, the highest percentages of the administered dose at $T_{\max}$ were present in whole blood, liver, skin and muscle (Figure 17). In females, the largest fractions of the dose were found in the GI contents, GI tract, liver and whole blood. The total amount of radioactivity recovered in the body at $T_{\max/2}$ decreased to approximately 57% and 29% of the administered

dose in males and females, respectively (Table 43). In male rats, the percentage of the dose found in the liver increased at $T_{\max/2}$ relative to $T_{\max}$, but percentages in other tissues decreased. In females, the tissue burden of ^{14}C at $T_{\max/2}$ either decreased or remained constant relative to $T_{\max}$.

In male rats at $T_{\max}$, the highest tissue concentrations of ^{14}C were found in liver, followed by blood and kidney (Table 44). In females at $T_{\max}$, the GI contents and tract contained the highest concentrations of ^{14}C , followed by kidney, liver and blood. In males at $T_{\max/2}$, tissue concentrations of ^{14}C decreased relative to $T_{\max}$, except in liver where the concentrations were similar at both time points (Table 45). In female rats, tissues concentrations were similar between sampling times for all tissues, except GI contents, where the concentration of ^{14}C decreased.

To further characterize tissue distribution of ^{14}C over time, tissue:blood concentration ratios were calculated and are presented in Figure 18. In male rats, tissue blood ratios greater than 1 were observed only in liver, and the liver:blood concentration ratio increased significantly between $T_{\max}$ and $T_{\max/2}$. In female rats, tissue:blood ratios greater than 1 were observed in the GI contents and kidney. In other tissues, ratios were close to 1, and in all tissues, concentration ratios either decreased or remained constant between $T_{\max}$ and $T_{\max/2}$.

Experiment 11: Tissue distribution of ^{14}C at plasma $T_{\max}$ and $T_{\max/2}$ in male and female rats following oral administration of 5 mg/kg ^{14}C -PFOA (Tables 46-49, Figures 19-20, Appendix O)

The body burden of ^{14}C at $T_{\max}$ following oral administration of 5 mg/kg ^{14}C -PFOA was approximately 88% and 37% of the administered dose in male and female rats, respectively (Table 46). The tissue distribution of ^{14}C at $T_{\max}$ in male and female rats was similar to that observed at the 1 mg/kg dose level, except that the proportion of the dose remaining in the GI contents in females was somewhat lower (Figure 19). A decrease in total body radioactivity similar to that observed following 1 mg/kg ^{14}C -PFOA was observed at $T_{\max/2}$ (Table 47). Changes in the tissue distribution of ^{14}C at $T_{\max/2}$ were also similar to those observed at the 1 mg/kg dose level, except that a clear decrease in liver ^{14}C burden was evident in female rats in this experiment.

For both male and female rats, the highest concentrations of ^{14}C were found in liver, kidney and blood at $T_{\max}$ and $T_{\max/2}$ (Tables 48-49). Liver:blood ^{14}C concentration ratios (Figure 20) in male rats at $T_{\max}$ were greater than 1, and increased between $T_{\max}$ and $T_{\max/2}$. Tissue:blood ratios for other tissues in males remained constant over this interval. Liver:blood ratios in male rats following 5 mg/kg PFOA were generally lower than were observed at the 1 mg/kg dose level. In females, tissue:blood ^{14}C concentration ratios were similar to those observed at 1 mg/kg, with the exception of the GI contents.

Experiment 12: Tissue distribution of ^{14}C at plasma $T_{\max}$ and $T_{\max/2}$ in male and female rats following oral administration of 25 mg/kg ^{14}C -PFOA (Tables 50-53, Figures 21-22, Appendix P)

In general, body ^{14}C burdens in male and female rats at $T_{\max}$ and $T_{\max/2}$ following administration of 25 mg/kg ^{14}C -PFOA were similar to those observed at lower dose levels (Tables 50-51). Moreover, the tissue distribution of the remaining dose at both sampling times was similar to lower dose groups for both sexes (Figure 21).

For both male and female rats, the highest concentrations of ^{14}C were found in liver, kidney and blood at $T_{\max}$ and $T_{\max/2}$ (Tables 52-53). The decrease in tissue concentration in female rats between $T_{\max}$ and $T_{\max/2}$ was somewhat lower than expected. This may have been due to the use of $T_{\max}$ and $T_{\max/2}$ to estimate $T_{\max/2}$. This method underestimated $T_{\max/2}$ for female rats at the 25 mg/kg dose level. Liver:blood ^{14}C concentration ratios (Figure 22) in male rats at $T_{\max}$ were significantly greater than 1, and increased between $T_{\max}$ and $T_{\max/2}$. Tissue:blood ratios for other tissues in males were less than 1 and remained constant over this interval. In females, the kidney:blood ratio was significantly greater than 1, and remained relatively constant between $T_{\max}$ and $T_{\max/2}$. For other tissues, the ratio was approximately 1 or less and did not change appreciably between sampling times.

CONCLUSIONS

The results of these studies demonstrate significant sex differences in tissues distribution, elimination, and pharmacokinetic behavior of PFOA in rats. Urinary excretion was the primary route of elimination of PFOA in both males and female, while fecal excretion played a relatively minor role. Elimination of PFOA by both routes was rapid and nearly complete in females. In males, elimination was much slower than in females, and up to 20% of the dose remained in the body after 28 days. PFOA-derived ^{14}C was not eliminated as $^{14}\text{CO}_2$ or as volatile organic compounds. Sex differences in excretion of PFOA were reflected in plasma pharmacokinetic parameters in male and female rats. Oral bioavailability of PFOA was approximately 100%. Plasma elimination was slow in male rats, and no evidence of dose-dependent elimination was observed. In females, plasma elimination was rapid and displayed biphasic behavior at the higher dose levels. In both males and females, the main tissues for distribution of PFOA were the blood, liver, and kidney. The blood:liver concentration ratio of PFOA in males increased over time, suggesting that this tissue may serve as a depot for PFOA in male rats. The results of these studies constitute a comprehensive description of PFOA toxicokinetics in male and female rats.

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.

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TABLES

TABLES

EXPLANATORY NOTES

ABBREVIATIONS:

AUC_{INF}	area under the plasma concentration vs. time curve, extrapolated to infinity
$AUC_{INF/D}$	AUC_{INF} , normalized to dose
Aux	auxiliary
Cl_p	plasma clearance
C_{max}	maximum plasma concentration
equiv	equivalent
hr or h	hour(s)
Lambda-Z	terminal elimination constant
μCi	microcurie, 2.22×10^6 dpm
m	minute(s)
NA	not applicable
ND	not detected
SD	standard deviation
$T_{1/2}$	terminal elimination half-life
T_{max}	time to C_{max}
$T_{max/2}$	time to $1/2 C_{max}$ following attainment of maximum concentrations

Table 1: Pilot Study – Dosing information for male and female rats

Test Substance	Nominal Dose	Sex	Animal Weight (g)		Dose Volume (mL)		Actual Dose Rate (mg/kg)		Radioactivity Received (μCi)	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
Pharmacokinetics										
PFOA	1 mg/kg	Male	253.7	20.7	0.96	0.02	0.78	0.05	NA	NA
		Female	228.7	4.0	0.89	0.01	0.80	0.01	NA	NA
Material Balance										
¹⁴ C-PFOA	25 mg/kg	Male	250.1	12.4	0.71	0.05	18.11	0.38	19.284	1.361
		Female	157.2	2.9	0.45	0.01	18.26	0.15	12.210	0.326

Table 2: Pilot Study – Pharmacokinetic parameters in male and female rats following oral gavage with 1 mg/kg PFOA

Parameter	Units	Males		Females	
		Mean	SD	Mean	SD
T _{max}	hr	7.00	7.07	0.50	0.00
C _{max}	(μ g/mL)	25.98	5.37	25.30	11.46
Lambda z	(1/hr)	0.0068	0.0006	0.24	0.02
T _{1/2}	(hr)	103.30	13.30	2.96	0.33
AUC _{INF}	(hr· μ g/mL)	3647.75	671.71	123.35	30.66
AUC _{INF/D}	(hr· μ g/mL/mg·kg)	4688.66	567.27	154.99	37.19
Cl _p	(mL·kg/hr)	0.21	0.03	6.64	1.59

Table 3: Pilot Study – Percent of dose recovered in urine in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

Timepoint	Male		Female	
	Mean	SD	Mean	SD
4 h	0.217	0.104	28.493	0.993
8 h	1.176	0.285	32.162	9.208
12 h	1.135	0.300	17.559	5.326
24 h	2.570	0.644	9.968	2.291
48 h	3.916	0.320	2.560	0.613
72 h	4.412	1.278	0.546	0.087
96 h	4.580	0.083	0.351	0.013
120 h	4.421	0.008	0.206	0.016
144 h	3.691	0.591	0.149	0.000
168 h	4.194	0.106	0.147	0.037
Total ^a	30.310	2.539	92.140	1.849

^a Totals are calculated from individual animal data.

n = 2

Table 4: Pilot Study – Percent of dose recovered in feces in male and female rats following oral gavage with 25 mg/kg ¹⁴C-PFOA

Timepoint	Male		Female	
	Mean	SD	Mean	SD
4 h	0.028	NA	NA	NA
8 h	0.045	NA	NA	NA
12 h	0.507	0.705	0.123	0.109
24 h	4.247	4.183	0.217	0.162
48 h	1.102	0.739	0.113	0.086
72 h	0.434	0.088	0.030	NA
96 h	0.501	0.380	0.014	0.006
120 h	0.477	0.394	0.025	NA
144 h	0.846	1.012	0.012	NA
168 h	0.313	0.298	0.028	0.008
Total ^a	8.462	2.057	0.528	0.419

^a Totals are calculated from individual animal data.

n = 2

Table 5: Pilot Study – Percent of dose recovered at 168 hours in tissues in male and female rats following oral gavage with 25 mg/kg ¹⁴C-PFOA

	Male		Female	
	Mean	SD	Mean	SD
prostate	0.034	0.006	NA	NA
carcass	18.619	2.603	0.288	NA
skin	0.525	0.211	NA	NA
whole blood	5.761	1.194	NA	NA
brain	0.025	0.002	NA	NA
fat	0.065	0.000	NA	NA
heart	0.201	0.004	NA	NA
lungs	0.415	0.065	NA	NA
spleen	0.046	0.006	NA	NA
liver	25.628	0.259	0.008	0.001
kidney	1.189	0.013	0.002	0.001
G.I. tract	0.988	0.132	NA	NA
G.I. contents	0.228	0.013	NA	NA
thymus	0.046	0.008	NA	NA
testes	0.263	0.033	NA	NA
ovaries	NA	NA	NA	NA
adrenals	0.008	0.001	NA	NA
uterus	NA	NA	NA	NA
muscle	0.223	0.044	NA	NA
bone	0.078	0.011	NA	NA
Total ^a	54.338	3.630	0.154	0.202

^a Totals are calculated from individual animal data.

n = 2

Table 6: Pilot Study – Concentration ($\mu\text{g equiv/g}$) in tissues in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

	Male		Female	
	Mean	SD	Mean	SD
prostate	3.009	0.137	NA	NA
carcass	3.755	0.393	0.060	NA
skin	7.149	0.559	NA	NA
whole blood	25.548	0.679	NA	NA
brain	0.570	0.007	NA	NA
fat	1.494	0.684	NA	NA
heart	7.890	0.222	NA	NA
lungs	11.657	0.181	NA	NA
spleen	3.049	0.210	NA	NA
liver	57.379	3.746	0.030	0.003
kidney	17.494	0.129	0.023	0.011
G.I. tract	3.771	0.345	NA	NA
G.I. contents	0.543	0.004	NA	NA
thymus	3.069	0.000	NA	NA
testes	3.855	0.166	NA	NA
ovaries	NA	NA	NA	NA
adrenals	4.348	0.354	NA	NA
uterus	NA	NA	NA	NA
muscle	2.115	0.351	NA	NA
bone	3.394	1.058	NA	NA

n = 4

Table 7: Pilot Study – Percent of dose recovered at 168 hours in cage wash and residual feed in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

	Male		Female	
	Mean	SD	Mean	SD
cage wash	0.820	0.274	0.605	0.306
residual feed	NA	NA	0.451	0.503
Total ^a	0.820	0.274	1.055	0.809

^a Totals are calculated from individual animal data.

n = 2

Table 8: Pilot Study – Overall mass balance in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

	Percent of Administered Dose			
	Male		Female	
	Mean	SD	Mean	SD
urine	30.310	2.539	92.140	1.849
feces	8.462	2.057	0.528	0.419
tissues	54.338	3.630	0.154	0.202
cage wash & residual feed	0.820	0.274	1.055	0.809
CO ₂ trap A	ND	ND	ND	ND
volatile organics	ND	ND	ND	ND
Total	93.929	3.422	93.902	2.581

Table 9: Material Balance – Dosing information for male and female rats

Test Substance	Nominal Dose	Sex	Animal Weight (g)		Dose Administered (g)		Actual Dose Rate (mg/kg)		Radioactivity Received (μCi)	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
Material Balance										
¹⁴ C-PFOA	1 mg/kg	Male	233.4	6.2	0.93	0.02	1.15	0.02	28.180	0.579
		Female	174.6	8.9	0.68	0.05	0.85	0.01	22.205	1.175
¹⁴ C-PFOA	5 mg/kg	Male	197.6	3.2	0.77	0.04	4.72	0.15	22.125	1.025
		Female	200.3	7.4	0.80	0.03	4.83	0.03	22.936	0.975
¹⁴ C-PFOA	25 mg/kg	Male	209.8	6.3	0.85	0.03	26.07	0.89	24.320	0.964
		Female	188.5	5.2	0.75	0.02	25.57	0.20	21.438	0.519
¹⁴ C-PFOA	1 mg/kg ^a	Male	343.2	11.1	1.34	0.06	0.92	0.02	39.994	1.935
		Female	243.5	11.0	0.97	0.03	0.94	0.01	29.043	0.966

^a14-day repeated dose with PFOA, followed by a single dose with ¹⁴C-PFOA.

Table 10: Percent of dose recovered in urine in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA

Timepoint	Male		Female	
	Mean	SD	Mean	SD
4 h	0.048	0.042	11.505	5.954
8 h	0.408	0.230	30.930	5.092
12 h	0.896	0.199	16.002	3.043
24 h	2.114	0.298	10.713	3.290
48 h	3.370	0.481	3.119	1.428
72 h	2.978	0.240	1.538	0.634
96 h	2.320	0.163	0.826	0.153
120 h	2.101	0.186	0.432	0.086
144 h	2.155	0.395	0.329	0.095
168 h	1.914	0.408	0.480	0.220
Day 8	1.735	0.338	NA	NA
Day 9	1.626	0.348	NA	NA
Day 10	1.750	0.363	NA	NA
Day 11	1.496	0.149	NA	NA
Day 12	1.472	0.275	NA	NA
Day 13	1.086	0.431	NA	NA
Day 14	1.191	0.323	NA	NA
Day 16	2.340	0.585	NA	NA
Day 18	2.457	0.248	NA	NA
Day 20	2.377	0.534	NA	NA
Day 22	2.272	0.718	NA	NA
Day 24	2.062	0.846	NA	NA
Day 26	1.499	0.140	NA	NA
Day 28	1.619	0.327	NA	NA
Total ^a	43.283	3.015	75.872	4.066

^a Totals are calculated from individual animal data.

n = 4

Table 11: Percent of dose recovered in feces in male and female rats following oral gavage with 1 mg/kg ¹⁴C-PFOA

Timepoint	Male		Female	
	Mean	SD	Mean	SD
4 h	NA	NA	NA	NA
8 h	2.269	NA	NA	NA
12 h	2.433	2.625	1.239	1.944
24 h	5.554	3.577	0.580	0.898
48 h	0.838	0.517	0.108	0.092
72 h	0.292	0.225	0.028	0.005
96 h	0.238	0.245	0.106	0.092
120 h	0.126	0.046	0.046	0.028
144 h	0.160	0.039	0.033	0.019
168 h	0.190	0.124	0.030	0.017
Day 8	0.255	0.268	NA	NA
Day 9	0.299	0.297	NA	NA
Day 10	0.190	0.177	NA	NA
Day 11	0.204	0.204	NA	NA
Day 12	0.098	0.035	NA	NA
Day 13	0.256	0.165	NA	NA
Day 14	0.227	0.159	NA	NA
Day 16	0.387	0.235	NA	NA
Day 18	0.232	0.128	NA	NA
Day 20	0.284	0.158	NA	NA
Day 22	0.309	0.193	NA	NA
Day 24	0.457	0.313	NA	NA
Day 26	0.262	0.195	NA	NA
Day 28	0.198	0.096	NA	NA
Total ^a	14.055	4.003	2.169	2.923

^a Totals are calculated from individual animal data.

n = 4

Table 12: Percent of dose recovered in tissues in male and female rats following oral gavage with 1 mg/kg ¹⁴C-PFOA

	Male (Day 28)		Female (168 Hours)	
	Mean	SD	Mean	SD
prostate	0.020	0.009	NA	NA
carcass	7.388	1.440	0.215	0.125
skin	0.090	0.030	0.001	NA
whole blood	1.265	0.387	0.004	0.002
brain	0.006	0.002	NA	NA
fat	0.017	0.007	NA	NA
heart	0.064	0.014	NA	NA
lungs	0.108	0.016	NA	NA
spleen	0.015	0.004	NA	NA
liver	13.400	2.467	0.013	0.003
kidney	0.522	0.132	0.002	0.001
G.I. tract	0.344	0.070	NA	NA
G.I. contents	0.061	0.012	0.003	NA
thyroid	0.002	0.001	NA	NA
thymus	0.011	0.004	NA	NA
testes	0.103	0.029	NA	NA
ovaries	NA	NA	NA	NA
adrenals	0.002	0.001	NA	NA
uterus	NA	NA	NA	NA
muscle	0.095	0.025	NA	NA
bone	0.032	0.011	NA	NA
Total ^a	23.545	4.062	0.232	0.125

^a Totals are calculated from individual animal data.

n = 4

Table 13: Concentration ($\mu\text{g equiv/g}$) in tissues in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA

	Male		Female	
	Mean	SD	Mean	SD
prostate	0.050	0.016	NA	NA
carcass	0.061	0.015	0.002	0.001
skin	0.115	0.029	0.001	NA
whole blood	0.357	0.099	0.001	0.000
brain	0.008	0.002	NA	NA
fat	0.014	0.007	NA	NA
heart	0.121	0.035	NA	NA
lungs	0.171	0.046	NA	NA
spleen	0.054	0.014	NA	NA
liver	1.987	0.427	0.002	0.000
kidney	0.357	0.054	0.002	0.001
G.I. tract	0.051	0.016	NA	NA
G.I. contents	0.008	0.003	0.000	NA
thyroid	0.066	0.034	NA	NA
thymus	0.047	0.014	NA	NA
testes	0.092	0.035	NA	NA
ovaries	NA	NA	NA	NA
adrenals	0.056	0.024	NA	NA
uterus	NA	NA	NA	NA
muscle	0.035	0.008	NA	NA
bone	0.054	0.011	NA	NA

n = 4

Table 14: Percent of dose recovered in cage wash and residual feed in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA

	Male (Day 28)		Female (168 Hours)	
	Mean	SD	Mean	SD
cage wash	2.212	0.528	2.854	1.287
residual feed	0.736	0.450	0.198	0.031
Total ^a	2.948	0.732	3.052	1.311

^a Totals are calculated from individual animal data.

n = 4

Table 15: Overall mass balance in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA

	Male		Female	
	Mean	SD	Mean	SD
urine	43.238	3.015	75.872	4.066
feces	14.055	4.003	2.169	2.923
tissues	23.545	4.062	0.232	0.125
cage wash & residual feed	2.948	0.732	3.052	1.311
Total	83.830	4.006	81.325	4.546

Table 16: Percent of dose recovered in urine in male and female rats following oral gavage with 5 mg/kg ^{14}C -PFOA

Timepoint	Male		Female	
	Mean	SD	Mean	SD
4 h	0.102	0.081	11.696	10.464
8 h	0.607	0.319	35.213	3.547
12 h	1.043	0.468	17.189	3.358
24 h	2.575	0.441	13.565	6.189
48 h	4.445	0.584	3.026	0.831
72 h	3.931	0.784	1.008	0.579
96 h	3.473	0.675	0.622	0.209
120 h	3.748	0.684	0.642	0.480
144 h	3.346	0.151	0.441	0.319
168 h	3.454	0.779	0.314	0.132
Day 8	2.925	0.212	NA	NA
Day 9	2.634	0.244	NA	NA
Day 10	2.674	0.248	NA	NA
Day 11	2.379	0.193	NA	NA
Day 12	2.241	0.284	NA	NA
Day 13	2.045	0.289	NA	NA
Day 14	1.869	0.298	NA	NA
Day 16	3.214	0.306	NA	NA
Day 18	3.379	0.336	NA	NA
Day 20	3.003	0.268	NA	NA
Day 22	2.788	0.314	NA	NA
Day 24	2.314	0.285	NA	NA
Day 26	2.258	0.151	NA	NA
Day 28	1.935	0.249	NA	NA
Total ^a	62.201	3.656	77.867	6.034

^a Totals are calculated from individual animal data.

n = 4

Table 17: Percent of dose recovered in feces in male and female rats following oral gavage with 5 mg/kg ^{14}C -PFOA

Timepoint	Male		Female	
	Mean	SD	Mean	SD
4 h	NA	NA	0.003	NA
8 h	NA	NA	NA	NA
12 h	1.027	1.989	1.134	0.069
24 h	0.740	0.249	3.934	5.118
48 h	0.536	0.381	0.560	0.630
72 h	0.580	0.489	0.341	0.357
96 h	0.355	0.314	0.146	0.169
120 h	0.197	0.094	0.119	0.141
144 h	0.176	0.078	0.106	0.131
168 h	0.140	0.039	0.114	0.112
Day 8	0.128	0.035	NA	NA
Day 9	0.111	0.027	NA	NA
Day 10	0.149	0.082	NA	NA
Day 11	0.145	0.051	NA	NA
Day 12	0.119	0.073	NA	NA
Day 13	0.088	0.030	NA	NA
Day 14	0.101	0.032	NA	NA
Day 16	0.204	0.082	NA	NA
Day 18	0.161	0.071	NA	NA
Day 20	0.124	0.027	NA	NA
Day 22	0.107	0.031	NA	NA
Day 24	0.120	0.049	NA	NA
Day 26	0.115	0.027	NA	NA
Day 28	0.148	0.091	NA	NA
Total ^a	5.568	1.779	5.886	5.387

^a Totals are calculated from individual animal data.

n = 4

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Table 18: Percent of dose recovered in tissues in male and female rats following oral gavage with 5 mg/kg ^{14}C -PFOA

	Male (Day 28)		Female (168 Hours)	
	Mean	SD	Mean	SD
prostate	0.015	0.003	NA	NA
carcass	6.677	1.214	0.121	0.045
skin	0.074	0.016	NA	NA
whole blood	1.183	0.201	NA	NA
brain	0.006	0.001	NA	NA
fat	0.018	0.002	NA	NA
heart	0.056	0.012	NA	NA
lungs	0.096	0.030	NA	NA
spleen	0.014	0.003	NA	NA
liver	10.904	1.390	0.016	0.002
kidney	0.388	0.031	0.002	0.000
G.I. tract	0.259	0.045	NA	NA
G.I. contents	0.055	0.015	NA	NA
thyroid	0.002	0.001	NA	NA
thymus	0.014	0.003	NA	NA
testes	0.093	0.014	NA	NA
ovaries	NA	NA	NA	NA
adrenals	0.006	0.006	NA	NA
uterus	NA	NA	NA	NA
muscle	0.065	0.008	NA	NA
bone	0.028	0.005	NA	NA
Total ^a	19.949	2.755	0.109	0.072

^a Totals are calculated from individual animal data.

n = 4

Table 19: Concentration ($\mu\text{g equiv/g}$) in tissues in male and female rats following oral gavage with 5 mg/kg ^{14}C -PFOA

	Male		Female	
	Mean	SD	Mean	SD
prostate	0.142	0.043	NA	NA
carcass	0.179	0.025	0.007	0.003
skin	0.345	0.073	NA	NA
whole blood	1.103	0.161	NA	NA
brain	0.027	0.005	NA	NA
fat	0.052	0.013	NA	NA
heart	0.349	0.061	NA	NA
lungs	0.492	0.081	NA	NA
spleen	0.159	0.013	NA	NA
liver	5.331	0.670	0.016	0.003
kidney	0.935	0.078	0.010	0.001
G.I. tract	0.165	0.031	NA	NA
G.I. contents	0.028	0.011	NA	NA
thyroid	0.176	0.049	NA	NA
thymus	0.145	0.012	NA	NA
testes	0.264	0.042	NA	NA
ovaries	NA	NA	NA	NA
adrenals	0.468	0.574	NA	NA
uterus	NA	NA	NA	NA
muscle	0.102	0.011	NA	NA
bone	0.174	0.023	NA	NA

n = 4

Table 20: Percent of dose recovered in cage wash and residual feed in male and female rats following oral gavage with 5 mg/kg ^{14}C -PFOA

	Male (Day 28)		Female (168 Hours)	
	Mean	SD	Mean	SD
cage wash	3.652	1.966	2.417	0.864
residual feed	0.377	0.434	0.541	0.450
Total ^a	3.935	2.362	2.958	0.845

^a Totals are calculated from individual animal data.

n = 4

Table 21: Overall mass balance in male and female rats following oral gavage with 5 mg/kg ^{14}C -PFOA

	Male		Female	
	Mean	SD	Mean	SD
urine	62.201	3.656	77.867	6.034
feces	5.568	1.779	5.886	5.387
tissues	19.949	2.755	0.109	0.072
cage wash & residual feed	3.935	2.362	2.958	0.845
Total	91.652	2.577	86.819	5.169

Table 22: Percent of dose recovered in urine in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

Timepoint	Male		Female	
	Mean	SD	Mean	SD
4 h	0.251	0.190	23.794	8.041
8 h	0.771	0.400	28.586	11.300
12 h	1.350	0.568	14.200	3.042
24 h	3.258	0.921	9.855	4.783
48 h	6.803	1.914	3.714	0.966
72 h	4.609	1.811	1.539	0.428
96 h	4.026	1.361	1.080	0.552
120 h	3.779	0.741	0.706	0.313
144 h	3.238	0.635	0.434	0.196
168 h	2.567	0.579	0.474	0.286
Day 8	2.066	0.527	NA	NA
Day 9	1.656	1.088	NA	NA
Day 10	1.856	0.362	NA	NA
Day 11	1.715	0.442	NA	NA
Day 12	1.539	0.489	NA	NA
Day 13	1.182	0.321	NA	NA
Day 14	1.124	0.381	NA	NA
Day 16	1.495	0.557	NA	NA
Day 18	1.151	0.435	NA	NA
Day 20	2.249	0.394	NA	NA
Day 22	1.953	0.256	NA	NA
Day 24	1.819	0.106	NA	NA
Day 26	1.522	0.339	NA	NA
Day 28	1.287	0.591	NA	NA
Total ^a	53.265	8.490	84.381	12.023

^a Totals are calculated from individual animal data.

n = 4

Table 23: Percent of dose recovered in feces in male and female rats following oral gavage with 25 mg/kg ¹⁴C-PFOA

Timepoint	Male		Female	
	Mean	SD	Mean	SD
4 h	0.020	NA	0.017	NA
8 h	0.181	0.249	0.002	NA
12 h	0.125	0.139	0.560	0.783
24 h	1.667	1.677	0.749	1.187
48 h	0.986	1.018	0.280	0.354
72 h	0.338	0.073	0.171	0.208
96 h	0.436	0.221	0.144	0.111
120 h	0.522	0.289	0.042	0.032
144 h	0.507	0.138	0.069	0.063
168 h	0.495	0.274	0.130	0.166
Day 8	0.722	0.414	NA	NA
Day 9	0.678	0.496	NA	NA
Day 10	0.933	0.418	NA	NA
Day 11	0.325	0.113	NA	NA
Day 12	0.319	0.247	NA	NA
Day 13	0.459	0.421	NA	NA
Day 14	0.421	0.332	NA	NA
Day 16	0.798	0.388	NA	NA
Day 18	1.320	0.335	NA	NA
Day 20	0.191	0.053	NA	NA
Day 22	0.307	0.184	NA	NA
Day 24	0.297	0.202	NA	NA
Day 26	0.322	0.073	NA	NA
Day 28	0.260	0.139	NA	NA
Total ^a	12.490	4.153	1.868	2.546

^a Totals are calculated from individual animal data.

n = 4

Table 24: Percent of dose recovered in tissues in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

	Male (Day 28)		Female (168 Hours)	
	Mean	SD	Mean	SD
prostate	0.010	0.004	NA	NA
carcass	5.355	2.637	0.188	0.068
skin	0.051	0.029	0.001	0.001
whole blood	0.769	0.366	NA	NA
brain	0.005	0.002	NA	NA
fat	0.014	0.007	NA	NA
heart	0.045	0.028	NA	NA
lungs	0.077	0.035	NA	NA
spleen	0.016	0.010	NA	NA
liver	5.521	1.636	0.015	0.008
kidney	0.389	0.183	0.003	0.000
G.I. tract	0.357	0.187	NA	NA
G.I. contents	0.056	0.034	NA	NA
thyroid	0.002	0.001	NA	NA
thymus	0.009	0.006	NA	NA
testes	0.068	0.031	NA	NA
ovaries	NA	NA	NA	NA
adrenals	0.003	0.002	NA	NA
uterus	NA	NA	NA	NA
muscle	0.041	0.016	NA	NA
bone	0.018	0.006	NA	NA
Total ^a	12.803	5.005	0.160	0.102

^a Totals are calculated from individual animal data.

n = 4

Table 25: Concentration ($\mu\text{g equiv/g}$) in tissues in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

	Male		Female	
	Mean	SD	Mean	SD
prostate	0.798	0.493	NA	NA
carcass	0.962	0.529	0.056	0.022
skin	1.790	0.905	0.024	0.016
whole blood	5.771	2.828	NA	NA
brain	0.139	0.068	NA	NA
fat	0.291	0.156	NA	NA
heart	1.863	1.029	NA	NA
lungs	2.658	1.375	NA	NA
spleen	1.248	0.903	NA	NA
liver	16.609	5.892	0.078	0.041
kidney	6.229	2.745	0.074	0.013
G.I. tract	1.166	0.755	NA	NA
G.I. contents	0.156	0.100	NA	NA
thyroid	1.164	0.671	NA	NA
thymus	0.854	0.577	NA	NA
testes	1.227	0.590	NA	NA
ovaries	NA	NA	NA	NA
adrenals	1.150	0.589	NA	NA
uterus	NA	NA	NA	NA
muscle	0.476	0.225	NA	NA
bone	0.707	0.274	NA	NA

n = 4

Table 26: Percent of dose recovered in cage wash and residual feed in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

	Male (Day 28)		Female (168 Hours)	
	Mean	SD	Mean	SD
cage wash	3.997	1.614	1.856	1.316
residual feed	1.347	1.850	4.996	7.569
Total ^a	5.344	3.336	6.852	8.360

^a Totals are calculated from individual animal data.

n = 4

Table 27: Overall mass balance in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

	Male		Female	
	Mean	SD	Mean	SD
urine	53.265	8.490	84.381	12.023
feces	12.490	4.153	1.868	2.546
tissues	12.803	5.005	0.160	0.102
cage wash & residual feed	5.344	3.336	6.852	8.360
Total	83.902	3.433	93.260	3.554

Table 28: Percent of dose recovered in urine in male and female rats after 14-day repeated administration of 1 mg/kg PFOA, followed by a 1 mg/kg challenge dose of ^{14}C -PFOA (day 15)

Timepoint	Male		Female	
	Mean	SD	Mean	SD
4 h	0.155	0.143	7.547	5.777
8 h	0.704	0.224	32.922	14.134
12 h	0.929	0.451	9.853	2.887
24 h	2.832	0.631	10.020	4.319
48 h	5.107	1.731	5.984	2.579
72 h	3.788	1.044	1.375	0.854
96 h	2.659	1.419	1.281	0.894
120 h	2.488	1.273	0.556	0.239
144 h	2.681	1.162	0.558	0.462
168 h	2.298	0.403	0.329	0.253
Day 8	1.784	0.629	NA	NA
Day 9	1.918	0.422	NA	NA
Day 10	1.561	0.637	NA	NA
Day 11	1.810	0.483	NA	NA
Day 12	1.871	0.620	NA	NA
Day 13	1.998	0.689	NA	NA
Day 14	2.279	0.434	NA	NA
Day 16	3.213	0.238	NA	NA
Day 18	2.905	0.344	NA	NA
Day 20	2.381	0.465	NA	NA
Day 22	2.035	0.531	NA	NA
Day 24	1.850	0.485	NA	NA
Day 26	1.744	0.264	NA	NA
Day 28	1.444	0.465	NA	NA
Total ^a	52.430	7.959	68.537	16.631

^a Totals are calculated from individual animal data.

n = 4

Table 29: Percent of dose recovered in feces in male and female rats following oral gavage with 1 mg/kg ¹⁴C-PFOA (repeat dose)

Timepoint	Male		Female	
	Mean	SD	Mean	SD
4 h	NA	NA	NA	NA
8 h	0.203	0.318	3.599	4.530
12 h	1.072	1.745	0.172	0.154
24 h	6.752	3.460	4.539	7.406
48 h	1.254	0.458	2.883	3.972
72 h	0.817	0.473	0.764	0.824
96 h	1.044	0.774	0.121	0.093
120 h	0.376	0.207	0.160	0.124
144 h	0.769	0.315	0.143	0.072
168 h	1.074	0.578	0.047	0.019
Day 8	1.150	0.714	NA	NA
Day 9	1.113	0.427	NA	NA
Day 10	1.060	1.170	NA	NA
Day 11	0.712	0.815	NA	NA
Day 12	0.465	0.433	NA	NA
Day 13	0.345	0.400	NA	NA
Day 14	0.096	0.036	NA	NA
Day 16	0.342	0.295	NA	NA
Day 18	0.202	0.053	NA	NA
Day 20	0.275	0.250	NA	NA
Day 22	0.319	0.242	NA	NA
Day 24	0.220	0.202	NA	NA
Day 26	0.076	0.021	NA	NA
Day 28	0.108	0.091	NA	NA
Total ^a	19.841	6.620	12.384	15.775

^a Totals are calculated from individual animal data.

n = 4

Table 30: Percent of dose recovered in tissues in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA (repeat dose)

	Male (Day 28)		Female (168 Hours)	
	Mean	SD	Mean	SD
prostate	0.008	0.004	NA	NA
carcass	5.226	1.886	0.262	0.075
skin	0.078	0.035	0.001	0.000
whole blood	0.977	0.573	0.004	0.001
brain	0.004	0.002	NA	NA
fat	0.019	0.006	NA	NA
heart	0.040	0.016	NA	NA
lungs	0.074	0.030	0.000	NA
spleen	0.012	0.006	NA	NA
liver	6.113	1.684	0.037	0.006
kidney	0.346	0.164	0.005	0.002
G.I. tract	0.177	0.083	NA	NA
G.I. contents	0.041	0.021	NA	NA
thyroid	0.001	0.001	NA	NA
thymus	0.012	0.006	NA	NA
testes	0.054	0.021	NA	NA
ovaries	NA	NA	NA	NA
adrenals	0.002	0.001	NA	NA
uterus	NA	NA	NA	NA
muscle	0.052	0.023	NA	NA
bone	0.019	0.007	NA	NA
Total ^a	13.251	4.430	0.309	0.083

^a Totals are calculated from individual animal data.

n = 4

Table 31: Concentration ($\mu\text{g equiv/g}$) in tissues in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA (repeat dose)

	Male		Female	
	Mean	SD	Mean	SD
prostate	0.022	0.011	NA	NA
carcass	0.042	0.016	0.003	0.001
skin	0.083	0.032	0.002	0.001
whole blood	0.293	0.147	0.001	0.000
brain	0.007	0.003	NA	NA
fat	0.009	0.003	NA	NA
heart	0.084	0.034	NA	NA
lungs	0.121	0.052	0.001	NA
spleen	0.036	0.015	NA	NA
liver	0.940	0.243	0.008	0.001
kidney	0.272	0.111	0.006	0.001
G.I. tract	0.038	0.018	NA	NA
G.I. contents	0.006	0.003	NA	NA
thyroid	0.034	0.018	NA	NA
thymus	0.042	0.021	NA	NA
testes	0.052	0.024	NA	NA
ovaries	NA	NA	NA	NA
adrenals	0.044	0.027	NA	NA
uterus	NA	NA	NA	NA
muscle	0.025	0.010	NA	NA
bone	0.032	0.011	NA	NA
n = 4				

Table 32: Percent of dose recovered in cage wash and residual feed in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA (repeat dose)

	Male (Day 28)		Female (168 Hours)	
	Mean	SD	Mean	SD
cage wash	2.265	1.170	3.643	1.982
residual feed	0.263	0.349	4.766	8.615
Total ^a	2.528	1.465	8.409	8.329

^a Totals are calculated from individual animal data.

n = 4

Table 33: Overall mass balance in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA (repeat dose)

	Percent of Administered Dose			
	Male		Female	
	Mean	SD	Mean	SD
urine	52.430	7.959	68.537	16.631
feces	19.841	6.620	12.384	15.775
tissues	13.251	4.430	0.309	0.083
cage wash & residual feed	2.528	1.465	8.409	8.329
Total	88.049	1.651	89.638	3.348

Table 34: Pharmacokinetics – Dosing information for male and female rats

Test Substance	Nominal Dose	Sex	Animal Weight (g)		Dose Volume (mL)		Actual Dose Rate (mg/kg)	
			Mean	SD	Mean	SD	Mean	SD
Pharmacokinetics								
PFOA	0.1 mg/kg	Male	216.3	11.2	0.86	0.04	0.112	0.000
		Female	176.4	8.6	0.71	0.03	0.113	0.000
PFOA	1 mg/kg ^a	Male	248.7	1.6	1.00	0.01	1.01	0.00
		Female	197.0	9.7	0.79	0.04	1.01	0.01
PFOA	1 mg/kg ^b	Male	248.3	9.3	0.50	0.02	1.11	0.01
		Female	200.6	2.7	0.40	0.01	1.11	0.01
PFOA	5 mg/kg	Male	218.0	3.4	0.87	0.01	5.51	0.02
		Female	187.3	3.6	0.75	0.01	5.53	0.02
PFOA	25 mg/kg	Male	225.0	3.7	0.90	0.01	26.76	0.31
		Female	194.8	14.4	0.78	0.06	26.94	0.09
PFOA	0.1 mg/kg ^c	Male	272.5	5.8	1.10	0.00	0.097	0.002
		Female	201.0	11.8	0.81	0.05	0.097	0.000

^aOral gavage^bIntravenous injection^cExtended time course

Table 35: Pharmacokinetic parameters in male and female rats following oral gavage with 0.1 mg/kg PFOA

Parameter	Units	Males		Females	
		Mean	SD	Mean	SD
T_{max}	hr	10.25	6.45	0.56	0.31
C_{max}	($\mu\text{g/mL}$)	0.598	0.127	0.67	0.07
Lambda z	(1/hr)	0.004	0.001	0.231	0.066
$T_{1/2}$	(hr)	201.774	37.489	3.206	0.905
AUC_{INF}	(hr· $\mu\text{g/mL}$)	123.224	35.476	3.584	0.666
$AUC_{INF/D}$	(hr· $\mu\text{g/mL/mg/kg}$)	1096.811	310.491	31.721	5.880
Cl_p	(mL/kg·hr)	0.962	0.240	32.359	6.025

Table 36: Pharmacokinetic parameters in male and female rats following oral gavage with 1 mg/kg PFOA

Parameter	Units	Males		Females	
		Mean	SD	Mean	SD
T _{max}	hr	9.00	3.83	1.13	0.63
C _{max}	(µg/mL)	8.431	1.161	4.782	1.149
Lambda z	(1/hr)	0.005	0.001	0.213	0.053
T _{1/2}	(hr)	138.343	31.972	3.457	1.111
AUC _{INF}	(hr·µg/mL)	1194.463	215.578	39.072	10.172
AUC _{INF/D}	(hr·µg/mL/mg/kg)	1176.009	206.316	38.635	10.093
Cl _p	(mL/kg·hr)	0.871	0.158	27.286	7.159

Table 37: Pharmacokinetic parameters in male and female rats following intravenous injection with 1 mg /kg PFOA

Parameter	Units	Males		Females	
		Mean	SD	Mean	SD
Lambda z	(1/hr)	0.004	0.000	0.250	0.047
T _{1/2}	(hr)	185.584	19.558	2.844	0.514
AUC _{INF}	(hr·μg/mL)	1249.817	113.167	33.998	7.601
AUC _{INF/D}	(hr·μg/mL/mg/kg)	1123.384	100.488	30.747	6.759
Cl _p	(mL/kg·hr)	0.896	0.082	34.040	9.230

Table 38: Pharmacokinetic parameters in male and female rats following oral gavage with 5 mg/kg PFOA

Parameter	Units	Males		Females	
		Mean	SD	Mean	SD
$T_{\max}$	hr	15.0	10.5	1.50	0.58
$C_{\max}$	($\mu\text{g/mL}$)	44.75	6.14	20.36	1.58
$\text{Lambda } z$	(1/hr)	0.0041	0.0007	0.15	0.02
$T_{1/2}$	(hr)	174.19	28.92	4.60	0.64
AUC_{INF}	(hr· $\mu\text{g/mL}$)	6733.70	1392.83	114.90	11.23
$\text{AUC}_{\text{INF}}/D$	(hr· $\mu\text{g/mL/mg/kg}$)	1221.89	250.28	20.78	2.01
Cl_p	(mL/kg·hr)	0.85	0.21	48.48	4.86

Table 39: Pharmacokinetic parameters in male and female rats following oral gavage with 25 mg/kg PFOA

Parameter	Units	Males		Females	
		Mean	SD	Mean	SD
$T_{\max}$	hr	7.5	6.2	1.25	0.87
$C_{\max}$	($\mu\text{g/mL}$)	160.00	11.95	132.65	45.95
Lambda z	(1/hr)	0.0046	0.0012	0.059	0.037
$T_{1/2}$	(hr)	157.47	38.39	16.22	9.90
AUC_{INF}	(hr· $\mu\text{g/mL}$)	25155.61	7276.96	795.76	187.51
$AUC_{\text{INF/D}}$	(hr· $\mu\text{g/mL/mg/kg}$)	942.65	284.67	29.54	6.92
Cl_p	(mL/kg·hr)	1.13	0.31	35.06	6.88

Table 40: Pharmacokinetic parameters in male and female rats following oral gavage with 0.1 mg/kg PFOA (extended time course)

Parameter	Units	Males		Females	
		Mean	SD	Mean	SD
$T_{\max}$	hr	5.5	7.0	1.25	0.50
$C_{\max}$	($\mu\text{g/mL}$)	1.08	0.42	0.52	0.08
Lambda z	(1/hr)	0.0026	0.0007	0.22	0.07
$T_{1/2}$	(hr)	277.10	56.62	3.44	1.26
AUC_{INF}	(hr· $\mu\text{g/mL}$)	206.38	59.03	3.34	0.32
$AUC_{\text{INF/D}}$	(hr· $\mu\text{g/mL/mg/kg}$)	2111.28	586.77	34.39	3.29
Cl_p	(mL/kg·hr)	0.51	0.17	29.30	3.06

Table 41: Tissue Distribution – Dosing information for male and female rats

Test Substance	Nominal Dose	Sex	Animal Weight (g)		Dose Volume (mL)		Actual Dose Rate (mg/kg)		Radioactivity Received (μCi)	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
T _{max}										
¹⁴ C-PFOA	1 mg/kg	Male	202.2	3.4	0.80	0.01	0.87	0.02	23.463	0.384
		Female	192.4	2.2	0.79	0.02	0.88	0.01	22.725	0.171
¹⁴ C-PFOA	5 mg/kg	Male	229.1	6.1	0.92	0.03	4.72	0.07	28.391	0.985
		Female	193.2	5.4	0.77	0.02	4.68	0.03	23.754	0.601
¹⁴ C-PFOA	25 mg/kg	Male	216.2	6.8	0.88	0.03	25.02	0.08	23.792	0.790
		Female	190.3	3.0	0.77	0.01	24.90	0.28	20.837	0.338
T _{max/2}										
¹⁴ C-PFOA	1 mg/kg	Male	203.2	2.4	0.81	0.02	0.88	0.01	23.942	0.517
		Female	189.5	6.4	0.76	0.02	0.89	0.01	22.548	0.620
¹⁴ C-PFOA	5 mg/kg	Male	225.1	7.6	0.90	0.03	4.71	0.02	27.822	0.922
		Female	192.3	9.6	0.78	0.04	4.72	0.05	23.838	1.214
¹⁴ C-PFOA	25 mg/kg	Male	218.3	7.6	0.88	0.03	24.95	0.12	23.948	0.900
		Female	193.2	4.1	0.78	0.02	24.90	0.09	21.149	0.444

Table 42: Percent of dose recovered at T_{max} in tissues in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA

	Male (10 h 30 m)		Female (1 h 15 m)	
	Mean	SD	Mean	SD
prostate	0.083	0.039	NA	NA
skin ^a	14.772	2.135	0.434	0.162
whole blood ^a	22.148	0.692	5.740	1.507
brain	0.071	0.018	0.037	0.009
fat ^a	2.281	0.467	0.134	0.032
heart	0.451	0.119	0.198	0.079
lungs	0.740	0.147	0.454	0.148
spleen	0.086	0.011	0.063	0.027
liver	21.708	5.627	7.060	1.266
kidney	1.949	0.402	3.288	0.948
G.I. tract	2.930	0.929	10.699	9.066
G.I. contents	2.083	0.625	21.956	13.477
thyroid	0.008	0.005	0.010	0.003
thymus	0.085	0.008	0.052	0.017
testes	0.755	0.079	NA	NA
ovaries	NA	NA	0.047	0.019
adrenals	0.019	0.004	0.014	0.005
muscle ^a	12.025	0.648	0.170	0.051
uterus	NA	NA	0.243	0.091
bone ^a	3.273	0.538	0.101	0.017
Total ^b	85.465	6.426	50.698	16.485

^a Percent recovery scaled to whole animal assuming the following:
 skin=19%, whole blood=7.4%, fat=7%, muscle=40.4%, bone=7.3% of
 body weight.

^b Totals are calculated from individual animal data.

n = 4

Table 43: Percent of dose recovered at $T_{\max/2}$ in tissues in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA

	Male (171 h)		Female (4 h)	
	Mean	SD	Mean	SD
prostate	0.030	0.002	NA	NA
skin ^a	6.061	0.274	0.403	0.096
whole blood ^a	8.232	1.218	4.438	1.625
brain	0.022	0.002	0.047	0.008
fat ^a	0.593	0.136	0.164	0.079
heart	0.195	0.024	0.253	0.055
lungs	0.341	0.043	0.546	0.082
spleen	0.045	0.006	0.058	0.006
liver	32.627	3.601	6.817	1.537
kidney	1.140	0.215	2.769	0.784
G.I. tract	0.980	0.300	8.462	6.519
G.I. contents	0.239	0.025	3.891	2.395
thyroid	0.004	0.003	0.016	0.021
thymus	0.051	0.018	0.058	0.024
testes	0.356	0.037	NA	NA
ovaries	NA	NA	0.048	0.006
adrenals	0.010	0.001	0.018	0.004
muscle ^a	4.984	0.745	0.258	0.089
uterus	NA	NA	0.374	0.247
bone ^a	1.120	0.094	0.153	0.052
Total ^b	57.026	3.379	28.772	10.976

^a Percent recovery scaled to whole animal assuming the following:
skin=19%, whole blood=7.4%, fat=7%, muscle=40.4%, bone=7.3% of
body weight.

^b Totals are calculated from individual animal data.

n = 4

Table 44: Concentration ($\mu\text{g equiv/g}$) at T_{max} in tissues in male and female rats following oral gavage with $1 \text{ mg/kg } ^{14}\text{C-PFOA}$

	Male (10 h 30 m)		Female (1 h 15 m)	
	Mean	SD	Mean	SD
prostate	0.454	0.110	NA	NA
skin	0.672	0.097	0.298	0.114
whole blood	2.587	0.024	1.717	0.569
brain	0.066	0.012	0.033	0.008
fat	0.281	0.050	0.142	0.064
heart	0.973	0.161	0.440	0.151
lungs	1.157	0.151	0.701	0.192
spleen	0.339	0.058	0.201	0.065
liver	4.627	0.729	1.938	0.260
kidney	1.710	0.302	3.073	0.852
G.I. tract	0.528	0.151	2.184	2.185
G.I. contents	0.218	0.025	9.170	5.910
thyroid	0.399	0.088	0.385	0.117
thymus	0.277	0.039	0.175	0.055
testes	0.540	0.051	NA	NA
ovaries	NA	NA	0.422	0.167
adrenals	0.531	0.130	0.238	0.076
uterus	NA	NA	0.410	0.231
muscle	0.257	0.008	0.119	0.035
bone	0.386	0.053	0.171	0.053

n = 4

Table 45: Concentration ($\mu\text{g equiv/g}$) at $T_{\text{max}/2}$ in tissues in male and female rats following oral gavage with $1 \text{ mg/kg } ^{14}\text{C-PFOA}$

	Male (171 h)		Female (4 h)	
	Mean	SD	Mean	SD
prostate	0.153	0.035	NA	NA
skin	0.280	0.011	0.415	0.073
whole blood	0.976	0.143	1.753	0.212
brain	0.021	0.001	0.041	0.005
fat	0.074	0.017	0.157	0.020
heart	0.339	0.027	0.533	0.067
lungs	0.416	0.025	0.853	0.098
spleen	0.125	0.008	0.227	0.028
liver	4.180	0.628	2.064	0.503
kidney	0.773	0.151	2.897	0.800
G.I. tract	0.140	0.010	1.567	1.154
G.I. contents	0.025	0.002	1.639	1.039
thyroid	0.298	0.187	1.289	2.094
thymus	0.141	0.033	0.219	0.109
testes	0.231	0.029	NA	NA
ovaries	NA	NA	0.465	0.063
adrenals	0.175	0.021	0.308	0.056
uterus	NA	NA	0.565	0.228
muscle	0.108	0.016	0.187	0.083
bone	0.135	0.012	0.188	0.015

n = 4

Table 46: Percent of dose recovered at T_{max} in tissues in male and female rats following oral gavage with 5 mg/kg ^{14}C -PFOA

	Male (10 h 30 m)		Female (1 h 15 m)	
	Mean	SD	Mean	SD
prostate	0.071	0.045	NA	NA
skin ^a	15.565	0.899	0.624	0.142
whole blood ^a	24.919	1.942	8.089	2.080
brain	0.051	0.021	0.066	0.019
fat ^a	2.815	0.225	0.220	0.111
heart	0.443	0.037	0.388	0.057
lungs	0.593	0.376	0.827	0.102
spleen	0.096	0.017	0.101	0.021
liver	18.750	2.434	11.190	2.192
kidney	2.170	0.354	4.293	0.771
G.I. tract	2.508	0.713	7.142	2.594
G.I. contents	2.632	0.934	2.896	2.305
thyroid	0.011	0.006	0.008	0.002
thymus	0.085	0.012	0.105	0.030
testes	0.693	0.180	NA	NA
ovaries	NA	NA	0.071	0.012
adrenals	0.022	0.004	0.026	0.005
muscle ^a	13.565	0.576	0.325	0.010
uterus	NA	NA	0.354	0.046
bone ^a	3.047	0.544	0.174	0.057
Total ^b	88.033	1.420	36.897	3.187

^a Percent recovery scaled to whole animal assuming the following:
 skin=19%, whole blood=7.4%, fat=7%, muscle=40.4%, bone=7.3% of
 body weight.

^b Totals are calculated from individual animal data.

n = 4

Table 47: Percent of dose recovered at $T_{\max}/2$ in tissues in male and female rats following oral gavage with 5 mg/kg ^{14}C -PFOA

	Male (171 h)		Female (4 h)	
	Mean	SD	Mean	SD
prostate	0.057	0.020	NA	NA
skin ^a	7.233	0.430	0.307	0.121
whole blood ^a	11.140	0.624	5.411	1.466
brain	0.023	0.008	0.045	0.010
fat ^a	0.916	0.205	0.110	0.069
heart	0.252	0.030	0.236	0.051
lungs	0.344	0.194	0.570	0.179
spleen	0.060	0.007	0.060	0.012
liver	25.231	1.289	7.176	0.982
kidney	1.212	0.115	2.685	0.736
G.I. tract	1.052	0.202	8.255	8.967
G.I. contents	0.270	0.028	5.601	6.165
thyroid	0.004	0.002	0.006	0.002
thymus	0.053	0.003	0.068	0.021
testes	0.372	0.062	NA	NA
ovaries	NA	NA	0.041	0.012
adrenals	0.009	0.001	0.015	0.004
muscle ^a	6.429	0.648	0.229	0.031
uterus	NA	NA	0.247	0.068
bone ^a	1.375	0.169	0.142	0.078
Total ^b	56.031	1.025	31.201	12.626

^a Percent recovery scaled to whole animal assuming the following:
skin=19%, whole blood=7.4%, fat=7%, muscle=40.4%, bone=7.3% of
body weight.

^b Totals are calculated from individual animal data.

n = 4

Table 48: Concentration ($\mu\text{g equiv/g}$) at T_{max} in tissues in male and female rats following oral gavage with 5 mg/kg ^{14}C -PFOA

	Male (10 h 30 m)		Female (1 h 15 m)	
	Mean	SD	Mean	SD
prostate	2.012	1.278	NA	NA
skin	3.865	0.224	2.778	0.474
whole blood	15.886	1.227	13.889	1.683
brain	0.310	0.028	0.330	0.073
fat	1.896	0.138	1.270	0.271
heart	5.386	0.369	4.501	0.783
lungs	6.996	0.744	6.992	0.873
spleen	2.014	0.146	1.725	0.269
liver	23.456	3.178	16.934	3.409
kidney	11.018	2.089	26.042	5.457
G.I. tract	2.789	0.609	7.938	2.405
G.I. contents	1.750	0.542	4.861	4.149
thyroid	3.042	0.836	2.389	0.256
thymus	1.922	0.286	1.689	0.127
testes	2.754	0.154	NA	NA
ovaries	NA	NA	3.708	0.442
adrenals	3.449	0.714	2.810	0.605
muscle	1.584	0.069	4.955	1.549
uterus	NA	NA	1.067	0.179
bone	1.966	0.333	1.360	0.259

n = 4

Table 49: Concentration ($\mu\text{g equiv/g}$) at $T_{\text{max}/2}$ in tissues in male and female rats following oral gavage with $5 \text{ mg/kg } ^{14}\text{C-PFOA}$

	Male (171 h)		Female (4 h)	
	Mean	SD	Mean	SD
prostate	1.032	0.157	NA	NA
skin	1.792	0.116	2.532	0.786
whole blood	7.085	0.393	9.065	1.406
brain	0.155	0.021	0.241	0.078
fat	0.616	0.138	0.868	0.200
heart	2.442	0.213	2.889	0.583
lungs	3.101	0.534	4.819	1.265
spleen	0.868	0.061	1.199	0.221
liver	18.242	1.611	11.295	1.064
kidney	4.459	0.564	15.737	2.948
G.I. tract	0.963	0.124	9.904	11.648
G.I. contents	0.175	0.027	12.202	12.659
thyroid	1.652	0.445	1.990	0.387
thymus	1.142	0.236	1.234	0.288
testes	1.244	0.211	NA	NA
ovaries	NA	NA	2.880	0.756
adrenals	1.115	0.183	2.053	0.330
muscle	0.749	0.077	4.578	1.065
uterus	NA	NA	0.767	0.242
bone	0.886	0.110	1.070	0.360

n = 4

Table 50: Percent of dose recovered at T_{max} in tissues in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

	Male (10 h 30 m)		Female (1 h 15 m)	
	Mean	SD	Mean	SD
prostate	0.067	0.018	NA	NA
skin ^a	13.836	0.969	0.380	0.166
whole blood ^a	22.905	1.177	7.158	2.232
brain	0.063	0.007	0.058	0.008
fat ^a	2.153	0.430	0.147	0.053
heart	0.461	0.053	0.317	0.035
lungs	0.863	0.103	0.678	0.067
spleen	0.106	0.015	0.091	0.007
liver	17.528	0.900	10.538	1.723
kidney	2.293	0.286	5.867	0.946
G.I. tract	2.784	0.608	6.923	1.846
G.I. contents	4.186	1.349	2.491	1.548
thyroid	0.009	0.002	0.009	0.003
thymus	0.120	0.025	0.091	0.032
testes	0.623	0.098	NA	NA
ovaries	NA	NA	0.071	0.012
adrenals	0.026	0.004	0.031	0.005
muscle ^a	12.855	0.841	0.441	0.116
uterus	NA	NA	0.358	0.124
bone ^a	3.062	0.438	0.157	0.072
Total ^b	83.937	3.680	35.803	2.554

^a Percent recovery scaled to whole animal assuming the following:
skin=19%, whole blood=7.4%, fat=7%, muscle=40.4%, bone=7.3% of
body weight.

^b Totals are calculated from individual animal data.

n = 4

Table 51: Percent of dose recovered at $T_{\max}/2$ in tissues in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

	Male (171 h)		Female (4 h)	
	Mean	SD	Mean	SD
prostate	0.028	0.012	NA	NA
skin ^a	5.419	0.237	0.415	0.175
whole blood ^a	7.904	1.032	6.407	1.406
brain	0.019	0.002	0.058	0.018
fat ^a	0.628	0.110	0.148	0.065
heart	0.164	0.032	0.287	0.069
lungs	0.303	0.057	0.775	0.204
spleen	0.042	0.005	0.070	0.002
liver	20.145	3.098	9.080	0.895
kidney	1.003	0.122	4.749	0.393
G.I. tract	0.808	0.189	3.547	1.306
G.I. contents	0.210	0.084	1.121	1.010
thyroid	0.005	0.001	0.007	0.002
thymus	0.045	0.010	0.077	0.020
testes	0.224	0.031	NA	NA
ovaries	NA	NA	0.070	0.012
adrenals	0.009	0.003	0.021	0.001
muscle ^a	4.253	0.358	0.304	0.099
uterus	NA	NA	0.365	0.029
bone ^a	0.906	0.100	0.181	0.090
Total ^b	42.112	4.740	27.680	2.569

^a Percent recovery scaled to whole animal assuming the following:
skin=19%, whole blood=7.4%, fat=7%, muscle=40.4%, bone=7.3% of
body weight.

^b Totals are calculated from individual animal data.

n = 4

Table 52: Concentration ($\mu\text{g equiv/g}$) at T_{max} in tissues in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

	Male (10 h 30 m)		Female (1 h 15 m)	
	Mean	SD	Mean	SD
prostate	12.048	3.283	NA	NA
skin	18.222	1.288	17.036	2.814
whole blood	77.460	4.180	73.097	4.272
brain	1.807	0.147	1.475	0.179
fat	7.700	1.560	8.428	2.738
heart	27.064	1.522	21.274	1.709
lungs	37.162	2.431	34.065	3.029
spleen	10.237	0.612	9.835	0.888
liver	104.841	6.548	92.592	10.198
kidney	58.898	6.203	159.165	15.051
G.I. tract	16.435	2.346	39.253	12.486
G.I. contents	14.361	3.941	33.918	19.210
thyroid	13.121	3.797	15.543	5.794
thymus	9.882	1.762	11.813	2.405
testes	14.333	1.314	NA	NA
ovaries	NA	NA	19.130	2.121
adrenals	17.271	1.927	15.727	2.063
muscle	7.964	0.546	23.816	6.137
uterus	NA	NA	5.439	0.611
bone	10.498	1.534	6.546	0.478

n = 4

Table 53: Concentration ($\mu\text{g equiv/g}$) at $T_{\text{max}/2}$ in tissues in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

	Male (171 h)		Female (4 h)	
	Mean	SD	Mean	SD
prostate	4.010	0.880	NA	NA
skin	7.114	0.302	16.653	2.934
whole blood	26.647	3.490	60.145	5.361
brain	0.536	0.064	1.551	0.457
fat	2.238	0.390	6.157	0.608
heart	8.192	1.192	18.171	3.540
lungs	10.614	1.505	32.621	5.884
spleen	3.007	0.234	8.385	0.469
liver	54.704	5.989	72.211	6.062
kidney	19.153	2.090	134.318	8.888
G.I. tract	3.546	0.697	25.265	19.676
G.I. contents	0.650	0.186	12.611	12.463
thyroid	7.776	3.364	17.409	5.319
thymus	3.421	0.463	7.423	0.691
testes	4.022	0.663	NA	NA
ovaries	NA	NA	18.721	2.802
adrenals	4.661	0.578	12.419	1.449
muscle	2.626	0.216	21.531	3.854
uterus	NA	NA	5.297	0.637
bone	3.095	0.341	6.893	1.631

n = 4

FIGURES

FIGURES

EXPLANATORY NOTES

ABBREVIATIONS:

%AD	percent of administered dose
C _{max}	maximum plasma concentration
F	female
hr	hour(s)
T _{max}	time to C _{max}
T _{max/2}	time to 1/2 C _{max} following attainment of maximum concentrations

Figure 1: Pilot Study – PFOA concentration in serial plasma samples from male and female rats following oral gavage with 1 mg/kg PFOA

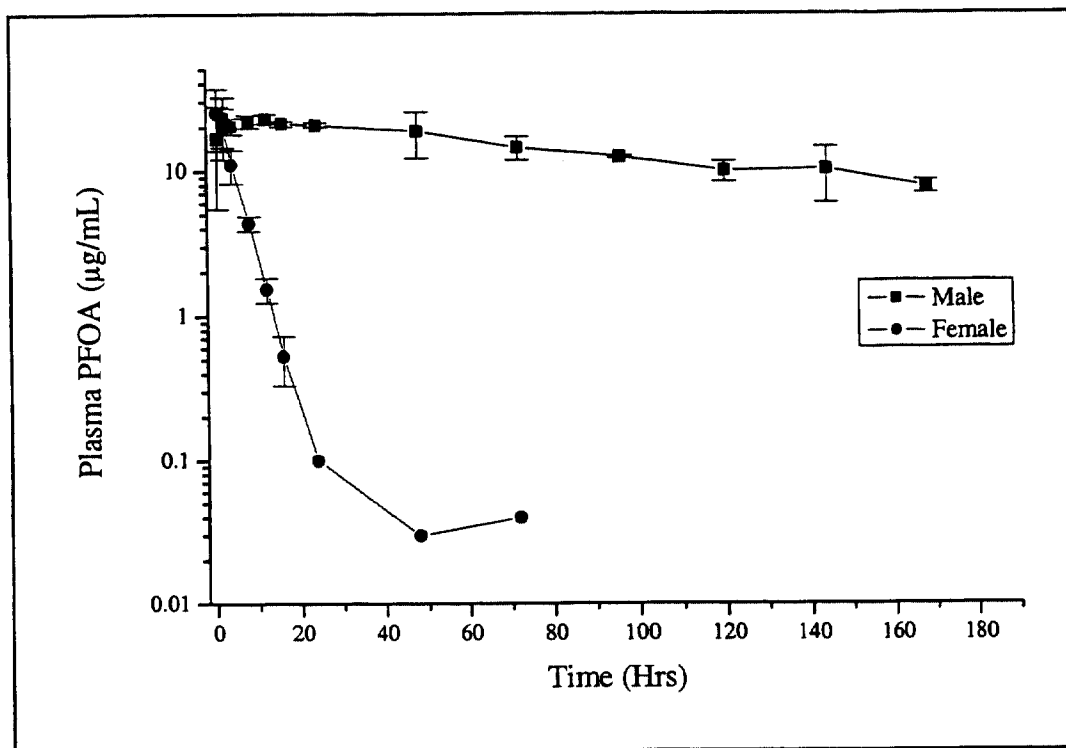
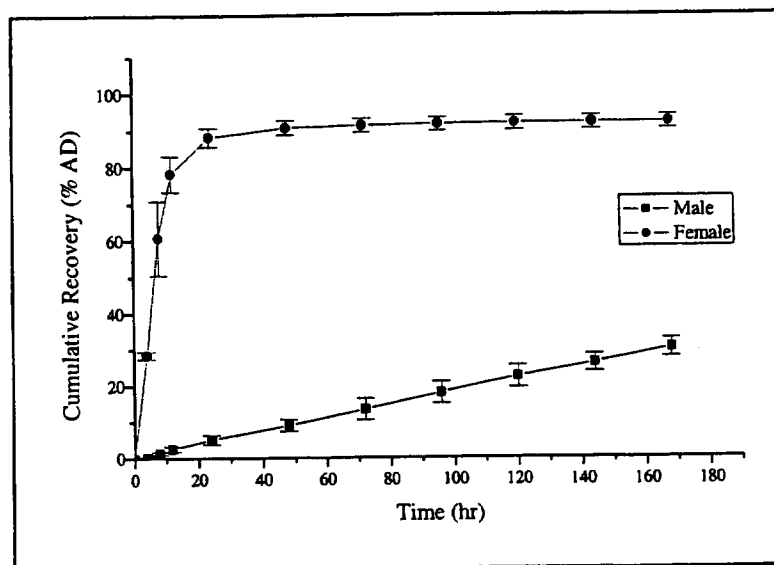


Figure 2: Pilot Study – Cumulative recovery of ^{14}C in urine and feces in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

Urine



Feces

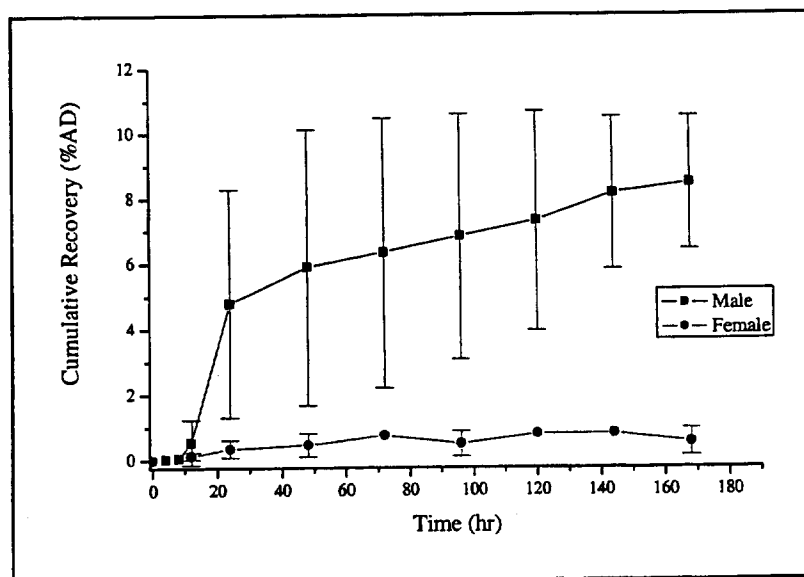
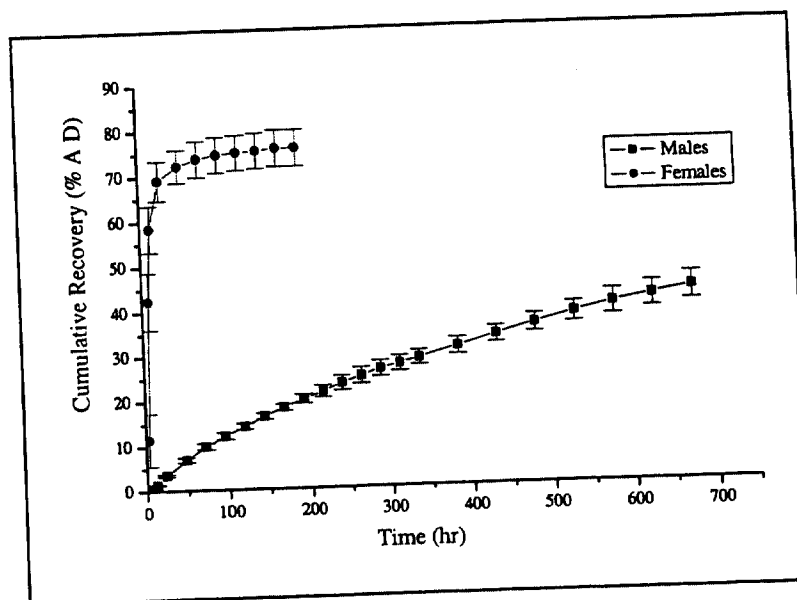


Figure 3: Cumulative recovery of ^{14}C in urine and feces in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA

Urine



Feces

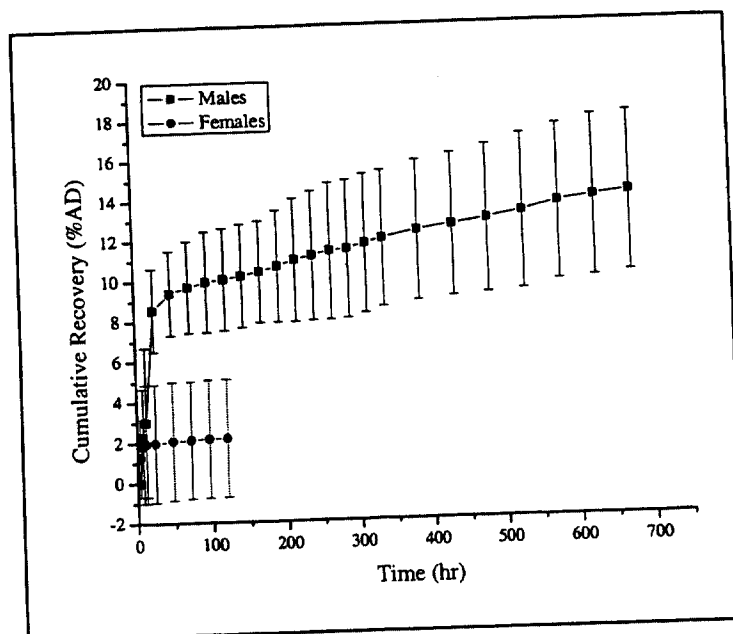


Figure 4: Terminal tissue:blood concentration ratio in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA

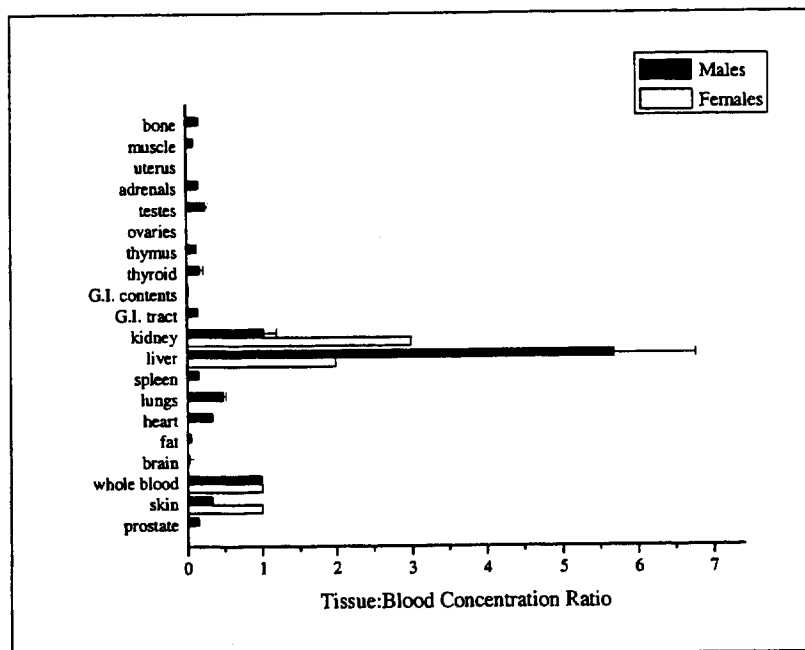
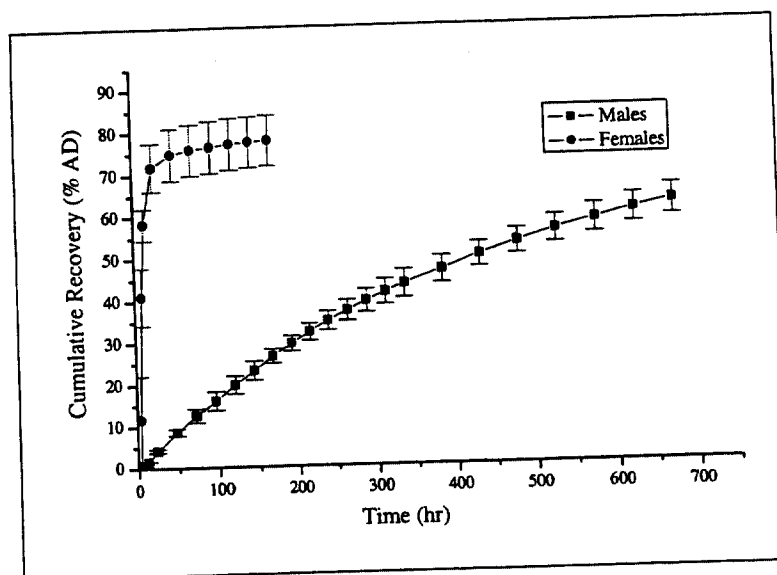
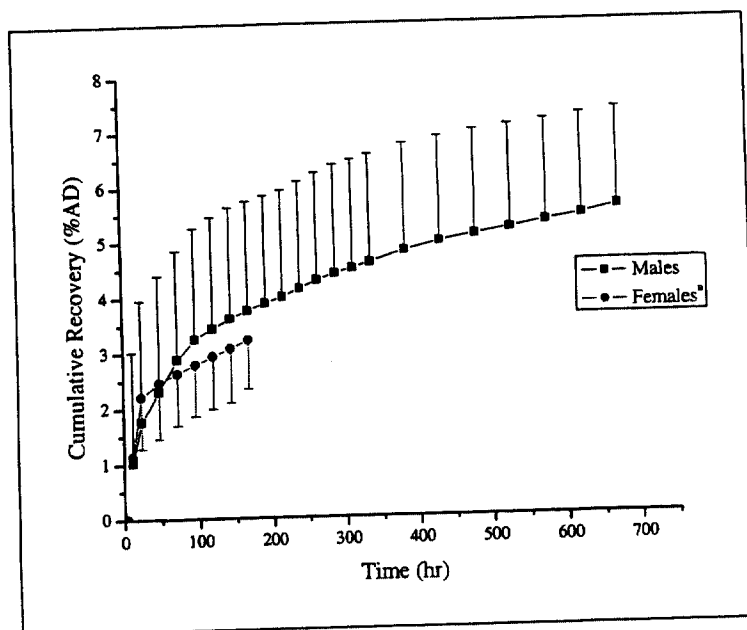


Figure 5: Cumulative recovery of ^{14}C in urine and feces in male and female rats following oral gavage with 5 mg/kg ^{14}C -PFOA

Urine

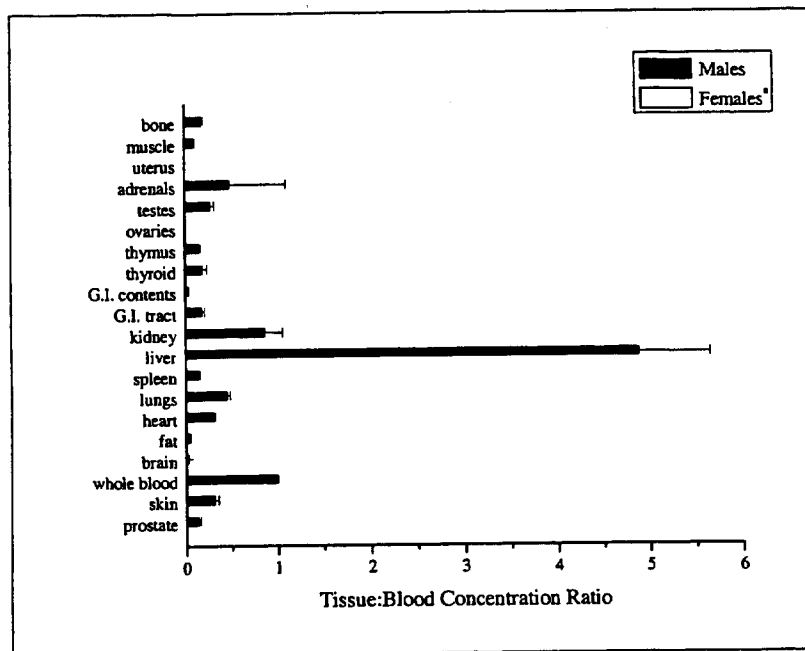


Feces



^a Animal 104F was omitted because of an extreme value for 24 hour fecal excretion, possibly due to contamination with urine.

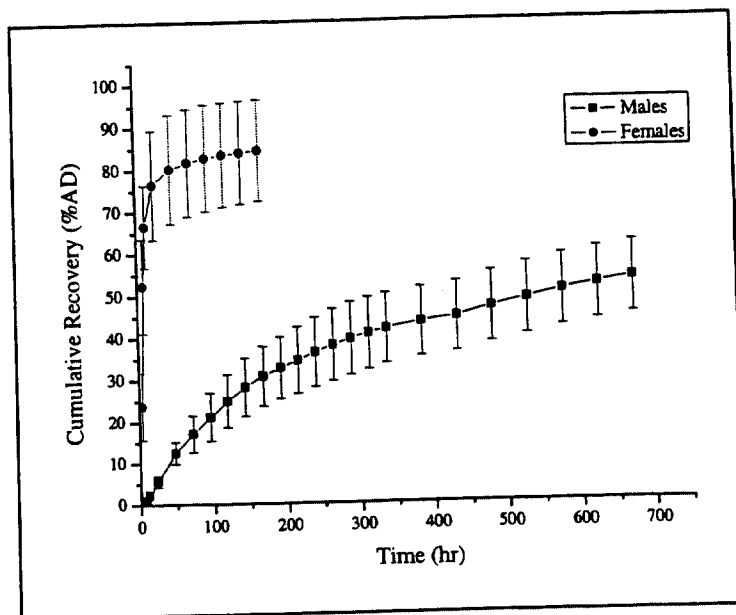
Figure 6: Terminal tissue:blood concentration ratio in male and female rats following oral gavage with 5 mg/kg ^{14}C -PFOA



* Whole blood concentration in females was below the detection limits for the assay. See Table 19 for tissue concentrations.

Figure 7: Cumulative recovery of ^{14}C in urine and feces in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

Urine



Feces

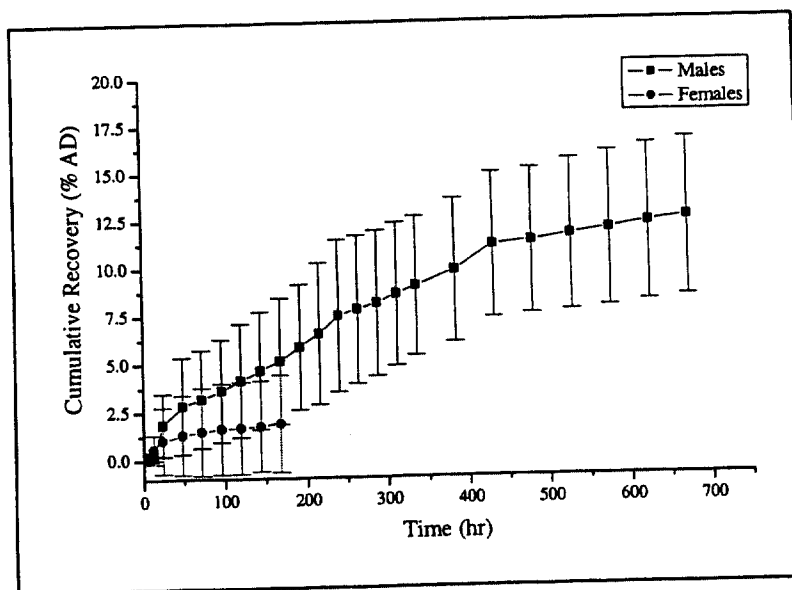
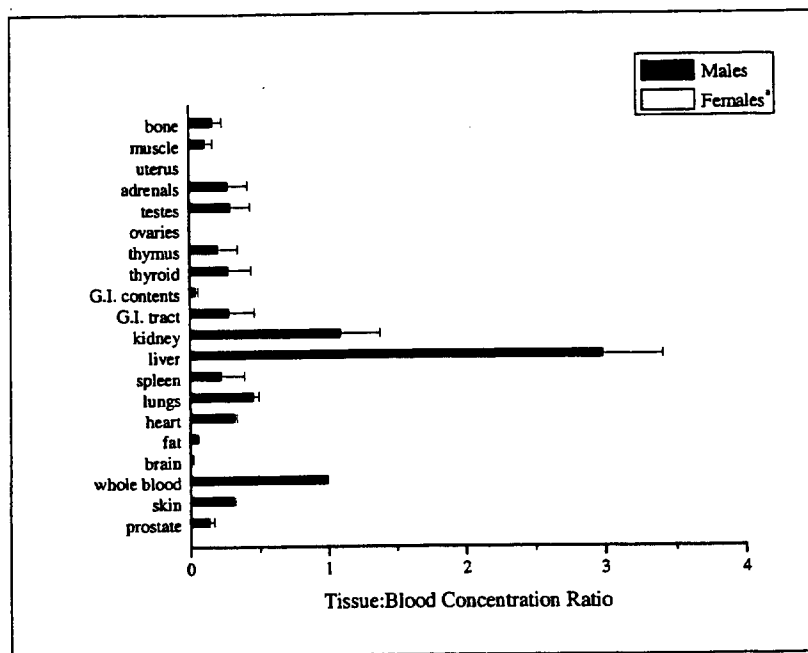


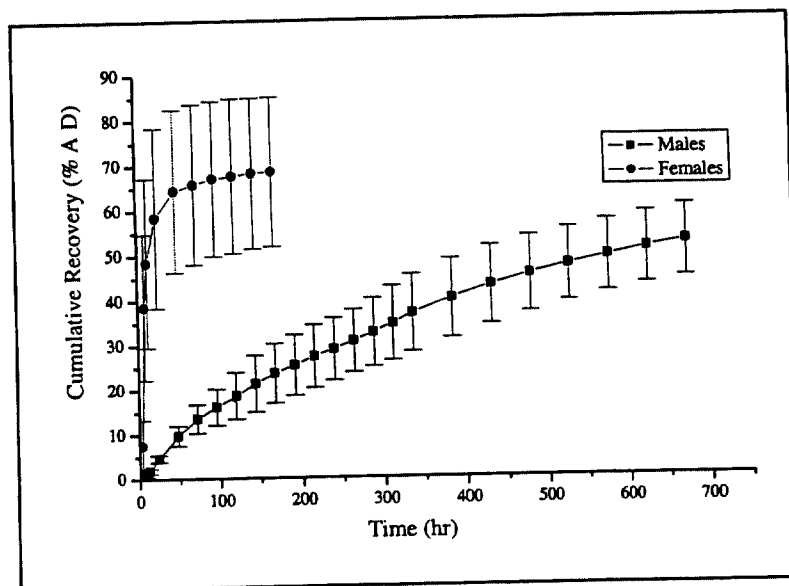
Figure 8: Terminal tissue:blood concentration ratio in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA



^a Whole blood concentration in females was below the detection limits for the assay.

Figure 9: Cumulative recovery of ^{14}C in urine and feces of male and female rats after 14-day repeated oral gavage with 1 mg/kg PFOA, followed by a 1 mg/kg challenge dose of ^{14}C -PFOA (day 15)

Urine



Feces

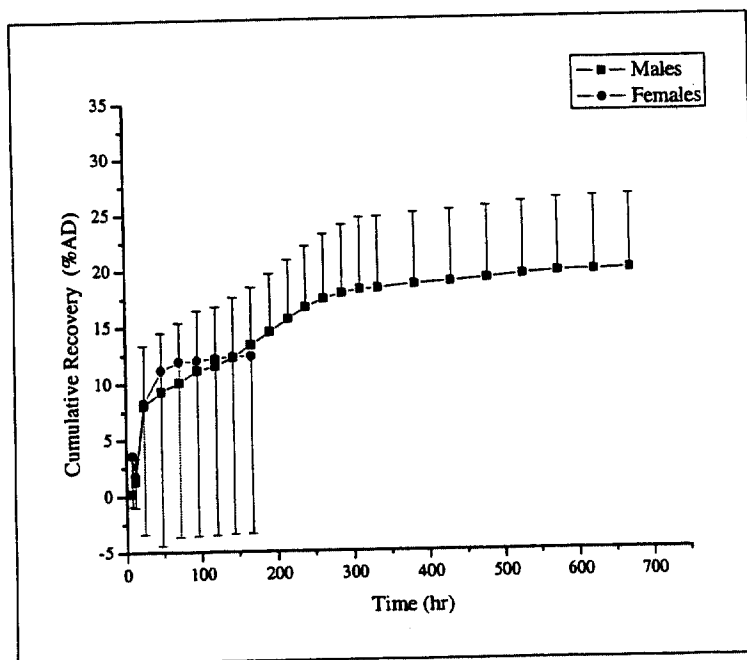


Figure 10: Terminal tissue:blood concentration ratio in male and female rats following 14-day repeated oral gavage with 1 mg/kg ^{14}C -PFOA

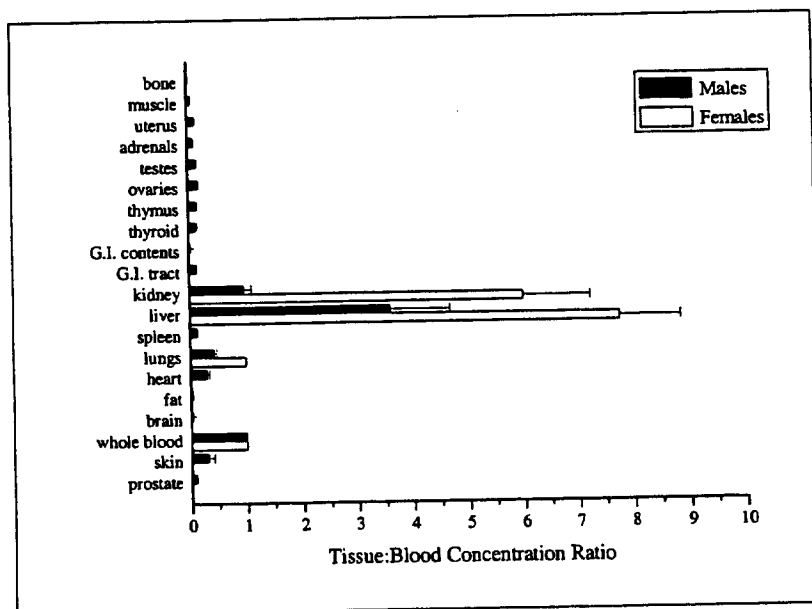
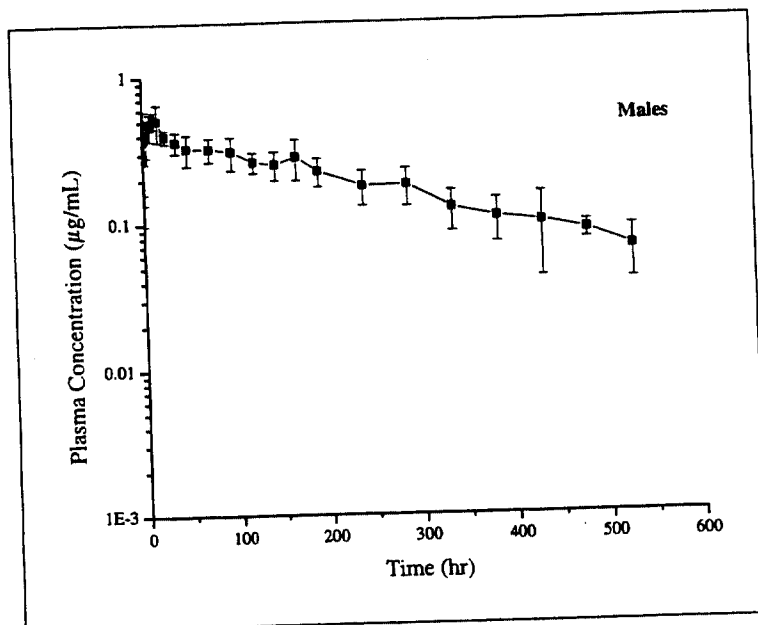


Figure 11: PFOA concentration in serial plasma samples from male and female rats following oral gavage with 0.1 mg/kg PFOA

Males



Females

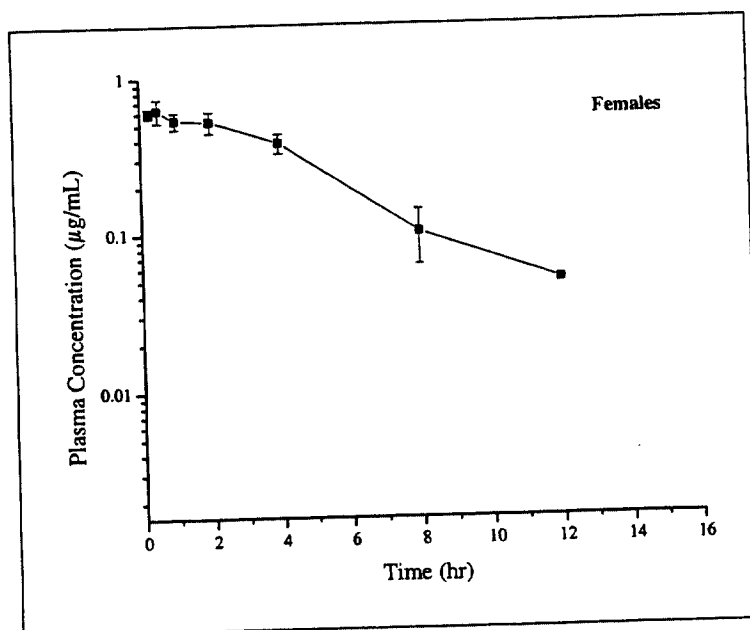
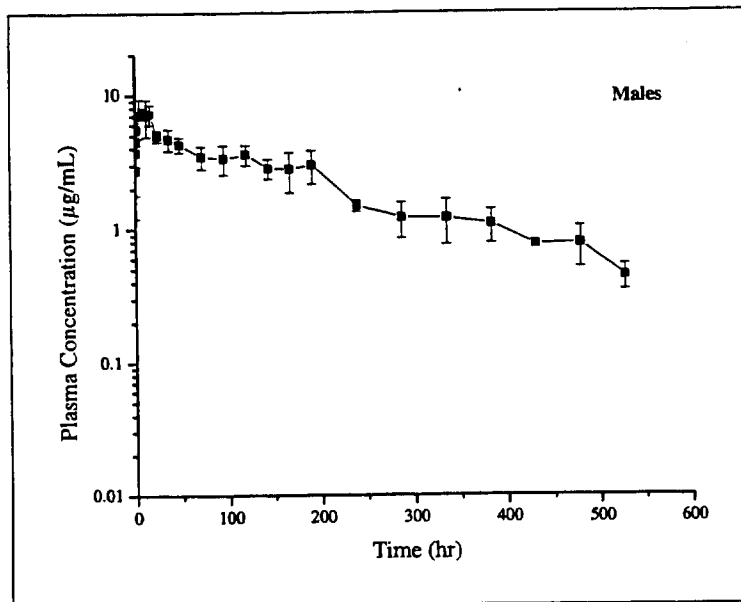


Figure 12: PFOA concentration in serial plasma samples from male and female rats following oral gavage with 1 mg/kg PFOA

Males



Females

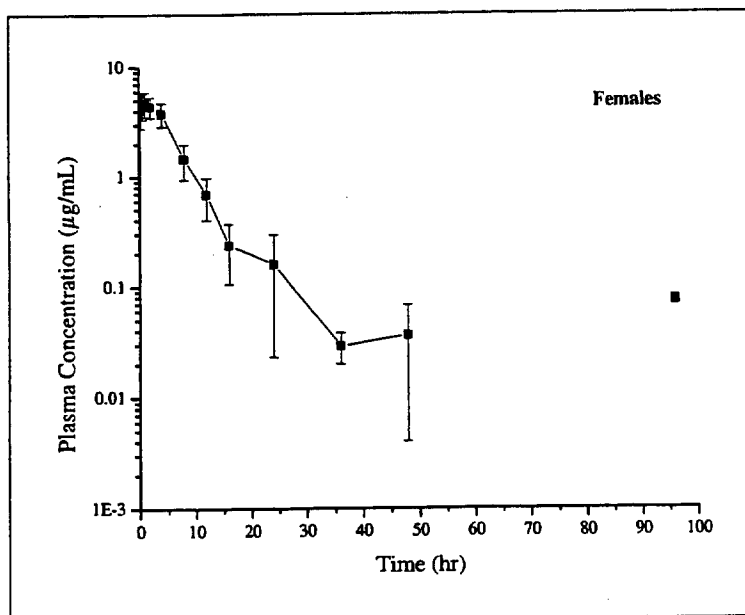
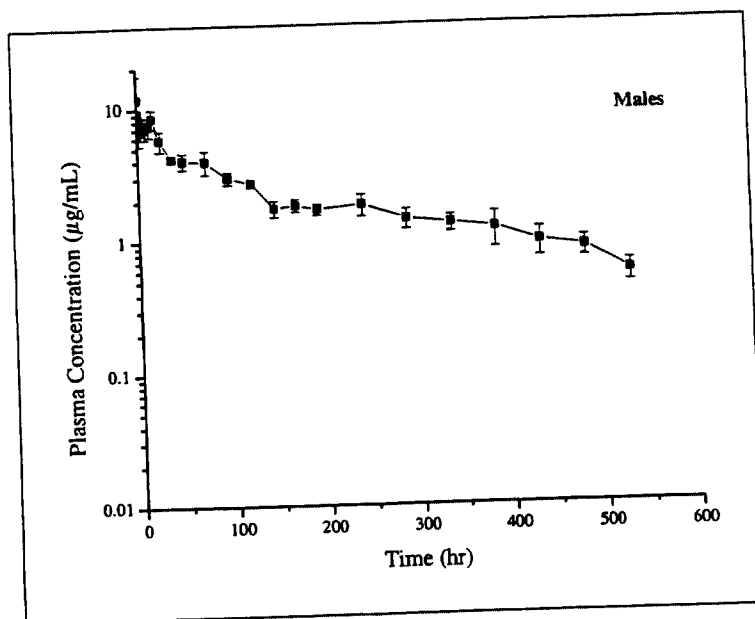


Figure 13: PFOA concentration in serial plasma samples from male and female rats following intravenous injection with 1 mg/kg PFOA

Males



Females

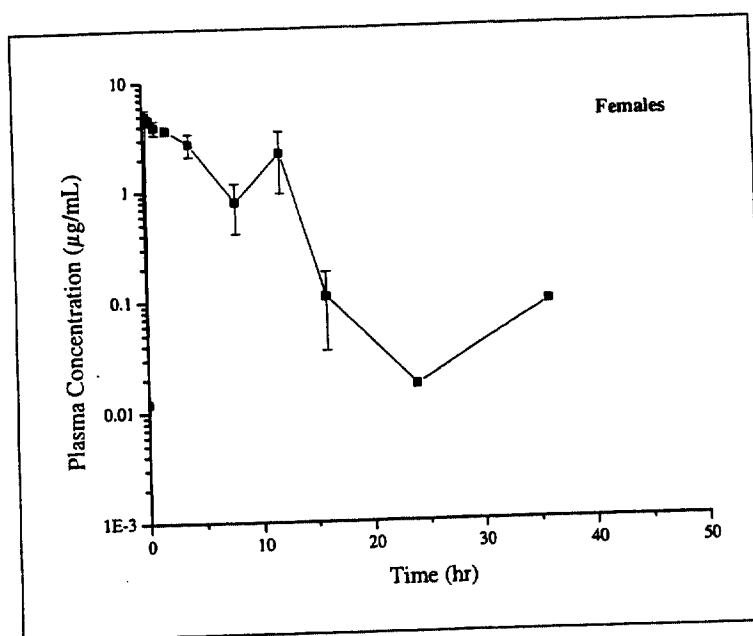
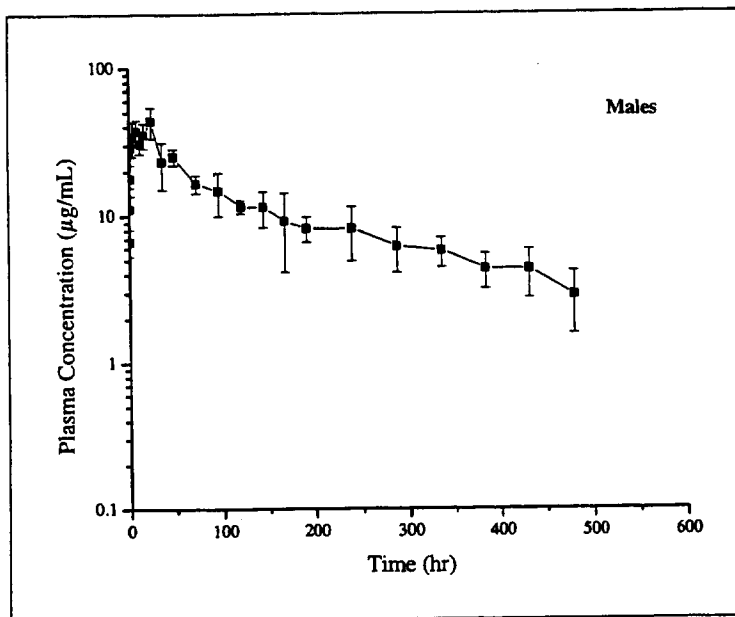


Figure 14: PFOA concentration in serial plasma samples from male and female rats following oral gavage with 5 mg/kg PFOA

Males



Females

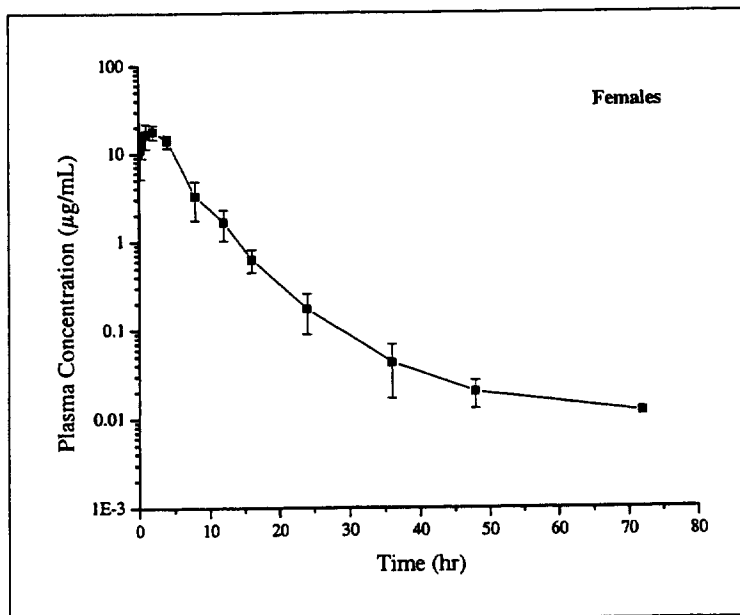
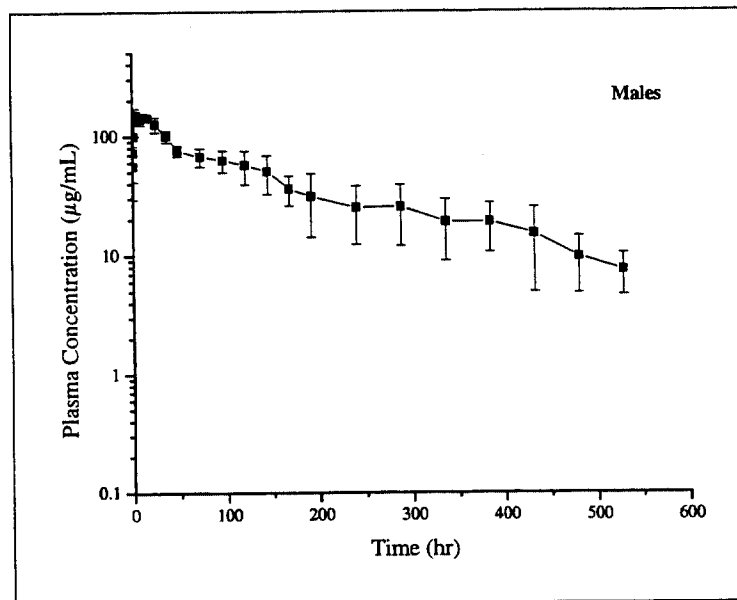


Figure 15: PFOA concentration in serial plasma samples from male and female rats following oral gavage with 25 mg/kg PFOA

Males



Females

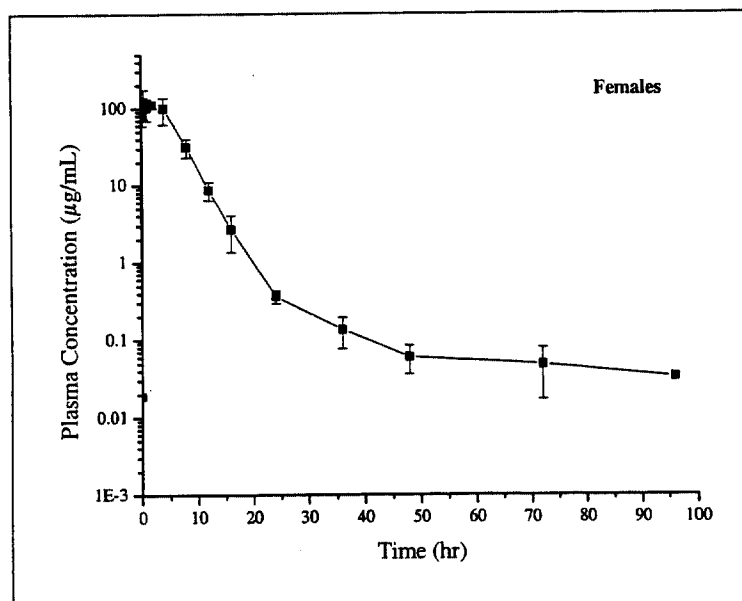
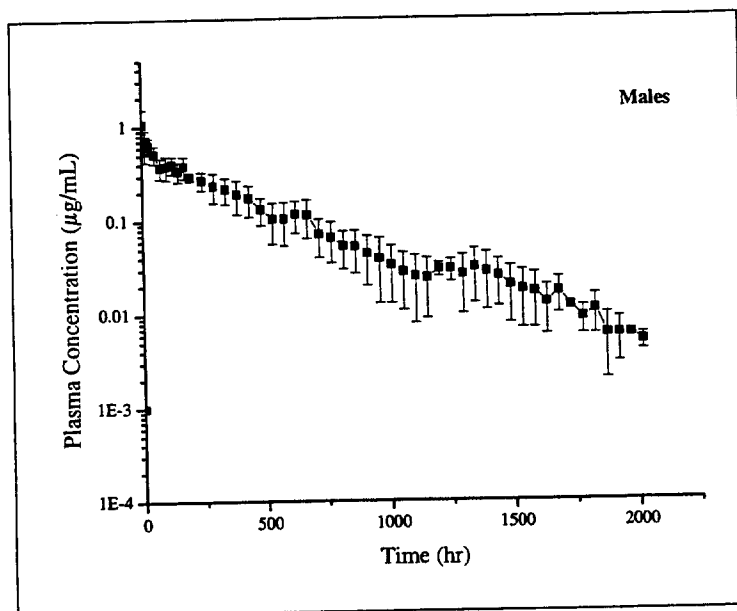


Figure 16: PFOA concentration in serial plasma samples from male and female rats following oral gavage with 0.1 mg/kg PFOA (extended time course)

Males



Females

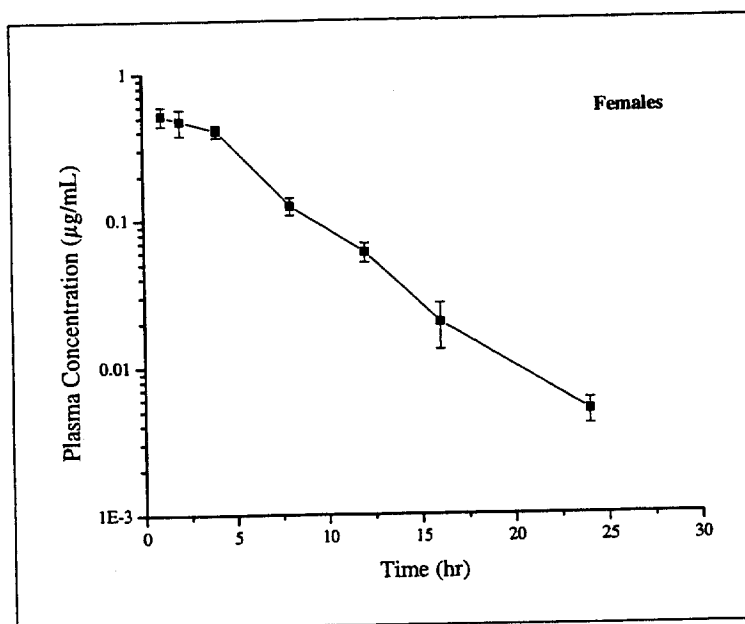
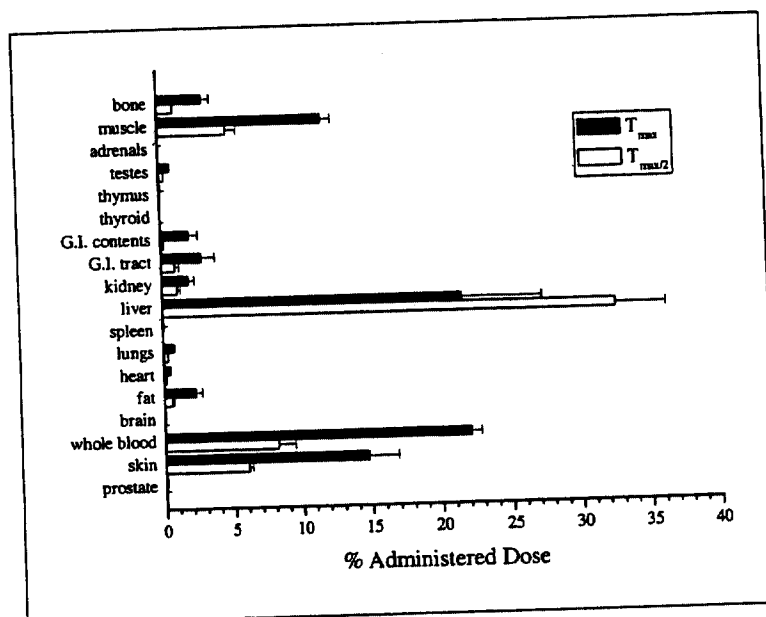


Figure 17: Tissue distribution of ^{14}C at $T_{\max}$ and $T_{\max/2}$ in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA

Males



Females

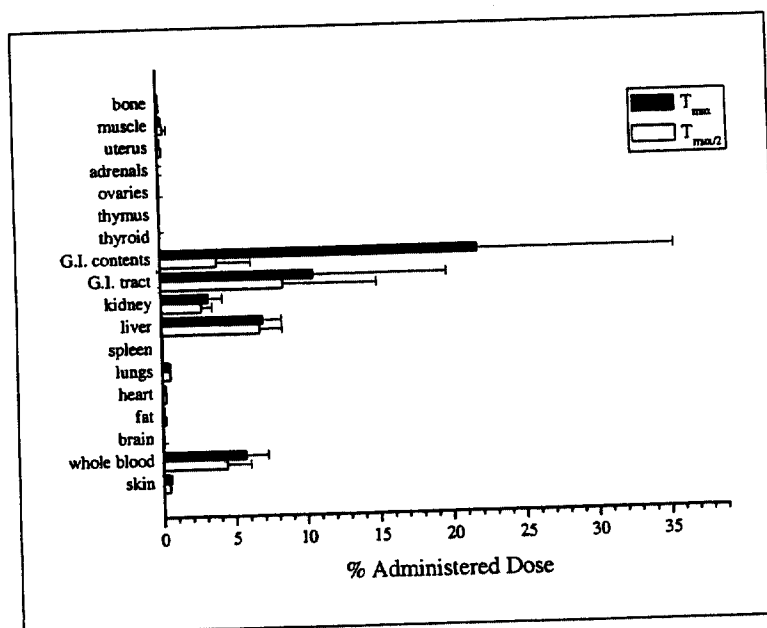
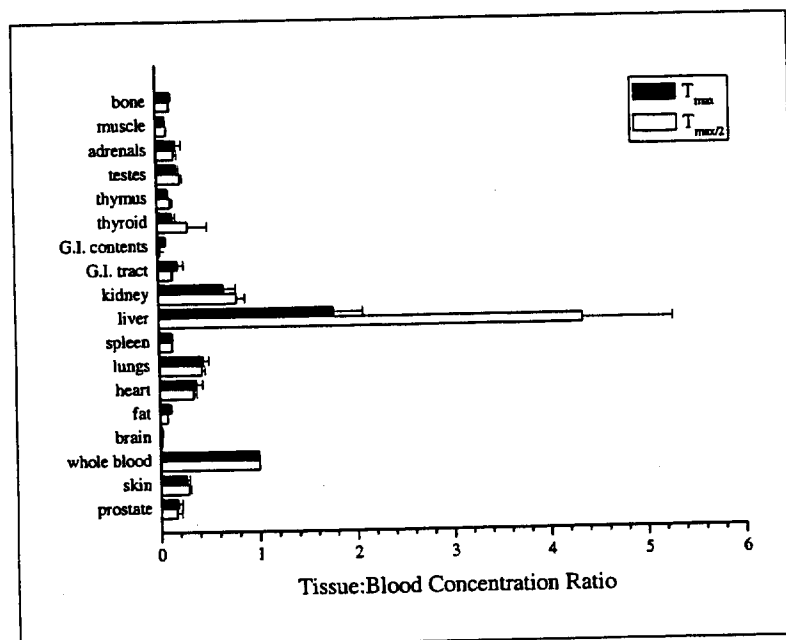


Figure 18: Tissue:blood concentration ratio at T_{max} and $T_{max/2}$ in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA

Males



Females

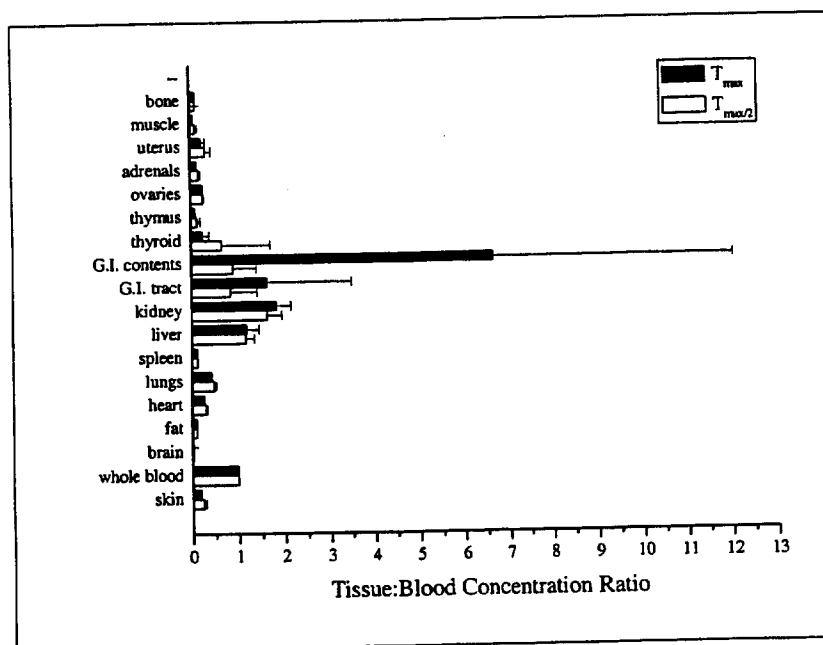
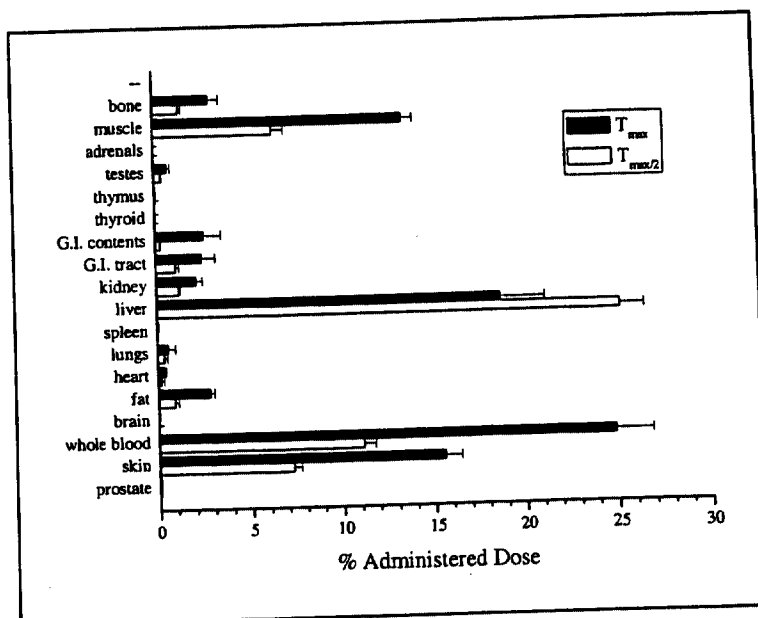


Figure 19: Tissue distribution of ^{14}C at T_{max} and $T_{\text{max}/2}$ in male and female rats following oral gavage with 5 mg/kg ^{14}C -PFOA

Males



Females

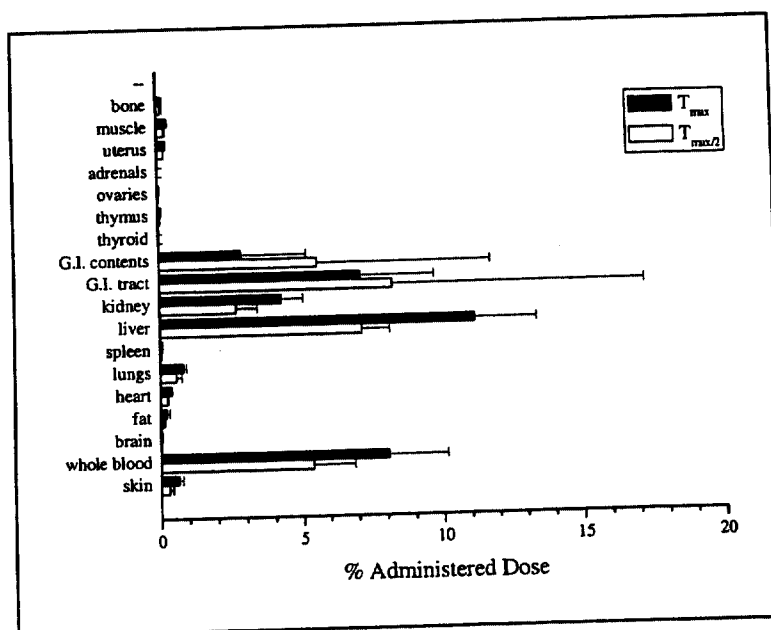
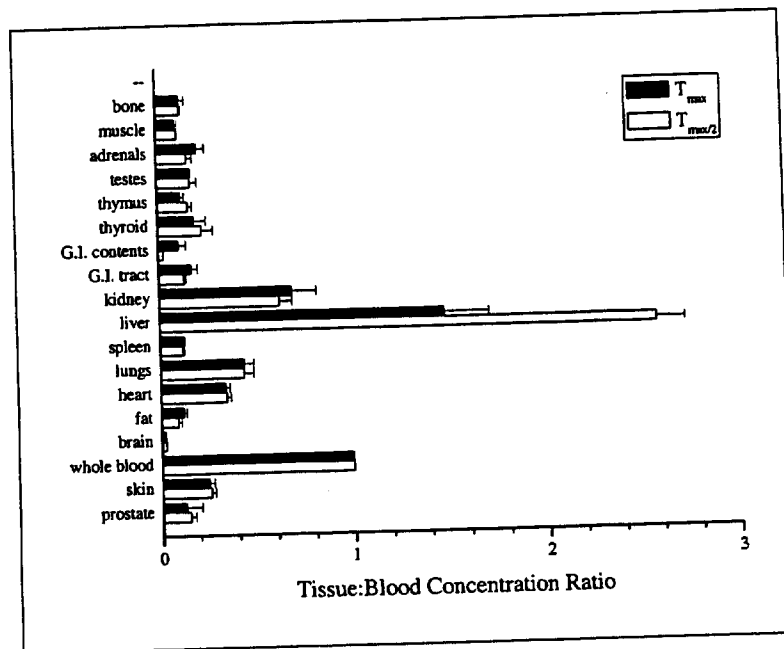


Figure 20: Tissue:blood concentration ratio at T_{max} and $T_{max/2}$ in male and female rats following oral gavage with 5 mg/kg ^{14}C -PFOA

Males



Females

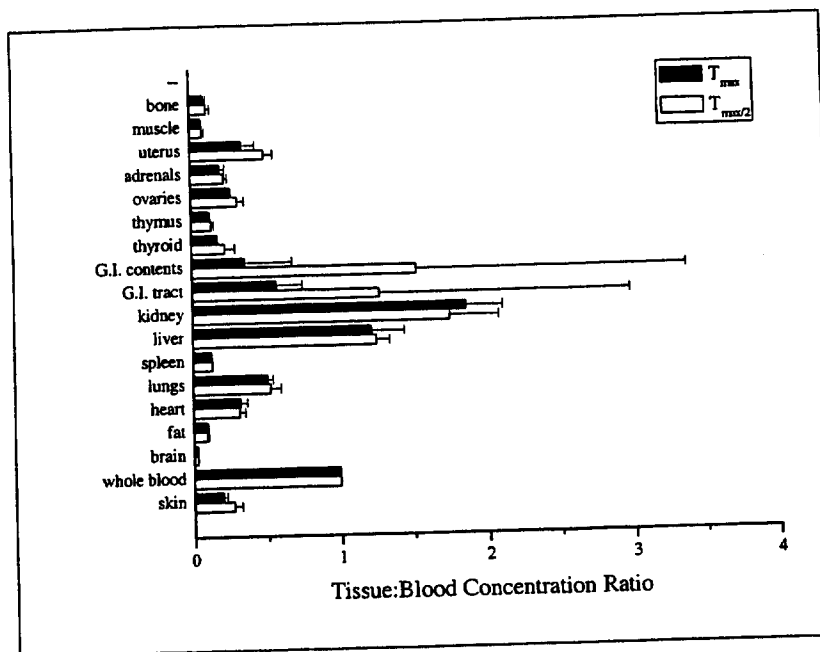
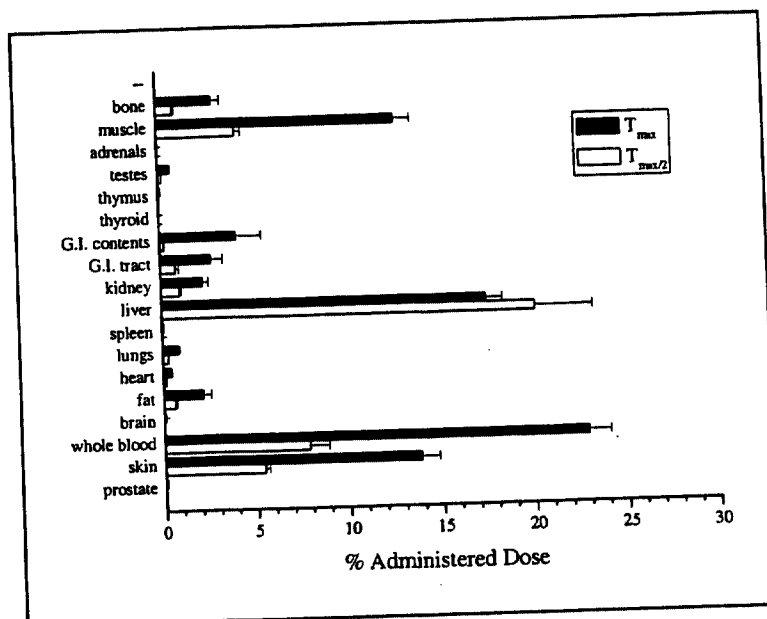


Figure 21: Tissue distribution of ^{14}C at $T_{\max}$ and $T_{\max/2}$ in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

Males



Females

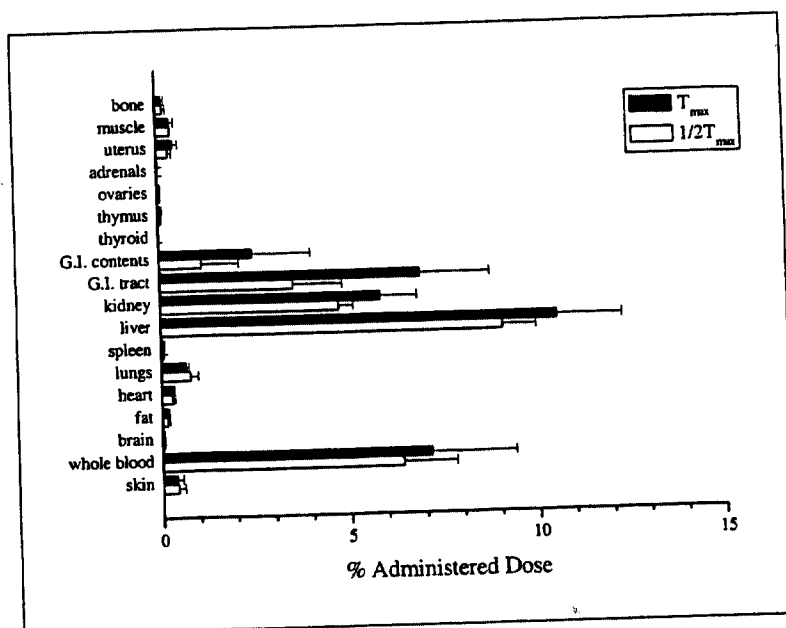
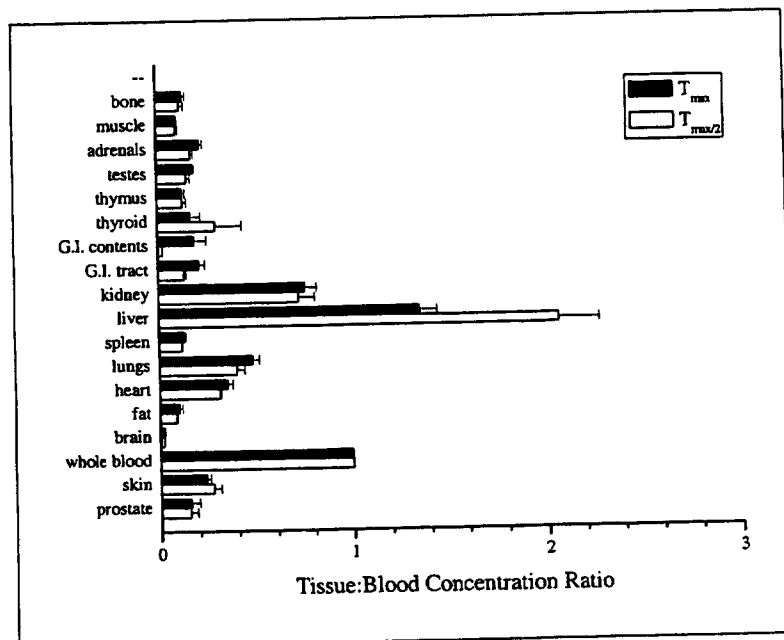
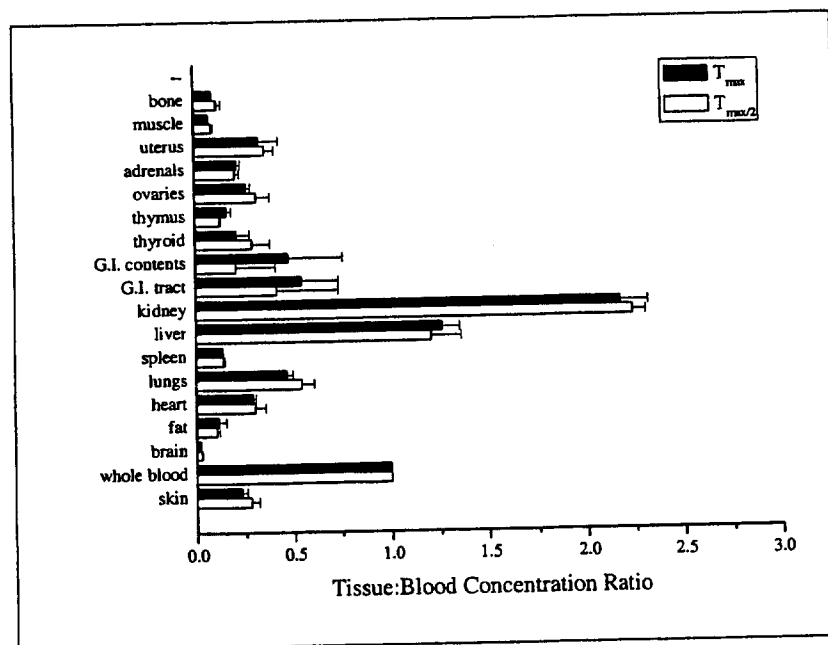


Figure 22: Tissue:blood concentration ratio at T_{max} and $T_{max/2}$ in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

Males



Females



APPENDICES

APPENDICES

EXPLANATORY NOTES

ABBREVIATIONS:

AUC _{INF}	area under the plasma concentration vs. time curve, extrapolated to infinity
AUC _{INF/D}	AUC _{INF} , normalized to dose
Cl _p	plasma clearance
C _{max}	maximum plasma concentration
equiv	equivalent
F	female
G.I.	gastrointestinal
hr or h	hour(s)
Lambda-Z	terminal elimination constant
LOD	limit of detection
LOQ	limit of quantitation
M	male
μCi	microcurie, 2.22x10 ⁶ dpm
m	minute(s)
NA	not applicable
NS	no sample
SD	standard deviation
T _½	terminal elimination half-life
T _{max}	time to C _{max}
T _{max/2}	time to ½ C _{max} following attainment of maximum concentrations

Appendix A
Certificates of Analysis

Sigma-Aldrich Certificate of Analysis

Page 1 of 1

**Certificate of Analysis**

TEST	SPECIFICATION	LOT {08316DO} RESULTS
Product Name	Pentadecafluorooctanoic acid, 96%	
Product Number	171468	
CAS Number	335671	
Formula	$\text{CF}_3(\text{CF}_2)_6\text{CO}_2\text{H}$	
Formula Weight	414.06	
APPEARANCE	WHITE TO OFF-WHITE POWDER	WHITE POWDER
INFRARED SPECTRUM	CONFORMS TO STRUCTURE AND STANDARD AS ILLUSTRATED	CONFORMS TO STRUCTURE AND STANDARD.
TITRATION	95.5% - 104.5% (WITH NaOH)	100.4% (WITH NaOH)
GAS LIQUID CHROMATOGRAPHY	95.5% (MINIMUM)	99.9%
TITRATION	2 % H ₂ O (MAXIMUM)	1.48% H ₂ O (WITH 'KARL FISCHER' REAGENT)
QUALITY CONTROL ACCEPTANCE DATE		JUNE 2001

David Swessel, Supervisor
Quality Control

Appendix B
Pilot Pharmacokinetics in Male and Female Rats
Following Oral Gavage with 1 mg/kg PFOA

Dosing information for male and female rats

Dose Concentration (mg/mL): 0.206
Nominal Dose Volume (mL/kg): 4.0
Nominal Dose Rate (mg/kg): 1.0

Male

Animal	Animal Weight (g)	Dose Volume (mL)	Actual Dose Rate (mg/kg)
651159	239.0	0.94	0.810
651161	268.3	0.97	0.745
Mean	253.7	0.96	0.778
Standard Deviation	20.7	0.02	0.046

Female

Animal	Animal Weight (g)	Dose Volume (mL)	Actual Dose Rate (mg/kg)
651162	231.5	0.89	0.792
651163	225.8	0.88	0.803
Mean	228.7	0.89	0.798
Standard Deviation	4.0	0.01	0.008

Concentration ($\mu\text{g/mL}$) in serial plasma in male and female rats following oral gavage with 1 mg/kg PFOA

Male

Time (h)	Animal Number		Mean	SD
	651159	651161		
0.5	24.64	8.88	16.76	11.1
2	29.78	17.44	23.61	8.7
4	22.40	19.00	20.70	2.4
8	23.74	20.88	22.31	2.0
12	24.18	22.18	23.18	1.4
16	21.86	20.90	21.38	0.7
24	21.40	20.68	21.04	0.5
48	23.56	14.46	19.01	6.4
72	16.46	12.78	14.62	2.6
96	12.58	12.56	12.57	0.0
120	11.14	9.04	10.09	1.5
144	13.34	7.40	10.37	4.2
168	8.39	7.44	7.92	0.7

Female

Time (h)	Animal Number		Mean	SD
	651162	651163		
0.5	17.20	33.40	25.30	11.5
2	14.32	25.08	19.70	7.6
4	9.06	13.16	11.11	2.9
8	4.05	4.71	4.38	0.5
12	1.76	1.31	1.53	0.3
16	0.67	0.39	0.53	0.2
24	0.12	0.09	0.10	0.0
48	0.05	0.01	0.03	0.0
72	0.07	0.01	0.04	0.0
96	0.00	0.00	0.00	0.0
120	0.00	0.00	0.00	0.0
144	0.01	0.00	0.00	0.0
168	0.00	0.00	0.00	0.0

Pharmacokinetic parameters in male and female rats following oral gavage with 1 mg/kg PFOA

Male

Animal #	T _{max} (hr)	C _{max} (μg/mL)	Lambda z (1/hr)	T _{1/2} (hr)	AUC _{INF} (hr·μg/mL)	AUC _{INF} /D (hr·μg/mL/mg·kg)	Cl _p (mL·kg/hr)
651159	2.00	29.78	0.0062	112.60	4122.72	5089.78	0.20
651161	12.00	22.18	0.0074	93.99	3172.78	4287.54	0.23
Mean	7.00	25.98	0.0068	103.30	3647.75	4688.66	0.21
SD	7.07	5.37	0.0006	13.30	671.71	567.27	0.03

Female

Animal #	T _{max} (hr)	C _{max} (μg/mL)	Lambda z (1/hr)	T _{1/2} (hr)	AUC _{INF} (hr·μg/mL)	AUC _{INF} /D (hr·μg/mL/mg·kg)	Cl _p (mL·kg/hr)
651162	0.50	17.20	0.22	3.19	101.67	128.69	7.77
651163	0.50	33.40	0.25	2.72	145.03	181.29	5.52
Mean	0.50	25.30	0.24	2.96	123.35	154.99	6.64
SD	0.00	11.46	0.02	0.33	30.66	37.19	1.59

Appendix C
Pilot Excretion and Material Balance in Male and Female Rats
Following Oral Gavage with 25 mg/kg ^{14}C -PFOA

Dosing information for male and female rats

Dose Concentration (mg/g): 6.369

Nominal Dose Volume (mL/kg): 4.0

Nominal Dose Rate (mg/kg): 25.0

Male

Animal	Animal Weight (g)	Dose Administered (g)	Actual Dose Rate (mg/kg)	Radioactivity Received (μ Ci)
101M	258.8	0.75	18.384	20.246
102M	241.3	0.68	17.843	18.322
Mean	250.1	0.71	18.114	19.284
Standard Deviation	12.4	0.05	0.382	1.361

Female

Animal	Animal Weight (g)	Dose Administered (g)	Actual Dose Rate (mg/kg)	Radioactivity Received (μ Ci)
101F	159.2	0.46	18.364	12.440
102F	155.1	0.44	18.151	11.980
Mean	157.2	0.45	18.257	12.210
Standard Deviation	2.9	0.01	0.150	0.326

Percent recovery of radioactivity in urine in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

Male

	Timepoint	101M	102M	Mean	SD
urine	4 h	0.290	0.143	0.217	0.104
urine	8 h	1.377	0.974	1.176	0.285
urine	12 h	1.347	0.923	1.135	0.300
urine	24 h	3.025	2.114	2.570	0.644
urine	48 h	4.142	3.689	3.916	0.320
urine	72 h	5.316	3.508	4.412	1.278
urine	96 h	4.639	4.521	4.580	0.083
urine	120 h	4.427	4.415	4.421	0.008
urine	144 h	3.273	4.109	3.691	0.591
urine	168 h	4.269	4.119	4.194	0.106
	Total	32.105	28.515	30.310	2.539

Female

	Timepoint	101F	102F	Mean	SD
urine	4 h	29.195	27.791	28.493	0.993
urine	8 h	38.673	25.651	32.162	9.208
urine	12 h	13.793	21.325	17.559	5.326
urine	24 h	8.348	11.588	9.968	2.291
urine	48 h	2.126	2.993	2.560	0.613
urine	72 h	0.484	0.607	0.546	0.087
urine	96 h	0.341	0.360	0.351	0.013
urine	120 h	0.217	0.195	0.206	0.016
urine	144 h	0.149	0.149	0.149	0.000
urine	168 h	0.121	0.173	0.147	0.037
	Total	93.447	90.832	92.140	1.849

Percent recovery of radioactivity in feces in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

Male

	Timepoint	101M	102M	Mean	SD
feces	4 h	0.028	NS	0.028	NA
feces	8 h	NS	0.045	0.045	NA
feces	12 h	1.005	0.008	0.507	0.705
feces	24 h	1.289	7.205	4.247	4.183
feces	48 h	0.579	1.624	1.102	0.739
feces	72 h	0.496	0.372	0.434	0.088
feces	96 h	0.770	0.232	0.501	0.380
feces	120 h	0.755	0.198	0.477	0.394
feces	144 h	1.561	0.130	0.846	1.012
feces	168 h	0.524	0.102	0.313	0.298
	Total	7.007	9.916	8.462	2.057

Female

	Timepoint	101F	102F	Mean	SD
feces	4 h	NS	NS	NA	NA
feces	8 h	NS	NS	NA	NA
feces	12 h	0.200	0.046	0.123	0.109
feces	24 h	0.331	0.102	0.217	0.162
feces	48 h	0.174	0.052	0.113	0.086
feces	72 h	0.030	<LOQ	0.030	NA
feces	96 h	0.018	0.009	0.014	0.006
feces	120 h	0.025	<LOQ	0.025	NA
feces	144 h	0.012	<LOQ	0.012	NA
feces	168 h	0.034	0.022	0.028	0.008
	Total	0.824	0.231	0.528	0.419

Percent recovery of radioactivity in tissues in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

Male

	Timepoint	101M	102M	Mean	SD
prostate	168 h	0.038	0.029	0.034	0.006
carcass	168 h	16.778	20.459	18.619	2.603
skin	168 h	0.674	0.375	0.525	0.211
whole blood	168 h	4.917	6.605	5.761	1.194
brain	168 h	0.023	0.026	0.025	0.002
fat	168 h	0.065	0.065	0.065	0.000
heart	168 h	0.198	0.204	0.201	0.004
lungs	168 h	0.369	0.461	0.415	0.065
spleen	168 h	0.041	0.050	0.046	0.006
liver	168 h	25.811	25.445	25.628	0.259
kidney	168 h	1.180	1.198	1.189	0.013
G.I. tract	168 h	0.895	1.081	0.988	0.132
G.I. contents	168 h	0.219	0.237	0.228	0.013
thymus	168 h	0.040	0.051	0.046	0.008
testes	168 h	0.239	0.286	0.263	0.033
adrenals	168 h	0.007	0.008	0.008	0.001
muscle	168 h	0.192	0.254	0.223	0.044
bone	168 h	0.085	0.070	0.078	0.011
Total		51.771	56.904	54.338	3.630

Female

	Timepoint	101F	102F	Mean	SD
carcass	168 h	<LOD	0.288	0.288	NA
skin	168 h	<LOQ	<LOD	NA	NA
whole blood	168 h	<LOQ	<LOD	NA	NA
brain	168 h	<LOD	<LOD	NA	NA
fat	168 h	<LOD	<LOD	NA	NA
heart	168 h	<LOD	<LOD	NA	NA
lungs	168 h	<LOD	<LOD	NA	NA
spleen	168 h	<LOD	<LOD	NA	NA
liver	168 h	0.009	0.007	0.008	0.001
kidney	168 h	0.002	0.001	0.002	0.001
G.I. tract	168 h	<LOD	<LOD	NA	NA
G.I. contents	168 h	<LOD	<LOD	NA	NA
thymus	168 h	<LOD	<LOD	NA	NA
ovaries	168 h	<LOD	<LOD	NA	NA
adrenals	168 h	<LOD	<LOD	NA	NA
uterus	168 h	<LOD	<LOD	NA	NA
muscle	168 h	<LOD	<LOD	NA	NA
bone	168 h	<LOD	<LOD	NA	NA
Total		0.011	0.296	0.154	0.202

Percent recovery of radioactivity in cage wash and residual feed in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA**Male**

	Timepoint	101M	102M	Mean	SD
cage wash	168 h	0.626	1.014	0.820	0.274
residual feed	168 h	NS	NS	NA	NA
	Total	0.626	1.014	0.820	0.274

Female

	Timepoint	101F	102F	Mean	SD
cage wash	168 h	0.821	0.388	0.605	0.306
residual feed	168 h	0.806	0.095	0.451	0.503
	Total	1.627	0.483	1.055	0.809

Percent recovery of radioactivity in CO₂ trap in male and female rats following oral gavage with 25 mg/kg ¹⁴C-PFOA

Male

	Timepoint	101M	102M	Mean	SD
CO ₂ trap A	24 h	<LOD	<LOD	NA	NA
CO ₂ trap A	48 h	<LOD	<LOD	NA	NA
CO ₂ trap A	72 h	<LOD	<LOD	NA	NA
CO ₂ trap A	96 h	<LOD	<LOD	NA	NA
CO ₂ trap A	120 h	<LOD	<LOD	NA	NA
CO ₂ trap A	144 h	<LOD	<LOD	NA	NA
CO ₂ trap A	168 h	<LOD	<LOD	NA	NA
	Total	NA	NA	NA	NA

Female

	Timepoint	101F	102F	Mean	SD
CO ₂ trap A	24 h	<LOD	<LOD	NA	NA
CO ₂ trap A	48 h	<LOD	<LOD	NA	NA
CO ₂ trap A	72 h	<LOD	<LOD	NA	NA
CO ₂ trap A	96 h	<LOD	<LOD	NA	NA
CO ₂ trap A	120 h	<LOD	<LOD	NA	NA
CO ₂ trap A	144 h	<LOD	<LOD	NA	NA
CO ₂ trap A	168 h	<LOD	<LOD	NA	NA
	Total	NA	NA	NA	NA

Percent recovery of radioactivity as volatile organics (VO) in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

Male

	Timepoint	101M	102M	Mean	SD
VO	24 h	<LOD	<LOD	NA	NA
VO	48 h	<LOD	<LOD	NA	NA
VO	72 h	<LOD	<LOD	NA	NA
VO	96 h	<LOD	<LOD	NA	NA
VO	120 h	<LOD	<LOD	NA	NA
VO	144 h	<LOD	<LOD	NA	NA
VO	168 h	<LOD	<LOD	NA	NA
	Total	NA	NA	NA	NA

Female

	Timepoint	101F	102F	Mean	SD
VO	24 h	<LOD	<LOD	NA	NA
VO	48 h	<LOD	<LOD	NA	NA
VO	72 h	<LOD	<LOD	NA	NA
VO	96 h	<LOD	<LOD	NA	NA
VO	120 h	<LOD	<LOD	NA	NA
VO	144 h	<LOD	<LOD	NA	NA
VO	168 h	<LOD	<LOD	NA	NA
	Total	NA	NA	NA	NA

Concentration ($\mu\text{g equiv/g}$) in tissues in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

Male

	Timepoint	101M	102M	Mean	SD
prostate	168 h	3.106	2.912	3.009	0.137
carcass	168 h	3.478	4.033	3.755	0.393
skin	168 h	6.753	7.544	7.149	0.559
whole blood	168 h	25.068	26.028	25.548	0.679
brain	168 h	0.575	0.565	0.570	0.007
fat	168 h	1.010	1.978	1.494	0.684
heart	168 h	7.733	8.047	7.890	0.222
lungs	168 h	11.530	11.785	11.657	0.181
spleen	168 h	3.197	2.900	3.049	0.210
liver	168 h	60.028	54.730	57.379	3.746
kidney	168 h	17.585	17.402	17.494	0.129
G.I. tract	168 h	3.527	4.015	3.771	0.345
G.I. contents	168 h	0.546	0.540	0.543	0.004
thymus	168 h	3.069	3.070	3.069	0.000
testes	168 h	3.738	3.972	3.855	0.166
adrenals	168 h	4.598	4.098	4.348	0.354
muscle	168 h	1.867	2.364	2.115	0.351
bone	168 h	4.142	2.645	3.394	1.058

Female

	Timepoint	101F	102F	Mean	SD
carcass	168 h	<LOD	0.060	0.060	NA
skin	168 h	<LOQ	<LOD	NA	NA
whole blood	168 h	<LOQ	<LOD	NA	NA
brain	168 h	<LOD	<LOD	NA	NA
fat	168 h	<LOD	<LOD	NA	NA
heart	168 h	<LOD	<LOD	NA	NA
lungs	168 h	<LOD	<LOD	NA	NA
spleen	168 h	<LOD	<LOD	NA	NA
liver	168 h	0.032	0.028	0.030	0.003
kidney	168 h	0.030	0.015	0.023	0.011
G.I. tract	168 h	<LOD	<LOD	NA	NA
G.I. contents	168 h	<LOD	<LOD	NA	NA
thymus	168 h	<LOD	<LOD	NA	NA
ovaries	168 h	<LOD	<LOD	NA	NA
adrenals	168 h	<LOD	<LOD	NA	NA
uterus	168 h	<LOD	<LOD	NA	NA
muscle	168 h	<LOD	<LOD	NA	NA
bone	168 h	<LOD	<LOD	NA	NA

Appendix D
Material Balance in Male and Female Rats
Following Oral Gavage with 1 mg/kg ^{14}C -PFOA

Dosing information for male and female rats

Male Dose Concentration (mg/g): 0.289
Female Dose Concentration (mg/g): 0.214
Nominal Dose Volume (mL/kg): 4.0
Nominal Dose Rate (mg/kg): 1.0

Male

Animal	Animal Weight (g)	Dose Administered (g)	Actual Dose Rate (mg/kg)	Radioactivity Received (μ Ci)
101M	240.9	0.93	1.119	28.301
102M	225.9	0.90	1.155	27.392
103M	232.6	0.93	1.157	28.240
104M	234.3	0.95	1.170	28.786
Mean	233.4	0.93	1.150	28.180
Standard Deviation	6.2	0.02	0.022	0.579

Female

Animal	Animal Weight (g)	Dose Administered (g)	Actual Dose Rate (mg/kg)	Radioactivity Received (μ Ci)
101F	172.0	0.70	0.852	21.973
102F	163.0	0.60	0.846	20.692
103F	182.2	0.70	0.858	23.446
104F	181.0	0.70	0.837	22.710
Mean	174.6	0.68	0.848	22.205
Standard Deviation	8.9	0.05	0.009	1.175

Perfluorooctanoic Acid: Toxicokinetics in the Rat

Percent recovery of radioactivity in urine in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA

Male

	Timepoint	101M	102M	103M	104M	Mean	SD
urine	4 h	0.038	0.024	0.110	0.020	0.048	0.042
urine	8 h	0.619	0.588	0.268	0.158	0.408	0.230
urine	12 h	0.626	1.040	0.867	1.051	0.896	0.199
urine	24 h	2.254	1.808	1.932	2.461	2.114	0.298
urine	48 h	2.915	3.001	3.705	3.858	3.370	0.481
urine	72 h	2.773	3.175	2.767	3.197	2.978	0.240
urine	96 h	2.174	2.278	2.272	2.554	2.320	0.163
urine	120 h	2.364	2.056	2.060	1.925	2.101	0.186
urine	144 h	2.133	1.726	2.682	2.079	2.155	0.395
urine	168 h	2.061	1.801	2.378	1.414	1.914	0.408
urine	Day 8	1.296	1.649	2.047	1.949	1.735	0.338
urine	Day 9	1.187	1.523	1.816	1.978	1.626	0.348
urine	Day 10	1.497	1.395	1.952	2.155	1.750	0.363
urine	Day 11	1.311	1.441	1.636	1.594	1.496	0.149
urine	Day 12	1.612	1.343	1.775	1.157	1.472	0.275
urine	Day 13	1.207	1.303	1.386	0.449	1.086	0.431
urine	Day 14	1.511	1.270	1.242	0.742	1.191	0.323
urine	Day 16	2.147	2.728	2.882	1.601	2.340	0.585
urine	Day 18	2.483	2.203	2.356	2.787	2.457	0.248
urine	Day 20	2.400	1.704	2.391	3.012	2.377	0.534
urine	Day 22	1.953	1.895	1.890	3.348	2.272	0.718
urine	Day 24	1.869	1.210	1.935	3.232	2.062	0.846
urine	Day 26	1.644	1.368	1.389	1.593	1.499	0.140
urine	Day 28	1.342	1.553	1.489	2.092	1.619	0.327
	Total	41.416	40.082	45.227	46.406	43.283	3.015

Female

	Timepoint	101F	102F	103F	104F	Mean	SD
urine	4 h	20.276	7.612	10.156	7.975	11.505	5.954
urine	8 h	27.003	27.422	37.996	31.297	30.930	5.092
urine	12 h	16.385	16.430	11.913	19.279	16.002	3.043
urine	24 h	8.052	11.912	8.060	14.826	10.713	3.290
urine	48 h	1.858	5.041	2.233	3.344	3.119	1.428
urine	72 h	0.875	1.285	1.618	2.373	1.538	0.634
urine	96 h	0.627	0.999	0.846	0.831	0.826	0.153
urine	120 h	0.314	0.498	0.495	0.420	0.432	0.086
urine	144 h	0.200	0.331	0.357	0.427	0.329	0.095
urine	168 h	0.205	0.425	0.569	0.721	0.480	0.220
	Total	75.795	71.955	74.243	81.493	75.872	4.066

Percent recovery of radioactivity in feces in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA

Male

	Timepoint	101M	102M	103M	104M	Mean	SD
feces	4 h	NS	NS	NS	NS	NA	NA
feces	8 h	NS	2.269	NS	NS	2.269	NA
feces	12 h	0.203	6.016	2.743	0.771	2.433	2.625
feces	24 h	10.313	1.634	5.019	5.249	5.554	3.577
feces	48 h	1.391	0.147	0.840	0.972	0.838	0.517
feces	72 h	0.627	0.181	0.217	0.143	0.292	0.225
feces	96 h	0.600	0.166	0.117	0.067	0.238	0.245
feces	120 h	0.178	0.087	0.151	0.086	0.126	0.046
feces	144 h	0.213	0.158	0.118	0.150	0.160	0.039
feces	168 h	0.212	0.069	0.125	0.353	0.190	0.124
feces	Day 8	0.653	0.174	0.109	0.084	0.255	0.268
feces	Day 9	0.694	0.363	0.070	0.070	0.299	0.297
feces	Day 10	0.455	0.123	0.086	0.096	0.190	0.177
feces	Day 11	0.506	0.099	0.066	0.145	0.204	0.204
feces	Day 12	0.147	0.073	0.073	0.097	0.098	0.035
feces	Day 13	0.378	0.050	0.196	0.401	0.256	0.165
feces	Day 14	0.217	0.066	0.180	0.446	0.227	0.159
feces	Day 16	0.609	0.122	0.259	0.558	0.387	0.235
feces	Day 18	0.363	0.112	0.319	0.133	0.232	0.128
feces	Day 20	0.485	0.098	0.284	0.270	0.284	0.158
feces	Day 22	0.578	0.204	0.315	0.140	0.309	0.193
feces	Day 24	0.541	0.212	0.211	0.865	0.457	0.313
feces	Day 26	0.494	0.119	0.083	0.351	0.262	0.195
feces	Day 28	0.165	0.144	0.141	0.341	0.198	0.096
	Total	20.022	12.686	11.722	11.788	14.055	4.003

Female

	Timepoint	101F	102F	103F	104F	Mean	SD
feces	4 h	NS	NS	NS	NS	NA	NA
feces	8 h	NS	NS	NS	NS	NA	NA
feces	12 h	0.275	0.265	4.155	0.261	1.239	1.944
feces	24 h	0.220	0.118	1.924	0.059	0.580	0.898
feces	48 h	0.095	0.075	0.237	0.023	0.108	0.092
feces	72 h	0.029	0.020	0.030	0.032	0.028	0.005
feces	96 h	0.071	0.233	0.102	0.017	0.106	0.092
feces	120 h	0.064	0.074	0.017	0.027	0.046	0.028
feces	144 h	0.052	0.026	0.044	0.010	0.033	0.019
feces	168 h	0.026	0.008	0.037	0.049	0.030	0.017
	Total	0.832	0.819	6.546	0.478	2.169	2.923

Percent recovery of radioactivity in tissues in male and female rats following oral gavage with 1 mg/kg ¹⁴C-PFOA

Male

	Timepoint	101M	102M	103M	104M	Mean	SD
prostate	Day 28	0.011	0.020	0.032	0.017	0.020	0.009
carcass	Day 28	6.129	8.078	9.086	6.260	7.388	1.440
skin	Day 28	0.065	0.105	0.125	0.066	0.090	0.030
whole blood	Day 28	0.878	1.614	1.582	0.986	1.265	0.387
brain	Day 28	0.004	0.008	0.008	0.005	0.006	0.002
fat	Day 28	0.008	0.017	0.024	0.020	0.017	0.007
heart	Day 28	0.049	0.075	0.076	0.055	0.064	0.014
lungs	Day 28	0.093	0.109	0.130	0.101	0.108	0.016
spleen	Day 28	0.011	0.016	0.020	0.011	0.015	0.004
liver	Day 28	14.379	12.553	16.212	10.455	13.400	2.467
kidney	Day 28	0.473	0.445	0.719	0.451	0.522	0.132
G.I. tract	Day 28	0.302	0.354	0.438	0.282	0.344	0.070
G.I. contents	Day 28	0.047	0.072	0.069	0.054	0.061	0.012
thyroid	Day 28	0.001	0.004	0.002	0.001	0.002	0.001
thymus	Day 28	0.008	0.014	0.013	0.007	0.011	0.004
testes	Day 28	0.079	0.138	0.114	0.080	0.103	0.029
adrenals	Day 28	0.001	0.003	0.003	0.002	0.002	0.001
muscle	Day 28	0.080	0.128	0.101	0.072	0.095	0.025
bone	Day 28	0.024	0.047	0.034	0.024	0.032	0.011
Total		22.642	23.800	28.788	18.949	23.545	4.062

Female

	Timepoint	101F	102F	103F	104F	Mean	SD
carcass	168 h	0.105	0.388	0.148	0.217	0.215	0.125
skin	168 h	<LOQ	<LOQ	0.001	<LOQ	0.001	NA
whole blood	168 h	<LOQ	0.002	0.005	<LOQ	0.004	0.002
brain	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
fat	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
heart	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
lungs	168 h	<LOD	<LOD	<LOQ	<LOD	NA	NA
spleen	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
liver	168 h	0.008	0.012	0.016	0.014	0.013	0.003
kidney	168 h	0.001	0.002	0.004	0.002	0.002	0.001
G.I. tract	168 h	<LOD	<LOD	<LOQ	<LOD	NA	NA
G.I. contents	168 h	<LOD	<LOQ	0.003	<LOD	0.003	NA
thyroid	168 h	<LOQ	<LOD	<LOD	<LOD	NA	NA
thymus	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
ovaries	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
adrenals	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
uterus	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
muscle	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
bone	168 h	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
Total		0.114	0.404	0.177	0.233	0.232	0.125

Percent recovery of radioactivity in cage wash and residual feed in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA

Male

	Timepoint	101M	102M	103M	104M	Mean	SD
cage wash	Day 28	1.813	2.912	1.794	2.328	2.212	0.528
residual feed	Day 28	0.513	0.490	0.531	1.411	0.736	0.450
	Total	2.326	3.402	2.325	3.739	2.948	0.732

Female

	Timepoint	101F	102F	103F	104F	Mean	SD
cage wash	168 h	3.183	2.131	4.510	1.592	2.854	1.287
residual feed	168 h	0.182	0.176	0.243	0.192	0.198	0.031
	Total	3.365	2.307	4.753	1.784	3.052	1.311

Concentration ($\mu\text{g equiv/g}$) in tissues in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA

Male

	Timepoint	101M	102M	103M	104M	Mean	SD
prostate	Day 28	0.033	0.057	0.070	0.041	0.050	0.016
carcass	Day 28	0.043	0.074	0.074	0.055	0.061	0.015
skin	Day 28	0.084	0.146	0.132	0.097	0.115	0.029
whole blood	Day 28	0.259	0.442	0.441	0.283	0.357	0.099
brain	Day 28	0.006	0.010	0.009	0.007	0.008	0.002
fat	Day 28	0.005	0.021	0.017	0.013	0.014	0.007
heart	Day 28	0.084	0.152	0.150	0.099	0.121	0.035
lungs	Day 28	0.117	0.220	0.194	0.151	0.171	0.046
spleen	Day 28	0.044	0.069	0.062	0.041	0.054	0.014
liver	Day 28	1.892	2.325	2.310	1.423	1.987	0.427
kidney	Day 28	0.324	0.377	0.423	0.304	0.357	0.054
G.I. tract	Day 28	0.033	0.065	0.063	0.042	0.051	0.016
G.I. contents	Day 28	0.006	0.012	0.010	0.006	0.008	0.003
thyroid	Day 28	0.036	0.098	0.093	0.039	0.066	0.034
thymus	Day 28	0.034	0.055	0.062	0.036	0.047	0.014
testes	Day 28	0.061	0.105	0.134	0.066	0.092	0.035
adrenals	Day 28	0.034	0.083	0.069	0.037	0.056	0.024
muscle	Day 28	0.027	0.044	0.039	0.029	0.035	0.008
bone	Day 28	0.048	0.070	0.055	0.046	0.054	0.011

Female

	Timepoint	101F	102F	103F	104F	Mean	SD
carcass	168 h	0.001	0.003	0.001	0.002	0.002	0.001
skin	168 h	<LOQ	<LOQ	0.001	<LOQ	0.001	NA
whole blood	168 h	<LOQ	0.000*	0.001	<LOQ	0.001	0.000
brain	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
fat	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
heart	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
lungs	168 h	<LOD	<LOD	<LOQ	<LOD	NA	NA
spleen	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
liver	168 h	0.001	0.002	0.002	0.002	0.002	0.000
kidney	168 h	0.001	0.001	0.003	0.001	0.002	0.001
G.I. tract	168 h	<LOD	<LOD	<LOQ	<LOD	NA	NA
G.I. contents	168 h	<LOD	<LOQ	0.000*	<LOD	0.000*	NA
thyroid	168 h	<LOQ	<LOD	<LOD	<LOD	NA	NA
thymus	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
ovaries	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
adrenals	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
uterus	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
muscle	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
bone	168 h	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA

*Value above LOD, but <0.001

Appendix E
Material Balance in Male and Female Rats
Following Oral Gavage with 5 mg/kg ^{14}C -PFOA

Dosing information for male and female rats

Dose Concentration (mg/g): 1.211
Nominal Dose Volume (mL/kg): 4.0
Nominal Dose Rate (mg/kg): 5.0

Male

Animal	Animal Weight (g)	Dose Administered (g)	Actual Dose Rate (mg/kg)	Radioactivity Received (μ Ci)
101M	198.0	0.78	4.787	22.476
102M	197.7	0.79	4.807	22.534
103M	201.2	0.80	4.795	22.878
104M	193.3	0.72	4.497	20.611
Mean	197.6	0.77	4.722	22.125
Standard Deviation	3.2	0.04	0.150	1.025

Female

Animal	Animal Weight (g)	Dose Administered (g)	Actual Dose Rate (mg/kg)	Radioactivity Received (μ Ci)
101F	197.8	0.79	4.835	22.677
102F	192.9	0.77	4.801	21.960
103F	210.5	0.85	4.865	24.285
104F	200.1	0.80	4.810	22.821
Mean	200.3	0.80	4.828	22.936
Standard Deviation	7.4	0.03	0.029	0.975

Percent recovery of radioactivity in urine in male and female rats following oral gavage with 5 mg/kg ^{14}C -PFOA

Male

	Timepoint	101M	102M	103M	104M	Mean	SD
urine	4 h	0.195	0.066	0.045	<LOD	0.102	0.081
urine	8 h	0.817	0.765	0.240	NS	0.607	0.319
urine	12 h	0.599	0.737	1.210	1.625	1.043	0.468
urine	24 h	2.231	2.179	2.813	3.076	2.575	0.441
urine	48 h	4.907	3.609	4.774	4.490	4.445	0.584
urine	72 h	4.188	2.764	4.340	4.432	3.931	0.784
urine	96 h	3.558	2.588	3.513	4.231	3.473	0.675
urine	120 h	3.357	4.265	2.985	4.383	3.748	0.684
urine	144 h	3.411	3.120	3.442	3.410	3.346	0.151
urine	168 h	3.434	4.547	2.759	3.075	3.454	0.779
urine	Day 8	3.160	2.646	2.972	2.920	2.925	0.212
urine	Day 9	2.763	2.298	2.619	2.856	2.634	0.244
urine	Day 10	2.866	2.357	2.597	2.877	2.674	0.248
urine	Day 11	2.403	2.134	2.372	2.605	2.379	0.193
urine	Day 12	2.359	1.816	2.414	2.373	2.241	0.284
urine	Day 13	2.197	1.657	2.004	2.320	2.045	0.289
urine	Day 14	1.987	1.435	1.941	2.113	1.869	0.298
urine	Day 16	3.555	3.300	3.181	2.818	3.214	0.306
urine	Day 18	3.608	3.691	3.255	2.963	3.379	0.336
urine	Day 20	3.352	2.835	3.069	2.755	3.003	0.268
urine	Day 22	3.248	2.544	2.651	2.710	2.788	0.314
urine	Day 24	2.587	1.978	2.510	2.179	2.314	0.285
urine	Day 26	2.257	2.273	2.067	2.436	2.258	0.151
urine	Day 28	2.060	1.680	1.781	2.220	1.935	0.249
	Total	65.099	57.284	61.554	64.867	62.201	3.656

Female

	Timepoint	101F	102F	103F	104F	Mean	SD
urine	4 h	4.296	NS	19.095	<LOD	11.696	10.464
urine	8 h	37.676	33.762	30.895	38.518	35.213	3.547
urine	12 h	16.617	19.676	12.663	19.801	17.189	3.358
urine	24 h	21.722	14.401	7.168	10.969	13.565	6.189
urine	48 h	3.828	3.616	2.564	2.095	3.026	0.831
urine	72 h	0.737	1.833	0.952	0.510	1.008	0.579
urine	96 h	0.807	0.696	0.662	0.323	0.622	0.209
urine	120 h	0.461	1.348	0.483	0.274	0.642	0.480
urine	144 h	0.219	0.909	0.375	0.261	0.441	0.319
urine	168 h	0.248	0.467	0.370	0.169	0.314	0.132
	Total	86.611	76.708	75.227	72.920	77.867	6.034

Perfluorooctanoic Acid: Toxicokinetics in the Rat

Percent recovery of radioactivity in feces in male and female rats following oral gavage with 5 mg/kg ^{14}C -PFOA

Male

	Timepoint	101M	102M	103M	104M	Mean	SD
feces	4 h	NS	NS	NS	NS	NA	NA
feces	8 h	NS	NS	NS	NS	NA	NA
feces	12 h	4.010	0.032	0.063	0.002	1.027	1.989
feces	24 h	1.027	0.742	0.770	0.420	0.740	0.249
feces	48 h	0.336	1.107	0.365	0.334	0.536	0.381
feces	72 h	0.204	1.228	0.200	0.688	0.580	0.489
feces	96 h	0.209	0.825	0.216	0.170	0.355	0.314
feces	120 h	0.120	0.328	0.137	0.204	0.197	0.094
feces	144 h	0.114	0.279	0.116	0.196	0.176	0.078
feces	168 h	0.090	0.135	0.151	0.185	0.140	0.039
feces	Day 8	0.098	0.112	0.124	0.177	0.128	0.035
feces	Day 9	0.085	0.117	0.095	0.146	0.111	0.027
feces	Day 10	0.084	0.265	0.099	0.146	0.149	0.082
feces	Day 11	0.100	0.218	0.131	0.131	0.145	0.051
feces	Day 12	0.070	0.228	0.083	0.094	0.119	0.073
feces	Day 13	0.058	0.129	0.077	0.089	0.088	0.030
feces	Day 14	0.061	0.140	0.103	0.101	0.101	0.032
feces	Day 16	0.221	0.129	0.152	0.312	0.204	0.082
feces	Day 18	0.084	0.175	0.133	0.251	0.161	0.071
feces	Day 20	0.095	0.137	0.107	0.155	0.124	0.027
feces	Day 22	0.079	0.089	0.109	0.149	0.107	0.031
feces	Day 24	0.062	0.129	0.180	0.108	0.120	0.049
feces	Day 26	0.078	0.131	0.137	0.113	0.115	0.027
feces	Day 28	0.065	0.154	0.273	0.101	0.148	0.091
	Total	7.350	6.829	3.821	4.272	5.568	1.779

Female

	Timepoint	101F	102F	103F	104F	Mean	SD
feces	4 h	NS	0.003	NS	NS	0.003	NA
feces	8 h	NS	NS	NS	NS	NA	NA
feces	12 h	NS	1.085	1.182	NS	1.134	0.069
feces	24 h	3.262	0.396	0.712	11.365	3.934	5.118
feces	48 h	0.319	0.145	0.277	1.499	0.560	0.630
feces	72 h	0.056	0.165	0.284	0.857	0.341	0.357
feces	96 h	0.026	0.029	0.386	0.142	0.146	0.169
feces	120 h	0.069	0.059	0.328	0.021	0.119	0.141
feces	144 h	0.047	0.072	0.297	0.006	0.106	0.131
feces	168 h	0.039	0.245	0.168	0.004	0.114	0.112
	Total	3.818	2.199	3.634	13.894	5.886	5.387

Percent recovery of radioactivity in tissues in male and female rats following oral gavage with 5 mg/kg ^{14}C -PFOA

Male

	Timepoint	101M	102M	103M	104M	Mean	SD
prostate	Day 28	0.010	0.017	0.016	0.015	0.015	0.003
carcass	Day 28	5.379	5.954	7.394	7.981	6.677	1.214
skin	Day 28	0.055	0.068	0.089	0.084	0.074	0.016
whole blood	Day 28	0.999	1.043	1.254	1.434	1.183	0.201
brain	Day 28	0.004	0.005	0.007	0.006	0.006	0.001
fat	Day 28	0.018	0.020	0.016	0.016	0.018	0.002
heart	Day 28	0.042	0.049	0.068	0.064	0.056	0.012
lungs	Day 28	0.055	0.092	0.121	0.116	0.096	0.030
spleen	Day 28	0.011	0.015	0.018	0.013	0.014	0.003
liver	Day 28	10.637	9.392	10.830	12.756	10.904	1.390
kidney	Day 28	0.381	0.397	0.350	0.423	0.388	0.031
G.I. tract	Day 28	0.201	0.250	0.275	0.308	0.259	0.045
G.I. contents	Day 28	0.054	0.039	0.051	0.076	0.055	0.015
thyroid	Day 28	0.001	0.002	0.003	0.002	0.002	0.001
thymus	Day 28	0.010	0.014	0.013	0.017	0.014	0.003
testes	Day 28	0.072	0.098	0.105	0.097	0.093	0.014
adrenals	Day 28	0.015	0.002	0.003	0.002	0.006	0.006
muscle	Day 28	0.056	0.060	0.073	0.070	0.065	0.008
bone	Day 28	0.021	0.028	0.032	0.030	0.028	0.005
Total		18.021	17.545	20.718	23.510	19.949	2.755

Female

	Timepoint	101F	102F	103F	104F	Mean	SD
carcass	168 h	0.109	0.170	0.083	<LOD	0.121	0.045
skin	168 h	<LOQ	<LOQ	<LOD	<LOD	NA	NA
whole blood	168 h	<LOQ	<LOQ	<LOQ	<LOD	NA	NA
brain	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
fat	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
heart	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
lungs	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
spleen	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
liver	168 h	0.016	0.018	0.018	0.013	0.016	0.002
kidney	168 h	0.002	0.002	0.002	0.002	0.002	0.000
G.I. tract	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
G.I. contents	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
thyroid	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
thymus	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
ovaries	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
adrenals	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
uterus	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
muscle	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
bone	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
Total		0.127	0.190	0.103	0.015	0.109	0.072

Percent recovery of radioactivity in cage wash and residual feed in male and female rats following oral gavage with 5 mg/kg ^{14}C -PFOA

Male

	Timepoint	101M	102M	103M	104M	Mean	SD
cage wash	Day 28	2.318	6.263	4.058	1.967	3.652	1.966
residual feed	Day 28	0.019	0.860	0.253	<LOD	0.377	0.434
	Total	2.337	7.123	4.311	1.967	3.935	2.362

Female

	Timepoint	101F	102F	103F	104F	Mean	SD
cage wash	168 h	1.578	3.102	3.219	1.768	2.417	0.864
residual feed	168 h	1.159	0.510	0.409	0.086	0.541	0.450
	Total	2.737	3.612	3.628	1.854	2.958	0.845

Concentration ($\mu\text{g equiv/g}$) in tissues in male and female rats following oral gavage with 5 mg/kg ^{14}C -PFOA

Male

	Timepoint	101M	102M	103M	104M	Mean	SD
prostate	Day 28	0.098	0.129	0.201	0.141	0.142	0.043
carcass	Day 28	0.151	0.166	0.203	0.197	0.179	0.025
skin	Day 28	0.245	0.342	0.416	0.377	0.345	0.073
whole blood	Day 28	0.941	0.987	1.241	1.244	1.103	0.161
brain	Day 28	0.022	0.023	0.032	0.029	0.027	0.005
fat	Day 28	0.037	0.047	0.068	0.057	0.052	0.013
heart	Day 28	0.289	0.303	0.409	0.394	0.349	0.061
lungs	Day 28	0.415	0.452	0.603	0.500	0.492	0.081
spleen	Day 28	0.142	0.160	0.173	0.162	0.159	0.013
liver	Day 28	5.504	4.653	6.187	4.979	5.331	0.670
kidney	Day 28	0.977	1.014	0.837	0.913	0.935	0.078
G.I. tract	Day 28	0.135	0.147	0.206	0.172	0.165	0.031
G.I. contents	Day 28	0.022	0.022	0.044	0.025	0.028	0.011
thyroid	Day 28	0.127	0.165	0.244	0.168	0.176	0.049
thymus	Day 28	0.128	0.155	0.146	0.152	0.145	0.012
testes	Day 28	0.211	0.260	0.313	0.273	0.264	0.042
adrenals	Day 28	1.328	0.131	0.221	0.191	0.468	0.574
muscle	Day 28	0.090	0.096	0.112	0.112	0.102	0.011
bone	Day 28	0.142	0.171	0.192	0.192	0.174	0.023

Female

	Timepoint	101F	102F	103F	104F	Mean	SD
carcass	168 h	0.006	0.010	0.004	<LOD	0.007	0.003
skin	168 h	<LOQ	<LOQ	<LOD	<LOD	NA	NA
whole blood	168 h	<LOQ	<LOQ	<LOQ	<LOD	NA	NA
brain	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
fat	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
heart	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
lungs	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
spleen	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
liver	168 h	0.015	0.019	0.016	0.012	0.016	0.003
kidney	168 h	0.008	0.011	0.011	0.009	0.010	0.001
G.I. tract	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
G.I. contents	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
thyroid	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
thymus	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
ovaries	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
adrenals	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
uterus	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
muscle	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
bone	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA

Appendix F
Material Balance in Male and Female Rats
Following Oral Gavage with 25 mg/kg ^{14}C -PFOA

Dosing information for male and female rats

Dose Concentration (mg/g): 6.447
Nominal Dose Volume (mL/kg): 4.0
Nominal Dose Rate (mg/kg): 25.0

Male

Animal	Animal Weight (g)	Dose Administered (g)	Actual Dose Rate (mg/kg)	Radioactivity Received (μ Ci)
301M	216.3	0.87	25.903	24.915
302M	201.8	0.81	25.815	23.166
303M	213.0	0.83	25.244	23.911
304M	208.1	0.88	27.326	25.287
Mean	209.8	0.85	26.072	24.320
Standard Deviation	6.3	0.03	0.885	0.964

Female

Animal	Animal Weight (g)	Dose Administered (g)	Actual Dose Rate (mg/kg)	Radioactivity Received (μ Ci)
301F	183.7	0.73	25.621	20.930
302F	196.0	0.77	25.395	22.134
303F	187.2	0.75	25.831	21.503
304F	187.2	0.74	25.452	21.188
Mean	188.5	0.75	25.574	21.438
Standard Deviation	5.2	0.02	0.196	0.519

Perfluorooctanoic Acid: Toxicokinetics in the Rat

Percent recovery of radioactivity in urine in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

Male

	Timepoint	301M	302M	303M	304M	Mean	SD
urine	4 h	0.223	0.218	0.054	0.510	0.251	0.190
urine	8 h	1.056	1.155	0.321	0.552	0.771	0.400
urine	12 h	1.569	1.757	0.509	1.563	1.350	0.568
urine	24 h	3.120	4.265	3.577	2.070	3.258	0.921
urine	48 h	9.291	6.501	6.788	4.632	6.803	1.914
urine	72 h	6.681	5.453	3.688	2.613	4.609	1.811
urine	96 h	5.610	4.712	2.866	2.916	4.026	1.361
urine	120 h	4.489	3.663	4.172	2.791	3.779	0.741
urine	144 h	4.040	3.380	2.992	2.540	3.238	0.635
urine	168 h	3.045	2.511	1.771	2.941	2.567	0.579
urine	Day 8	2.668	1.857	1.451	2.288	2.066	0.527
urine	Day 9	2.539	1.734	0.102	2.250	1.656	1.088
urine	Day 10	2.179	2.109	1.397	1.738	1.856	0.362
urine	Day 11	1.879	2.261	1.433	1.288	1.715	0.442
urine	Day 12	1.334	2.170	1.022	1.631	1.539	0.489
urine	Day 13	1.057	1.036	0.973	1.661	1.182	0.321
urine	Day 14	0.662	1.285	1.000	1.548	1.124	0.381
urine	Day 16	0.993	1.876	1.042	2.069	1.495	0.557
urine	Day 18	0.826	1.717	0.792	1.268	1.151	0.435
urine	Day 20	1.927	2.803	2.012	2.255	2.249	0.394
urine	Day 22	1.812	2.309	1.730	1.959	1.953	0.256
urine	Day 24	1.731	1.814	1.763	1.969	1.819	0.106
urine	Day 26	1.229	1.804	1.228	1.826	1.522	0.339
urine	Day 28	0.703	1.707	0.860	1.878	1.287	0.591
	Total	60.663	60.097	43.543	48.756	53.265	8.490

Female

	Timepoint	301F	302F	303F	304F	Mean	SD
urine	4 h	35.531	19.430	22.344	17.871	23.794	8.041
urine	8 h	24.640	19.922	24.573	45.210	28.586	11.300
urine	12 h	9.742	16.571	15.024	15.463	14.200	3.042
urine	24 h	8.623	3.696	14.514	12.587	9.855	4.783
urine	48 h	3.079	3.371	5.152	3.254	3.714	0.966
urine	72 h	1.887	1.510	1.812	0.945	1.539	0.428
urine	96 h	1.833	0.989	0.994	0.503	1.080	0.552
urine	120 h	0.487	1.022	0.923	0.391	0.706	0.313
urine	144 h	0.276	0.651	0.548	0.261	0.434	0.196
urine	168 h	0.202	0.715	0.727	0.251	0.474	0.286
	Total	86.300	67.877	86.611	96.736	84.381	12.023

Percent recovery of radioactivity in feces in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

Male

	Timepoint	301M	302M	303M	304M	Mean	SD
feces	4 h	NS	NS	0.020	NS	0.020	NA
feces	8 h	0.005	0.357	NS	NS	0.181	0.249
feces	12 h	0.072	NS	0.020	0.283	0.125	0.139
feces	24 h	0.275	2.241	3.783	0.367	1.667	1.677
feces	48 h	0.343	0.445	2.500	0.657	0.986	1.018
feces	72 h	0.266	0.288	0.382	0.417	0.338	0.073
feces	96 h	0.192	0.304	0.630	0.616	0.436	0.221
feces	120 h	0.222	0.430	0.912	0.523	0.522	0.289
feces	144 h	0.333	0.467	0.649	0.578	0.507	0.138
feces	168 h	0.394	0.638	0.786	0.163	0.495	0.274
feces	Day 8	0.935	1.141	0.620	0.190	0.722	0.414
feces	Day 9	0.411	1.074	1.113	0.112	0.678	0.496
feces	Day 10	0.519	1.467	1.046	0.701	0.933	0.418
feces	Day 11	0.342	0.387	0.161	0.411	0.325	0.113
feces	Day 12	0.621	0.411	0.173	0.070	0.319	0.247
feces	Day 13	0.729	0.905	0.073	0.127	0.459	0.421
feces	Day 14	0.797	0.601	0.104	0.182	0.421	0.332
feces	Day 16	0.979	1.246	0.584	0.383	0.798	0.388
feces	Day 18	1.456	1.725	0.985	1.115	1.320	0.335
feces	Day 20	0.160	0.157	0.269	0.177	0.191	0.053
feces	Day 22	0.083	0.436	0.478	0.230	0.307	0.184
feces	Day 24	0.111	0.577	0.200	0.300	0.297	0.202
feces	Day 26	0.221	0.375	0.375	0.317	0.322	0.073
feces	Day 28	0.386	0.144	0.375	0.136	0.260	0.139
	Total	9.852	15.816	16.238	8.055	12.490	4.153

Female

	Timepoint	301F	302F	303F	304F	Mean	SD
feces	4 h	NS	NS	NS	0.017	0.017	NA
feces	8 h	NS	NS	NS	0.002	0.002	NA
feces	12 h	NS	1.113	NS	0.006	0.560	0.783
feces	24 h	0.102	2.529	0.147	0.219	0.749	1.187
feces	48 h	0.123	0.808	0.129	0.059	0.280	0.354
feces	72 h	0.127	0.477	0.043	0.037	0.171	0.208
feces	96 h	0.195	0.275	0.059	0.045	0.144	0.111
feces	120 h	0.059	0.078	0.009	0.020	0.042	0.032
feces	144 h	0.158	0.023	0.068	0.026	0.069	0.063
feces	168 h	0.072	0.376	0.016	0.054	0.130	0.166
	Total	0.836	5.679	0.471	0.485	1.868	2.546

Perfluorooctanoic Acid: Toxicokinetics in the Rat

Percent recovery of radioactivity in tissues in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

Male

	Timepoint	301M	302M	303M	304M	Mean	SD
prostate	Day 28	0.008	0.006	0.008	0.016	0.010	0.004
carcass	Day 28	3.752	3.935	4.446	9.285	5.355	2.637
skin	Day 28	0.026	0.043	0.043	0.093	0.051	0.029
whole blood	Day 28	0.291	0.746	0.862	1.175	0.769	0.366
brain	Day 28	0.004	0.003	0.005	0.008	0.005	0.002
fat	Day 28	0.012	0.009	0.011	0.025	0.014	0.007
heart	Day 28	0.031	0.030	0.031	0.087	0.045	0.028
lungs	Day 28	0.060	0.056	0.064	0.129	0.077	0.035
spleen	Day 28	0.008	0.008	0.030	0.016	0.016	0.010
liver	Day 28	4.469	4.553	5.128	7.935	5.521	1.636
kidney	Day 28	0.270	0.225	0.434	0.628	0.389	0.183
G.I. tract	Day 28	0.195	0.214	0.587	0.432	0.357	0.187
G.I. contents	Day 28	0.022	0.033	0.095	0.072	0.056	0.034
thyroid	Day 28	0.001	0.001	0.003	0.002	0.002	0.001
thymus	Day 28	0.006	0.008	0.005	0.018	0.009	0.006
testes	Day 28	0.054	0.039	0.067	0.110	0.068	0.031
adrenals	Day 28	0.001	0.002	0.002	0.005	0.003	0.002
muscle	Day 28	0.033	0.032	0.034	0.064	0.041	0.016
bone	Day 28	0.016	0.014	0.015	0.026	0.018	0.006
Total		9.259	9.957	11.870	20.126	12.803	5.005

Female

	Timepoint	301F	302F	303F	304F	Mean	SD
carcass	168 h	<LOQ	0.172	0.263	0.129	0.188	0.068
skin	168 h	0.001	0.001	0.002	0.001	0.001	0.001
whole blood	168 h	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
brain	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
fat	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
heart	168 h	<LOD	<LOD	<LOD	<LOQ	NA	NA
lungs	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
spleen	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
liver	168 h	0.020	0.019	0.003	0.018	0.015	0.008
kidney	168 h	0.003	0.003	<LOD	0.003	0.003	0.000
G.I. tract	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
G.I. contents	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
thyroid	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
thymus	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
ovaries	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
adrenals	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
uterus	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
muscle	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
bone	168 h	<LOD	<LOD	<LOQ	<LOQ	NA	NA
Total		0.024	0.195	0.268	0.151	0.160	0.102

Percent recovery of radioactivity in cage wash and residual feed in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA**Male**

	Timepoint	301M	302M	303M	304M	Mean	SD
cage wash	Day 28	3.125	2.412	6.099	4.351	3.997	1.614
residual feed	Day 28	0.002	0.716	4.082	0.589	1.347	1.850
	Total	3.127	3.128	10.181	4.940	5.344	3.336

Female

	Timepoint	301F	302F	303F	304F	Mean	SD
cage wash	168 h	0.694	3.145	2.835	0.749	1.856	1.316
residual feed	168 h	3.661	16.071	0.052	0.201	4.996	7.569
	Total	4.355	19.216	2.887	0.950	6.852	8.360

Perfluorooctanoic Acid: Toxicokinetics in the Rat

Concentration ($\mu\text{g equiv/g}$) in tissues in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

Male

	Timepoint	301M	302M	303M	304M	Mean	SD
prostate	Day 28	0.714	0.425	0.538	1.516	0.798	0.493
carcass	Day 28	0.655	0.615	0.836	1.742	0.962	0.529
skin	Day 28	1.353	1.136	1.548	3.125	1.790	0.905
whole blood	Day 28	4.108	3.934	5.098	9.943	5.771	2.828
brain	Day 28	0.106	0.084	0.130	0.238	0.139	0.068
fat	Day 28	0.232	0.139	0.289	0.506	0.291	0.156
heart	Day 28	1.343	1.207	1.507	3.396	1.863	1.029
lungs	Day 28	2.085	1.672	2.181	4.693	2.658	1.375
spleen	Day 28	0.564	0.522	2.432	1.474	1.248	0.903
liver	Day 28	14.266	11.108	16.192	24.870	16.609	5.892
kidney	Day 28	4.434	3.468	7.674	9.338	6.229	2.745
G.I. tract	Day 28	0.576	0.516	2.077	1.496	1.166	0.755
G.I. contents	Day 28	0.075	0.076	0.282	0.189	0.156	0.100
thyroid	Day 28	0.623	0.545	1.748	1.742	1.164	0.671
thymus	Day 28	0.529	0.492	0.686	1.710	0.854	0.577
testes	Day 28	1.020	0.649	1.195	2.044	1.227	0.590
adrenals	Day 28	0.784	0.886	0.902	2.030	1.150	0.589
muscle	Day 28	0.382	0.322	0.390	0.810	0.476	0.225
bone	Day 28	0.566	0.537	0.609	1.115	0.707	0.274

Female

	Timepoint	301F	302F	303F	304F	Mean	SD
carcass	168 h	<LOQ	0.053	0.080	0.036	0.056	0.022
skin	168 h	0.019	0.015	0.048	0.014	0.024	0.016
whole blood	168 h	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
brain	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
fat	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
heart	168 h	<LOD	<LOD	<LOD	<LOQ	NA	NA
lungs	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
spleen	168 h	<LOD	<LOD	<LOD	<LOD	0.078	0.041
liver	168 h	0.092	0.117	0.021	0.079	0.074	0.013
kidney	168 h	0.088	0.067	<LOD	0.065	NA	NA
G.I. tract	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
G.I. contents	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
thyroid	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
thymus	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
ovaries	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
adrenals	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
uterus	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
muscle	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
bone	168 h	<LOD	<LOD	<LOQ	<LOQ	NA	NA

Appendix G
Material Balance in Male and Female Rats
Following Oral Gavage with 1 mg/kg ^{14}C -PFOA
(14 day-repeated dose)

Dosing information for male and female rats

Dose Concentration (mg/g): 0.236
 Nominal Dose Volume (mL/kg): 4.0
 Nominal Dose Rate (mg/kg): 1.0

Male

Animal	Animal Weight ^a (g)	Dose Administered (g)	Actual Dose Rate (mg/kg)	Radioactivity Received (μ Ci)
501M	332.9	1.28	0.906	38.186
502M	334.9	1.29	0.907	38.455
503M	349.2	1.39	0.942	41.652
504M	355.8	1.40	0.925	41.682
Mean	343.2	1.34	0.920	39.994
Standard Deviation	11.1	0.06	0.017	1.935

^a Body weights at time of administration of ¹⁴C-PFOA challenge dose. At the initiation of the 14-day repeat dosing, male body weights were 280-294 g.

Female

Animal	Animal Weight ^a (g)	Dose Administered (g)	Actual Dose Rate (mg/kg)	Radioactivity Received (μ Ci)
505F	232.9	0.94	0.954	28.117
506F	257.5	1.01	0.922	30.059
507F	237.0	0.95	0.944	28.326
508F	246.6	0.99	0.950	29.671
Mean	243.5	0.97	0.942	29.043
Standard Deviation	11.0	0.03	0.014	0.966

^a Body weights at time of administration of ¹⁴C-PFOA challenge dose. At the initiation of the 14-day repeat dosing, female body weights were 245-255 g.

Percent recovery of radioactivity in urine in male and female rats following oral gavage with 1 mg/kg ¹⁴C-PFOA (repeated dose)

Male

	Timepoint	501M	502M	503M	504M	Mean	SD
urine	4 h	0.318	0.231	0.029	0.041	0.155	0.143
urine	8 h	1.024	0.584	0.523	0.683	0.704	0.224
urine	12 h	1.124	0.645	1.467	0.479	0.929	0.451
urine	24 h	2.695	2.046	3.036	3.550	2.832	0.631
urine	48 h	6.099	3.159	4.214	6.954	5.107	1.731
urine	72 h	3.608	2.605	3.794	5.143	3.788	1.044
urine	96 h	1.147	1.893	3.265	4.332	2.659	1.419
urine	120 h	1.592	1.239	3.247	3.874	2.488	1.273
urine	144 h	1.934	1.619	2.984	4.188	2.681	1.162
urine	168 h	2.025	1.887	2.714	2.564	2.298	0.403
urine	Day 8	0.980	1.881	2.512	1.764	1.784	0.629
urine	Day 9	2.291	1.315	1.977	2.089	1.918	0.422
urine	Day 10	2.082	1.096	2.135	0.929	1.561	0.637
urine	Day 11	1.956	1.562	2.415	1.308	1.810	0.483
urine	Day 12	1.852	1.018	2.157	2.458	1.871	0.620
urine	Day 13	2.078	1.092	2.052	2.770	1.998	0.689
urine	Day 14	2.619	1.749	2.098	2.648	2.279	0.434
urine	Day 16	3.136	2.911	3.378	3.425	3.213	0.238
urine	Day 18	3.369	2.832	2.878	2.540	2.905	0.344
urine	Day 20	2.751	2.509	2.563	1.701	2.381	0.465
urine	Day 22	2.212	2.361	2.322	1.243	2.035	0.531
urine	Day 24	2.241	1.848	2.143	1.166	1.850	0.485
urine	Day 26	1.936	1.700	1.952	1.388	1.744	0.264
urine	Day 28	1.009	1.517	2.065	1.184	1.444	0.465
Total		52.078	41.299	57.920	58.421	52.430	7.959

Female

	Timepoint	505F	506F	507F	508F	Mean	SD
urine	4 h	7.619	13.288	1.735	NS	7.547	5.777
urine	8 h	50.468	25.271	37.566	18.383	32.922	14.134
urine	12 h	13.253	11.104	8.256	6.798	9.853	2.887
urine	24 h	9.275	16.269	6.492	8.044	10.020	4.319
urine	48 h	2.574	7.575	5.454	8.331	5.984	2.579
urine	72 h	0.737	2.196	0.545	2.021	1.375	0.854
urine	96 h	0.325	1.729	0.774	2.294	1.281	0.894
urine	120 h	0.239	0.725	0.755	0.504	0.556	0.239
urine	144 h	0.054	0.556	0.450	1.171	0.558	0.462
urine	168 h	0.036	0.532	0.199	0.549	0.329	0.253
Total		84.580	79.245	62.226	48.095	68.537	16.631

Percent recovery of radioactivity in feces in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA (repeated dose)

Male

	Timepoint	501M	502M	503M	504M	Mean	SD
		NS	NS	NS	NS	NA	NA
feces	4 h	NS	NS	NS	NS	0.203	0.318
feces	8 h	0.023	0.678	0.092	0.019	1.072	1.745
feces	12 h	0.028	3.681	0.222	0.355	6.752	3.460
feces	24 h	6.962	11.323	3.029	5.692	1.254	0.458
feces	48 h	0.820	1.243	1.890	1.062	0.817	0.473
feces	72 h	1.501	0.754	0.564	0.450	1.044	0.774
feces	96 h	2.202	0.742	0.601	0.631	0.376	0.207
feces	120 h	0.554	0.162	0.234	0.553	0.769	0.315
feces	144 h	1.206	0.656	0.464	0.749	1.074	0.578
feces	168 h	1.075	0.638	0.693	1.890	1.150	0.714
feces	Day 8	1.402	0.733	0.434	2.032	1.113	0.427
feces	Day 9	0.599	1.368	0.938	1.546	1.060	1.170
feces	Day 10	0.335	0.740	0.372	2.793	0.712	0.815
feces	Day 11	0.343	0.525	0.077	1.902	0.465	0.433
feces	Day 12	0.177	1.082	0.151	0.449	0.345	0.400
feces	Day 13	0.201	0.940	0.154	0.083	0.096	0.036
feces	Day 14	0.148	0.083	0.088	0.065	0.342	0.295
feces	Day 16	0.784	0.212	0.183	0.189	0.202	0.053
feces	Day 18	0.133	0.251	0.235	0.187	0.275	0.250
feces	Day 20	0.101	0.158	0.195	0.646	0.319	0.242
feces	Day 22	0.321	0.154	0.141	0.660	0.220	0.202
feces	Day 24	0.066	0.184	0.115	0.514	0.076	0.021
feces	Day 26	0.050	0.099	0.086	0.067	0.108	0.091
feces	Day 28	0.060	0.239	0.098	0.036		
	Total	19.091	26.645	11.056	22.570	19.841	6.620

Female

	Timepoint	505F	506F	507F	508F	Mean	SD
		NS	NS	NS	NS	NA	NA
feces	4 h	NS	NS	NS	NS	3.599	4.530
feces	8 h	0.005	0.110	4.752	9.527	0.172	0.154
feces	12 h	0.003	0.211	0.303	<LOD	4.539	7.406
feces	24 h	0.396	0.014	2.188	15.556	2.883	3.972
feces	48 h	0.234	0.823	1.702	8.771	0.764	0.824
feces	72 h	0.077	0.615	1.954	0.409	0.121	0.093
feces	96 h	0.029	0.216	0.055	0.185	0.160	0.124
feces	120 h	0.076	0.163	0.067	0.334	0.143	0.072
feces	144 h	0.099	0.073	0.233	0.167	0.047	0.019
feces	168 h	0.029	0.032	0.063	0.065		
	Total	0.948	2.257	11.317	35.014	12.384	15.775

Perfluorooctanoic Acid: Toxicokinetics in the Rat

Percent recovery of radioactivity in tissues in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA (repeated dose)

Male

	Timepoint	501M	502M	503M	504M	Mean	SD
prostate	Day 28	0.008	0.009	0.012	0.003	0.008	0.004
carcass	Day 28	4.723	6.354	7.029	2.798	5.226	1.886
skin	Day 28	0.077	0.085	0.117	0.031	0.078	0.035
whole blood	Day 28	0.660	1.176	1.683	0.387	0.977	0.573
brain	Day 28	0.003	0.006	0.006	0.002	0.004	0.002
fat	Day 28	0.017	0.028	0.016	0.015	0.019	0.006
heart	Day 28	0.033	0.055	0.051	0.020	0.040	0.016
lungs	Day 28	0.057	0.092	0.105	0.041	0.074	0.030
spleen	Day 28	0.008	0.014	0.019	0.005	0.012	0.006
liver	Day 28	5.932	7.714	6.969	3.837	6.113	1.684
kidney	Day 28	0.268	0.400	0.546	0.169	0.346	0.164
G.I. tract	Day 28	0.123	0.281	0.205	0.098	0.177	0.083
G.I. contents	Day 28	0.032	0.047	0.068	0.018	0.041	0.021
thyroid	Day 28	0.001	0.001	0.002	0.000	0.001	0.001
thymus	Day 28	0.007	0.019	0.014	0.006	0.012	0.006
testes	Day 28	0.044	0.069	0.073	0.028	0.054	0.021
adrenals	Day 28	0.002	0.001	0.002	0.001	0.002	0.001
muscle	Day 28	0.036	0.063	0.078	0.029	0.052	0.023
bone	Day 28	0.013	0.027	0.023	0.014	0.019	0.007
Total		12.044	16.441	17.018	7.502	13.251	4.430

Female

	Timepoint	505F	506F	507F	508F	Mean	SD
carcass	168 h	0.240	0.291	0.170	0.346	0.262	0.075
skin	168 h	0.001	<LOQ	<LOQ	0.001	0.001	0.000
whole blood	168 h	0.004	0.005	0.003	0.005	0.004	0.001
brain	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
fat	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
heart	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
lungs	168 h	<LOQ	<LOD	<LOQ	0.000	0.000	NA
spleen	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
liver	168 h	0.037	0.043	0.028	0.040	0.037	0.006
kidney	168 h	0.006	0.006	0.003	0.006	0.005	0.002
G.I. tract	168 h	<LOQ	<LOD	<LOQ	<LOQ	NA	NA
G.I. contents	168 h	<LOQ	<LOD	<LOQ	<LOQ	NA	NA
thyroid	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
thymus	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
ovaries	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
adrenals	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
uterus	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
muscle	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
bone	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
Total		0.288	0.345	0.204	0.398	0.309	0.083

Percent recovery of radioactivity in cage wash and residual feed in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA (repeated dose)

Male

	Timepoint	501M	502M	503M	504M	Mean	SD
cage wash	Day 28	3.912	1.354	2.276	1.516	2.265	1.170
residual feed	Day 28	0.755	0.268	0.009	0.021	0.263	0.349
	Total	4.667	1.622	2.285	1.537	2.528	1.465

Female

	Timepoint	505F	506F	507F	508F	Mean	SD
cage wash	168 h	1.558	3.852	2.904	6.259	3.643	1.982
residual feed	168 h	0.170	1.223	17.662	0.007	4.766	8.615
	Total	1.728	5.075	20.566	6.266	8.409	8.329

Perfluorooctanoic Acid: Toxicokinetics in the Rat

Concentration ($\mu\text{g equiv/g}$) in tissues in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA (repeated dose)

Male

	Timepoint	501M	502M	503M	504M	Mean	SD
prostate	Day 28	0.020	0.022	0.037	0.010	0.022	0.011
carcass	Day 28	0.036	0.052	0.056	0.022	0.042	0.016
skin	Day 28	0.057	0.125	0.090	0.058	0.083	0.032
whole blood	Day 28	0.209	0.390	0.441	0.131	0.293	0.147
brain	Day 28	0.005	0.009	0.009	0.003	0.007	0.003
fat	Day 28	0.008	0.011	0.011	0.004	0.009	0.003
heart	Day 28	0.068	0.120	0.103	0.044	0.084	0.034
lungs	Day 28	0.097	0.169	0.159	0.060	0.121	0.052
spleen	Day 28	0.028	0.049	0.049	0.019	0.036	0.015
liver	Day 28	0.929	1.144	1.084	0.601	0.940	0.243
kidney	Day 28	0.215	0.325	0.397	0.149	0.272	0.111
G.I. tract	Day 28	0.029	0.053	0.054	0.017	0.038	0.018
G.I. contents	Day 28	0.004	0.007	0.010	0.003	0.006	0.003
thyroid	Day 28	0.030	0.026	0.060	0.021	0.034	0.018
thymus	Day 28	0.034	0.065	0.052	0.018	0.042	0.021
testes	Day 28	0.037	0.070	0.075	0.027	0.052	0.024
adrenals	Day 28	0.025	0.049	0.079	0.021	0.044	0.027
muscle	Day 28	0.018	0.033	0.033	0.015	0.025	0.010
bone	Day 28	0.026	0.039	0.044	0.020	0.032	0.011

Female

	Timepoint	505F	506F	507F	508F	Mean	SD
carcass	168 h	0.003	0.003	0.002	0.004	0.003	0.001
skin	168 h	0.001	<LOQ	<LOQ	0.002	0.002	0.001
whole blood	168 h	0.001	0.001	0.001	0.001	0.001	0.000
brain	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
fat	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
heart	168 h	<LOD	<LOD	<LOQ	0.001	0.001	NA
lungs	168 h	<LOQ	<LOD	<LOD	<LOD	NA	NA
spleen	168 h	<LOD	<LOD	<LOD	<LOD	0.008	0.001
liver	168 h	0.009	0.008	0.006	0.008	0.006	0.001
kidney	168 h	0.007	0.006	0.004	0.007	0.006	0.001
G.I. tract	168 h	<LOQ	<LOD	<LOQ	<LOQ	NA	NA
G.I. contents	168 h	<LOQ	<LOD	<LOQ	<LOQ	NA	NA
thyroid	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
thymus	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
ovaries	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
adrenals	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
uterus	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
muscle	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA
bone	168 h	<LOD	<LOD	<LOD	<LOD	NA	NA

Appendix H
Pharmacokinetics in Male and Female Rats
Following Oral Gavage with 0.1 mg/kg PFOA

Dosing information for male and female rats

Dose Concentration (mg/mL): 0.028
Nominal Dose Volume (mL/kg): 4.0
Nominal Dose Rate (mg/kg): 0.1

Male

Animal	Animal Weight (g)	Dose Volume (mL)	Actual Dose Rate (mg/kg)
652092	223.3	0.89	0.112
652093	228.3	0.91	0.112
652095	205.9	0.82	0.112
652096	207.5	0.83	0.113
Mean	216.3	0.86	0.112
Standard Deviation	11.2	0.04	0.000

Female

Animal	Animal Weight (g)	Dose Volume (mL)	Actual Dose Rate (mg/kg)
652100	179.8	0.72	0.113
652101	164.5	0.66	0.113
652102	184.6	0.74	0.113
652105	176.5	0.71	0.113
Mean	176.4	0.71	0.113
Standard Deviation	8.6	0.03	0.000

Perfluorooctanoic Acid: Toxicokinetics in the Rat

Concentration ($\mu\text{g/mL}$) in serial plasma in male and female rats following oral gavage with 0.1 mg/kg PFOA

Male

Time (h)	Animal				Mean	SD
	652092	652093	652095	652096		
0	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
0.25	0.438	0.105	0.141	0.442	0.282	0.184
0.5	0.438	0.125	0.198	0.448	0.302	0.165
1	0.376	0.185	0.267	0.676	0.376	0.215
2	0.452	0.214	0.376	0.509	0.388	0.128
4	0.445	0.239	0.425	0.506	0.404	0.115
8	0.468	0.339	0.491	0.570	0.467	0.096
12	0.573	0.429	0.501	0.565	0.517	0.067
16	0.430	0.387	0.714	0.512	0.511	0.145
24	0.383	0.347	0.443	0.421	0.399	0.042
36	0.291	0.360	0.371	0.434	0.364	0.059
48	0.272	0.279	0.322	0.441	0.328	0.078
72	0.255	0.320	0.320	0.402	0.324	0.060
96	0.240	0.245	0.367	0.390	0.311	0.079
120	0.219	0.233	0.304	0.290	0.262	0.042
144	0.189	0.220	0.309	0.288	0.251	0.056
168	0.221	0.199	0.247	0.345	0.253	0.064
192	0.194	0.177	0.241	0.287	0.225	0.049
240	0.136	0.148	0.181	0.242	0.177	0.047
288	0.145	0.147	0.176	0.255	0.181	0.052
336	0.094	0.108	0.117	0.182	0.125	0.039
384	0.083	0.085	0.102	0.160	0.108	0.036
432	0.070	0.059	0.087	0.186	0.100	0.058
480	0.063	0.057	0.081	0.148	0.087	0.042
528	0.040	0.053	0.067	0.092	0.063	0.022

Female

Time (h)	Animal				Mean	SD
	652100	652101	652102	652105		
0	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
0.25	0.651	0.566	0.591	NA	0.603	0.043
0.50	0.512	0.648	0.770	0.591	0.630	0.109
1	0.577	0.487	0.481	0.611	0.539	0.065
2	0.504	0.619	0.564	0.425	0.528	0.083
4	0.318	0.422	0.352	0.431	0.381	0.055
8	0.073	0.146	<LOQ	0.087	0.102	0.039
16	<LOQ	0.050	<LOQ	<LOQ	0.050	NA
24	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
36	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
48	<LOQ	<LOQ	NS	<LOQ	NA	NA
72	<LOQ	<LOQ	NS	<LOQ	NA	NA
96	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA

Pharmacokinetic parameters in male and female rats following oral gavage with 0.1 mg/kg PFOA

Male

Animal	T _{max} (hr)	C _{max} (μg/mL)	Lambda z (1/hr)	T _{1/2} (hr)	AUC _{INF} (hr·μg/mL)	AUC _{INF} /D (hr·μg/mL/mg/kg)	Cl _p (mL/kg·hr)
652092	12.0	0.573	0.004	184.559	95.469	852.404	1.173
652093	12.0	0.429	0.004	177.376	98.863	882.701	1.133
652095	16.0	0.714	0.004	187.517	126.328	1127.931	0.887
652096	1.0	0.676	0.003	257.643	172.235	1524.207	0.656
Mean	10.25	0.598	0.004	201.774	123.224	1096.811	0.962
SD	6.45	0.127	0.001	37.489	35.476	310.491	0.240

Female

Animal	T _{max} (hr)	C _{max} (μg/mL)	Lambda z (1/hr)	T _{1/2} (hr)	AUC _{INF} (hr·μg/mL)	AUC _{INF} /D (hr·μg/mL/mg/kg)	Cl _p (mL/kg·hr)
652100	0.25	0.651	0.303	2.291	2.885	25.529	39.171
652101	0.50	0.648	0.170	4.098	4.316	38.193	26.182
652102	0.50	0.770	0.180	3.860	3.956	35.006	28.567
652105	1.00	0.611	0.270	2.576	3.182	28.156	35.517
Mean	0.56	0.67	0.231	3.206	3.584	31.721	32.359
SD	0.31	0.07	0.066	0.905	0.666	5.880	6.025

Appendix I
Pharmacokinetics in Male and Female Rats
Following Oral Gavage with 1 mg/kg PFOA

Dosing information for male and female rats

Dose Concentration (mg/mL): 0.253
Nominal Dose Volume (mL/kg): 4.0
Nominal Dose Rate (mg/kg): 1.0

Male

Animal	Animal Weight (g)	Dose Volume (mL)	Actual Dose Rate (mg/kg)
653745	250.0	1.00	1.014
653746	246.4	0.99	1.018
653747	248.7	0.99	1.009
653749	249.6	1.00	1.015
Mean	248.7	1.00	1.014
Standard Deviation	1.6	0.01	0.004

Female

Animal	Animal Weight (g)	Dose Volume (mL)	Actual Dose Rate (mg/kg)
653759	200.4	0.80	1.010
653760	201.3	0.81	1.018
653761	182.6	0.73	1.011
653762	203.5	0.81	1.007
Mean	197.0	0.79	1.012
Standard Deviation	9.7	0.04	0.005

Concentration ($\mu\text{g/mL}$) in serial plasma in male and female rats following oral gavage with 1 mg/kg PFOA

Male

Time (h)	Animal				Mean	SD
	653745	653746	653747	653749		
0	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
0.25	2.054	2.198	1.688	5.016	2.739	1.533
0.5	3.096	2.978	2.252	6.580	3.727	1.939
1	4.860	3.920	2.768	6.312	4.465	1.499
2	6.848	5.056	3.952	6.376	5.558	1.312
4	9.128	7.798	3.818	7.418	7.041	2.270
8	8.042	7.910	6.800	6.698	7.363	0.712
12	5.098	8.414	5.372	9.380	7.066	2.154
16	6.228	6.890	6.782	9.014	7.229	1.225
24	5.724	4.764	4.792	4.624	4.976	0.504
36	4.222	4.514	4.132	5.956	4.706	0.849
48	4.230	4.754	3.540	4.656	4.295	0.552
72	2.892	3.960	2.904	4.126	3.471	0.665
96	2.580	3.402	3.006	4.522	3.378	0.834
120	3.048	3.142	3.836	4.368	3.599	0.622
144	2.136	2.930	3.250	2.994	2.828	0.481
168	1.610	3.852	2.746	2.932	2.785	0.921
192	2.152	3.952	3.434	2.444	2.996	0.841
240	NS*	1.636	1.358	1.471	1.488	0.140
288	NS	1.507	0.811	1.315	1.211	0.360
336	NS	1.680	0.801	1.135	1.205	0.443
384	NS	1.425	0.828	1.013	1.089	0.305
432	NS	0.802	0.711	0.796	0.770	0.051
480	NS	1.077	0.579	0.681	0.779	0.263
528	NS	0.561	0.384	0.397	0.447	0.098

*Animal # 653745 was found dead on day nine

Female

Time (h)	Animal				Mean	SD
	653759	653760	653761	653762		
0	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
0.25	3.263	4.356	5.914	2.929	4.116	1.345
0.50	3.602	4.314	6.315	3.977	4.552	1.211
1	4.138	4.358	6.487	3.909	4.723	1.190
2	4.307	4.245	5.604	3.399	4.389	0.910
4	4.278	3.404	4.802	2.719	3.801	0.923
8	1.609	1.384	2.025	0.788	1.452	0.516
12	0.645	0.494	1.108	0.510	0.689	0.287
16	0.219	0.189	0.421	0.115	0.236	0.131
24	0.255	<LOQ	0.063	<LOQ	0.159	0.136
36	<LOQ	<LOQ	0.036	0.023	0.029	0.009
48	<LOQ	<LOQ	0.013	0.058	0.036	0.032
72	<LOQ	<LOQ	<LOQ	NS	NA	NA
96	0.070	<LOQ	NS	0.080	0.075	0.007

Pharmacokinetic parameters in male and female rats following oral gavage with 1 mg/kg PFOA

Male

Animal	T _{max} (hr)	C _{max} (μg/mL)	Lambda z (1/hr)	T _{1/2} (hr)	AUC _{INF} (hr·μg/mL)	AUC _{INF} /D (hr·μg/mL/mg/kg)	Cl _p (mL/kg·hr)
653745	4.0	9.128	0.007	98.054	941.580	932.258	1.073
653746	12.0	8.414	0.004	176.052	1432.625	1404.534	0.712
653747	8.0	6.800	0.005	142.647	1105.277	1094.334	0.914
653749	12.0	9.380	0.005	136.620	1298.369	1272.911	0.786
Mean	9.00	8.431	0.005	138.343	1194.463	1176.009	0.871
SD	3.83	1.161	0.001	31.972	215.578	206.316	0.158

Female

Animal	T _{max} (hr)	C _{max} (μg/mL)	Lambda z (1/hr)	T _{1/2} (hr)	AUC _{INF} (hr·μg/mL)	AUC _{INF} /D (hr·μg/mL/mg/kg)	Cl _p (mL/kg·hr)
653759	2.00	4.307	0.246	2.822	47.894	47.420	21.088
653760	1.00	4.358	0.242	2.858	31.224	30.672	32.603
653761	1.00	6.487	0.135	5.118	47.818	47.298	21.143
653762	0.50	3.977	0.229	3.029	29.350	29.149	34.310
Mean	1.13	4.782	0.213	3.457	39.072	38.635	27.286
SD	0.63	1.149	0.053	1.111	10.172	10.093	7.159

Appendix J
Pharmacokinetics in Male and Female Rats
Following Intravenous Injection with 1 mg/kg PFOA

Dosing information for male and female rats

Dose Concentration (mg/mL): 0.554

Nominal Dose Volume (mL/kg): 2.0

Nominal Dose Rate (mg/kg): 1.0

Male

Animal	Animal Weight (g)	Dose Volume (mL)	Actual Dose Rate (mg/kg)
653740	253.2	0.51	1.116
653742	256.4	0.51	1.102
653743	235.2	0.47	1.108
653744	248.5	0.50	1.115
Mean	248.3	0.50	1.110
Standard Deviation	9.3	0.02	0.007

Female

Animal	Animal Weight (g)	Dose Volume (mL)	Actual Dose Rate (mg/kg)
653752	201.8	0.40	1.099
653754	202.7	0.41	1.121
653758	201.2	0.40	1.102
653763	196.7	0.39	1.099
Mean	200.6	0.40	1.105
Standard Deviation	2.7	0.01	0.011

Concentration ($\mu\text{g/mL}$) in serial plasma in male and female rats following intravenous injection with 1 mg/kg PFOA

Male

Time (h)	Animal				Mean	SD
	653740	653742	653743	653744		
0	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
0.25	20.170	11.158	8.144	7.884	11.839	5.749
0.5	9.380	6.470	8.454	7.444	7.937	1.258
1	9.202	9.920	5.562	12.480	9.291	2.856
2	6.106	8.212	5.016	8.606	6.985	1.711
4	6.702	8.916	6.568	7.264	7.363	1.079
8	5.658	6.832	8.426	7.192	7.027	1.140
12	5.542	7.942	8.230	7.852	7.392	1.243
16	8.656	7.330	10.408	7.574	8.492	1.401
24	6.972	6.034	5.736	4.480	5.806	1.029
36	3.984	4.450	4.224	4.090	4.187	0.201
48	4.104	4.468	3.252	4.358	4.046	0.551
72	4.642	3.158	4.654	3.426	3.970	0.791
96	3.222	2.892	3.200	2.550	2.966	0.316
120	2.818	2.630	2.468	2.890	2.702	0.190
144	1.852	2.037	1.600	1.493	1.745	0.246
168	1.687	1.752	1.466	1.964	1.717	0.205
192	1.741	1.694	1.481	1.874	1.697	0.163
240	2.295	1.498	1.663	1.864	1.830	0.344
288	1.695	1.381	1.122	1.481	1.420	0.238
336	1.403	1.372	1.030	1.431	1.309	0.188
384	1.677	1.161	0.802	1.161	1.200	0.360
432	1.108	1.153	0.669	0.843	0.943	0.228
480	0.864	0.989	0.696	0.812	0.840	0.121
528	0.652	0.699	0.449	0.565	0.591	0.110

Female

Time (h)	Animal				Mean	SD
	653752	653754	653758	653763		
0	<LOQ	<LOQ	<LOQ	0.012	0.012	NA
0.25	4.431	5.525	4.274	5.637	4.967	0.714
0.50	4.709	4.825	3.830	4.751	4.529	0.468
1	3.704	4.728	3.280	4.052	3.941	0.612
2	3.261	4.041	3.610	3.789	3.675	0.328
4	2.593	3.415	1.898	3.050	2.739	0.654
8	0.833	1.271	0.335	0.729	0.792	0.385
12	3.940	1.798	0.953	2.127	2.204	1.258
16	0.121	0.197	0.022	0.091	0.108	0.073
24	<LOQ	0.017	<LOQ	<LOQ	0.017	NA
36	<LOQ	<LOQ	<LOQ	0.092	0.092	NA
48	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
72	<LOQ	0.065	0.019	<LOQ	0.042	0.032
96	<LOQ	<LOQ	<LOQ	<LOD	NA	NA

Pharmacokinetic parameters in male and female rats following intravenous injection with 1 mg/kg PFOA

Male

Animal	Lambda z (1/hr)	T _{1/2} (hr)	AUC _{INF} (hr·μg/mL)	AUC _{INF} /D (hr·μg/mL/mg/kg)	Cl _p (mL/kg·hr)
653740	0.004	194.339	1374.590	1227.313	0.815
653742	0.004	200.779	1293.389	1175.808	0.851
653743	0.004	156.978	1107.407	997.664	1.002
653744	0.004	190.240	1223.881	1092.751	0.915
Mean	0.004	185.584	1249.817	1123.384	0.896
SD	0.000	19.558	113.167	100.488	0.082

Female

Animal	Lambda z (1/hr)	T _{1/2} (hr)	AUC _{INF} (hr·μg/mL)	AUC _{INF} /D (hr·μg/mL/mg/kg)	Cl _p (mL/kg·hr)
653752	0.216	3.211	38.774	35.249	28.370
653754	0.268	2.584	39.558	35.320	28.313
653758	0.308	2.251	23.078	20.980	47.665
653763	0.208	3.331	34.581	31.437	31.810
Mean	0.250	2.844	33.998	30.747	34.040
SD	0.047	0.514	7.601	6.759	9.230

Appendix K
Pharmacokinetics in Male and Female Rats
Following Oral Gavage with 5 mg/kg PFOA

Dosing information for male and female rats

Dose Concentration (mg/mL): 1.380
Nominal Dose Volume (mL/kg): 4.0
Nominal Dose Rate (mg/kg): 5.0

Male

Animal	Animal Weight (g)	Dose Volume (mL)	Actual Dose Rate (mg/kg)
654601	216.0	0.86	5.496
654602	223.0	0.89	5.509
654603	216.0	0.86	5.496
654604	217.0	0.87	5.535
Mean	218.0	0.87	5.509
Standard Deviation	3.4	0.01	0.018

Female

Animal	Animal Weight (g)	Dose Volume (mL)	Actual Dose Rate (mg/kg)
654605	184.0	0.74	5.552
654606	188.0	0.75	5.507
654608	192.0	0.77	5.536
654610	185.0	0.74	5.522
Mean	187.3	0.75	5.529
Standard Deviation	3.6	0.01	0.019

Concentration ($\mu\text{g/mL}$) in serial plasma in male and female rats following oral gavage with 5 mg/kg PFOA

Male

Time (h)	Animal				Mean	SD
	654601	654602	654603	654604		
0	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
0.25	6.72	7.216	4.808	8.024	6.692	1.366
0.5	17.456	10.136	7.132	9.712	11.109	4.435
1	19.728	14.128	14.632	22.896	17.846	4.211
2	24.976	27.24	31.612	32.08	28.977	3.445
4	24.74	41.148	27.776	42.204	33.967	8.998
8	38.02	33.036	31.604	47.128	37.447	7.015
12	35.112	26.284	27.404	33.804	30.651	4.452
16	36.472	25.492	38.368	40.98	35.328	6.813
24	31.968	NS	50.812	49.02	43.933	10.401
48	16.412	26.408	16.788	33.272	23.220	8.143
72	24.088	25.6	21.792	29.348	25.207	3.174
96	14.456	19.632	15.38	16.496	16.491	2.254
120	9.531	12.967	15.676	20.903	14.769	4.800
144	9.916	12.067	12.666	11.497	11.537	1.181
168	7.855	12.846	10.105	14.831	11.409	3.061
192	5.618	11.481	12.127	12.746	9.182	5.040
240	5.779	9.067	8.807	9.07	8.181	1.606
288	3.92	11.542	7.635	9.601	8.175	3.254
336	3.874	8.903	5.868	6.065	6.178	2.069
384	3.792	6.347	6.45	6.473	5.766	1.317
432	2.868	5.454	3.997	5.036	4.339	1.156
480	2.106	5.783	4.686	4.737	4.328	1.565
528	1.403	3.877	3.367	3.102	2.937	1.072

Female

Time (h)	Animal				Mean	SD
	654605	654606	654608	654610		
0	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
0.25	16.795	15.055	5.230	6.705	10.946	5.824
0.50	18.910	14.965	9.665	9.730	13.318	4.480
1	21.450	19.780	9.935	15.055	16.555	5.178
2	17.455	13.640	18.405	21.810	17.828	3.360
4	14.195	10.595	15.675	15.465	13.983	2.351
8	1.793	2.178	4.910	4.201	3.270	1.520
12	0.730	1.738	2.144	2.002	1.653	0.638
16	0.385	0.754	0.765	0.604	0.627	0.177
24	0.248	0.242	0.122	0.081	0.173	0.084
36	0.028	0.080	0.024	0.042	0.043	0.026
48	<LOQ	0.028	0.015	0.017	0.020	0.007
72	0.012	<LOQ	<LOQ	<LOQ	0.012	NA
96	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA

Pharmacokinetic parameters in male and female rats following oral gavage with 5 mg/kg PFOA

Male

Animal	T _{max} (hr)	C _{max} (μg/mL)	Lambda z (1/hr)	T _{1/2} (hr)	AUC _{INF} (hr·μg/mL)	AUC _{INF} /D (hr·μg/mL/mg/kg)	Cl _p (mL/kg·hr)
654601	8.0	38.02	0.0050	139.61	4722.52	859.26	1.16
654602	4.0	41.15	0.0034	201.71	7505.93	1362.48	0.73
654603	24.0	50.81	0.0036	194.02	6899.71	1255.41	0.80
654604	24.0	49.02	0.0043	161.42	7806.62	1410.41	0.71
Mean	15.0	44.75	0.0041	174.19	6733.70	1221.89	0.85
SD	10.5	6.14	0.0007	28.92	1392.83	250.28	0.21

Female

Animal	T _{max} (hr)	C _{max} (μg/mL)	Lambda z (1/hr)	T _{1/2} (hr)	AUC _{INF} (hr·μg/mL)	AUC _{INF} /D (hr·μg/mL/mg/kg)	Cl _p (mL/kg·hr)
654605	1.0	21.450	0.169	4.103	111.998	20.173	49.573
654606	1.0	19.780	0.126	5.521	100.407	18.233	54.847
654608	2.0	18.405	0.163	4.261	121.502	21.948	45.563
654610	2.0	21.810	0.153	4.536	125.685	22.761	43.935
Mean	1.50	20.36	0.15	4.60	114.90	20.78	48.48
SD	0.58	1.58	0.02	0.64	11.23	2.01	4.86

Appendix L
Pharmacokinetics in Male and Female Rats
Following Oral Gavage with 25 mg/kg PFOA

Dosing information for male and female rats

Dose Concentration (mg/mL): 6.726

Nominal Dose Volume (mL/kg): 4.0

Nominal Dose Rate (mg/kg): 25.0

Male

Animal	Animal Weight (g)	Dose Volume (mL)	Actual Dose Rate (mg/kg)
655168	225.0	0.90	26.90
655169	221.0	0.88	26.78
655170	224.0	0.90	27.02
655172	230.0	0.90	26.32
Mean	225.0	0.90	26.76
SD	3.7	0.01	0.31

Female

Animal	Animal Weight (g)	Dose Volume (mL)	Actual Dose Rate (mg/kg)
655175	182.0	0.73	26.98
655176	183.0	0.73	26.83
655177	210.0	0.84	26.90
655178	204.0	0.82	27.04
Mean	194.8	0.78	26.94
SD	14.4	0.06	0.09

Concentration ($\mu\text{g/mL}$) in serial plasma in male and female rats following oral gavage with 25 mg/kg PFOA

Male

Time (h)	Animal				Mean	SD
	655168	655169	655170	655172		
0	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
0.25	16.375	70.375	67.725	70.175	56.163	26.552
0.5	26.925	97.400	81.575	85.525	72.856	31.351
1	56.175	115.475	106.500	121.650	99.950	29.839
2	91.575	177.525	131.375	144.000	136.119	35.512
4	156.875	153.175	149.225	143.925	150.800	5.547
8	120.800	134.550	143.725	154.775	138.463	14.388
12	134.500	155.200	136.250	150.975	144.231	10.395
16	136.550	151.425	150.825	135.325	143.531	8.786
24	103.175	147.225	134.375	122.775	126.888	18.698
48	90.425	104.900	91.125	114.775	100.306	11.724
72	75.775	85.050	65.600	76.250	75.669	7.953
96	61.275	63.250	60.500	84.775	67.450	11.608
120	53.025	59.150	57.325	81.750	62.813	12.883
144	42.250	54.075	50.325	83.200	57.463	17.854
168	47.175	46.825	32.875	75.575	50.613	17.925
192	36.875	37.325	23.000	47.475	36.169	10.051
240	25.525	27.825	15.975	55.650	31.244	17.061
288	21.275	22.675	13.250	43.475	25.169	12.891
336	21.475	25.775	11.150	43.500	25.475	13.493
384	13.195	21.960	9.225	32.075	19.114	10.147
432	22.395	18.525	7.715	27.690	19.081	8.458
480	9.385	15.700	6.280	29.410	15.194	10.256
528	8.050	10.160	4.445	15.930	9.646	4.808

Female

Time (h)	Animal				Mean	SD
	655175	655176	655177	655178		
0	<LOQ	<LOQ	<LOQ	0.019	0.019	NA
0.25	68.020	62.380	79.860	106.400	79.165	19.563
0.50	200.270	101.140	95.090	99.930	124.108	50.842
1	145.180	80.530	74.110	106.720	101.635	32.275
2	125.270	97.560	122.240	106.950	113.005	13.050
4	154.950	88.640	87.100	68.240	99.733	37.962
8	33.578	19.192	37.070	36.072	31.478	8.321
12	11.726	9.130	6.624	7.072	8.638	2.330
16	4.671	2.257	2.014	1.803	2.686	1.336
24	0.349	0.381	0.446	0.276	0.363	0.070
36	0.067	0.203	0.109	0.160	0.135	0.059
48	0.056	0.096	0.044	0.046	0.060	0.024
72	0.058	0.013	0.074	<LOD	0.048	0.031
96	0.033	<LOD	<LOD	<LOD	0.033	NA

Pharmacokinetic parameters in male and female rats following oral gavage with 25 mg/kg PFOA

Male

Animal	T _{max} (hr)	C _{max} (µg/mL)	Lambda z (1/hr)	T _{1/2} (hr)	AUC _{INF} (hr·µg/mL)	AUC _{INF} /D (hr·µg/mL/mg/kg)	Cl _p (mL/kg·hr)
655168	4.0	156.875	0.0047	147.100	21698.88	806.65	1.240
655169	2.0	177.525	0.0042	165.499	25579.15	955.16	1.047
655170	16.0	150.825	0.0062	112.565	18242.08	675.13	1.481
655172	8.0	154.775	0.0034	204.712	35102.32	1333.67	0.750
Mean	7.5	160.00	0.0046	157.47	25155.61	942.65	1.13
SD	6.2	11.95	0.0012	38.39	7276.96	284.67	0.31

Female

Animal	T _{max} (hr)	C _{max} (µg/mL)	Lambda z (1/hr)	T _{1/2} (hr)	AUC _{INF} (hr·µg/mL)	AUC _{INF} /D (hr·µg/mL/mg/kg)	Cl _p (mL/kg·hr)
655175	0.5	200.270	0.025	28.157	1071.376	39.710	25.183
655176	0.5	101.140	0.071	9.738	661.311	24.648	40.571
655177	2.0	122.240	0.034	20.366	752.314	27.967	35.756
655178	2.0	106.950	0.105	6.625	698.043	25.815	38.737
Mean	1.25	132.65	0.059	16.22	795.76	29.54	35.06
SD	0.87	45.95	0.037	9.90	187.51	6.92	6.88

Appendix M
Pharmacokinetics in Male and Female Rats
Following Oral Gavage with 0.1 mg/kg PFOA (extended time course)

Dosing information for male and female rats

Dose Concentration (mg/mL): 0.024

Nominal Dose Volume (mL/kg): 4.0

Nominal Dose Rate (mg/kg): 0.1

Male

Animal	Animal Weight (g)	Dose Volume (mL)	Actual Dose Rate (mg/kg)
659277	267.0	1.10	0.099
659278	274.0	1.10	0.097
659279	280.0	1.10	0.095
659280	269.0	1.10	0.099
Mean	272.5	1.10	0.097
SD	5.8	0.00	0.002

Female

Animal	Animal Weight (g)	Dose Volume (mL)	Actual Dose Rate (mg/kg)
659283	184.0	0.74	0.097
659285	209.0	0.84	0.097
659286	209.0	0.84	0.097
659288	202.0	0.81	0.097
Mean	201.0	0.81	0.097
SD	11.8	0.05	0.000

Concentration ($\mu\text{g/mL}$) in serial plasma in male rats following oral gavage with 0.1 mg/kg PFOA (extended time course)

Time (h)	Animal				Mean	SD
	659277	659278	659279	659280		
0	<LOQ	0.001	<LOQ	<LOQ	0.001	NA
1	0.557	0.836	0.619	0.844	0.714	0.148
2	1.692	0.912	0.634	1.004	1.060	0.449
4	0.641	0.726	0.635	0.640	0.660	0.044
8	0.569	0.759	0.488	0.764	0.645	0.139
12	0.418	0.824	0.502	0.927	0.668	0.246
16	0.539	0.748	0.722	0.771	0.695	0.106
24	0.502	0.770	0.633	0.668	0.643	0.111
48	0.395	0.642	0.462	0.566	0.516	0.110
72	0.360	0.356	0.274	0.495	0.371	0.092
96	0.276	0.516	0.317	0.413	0.381	0.107
120	0.358	0.448	0.305	0.490	0.400	0.084
144	0.277	0.429	0.267	0.380	0.338	0.079
168	0.324	0.442	0.273	0.485	0.381	0.099
192	0.310	0.314	0.247	0.304	0.294	0.031
240	0.260	0.304	0.193	0.321	0.269	0.057
288	0.211	0.322	0.134	0.272	0.235	0.081
336	0.235	0.251	0.119	0.260	0.216	0.066
384	0.155	0.230	0.104	0.272	0.191	0.075
432	0.196	0.215	0.079	0.200	0.172	0.063
480	0.126	0.169	0.073	0.155	0.131	0.042
528	0.126	0.106	0.036	0.148	0.104	0.048
576	0.145	0.116	0.031	0.123	0.104	0.050
624	0.128	0.146	0.053	0.138	0.116	0.043
672	0.112	0.143	0.045	0.157	0.114	0.050
720	0.075	0.083	0.028	0.099	0.071	0.031
768	0.071	0.086	0.021	0.083	0.065	0.030
816	0.062	0.063	0.018	0.069	0.053	0.023
864	0.064	0.067	0.015	0.061	0.052	0.025
912	0.050	0.068	0.010	0.049	0.044	0.024
960	0.040	0.070	0.007	0.041	0.039	0.026
1008	0.037	0.049	0.004	0.041	0.033	0.020
1056	0.036	0.038	0.003	0.034	0.028	0.017
1104	0.030	0.040	0.001	0.028	0.025	0.017
1152	0.031	0.037	0.003	0.026	0.024	0.015
1200	0.029	0.036	<LOQ	0.026	0.030	0.005
1248	0.023	0.039	<LOQ	0.028	0.030	0.008
1296	0.037	0.017	0.008	0.042	0.026	0.016
1344	0.028	0.047	0.006	0.042	0.031	0.018
1392	0.030	0.042	0.003	0.037	0.028	0.017
1440	0.023	0.038	0.008	0.031	0.025	0.013
1488	0.019	0.030	0.003	0.027	0.020	0.012
1536	0.015	0.028	0.004	0.026	0.018	0.011
1584	0.021	0.027	0.003	0.019	0.017	0.010
1632	0.006	0.020	<LOQ	0.012	0.013	0.007
1680	0.014	0.026	<LOQ	0.012	0.017	0.007
1728	<LOQ	0.011	<LOQ	0.012	0.012	0.001
1776	<LOQ	0.011	<LOQ	0.008	0.009	0.003
1824	0.006	0.013	<LOQ	0.014	0.011	0.005
1872	0.001	0.008	<LOQ	0.009	0.006	0.004
1920	<LOQ	0.008	<LOQ	0.004	0.006	0.003
1968	<LOQ	0.006	<LOQ	0.006	0.006	0.000
2016	<LOQ	0.005	<LOQ	0.004	0.005	0.001

Concentration ($\mu\text{g equiv/g}$) in serial plasma in female rats following oral gavage with 0.1 mg/kg PFOA (extended time course)

Time (h)	Animal				Mean	SD
	659283	659285	659286	659288		
0	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
1	0.427	0.587	0.575	0.478	0.517	0.077
2	0.344	0.503	0.570	0.479	0.474	0.095
4	0.349	0.408	0.436	0.427	0.405	0.039
8	0.101	0.134	0.121	0.139	0.124	0.017
12	NS	0.066	0.050	0.065	0.060	0.009
16	0.028	0.021	0.011	0.021	0.020	0.007
24	0.005	0.004	<LOQ	<LOQ	0.005	0.001
36	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
48	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
72	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
96	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
120	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
144	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
168	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
192	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
240	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA
312	<LOQ	<LOQ	<LOQ	<LOQ	NA	NA

Pharmacokinetic parameters in male and female rats following oral gavage with 0.1 mg/kg PFOA (extended time course)

Male

Animal	T _{max} (hr)	C _{max} (μg/mL)	Lambda z (1/hr)	T _{1/2} (hr)	AUC _{INF} (hr·μg/mL)	AUC _{INF} /D (hr·μg/mL/mg/kg)	Cl _p (mL/kg·hr)
659277	2.0	1.692	0.0024	294.8	197.67	1996.62	0.50
659278	2.0	0.912	0.0022	319.5	253.70	2615.48	0.38
659279	16.0	0.722	0.0036	193.7	126.28	1329.28	0.75
659280	2.0	1.004	0.0023	300.5	247.87	2503.71	0.40
Mean	5.5	1.08	0.0026	277.10	206.38	2111.28	0.51
SD	7.0	0.42	0.0007	56.62	59.03	586.77	0.17

Female

Animal	T _{max} (hr)	C _{max} (μg/mL)	Lambda z (1/hr)	T _{1/2} (hr)	AUC _{INF} (hr·μg/mL)	AUC _{INF} /D (hr·μg/mL/mg/kg)	Cl _p (mL/kg·hr)
659283	1.0	0.427	0.20	3.40	2.87	29.57	33.8
659285	1.0	0.587	0.13	5.21	3.58	36.89	27.1
659286	1.0	0.575	0.30	2.31	3.48	35.87	27.9
659288	2.0	0.479	0.25	2.82	3.42	35.24	28.4
Mean	1.25	0.52	0.22	3.44	3.34	34.39	29.30
SD	0.50	0.08	0.07	1.26	0.32	3.29	3.06

Appendix N
Tissue Distribution at $T_{\max}$ and $T_{\max/2}$ in Male and Female Rats
Following Oral Gavage with 1 mg/kg ^{14}C -PFOA

Dosing information for male and female rats

Dose Concentration (mg/g): 0.220

Nominal Dose Volume (mL/kg): 4.0

Nominal Dose Rate (mg/kg): 1.0

Male

Animal	Animal Weight (g)	Dose Administered (g)	Actual Dose Rate (mg/kg)	Radioactivity Received (μ Ci)
T_{max}				
401M	201.2	0.80	0.877	23.684
402M	198.2	0.79	0.876	23.301
403M	206.2	0.78	0.831	23.006
404M	203.2	0.81	0.875	23.861
Mean	202.2	0.80	0.865	23.463
Standard Deviation	3.4	0.01	0.022	0.384
T_{max/2}				
405M	206.4	0.84	0.889	24.628
406M	202.1	0.80	0.874	23.713
407M	203.3	0.81	0.880	24.008
408M	200.9	0.79	0.869	23.418
Mean	203.2	0.81	0.878	23.942
Standard Deviation	2.4	0.02	0.009	0.517

Female

Animal	Animal Weight (g)	Dose Administered (g)	Actual Dose Rate (mg/kg)	Radioactivity Received (μ Ci)
T_{max}				
409F	193.1	0.80	0.872	22.593
410F	193.2	0.80	0.882	22.858
411F	194.2	0.78	0.878	22.888
412F	189.2	0.77	0.889	22.563
Mean	192.4	0.79	0.880	22.725
Standard Deviation	2.2	0.02	0.007	0.171
T_{max/2}				
413F	192.1	0.78	0.894	23.035
414F	180.6	0.73	0.893	21.649
415F	195.5	0.78	0.871	22.858
416F	189.6	0.77	0.890	22.652
Mean	189.5	0.76	0.887	22.548
Standard Deviation	6.4	0.02	0.011	0.620

Percent recovery of radioactivity at T_{max} in tissues in male and female rats following oral gavage with 1 mg/kg ¹⁴C-PFOA

Male

	Timepoint	401M	402M	403M	404M	Mean	SD
prostate	10 h 30 m	0.070	0.034	0.115	0.114	0.083	0.039
skin ^a	10 h 30 m	16.470	11.648	15.385	15.585	14.772	2.135
whole blood ^a	10 h 30 m	21.816	22.028	23.151	21.596	22.148	0.692
brain	10 h 30 m	0.064	0.058	0.098	0.063	0.071	0.018
fat ^a	10 h 30 m	1.913	2.260	2.946	2.005	2.281	0.467
heart	10 h 30 m	0.487	0.345	0.603	0.369	0.451	0.119
lungs	10 h 30 m	0.717	0.656	0.953	0.632	0.740	0.147
spleen	10 h 30 m	0.079	0.086	0.101	0.078	0.086	0.011
liver	10 h 30 m	25.170	15.970	17.973	27.718	21.708	5.627
kidney	10 h 30 m	1.718	2.073	1.550	2.455	1.949	0.402
G.I. tract	10 h 30 m	1.857	2.502	3.931	3.431	2.930	0.929
G.I. contents	10 h 30 m	1.564	2.371	2.827	1.568	2.083	0.625
thyroid	10 h 30 m	0.010	0.004	0.013	0.004	0.008	0.005
thymus	10 h 30 m	0.079	0.080	0.097	0.085	0.085	0.008
testes	10 h 30 m	0.761	0.765	0.843	0.650	0.755	0.079
adrenals	10 h 30 m	0.015	0.017	0.025	0.018	0.019	0.004
muscle ^a	10 h 30 m	11.612	11.994	12.951	11.543	12.025	0.648
bone ^a	10 h 30 m	2.973	3.218	4.046	2.853	3.273	0.538
Total		87.375	76.109	87.608	90.767	85.465	6.426

^a Percent recovery scaled to whole animal assuming the following: skin=19%, whole blood=7.4%, fat=7%, muscle=40.4%, bone=7.3% of body weight.

Female

	Timepoint	409F	410F	411F	412F	Mean	SD
skin ^a	1 h 15 m	0.495	0.631	0.268	0.341	0.434	0.162
whole blood ^a	1 h 15 m	7.509	6.355	4.067	5.028	5.740	1.507
brain	1 h 15 m	0.048	0.038	0.033	0.027	0.037	0.009
fat	1 h 15 m	0.163	0.161	0.107	0.105	0.134	0.032
heart	1 h 15 m	0.199	0.309	0.134	0.151	0.198	0.079
lungs	1 h 15 m	0.592	0.562	0.285	0.376	0.454	0.148
spleen	1 h 15 m	0.077	0.095	0.040	0.041	0.063	0.027
liver	1 h 15 m	6.724	8.932	6.233	6.349	7.060	1.266
kidney	1 h 15 m	3.706	4.256	3.154	2.037	3.288	0.948
G.I. tract	1 h 15 m	4.482	4.365	23.647	10.301	10.699	9.066
G.I. contents	1 h 15 m	21.336	3.325	29.125	34.039	21.956	13.477
thyroid	1 h 15 m	0.009	0.010	0.013	0.007	0.010	0.003
thymus	1 h 15 m	0.068	0.066	0.038	0.037	0.052	0.017
ovaries	1 h 15 m	0.046	0.075	0.034	0.034	0.047	0.019
adrenals	1 h 15 m	0.021	0.014	0.012	0.009	0.014	0.005
uterus	1 h 15 m	0.209	0.186	0.094	0.189	0.170	0.051
muscle ^a	1 h 15 m	0.225	0.372	0.213	0.161	0.243	0.091
bone ^a	1 h 15 m	0.091	0.125	0.086	0.100	0.101	0.017
Total		46.000	29.877	67.583	59.332	50.698	16.485

^a Percent recovery scaled to whole animal assuming the following: skin=19%, whole blood=7.4%, fat=7%, muscle=40.4%, bone=7.3% of body weight.

Perfluorooctanoic Acid: Toxicokinetics in the Rat

Percent recovery of radioactivity at $T_{max/2}$ in tissues in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA

Male

	Timepoint	405M	406M	407M	408M	Mean	SD
prostate	171 h	0.030	0.028	0.032	0.030	0.030	0.002
skin ^a	171 h	5.843	6.460	5.939	6.002	6.061	0.274
whole blood ^a	171 h	7.624	9.975	8.108	7.219	8.232	1.218
brain	171 h	0.021	0.020	0.025	0.020	0.022	0.002
fat ^a	171 h	0.438	0.753	0.535	0.645	0.593	0.136
heart	171 h	0.174	0.210	0.220	0.175	0.195	0.024
lungs	171 h	0.322	0.404	0.323	0.313	0.341	0.043
spleen	171 h	0.045	0.053	0.039	0.041	0.045	0.006
liver	171 h	37.037	30.266	34.029	29.176	32.627	3.601
kidney	171 h	0.841	1.329	1.256	1.134	1.140	0.215
G.I. tract	171 h	0.649	1.332	1.105	0.835	0.980	0.300
G.I. contents	171 h	0.203	0.244	0.249	0.260	0.239	0.025
thyroid	171 h	0.003	0.002	0.009	0.003	0.004	0.003
thymus	171 h	0.036	0.075	0.037	0.056	0.051	0.018
testes	171 h	0.301	0.375	0.378	0.368	0.356	0.037
adrenals	171 h	0.008	0.010	0.011	0.009	0.010	0.001
muscle ^a	171 h	4.460	6.089	4.681	4.704	4.984	0.745
bone ^a	171 h	1.161	1.229	1.068	1.020	1.120	0.094
Total		59.196	58.854	58.044	52.010	57.026	3.379

^a Percent recovery scaled to whole animal assuming the following: skin=19%, whole blood=7.4%, fat=7%, muscle=40.4%, bone=7.3% of body weight.

Female

	Timepoint	413F	414F	415F	416F	Mean	SD
skin ^a	4 h	0.270	0.396	0.456	0.488	0.403	0.096
whole blood ^a	4 h	3.406	6.470	4.995	2.882	4.438	1.625
brain	4 h	0.047	0.040	0.059	0.043	0.047	0.008
fat	4 h	0.070	0.141	0.186	0.259	0.164	0.079
heart	4 h	0.252	0.316	0.261	0.183	0.253	0.055
lungs	4 h	0.512	0.667	0.519	0.484	0.546	0.082
spleen	4 h	0.050	0.060	0.063	0.058	0.058	0.006
liver	4 h	4.571	7.984	7.582	7.131	6.817	1.537
kidney	4 h	2.047	3.147	2.192	3.688	2.769	0.784
G.I. tract	4 h	2.950	13.010	2.781	15.108	8.462	6.519
G.I. contents	4 h	1.158	5.193	2.731	6.480	3.891	2.395
thyroid	4 h	0.006	0.047	0.005	0.006	0.016	0.021
thymus	4 h	0.079	0.027	0.075	0.049	0.058	0.024
ovaries	4 h	0.057	0.045	0.049	0.042	0.048	0.006
adrenals	4 h	0.022	0.020	0.018	0.013	0.018	0.004
uterus	4 h	0.322	0.289	0.126	0.296	0.258	0.089
muscle ^a	4 h	0.262	0.290	0.741	0.204	0.374	0.247
bone ^a	4 h	0.116	0.226	0.115	0.155	0.153	0.052
Total		16.197	38.368	22.954	37.569	28.772	10.976

^a Percent recovery scaled to whole animal assuming the following: skin=19%, whole blood=7.4%, fat=7%, muscle=40.4%, bone=7.3% of body weight.

Concentration ($\mu\text{g equiv/g}$) at T_{max} in tissues in male and female rats following oral gavage with 1 mg/kg ^{14}C -PFOA

Male

	Timepoint	401M	402M	403M	404M	Mean	SD
prostate	10 h 30 m	0.473	0.306	0.572	0.464	0.454	0.110
skin	10 h 30 m	0.760	0.537	0.673	0.718	0.672	0.097
whole blood	10 h 30 m	2.586	2.607	2.601	2.553	2.587	0.024
brain	10 h 30 m	0.058	0.061	0.083	0.062	0.066	0.012
fat	10 h 30 m	0.240	0.283	0.350	0.251	0.281	0.050
heart	10 h 30 m	0.978	0.854	1.200	0.862	0.973	0.161
lungs	10 h 30 m	1.074	1.128	1.379	1.048	1.157	0.151
spleen	10 h 30 m	0.319	0.325	0.422	0.289	0.339	0.058
liver	10 h 30 m	4.808	4.814	3.589	5.298	4.627	0.729
kidney	10 h 30 m	1.512	1.739	1.464	2.126	1.710	0.302
G.I. tract	10 h 30 m	0.397	0.435	0.734	0.547	0.528	0.151
G.I. contents	10 h 30 m	0.191	0.223	0.250	0.209	0.218	0.025
thyroid	10 h 30 m	0.419	0.279	0.489	0.410	0.399	0.088
thymus	10 h 30 m	0.325	0.275	0.279	0.230	0.277	0.039
testes	10 h 30 m	0.578	0.558	0.560	0.465	0.540	0.051
adrenals	10 h 30 m	0.482	0.466	0.725	0.452	0.531	0.130
muscle	10 h 30 m	0.252	0.260	0.266	0.250	0.257	0.008
bone	10 h 30 m	0.357	0.386	0.461	0.342	0.386	0.053

Female

	Timepoint	409F	410F	411F	412F	Mean	SD
skin	1 h 15 m	0.336	0.441	0.188	0.228	0.298	0.114
whole blood	1 h 15 m	2.040	2.355	1.242	1.231	1.717	0.569
brain	1 h 15 m	0.042	0.038	0.028	0.026	0.033	0.008
fat	1 h 15 m	0.149	0.228	0.081	0.109	0.142	0.064
heart	1 h 15 m	0.484	0.635	0.314	0.326	0.440	0.151
lungs	1 h 15 m	0.879	0.855	0.521	0.551	0.701	0.192
spleen	1 h 15 m	0.246	0.267	0.152	0.138	0.201	0.065
liver	1 h 15 m	1.964	2.294	1.788	1.707	1.938	0.260
kidney	1 h 15 m	3.585	3.879	2.863	1.967	3.073	0.852
G.I. tract	1 h 15 m	0.750	0.754	5.365	1.869	2.184	2.185
G.I. contents	1 h 15 m	7.648	1.575	15.001	12.457	9.170	5.910
thyroid	1 h 15 m	0.256	0.370	0.540	0.376	0.385	0.117
thymus	1 h 15 m	0.217	0.225	0.143	0.114	0.175	0.055
ovaries	1 h 15 m	0.438	0.652	0.314	0.283	0.422	0.167
adrenals	1 h 15 m	0.319	0.287	0.172	0.173	0.238	0.076
uterus	1 h 15 m	0.744	0.384	0.240	0.271	0.410	0.231
muscle	1 h 15 m	0.134	0.161	0.091	0.091	0.119	0.035
bone	1 h 15 m	0.160	0.245	0.162	0.118	0.171	0.053

Concentration ($\mu\text{g equiv/g}$) at $T_{\text{max}/2}$ in tissues in male and female rats following oral gavage with $1 \text{ mg/kg } ^{14}\text{C-PFOA}$

Male

	Timepoint	405M	406M	407M	408M	Mean	SD
prostate	171 h	0.132	0.126	0.150	0.204	0.153	0.035
skin	171 h	0.273	0.297	0.275	0.274	0.280	0.011
whole blood	171 h	0.916	1.178	0.964	0.847	0.976	0.143
brain	171 h	0.021	0.020	0.022	0.020	0.021	0.001
fat	171 h	0.056	0.094	0.067	0.080	0.074	0.017
heart	171 h	0.312	0.363	0.362	0.318	0.339	0.027
lungs	171 h	0.418	0.445	0.417	0.383	0.416	0.025
spleen	171 h	0.127	0.135	0.118	0.121	0.125	0.008
liver	171 h	5.070	3.828	4.161	3.663	4.180	0.628
kidney	171 h	0.606	0.955	0.827	0.703	0.773	0.151
G.I. tract	171 h	0.129	0.147	0.148	0.134	0.140	0.010
G.I. contents	171 h	0.024	0.028	0.024	0.024	0.025	0.002
thyroid	171 h	0.216	0.198	0.578	0.199	0.298	0.187
thymus	171 h	0.130	0.189	0.115	0.130	0.141	0.033
testes	171 h	0.196	0.255	0.253	0.220	0.231	0.029
adrenals	171 h	0.144	0.187	0.180	0.189	0.175	0.021
muscle	171 h	0.098	0.132	0.102	0.101	0.108	0.016
bone	171 h	0.141	0.147	0.129	0.121	0.135	0.012

Female

	Timepoint	413F	414F	415F	416F	Mean	SD
skin	4 h	0.491	0.461	0.337	0.371	0.415	0.073
whole blood	4 h	1.530	1.990	1.626	1.866	1.753	0.212
brain	4 h	0.041	0.037	0.049	0.037	0.041	0.005
fat	4 h	0.141	0.187	0.149	0.150	0.157	0.020
heart	4 h	0.512	0.632	0.507	0.482	0.533	0.067
lungs	4 h	0.803	1.000	0.810	0.799	0.853	0.098
spleen	4 h	0.211	0.269	0.215	0.213	0.227	0.028
liver	4 h	1.379	2.538	2.020	2.319	2.064	0.503
kidney	4 h	1.991	3.144	2.587	3.868	2.897	0.800
G.I. tract	4 h	0.609	2.522	0.529	2.610	1.567	1.154
G.I. contents	4 h	0.577	2.074	1.024	2.880	1.639	1.039
thyroid	4 h	0.238	4.430	0.244	0.244	1.289	2.094
thymus	4 h	0.321	0.089	0.295	0.171	0.219	0.109
ovaries	4 h	0.422	0.558	0.447	0.434	0.465	0.063
adrenals	4 h	0.296	0.375	0.323	0.240	0.308	0.056
uterus	4 h	0.663	0.494	0.286	0.817	0.565	0.228
muscle	4 h	0.130	0.181	0.306	0.131	0.187	0.083
bone	4 h	0.172	0.207	0.183	0.192	0.188	0.015

Appendix O
Tissue Distribution at T_{max} and $T_{max/2}$ in Male and Female Rats
Following Oral Gavage with 5 mg/kg ^{14}C -PFOA

Perfluorooctanoic Acid: Toxicokinetics in the Rat

Dosing information for male and female rats

Dose Concentration (mg/g): 1.171
 Nominal Dose Volume (mL/kg): 4.0
 Nominal Dose Rate (mg/kg): 5.0

Male

Animal	Animal Weight (g)	Dose Administered (g)	Actual Dose Rate (mg/kg)	Radioactivity Received (μ Ci)
T_{max}				
417M	233.2	0.94	4.727	28.944
418M	220.1	0.88	4.667	26.976
419M	232.4	0.93	4.667	28.483
420M	230.8	0.95	4.811	29.160
Mean	229.1	0.92	4.718	28.391
Standard Deviation	6.1	0.03	0.068	0.985
$T_{max/2}$				
421M	216.2	0.87	4.708	26.730
422M	234.5	0.94	4.690	28.883
423M	223.4	0.89	4.688	27.499
424M	226.4	0.92	4.739	28.175
Mean	225.1	0.90	4.706	27.822
Standard Deviation	7.6	0.03	0.024	0.922

Female

Animal	Animal Weight (g)	Dose Administered (g)	Actual Dose Rate (mg/kg)	Radioactivity Received (μ Ci)
T_{max}				
425F	187.7	0.75	4.687	23.100
426F	190.6	0.76	4.677	23.408
427F	194.5	0.78	4.722	24.115
428F	200.1	0.79	4.642	24.392
Mean	193.2	0.77	4.682	23.754
Standard Deviation	5.4	0.02	0.033	0.601
$T_{max/2}$				
429F	204.9	0.83	4.751	25.561
430F	184.7	0.74	4.718	22.885
431F	184.8	0.75	4.760	23.100
432F	194.8	0.77	4.654	23.808
Mean	192.3	0.78	4.721	23.838
Standard Deviation	9.6	0.04	0.048	1.214

Percent recovery of radioactivity at T_{max} in tissues in male and female rats following oral gavage with 5 mg/kg ¹⁴C-PFOA

Male

	Timepoint	417M	418M	419M	420M	Mean	SD
prostate	10 h 30 m	0.020	0.049	0.123	0.090	0.071	0.045
skin*	10 h 30 m	14.877	14.875	16.766	15.742	15.565	0.899
whole blood*	10 h 30 m	23.248	27.499	23.612	25.317	24.919	1.942
brain	10 h 30 m	0.053	0.061	0.068	0.020	0.051	0.021
fat*	10 h 30 m	3.046	2.919	2.773	2.521	2.815	0.225
heart	10 h 30 m	0.400	0.459	0.485	0.426	0.443	0.037
lungs	10 h 30 m	0.753	0.846	0.740	0.034	0.593	0.376
spleen	10 h 30 m	0.101	0.117	0.089	0.077	0.096	0.017
liver	10 h 30 m	22.078	16.355	18.794	17.773	18.750	2.434
kidney	10 h 30 m	1.833	1.912	2.372	2.563	2.170	0.354
G.I. tract	10 h 30 m	1.984	2.644	1.941	3.463	2.508	0.713
G.I. contents	10 h 30 m	2.699	1.316	3.031	3.480	2.632	0.934
thyroid	10 h 30 m	0.019	0.008	0.009	0.007	0.011	0.006
thymus	10 h 30 m	0.101	0.080	0.086	0.073	0.085	0.012
testes	10 h 30 m	0.638	0.899	0.759	0.475	0.693	0.180
adrenals	10 h 30 m	0.020	0.017	0.025	0.024	0.022	0.004
muscle*	10 h 30 m	13.827	12.851	14.188	13.394	13.565	0.576
bone*	10 h 30 m	3.445	3.243	3.257	2.242	3.047	0.544
Total		89.142	86.150	89.118	87.721	88.033	1.420

* Percent recovery scaled to whole animal assuming the following: skin=19%, whole blood=7.4%, fat=7%, muscle=40.4%, bone=7.3% of body weight.

Female

	Timepoint	425F	426F	427F	428F	Mean	SD
skin*	1 h 15 m	0.786	0.444	0.665	0.600	0.624	0.142
whole blood*	1 h 15 m	9.284	6.015	10.381	6.675	8.089	2.080
brain	1 h 15 m	0.086	0.042	0.077	0.060	0.066	0.019
fat	1 h 15 m	0.154	0.196	0.148	0.383	0.220	0.111
heart	1 h 15 m	0.425	0.308	0.431	0.388	0.388	0.057
lungs	1 h 15 m	0.863	0.683	0.923	0.838	0.827	0.102
spleen	1 h 15 m	0.093	0.076	0.122	0.113	0.101	0.021
liver	1 h 15 m	11.414	9.858	14.190	9.296	11.190	2.192
kidney	1 h 15 m	3.676	3.825	4.289	5.380	4.293	0.771
G.I. tract	1 h 15 m	3.863	9.744	6.376	8.584	7.142	2.594
G.I. contents	1 h 15 m	0.722	4.915	1.086	4.862	2.896	2.305
thyroid	1 h 15 m	0.011	0.006	0.009	0.007	0.008	0.002
thymus	1 h 15 m	0.103	0.087	0.081	0.147	0.105	0.030
ovaries	1 h 15 m	0.079	0.056	0.082	0.066	0.071	0.012
adrenals	1 h 15 m	0.022	0.022	0.029	0.031	0.026	0.005
uterus	1 h 15 m	0.336	0.318	0.315	0.331	0.325	0.010
muscle*	1 h 15 m	0.335	0.300	0.404	0.375	0.354	0.046
bone*	1 h 15 m	0.146	0.191	0.114	0.246	0.174	0.057
Total		32.398	37.086	39.722	38.382	36.897	3.187

* Percent recovery scaled to whole animal assuming the following: skin=19%, whole blood=7.4%, fat=7%, muscle=40.4%, bone=7.3% of body weight.

Percent recovery of radioactivity at $T_{max/2}$ in tissues in male and female rats following oral gavage with 5 mg/kg ^{14}C -PFOA

Male

	Timepoint	421M	422M	423M	424M	Mean	SD
prostate	171 h	0.045	0.071	0.077	0.035	0.057	0.020
skin ^a	171 h	7.317	7.072	6.761	7.780	7.233	0.430
whole blood ^a	171 h	10.510	10.810	11.936	11.305	11.140	0.624
brain	171 h	0.012	0.025	0.030	0.024	0.023	0.008
fat ^a	171 h	0.670	1.138	0.839	1.016	0.916	0.205
heart	171 h	0.245	0.235	0.296	0.232	0.252	0.030
lungs	171 h	0.075	0.339	0.522	0.441	0.344	0.194
spleen	171 h	0.062	0.053	0.057	0.069	0.060	0.007
liver	171 h	27.111	24.563	24.990	24.260	25.231	1.289
kidney	171 h	1.064	1.222	1.215	1.346	1.212	0.115
G.I. tract	171 h	0.790	1.238	0.997	1.181	1.052	0.202
G.I. contents	171 h	0.255	0.240	0.304	0.282	0.270	0.028
thyroid	171 h	0.005	0.002	0.007	0.003	0.004	0.002
thymus	171 h	0.052	0.049	0.054	0.056	0.053	0.003
testes	171 h	0.400	0.445	0.310	0.332	0.372	0.062
adrenals	171 h	0.011	0.008	0.008	0.009	0.009	0.001
muscle ^a	171 h	5.754	6.018	6.822	7.123	6.429	0.648
bone ^a	171 h	1.180	1.287	1.535	1.496	1.375	0.169
Total		55.558	54.815	56.760	56.990	56.031	1.025

^a Percent recovery scaled to whole animal assuming the following: skin=19%, whole blood=7.4%, fat=7%, muscle=40.4%, bone=7.3% of body weight.

Female

	Timepoint	429F	430F	431F	432F	Mean	SD
skin ^a	4 h	0.336	0.326	0.138	0.426	0.307	0.121
whole blood ^a	4 h	6.530	4.650	3.722	6.740	5.411	1.466
brain	4 h	0.045	0.054	0.031	0.051	0.045	0.010
fat	4 h	0.040	0.131	0.072	0.196	0.110	0.069
heart	4 h	0.275	0.250	0.161	0.259	0.236	0.051
lungs	4 h	0.529	0.638	0.345	0.767	0.570	0.179
spleen	4 h	0.055	0.072	0.045	0.068	0.060	0.012
liver	4 h	7.010	7.008	6.163	8.522	7.176	0.982
kidney	4 h	2.439	1.970	2.621	3.710	2.685	0.736
G.I. tract	4 h	4.052	5.558	21.515	1.893	8.255	8.967
G.I. contents	4 h	0.352	2.739	14.420	4.894	5.601	6.165
thyroid	4 h	0.003	0.007	0.008	0.004	0.006	0.002
thymus	4 h	0.053	0.074	0.050	0.094	0.068	0.021
ovaries	4 h	0.043	0.051	0.023	0.046	0.041	0.012
adrenals	4 h	0.013	0.020	0.010	0.016	0.015	0.004
uterus	4 h	0.229	0.199	0.214	0.272	0.229	0.031
muscle ^a	4 h	0.231	0.314	0.160	0.284	0.247	0.068
bone ^a	4 h	0.101	0.212	0.053	0.203	0.142	0.078
Total		22.336	24.273	49.751	28.445	31.201	12.626

^a Percent recovery scaled to whole animal assuming the following: skin=19%, whole blood=7.4%, fat=7%, muscle=40.4%, bone=7.3% of body weight.

Concentration ($\mu\text{g equiv/g}$) at T_{max} in tissues in male and female rats following oral gavage with 5 mg/kg ^{14}C -PFOA

Male

	Timepoint	417M	418M	419M	420M	Mean	SD
prostate	10 h 30 m	0.291	1.792	3.041	2.926	2.012	1.278
skin	10 h 30 m	3.701	3.654	4.118	3.986	3.865	0.224
whole blood	10 h 30 m	14.849	17.344	14.892	16.461	15.886	1.227
brain	10 h 30 m	0.282	0.316	0.346	0.297	0.310	0.028
fat	10 h 30 m	2.056	1.947	1.849	1.733	1.896	0.138
heart	10 h 30 m	4.850	5.682	5.550	5.461	5.386	0.369
lungs	10 h 30 m	6.579	6.683	6.610	8.110	6.996	0.744
spleen	10 h 30 m	1.847	2.036	1.973	2.199	2.014	0.146
liver	10 h 30 m	24.514	20.607	21.231	27.471	23.456	3.178
kidney	10 h 30 m	8.938	9.924	11.480	13.730	11.018	2.089
G.I. tract	10 h 30 m	2.449	2.586	2.425	3.695	2.789	0.609
G.I. contents	10 h 30 m	1.698	1.047	1.902	2.352	1.750	0.542
thyroid	10 h 30 m	4.105	2.362	2.387	3.315	3.042	0.836
thymus	10 h 30 m	2.274	1.890	1.576	1.948	1.922	0.286
testes	10 h 30 m	2.567	2.943	2.742	2.764	2.754	0.154
adrenals	10 h 30 m	2.736	3.289	3.332	4.441	3.449	0.714
muscle	10 h 30 m	1.618	1.485	1.639	1.595	1.584	0.069
bone	10 h 30 m	2.230	2.073	2.082	1.478	1.966	0.333

Female

	Timepoint	425F	426F	427F	428F	Mean	SD
skin	1 h 15 m	2.776	2.232	2.717	3.387	2.778	0.474
whole blood	1 h 15 m	13.308	11.813	15.618	14.816	13.889	1.683
brain	1 h 15 m	0.402	0.237	0.371	0.309	0.330	0.073
fat	1 h 15 m	1.236	0.902	1.428	1.513	1.270	0.271
heart	1 h 15 m	5.117	3.446	5.073	4.370	4.501	0.783
lungs	1 h 15 m	7.439	5.688	7.518	7.324	6.992	0.873
spleen	1 h 15 m	1.792	1.327	1.902	1.876	1.725	0.269
liver	1 h 15 m	16.406	16.200	21.643	13.487	16.934	3.409
kidney	1 h 15 m	20.184	22.608	30.506	30.869	26.042	5.457
G.I. tract	1 h 15 m	4.674	8.584	8.056	10.441	7.938	2.405
G.I. contents	1 h 15 m	1.357	7.769	1.240	9.079	4.861	4.149
thyroid	1 h 15 m	2.414	2.034	2.467	2.641	2.389	0.256
thymus	1 h 15 m	1.602	1.614	1.666	1.876	1.689	0.127
ovaries	1 h 15 m	3.712	3.083	3.990	4.047	3.708	0.442
adrenals	1 h 15 m	3.122	1.905	3.065	3.150	2.810	0.605
uterus	1 h 15 m	4.717	3.327	4.713	7.061	4.955	1.549
muscle	1 h 15 m	1.053	0.835	1.109	1.269	1.067	0.179
bone	1 h 15 m	1.560	1.044	1.253	1.584	1.360	0.259

Concentration ($\mu\text{g equiv/g}$) at $T_{\text{max}/2}$ in tissues in male and female rats following oral gavage with 5 mg/kg ^{14}C -PFOA

Male

	Timepoint	421M	422M	423M	424M	Mean	SD
prostate	171 h	1.051	1.227	1.003	0.846	1.032	0.157
skin	171 h	1.813	1.746	1.668	1.941	1.792	0.116
whole blood	171 h	6.687	6.852	7.561	7.240	7.085	0.393
brain	171 h	0.132	0.180	0.164	0.144	0.155	0.021
fat	171 h	0.450	0.763	0.562	0.688	0.616	0.138
heart	171 h	2.285	2.447	2.742	2.294	2.442	0.213
lungs	171 h	2.743	2.679	3.841	3.142	3.101	0.534
spleen	171 h	0.808	0.887	0.945	0.831	0.868	0.061
liver	171 h	17.572	17.541	20.646	17.207	18.242	1.611
kidney	171 h	3.740	4.463	4.515	5.119	4.459	0.564
G.I. tract	171 h	0.844	0.873	1.100	1.035	0.963	0.124
G.I. contents	171 h	0.139	0.168	0.197	0.195	0.175	0.027
thyroid	171 h	1.142	1.514	1.745	2.206	1.652	0.445
thymus	171 h	0.853	1.064	1.394	1.258	1.142	0.236
testes	171 h	1.192	1.548	1.063	1.172	1.244	0.211
adrenals	171 h	1.157	1.253	0.847	1.202	1.115	0.183
muscle	171 h	0.671	0.699	0.792	0.836	0.749	0.077
bone	171 h	0.761	0.827	0.986	0.971	0.886	0.110

Female

	Timepoint	429F	430F	431F	432F	Mean	SD
skin	4 h	2.479	2.921	1.458	3.270	2.532	0.786
whole blood	4 h	9.103	9.556	7.136	10.466	9.065	1.406
brain	4 h	0.246	0.318	0.133	0.269	0.241	0.078
fat	4 h	0.936	0.793	0.639	1.107	0.868	0.200
heart	4 h	3.213	3.285	2.030	3.026	2.889	0.583
lungs	4 h	4.703	5.630	3.077	5.867	4.819	1.265
spleen	4 h	1.144	1.337	0.911	1.403	1.199	0.221
liver	4 h	11.674	11.509	9.767	12.229	11.295	1.064
kidney	4 h	15.742	12.594	14.933	19.679	15.737	2.948
G.I. tract	4 h	4.921	4.924	27.291	2.482	9.904	11.648
G.I. contents	4 h	0.637	11.051	30.066	7.052	12.202	12.659
thyroid	4 h	2.023	2.323	2.174	1.439	1.990	0.387
thymus	4 h	0.986	1.492	0.983	1.475	1.234	0.288
ovaries	4 h	2.540	3.635	1.986	3.359	2.880	0.756
adrenals	4 h	2.122	2.405	1.609	2.076	2.053	0.330
uterus	4 h	4.998	4.197	3.318	5.799	4.578	1.065
muscle	4 h	0.686	0.939	0.461	0.982	0.767	0.242
bone	4 h	1.145	1.223	0.547	1.364	1.070	0.360

Appendix P
Tissue Distribution at T_{max} and $T_{max/2}$ in Male and Female Rats
Following Oral Gavage with 25 mg/kg ^{14}C -PFOA

Dosing information for male and female rats

Dose Concentration (mg/g): 6.166
 Nominal Dose Volume (mL/kg): 4.0
 Nominal Dose Rate (mg/kg): 25.0

Male

Animal	Animal Weight (g)	Dose Administered (g)	Actual Dose Rate (mg/kg)	Radioactivity Received (μ Ci)
T_{max}				
433M	226.3	0.92	25.096	24.972
434M	211.6	0.86	25.090	23.345
435M	214.1	0.87	24.970	23.508
436M	212.9	0.86	24.937	23.345
Mean	216.2	0.88	25.023	23.792
Standard Deviation	6.8	0.03	0.082	0.790
T_{max/2}				
437M	216.5	0.87	24.864	23.670
438M	215.3	0.88	25.060	23.724
439M	229.3	0.93	25.036	25.243
440M	212.1	0.85	24.828	23.155
Mean	218.3	0.88	24.947	23.948
Standard Deviation	7.6	0.03	0.118	0.900

Female

Animal	Animal Weight (g)	Dose Administered (g)	Actual Dose Rate (mg/kg)	Radioactivity Received (μ Ci)
T_{max}				
441F	189.4	0.78	25.297	21.067
442F	194.7	0.78	24.735	21.176
443F	188.6	0.76	24.685	20.471
444F	188.5	0.76	24.894	20.634
Mean	190.3	0.77	24.902	20.837
Standard Deviation	3.0	0.01	0.278	0.338
T_{max/2}				
445F	187.2	0.76	24.902	20.498
446F	194.1	0.78	24.875	21.230
447F	194.9	0.79	25.026	21.447
448F	196.4	0.79	24.803	21.420
Mean	193.2	0.78	24.901	21.149
Standard Deviation	4.1	0.02	0.093	0.444

Percent recovery of radioactivity at T_{max} in tissues in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

Male

	Timepoint	433M	434M	435M	436M	Mean	SD
prostate	10 h 30 m	0.093	0.064	0.058	0.053	0.067	0.018
skin*	10 h 30 m	12.804	15.036	14.136	13.367	13.836	0.969
whole blood*	10 h 30 m	23.459	24.118	21.382	22.659	22.905	1.177
brain	10 h 30 m	0.072	0.057	0.063	0.059	0.063	0.007
fat*	10 h 30 m	2.748	2.178	1.904	1.782	2.153	0.430
heart	10 h 30 m	0.431	0.501	0.509	0.402	0.461	0.053
lungs	10 h 30 m	0.994	0.802	0.762	0.893	0.863	0.103
spleen	10 h 30 m	0.120	0.113	0.085	0.104	0.106	0.015
liver	10 h 30 m	16.443	17.822	18.576	17.272	17.528	0.900
kidney	10 h 30 m	2.178	2.654	1.982	2.359	2.293	0.286
G.I. tract	10 h 30 m	2.107	3.559	2.885	2.583	2.784	0.608
G.I. contents	10 h 30 m	2.927	4.029	6.087	3.702	4.186	1.349
thyroid	10 h 30 m	0.011	0.007	0.007	0.009	0.009	0.002
thymus	10 h 30 m	0.129	0.126	0.142	0.084	0.120	0.025
testes	10 h 30 m	0.559	0.696	0.520	0.716	0.623	0.098
adrenals	10 h 30 m	0.024	0.031	0.023	0.025	0.026	0.004
muscle*	10 h 30 m	13.506	13.583	12.496	11.836	12.855	0.841
bone*	10 h 30 m	3.363	3.462	2.908	2.513	3.062	0.438
Total		81.968	88.838	84.525	80.418	83.937	3.680

* Percent recovery scaled to whole animal assuming the following: skin=19%, whole blood=7.4%, fat=7%, muscle=40.4%, bone=7.3% of body weight.

Female

	Timepoint	441F	442F	443F	444F	Mean	SD
skin*	1 h 15 m	0.222	0.386	0.303	0.608	0.380	0.166
whole blood*	1 h 15 m	8.178	4.221	9.428	6.803	7.158	2.232
brain	1 h 15 m	0.060	0.049	0.068	0.055	0.058	0.008
fat	1 h 15 m	0.110	0.168	0.097	0.212	0.147	0.053
heart	1 h 15 m	0.342	0.304	0.273	0.348	0.317	0.035
lungs	1 h 15 m	0.692	0.580	0.722	0.718	0.678	0.067
spleen	1 h 15 m	0.091	0.086	0.086	0.101	0.091	0.007
liver	1 h 15 m	9.798	9.253	10.023	13.076	10.538	1.723
kidney	1 h 15 m	6.648	4.828	5.302	6.689	5.867	0.946
G.I. tract	1 h 15 m	5.309	8.941	8.036	5.405	6.923	1.846
G.I. contents	1 h 15 m	2.845	3.229	3.666	0.225	2.491	1.548
thyroid	1 h 15 m	0.008	0.005	0.008	0.013	0.009	0.003
thymus	1 h 15 m	0.104	0.070	0.060	0.130	0.091	0.032
ovaries	1 h 15 m	0.084	0.056	0.076	0.067	0.071	0.012
adrenals	1 h 15 m	0.029	0.028	0.030	0.038	0.031	0.005
uterus	1 h 15 m	0.438	0.410	0.597	0.319	0.441	0.116
muscle*	1 h 15 m	0.209	0.347	0.363	0.513	0.358	0.124
bone*	1 h 15 m	0.093	0.149	0.126	0.259	0.157	0.072
Total		35.260	33.110	39.264	35.579	35.803	2.554

* Percent recovery scaled to whole animal assuming the following: skin=19%, whole blood=7.4%, fat=7%, muscle=40.4%, bone=7.3% of body weight.

Percent recovery of radioactivity at $T_{max/2}$ in tissues in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

Male

	Timepoint	437M	438M	439M	440M	Mean	SD
prostate	171 h	0.034	0.014	0.040	0.022	0.028	0.012
skin ^a	171 h	5.384	5.100	5.635	5.557	5.419	0.237
whole blood ^a	171 h	8.988	7.418	8.500	6.709	7.904	1.032
brain	171 h	0.020	0.020	0.019	0.015	0.019	0.002
fat ^a	171 h	0.781	0.607	0.606	0.518	0.628	0.110
heart	171 h	0.207	0.141	0.170	0.139	0.164	0.032
lungs	171 h	0.367	0.317	0.298	0.230	0.303	0.057
spleen	171 h	0.046	0.036	0.045	0.041	0.042	0.005
liver	171 h	24.179	20.536	19.067	16.799	20.145	3.098
kidney	171 h	1.135	1.038	0.996	0.843	1.003	0.122
G.I. tract	171 h	0.915	1.018	0.631	0.667	0.808	0.189
G.I. contents	171 h	0.287	0.163	0.273	0.116	0.210	0.084
thyroid	171 h	0.006	0.005	0.004	0.003	0.005	0.001
thymus	171 h	0.055	0.051	0.039	0.035	0.045	0.010
testes	171 h	0.252	0.247	0.207	0.189	0.224	0.031
adrenals	171 h	0.013	0.009	0.007	0.005	0.009	0.003
muscle ^a	171 h	4.773	4.184	3.961	4.095	4.253	0.358
bone ^a	171 h	0.943	1.005	0.769	0.905	0.906	0.100
Total		48.385	41.909	41.267	36.888	42.112	4.740

^a Percent recovery scaled to whole animal assuming the following: skin=19%, whole blood=7.4%, fat=7%, muscle=40.4%, bone=7.3% of body weight.

Female

	Timepoint	445F	446F	447F	448F	Mean	SD
skin ^a	4 h	0.238	0.505	0.302	0.614	0.415	0.175
whole blood ^a	4 h	7.097	4.332	7.408	6.790	6.407	1.406
brain	4 h	0.055	0.056	0.083	0.039	0.058	0.018
fat	4 h	0.091	0.209	0.091	0.199	0.148	0.065
heart	4 h	0.282	0.376	0.283	0.208	0.287	0.069
lungs	4 h	0.803	1.020	0.753	0.524	0.775	0.204
spleen	4 h	0.072	0.071	0.068	0.067	0.070	0.002
liver	4 h	8.299	9.076	10.334	8.611	9.080	0.895
kidney	4 h	4.990	4.942	4.903	4.162	4.749	0.393
G.I. tract	4 h	4.880	4.357	2.914	2.036	3.547	1.306
G.I. contents	4 h	2.590	0.535	0.967	0.391	1.121	1.010
thyroid	4 h	0.009	0.008	0.004	0.007	0.007	0.002
thymus	4 h	0.080	0.104	0.060	0.062	0.077	0.020
ovaries	4 h	0.055	0.084	0.074	0.068	0.070	0.012
adrenals	4 h	0.022	0.021	0.020	0.020	0.021	0.001
uterus	4 h	0.435	0.195	0.289	0.297	0.304	0.099
muscle ^a	4 h	0.338	0.406	0.352	0.363	0.365	0.029
bone ^a	4 h	0.104	0.305	0.125	0.189	0.181	0.090
Total		30.440	26.602	29.030	24.647	27.680	2.569

^a Percent recovery scaled to whole animal assuming the following: skin=19%, whole blood=7.4%, fat=7%, muscle=40.4%, bone=7.3% of body weight.

Concentration ($\mu\text{g equiv/g}$) at T_{max} in tissues in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

Male

	Timepoint	433M	434M	435M	436M	Mean	SD
prostate	10 h 30 m	16.536	10.556	12.205	8.895	12.048	3.283
skin	10 h 30 m	16.911	19.856	18.578	17.544	18.222	1.288
whole blood	10 h 30 m	79.555	81.775	72.151	76.359	77.460	4.180
brain	10 h 30 m	2.028	1.727	1.731	1.744	1.807	0.147
fat	10 h 30 m	9.853	7.806	6.792	6.348	7.700	1.560
heart	10 h 30 m	25.768	29.032	27.495	25.962	27.064	1.522
lungs	10 h 30 m	39.555	35.354	34.800	38.938	37.162	2.431
spleen	10 h 30 m	10.878	9.963	9.519	10.589	10.237	0.612
liver	10 h 30 m	104.969	104.531	96.916	112.946	104.841	6.548
kidney	10 h 30 m	54.316	65.723	53.015	62.540	58.898	6.203
G.I. tract	10 h 30 m	13.998	19.390	17.098	15.253	16.435	2.346
G.I. contents	10 h 30 m	10.379	12.655	19.618	14.793	14.361	3.941
thyroid	10 h 30 m	14.447	9.435	10.757	17.845	13.121	3.797
thymus	10 h 30 m	10.679	11.774	7.675	9.400	9.882	1.762
testes	10 h 30 m	15.564	15.111	12.606	14.049	14.333	1.314
adrenals	10 h 30 m	19.135	18.001	14.601	17.347	17.271	1.927
muscle	10 h 30 m	8.390	8.436	7.724	7.306	7.964	0.546
bone	10 h 30 m	11.560	11.901	9.946	8.586	10.498	1.534

Female

	Timepoint	441F	442F	443F	444F	Mean	SD
skin	1 h 15 m	16.938	13.873	16.616	20.719	17.036	2.814
whole blood	1 h 15 m	72.495	68.907	71.931	79.054	73.097	4.272
brain	1 h 15 m	1.458	1.264	1.703	1.476	1.475	0.179
fat	1 h 15 m	6.606	5.883	11.868	9.355	8.428	2.738
heart	1 h 15 m	22.800	19.379	20.280	22.636	21.274	1.709
lungs	1 h 15 m	35.975	29.665	34.466	36.153	34.065	3.029
spleen	1 h 15 m	10.116	8.980	9.289	10.955	9.835	0.888
liver	1 h 15 m	91.459	78.829	97.762	102.318	92.592	10.198
kidney	1 h 15 m	156.202	139.072	169.866	171.518	159.165	15.051
G.I. tract	1 h 15 m	30.144	46.167	53.284	27.417	39.253	12.486
G.I. contents	1 h 15 m	41.312	55.170	29.353	9.838	33.918	19.210
thyroid	1 h 15 m	12.153	9.705	17.651	22.662	15.543	5.794
thymus	1 h 15 m	11.542	10.574	9.866	15.270	11.813	2.405
ovaries	1 h 15 m	16.842	17.827	20.687	21.164	19.130	2.121
adrenals	1 h 15 m	13.847	14.588	15.937	18.536	15.727	2.063
uterus	1 h 15 m	19.232	32.332	24.272	19.429	23.816	6.137
muscle	1 h 15 m	5.131	5.050	5.224	6.349	5.439	0.611
bone	1 h 15 m	6.791	5.857	6.928	6.609	6.546	0.478

Concentration ($\mu\text{g equiv/g}$) at $T_{\text{max}/2}$ in tissues in male and female rats following oral gavage with 25 mg/kg ^{14}C -PFOA

Male

	Timepoint	437M	438M	439M	440M	Mean	SD
prostate	171 h	4.283	5.072	3.680	3.004	4.010	0.880
skin	171 h	7.046	6.726	7.425	7.261	7.114	0.302
whole blood	171 h	30.200	25.120	28.758	22.510	26.647	3.490
brain	171 h	0.561	0.592	0.549	0.444	0.536	0.064
fat	171 h	2.774	2.175	2.166	1.838	2.238	0.390
heart	171 h	9.524	7.347	8.858	7.039	8.192	1.192
lungs	171 h	11.723	11.473	10.834	8.427	10.614	1.505
spleen	171 h	3.221	3.031	3.101	2.677	3.007	0.234
liver	171 h	56.472	59.199	57.258	45.887	54.704	5.989
kidney	171 h	20.305	21.206	18.655	16.448	19.153	2.090
G.I. tract	171 h	4.008	3.406	4.150	2.619	3.546	0.697
G.I. contents	171 h	0.629	0.598	0.907	0.466	0.650	0.186
thyroid	171 h	7.776	12.532	5.498	5.297	7.776	3.364
thymus	171 h	3.371	3.920	3.579	2.815	3.421	0.463
testes	171 h	4.662	4.424	3.820	3.182	4.022	0.663
adrenals	171 h	4.914	4.993	4.941	3.795	4.661	0.578
muscle	171 h	2.938	2.596	2.455	2.516	2.626	0.216
bone	171 h	3.213	3.449	2.639	3.078	3.095	0.341

Female

	Timepoint	445F	446F	447F	448F	Mean	SD
skin	4 h	13.924	19.713	18.605	14.371	16.653	2.934
whole blood	4 h	61.232	60.929	65.639	52.779	60.145	5.361
brain	4 h	1.488	1.437	2.184	1.095	1.551	0.457
fat	4 h	5.748	7.054	5.817	6.008	6.157	0.608
heart	4 h	18.813	22.809	16.459	14.601	18.171	3.540
lungs	4 h	36.513	35.611	34.476	23.884	32.621	5.884
spleen	4 h	8.529	8.108	8.977	7.924	8.385	0.469
liver	4 h	69.455	65.237	78.901	75.252	72.211	6.062
kidney	4 h	139.298	134.958	141.409	121.609	134.318	8.888
G.I. tract	4 h	53.753	22.141	15.616	9.548	25.265	19.676
G.I. contents	4 h	31.034	8.983	6.624	3.804	12.611	12.463
thyroid	4 h	11.702	24.562	16.474	16.897	17.409	5.319
thymus	4 h	7.010	8.218	7.760	6.703	7.423	0.691
ovaries	4 h	17.229	21.763	15.614	20.279	18.721	2.802
adrenals	4 h	12.446	10.894	14.362	11.972	12.419	1.449
uterus	4 h	19.110	19.728	27.286	20.002	21.531	3.854
muscle	4 h	4.643	6.105	5.470	4.971	5.297	0.637
bone	4 h	6.286	8.955	7.238	5.094	6.893	1.631

CONTAIN NO CBI