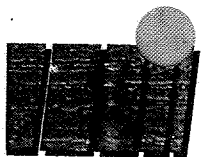


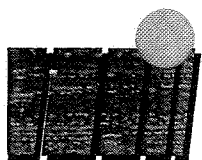
Abstract

Perfluorooctanoic acid (PFOA) is a Fluoroorganic surfactant that has been used in the production of a variety of Fluoropolymers. Considerable focus has been placed on describing the bioexposure potential of PFOA because of a recent decision to remove another Fluoroorganic compound, perfluorooctanyl sulfonate (PFOS), from the marketplace. In order to compare the bioexposure potential of PFOA and PFOS, male rats were dosed once per day for 10 days and followed for 94 days. Blood was drawn and analyzed for total Fluorine on days 1, 5, 10, 13, 24, 52 and 94. Noncompartmental analysis of the blood data was conducted using a WinNonlin mathematical software package. There was considerable difference in PFOA and PFOS blood kinetics as determined by peak blood concentrations and total exposure as determined by area under the curve (AUC) for doses normalized to 0.1 mmol/Kg body weight. The maximum concentration (C_{max}) in blood was 518 and 990 μM equivalents of PFOA and PFOS, respectively. The PFOS AUC in blood was 8 times higher than the PFOA AUC based on a normalized dose of 0.1 mmol/Kg. The terminal half-life in blood was 40.5 days for PFOS as compared to 8.3 days for PFOA. While PFOA and PFOS are both Fluoroorganic materials with surfactant properties, comparison of PFOA and PFOS blood kinetics following repeated oral dosing illustrates that PFOA and PFOS are kinetically different in the rat.



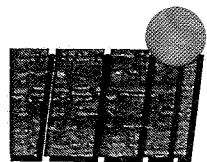
Introduction

Perfluorooctanoic acid (PFOA) is a Fluoroorganic surfactant that has been used in the production of a variety of Fluoropolymers. Considerable focus has been placed on describing the bioexposure potential of PFOA because of a recent decision to remove another Fluoroorganic compound, perfluorooctanyl sulfonate (PFOS), from the marketplace. In order to compare the bioexposure potential of PFOA and PFOS, male rats were dosed once per day for 10 days and followed for 94 days. Blood was analyzed for the total Fluorine content and used to compare the behavior of PFOS and PFOA in blood following oral dosing.



Materials and Methods

Male Crl:CD[®](SD)IGS BR rats were used in this study. Rats were purchased from Charles River Laboratories, Inc., Raleigh, North Carolina and were housed singly in stainless steel, wire-mesh cages suspended above cage boards. Animal rooms were maintained on an approximate 12-hour light/dark cycle (fluorescent light) and at a temperature of $23 \pm 1^{\circ}\text{C}$ and a relative humidity of $50 \pm 10\%$. Tap water was provided *ad libitum*. All rats were fed PMI Nutrition International, Inc. Certified Rodent LabDiet[®] 5002 chow. PFOS and PFOA were provided as solid compounds and were suspended as emulsions in their respective vehicles. Corn oil was used as the vehicle for PFOA. It was necessary to dissolve PFOS in acetone before suspending it in corn oil. The ratio of acetone to corn oil was 20:80. The dose volumes did not exceed 1 mL/100 g of body weight. The dosing suspensions were stirred on a magnetic stir plate throughout the dosing procedure to maintain homogeneity. Negative control groups were used in this study. Corn oil and corn oil:acetone (80:20) were chosen as the negative controls because they were the vehicles for the PFOA and PFOS, respectively. Control rats were dosed in a room separate from the rats dosed with the test substances. Approximately 2 hours after the first dose, 1-2 mL of blood was collected into EDTA tubes from the orbital sinus of each rat. At all other selected time points, 5 rats/group were euthanized by carbon dioxide, and blood was collected at test days 5, 10, 13, 24, 52 and 94.

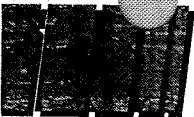


Materials and Methods (continued)

Five to 10 mL of blood was collected into EDTA tubes at sacrifice. The blood from all rats was refrigerated until analyzed for total Fluorine. The total Fluorine content of the blood samples was determined using a Wickbold torch combustion method, followed by analysis with a Fluoride ion selective electrode. The liquid blood was decomposed or volatilized in the presence of wet oxygen and swept through an oxy-hydrogen flame in a closed quartz apparatus. The combustion products were collected in an aqueous absorbing solution and analyzed using a Fluoride ion selective electrode.

Noncompartmental analysis was conducted on blood fluorine data derived from rats using WinNonlin Version 3.0 software (Pharsight Corp, Mountain View, CA).

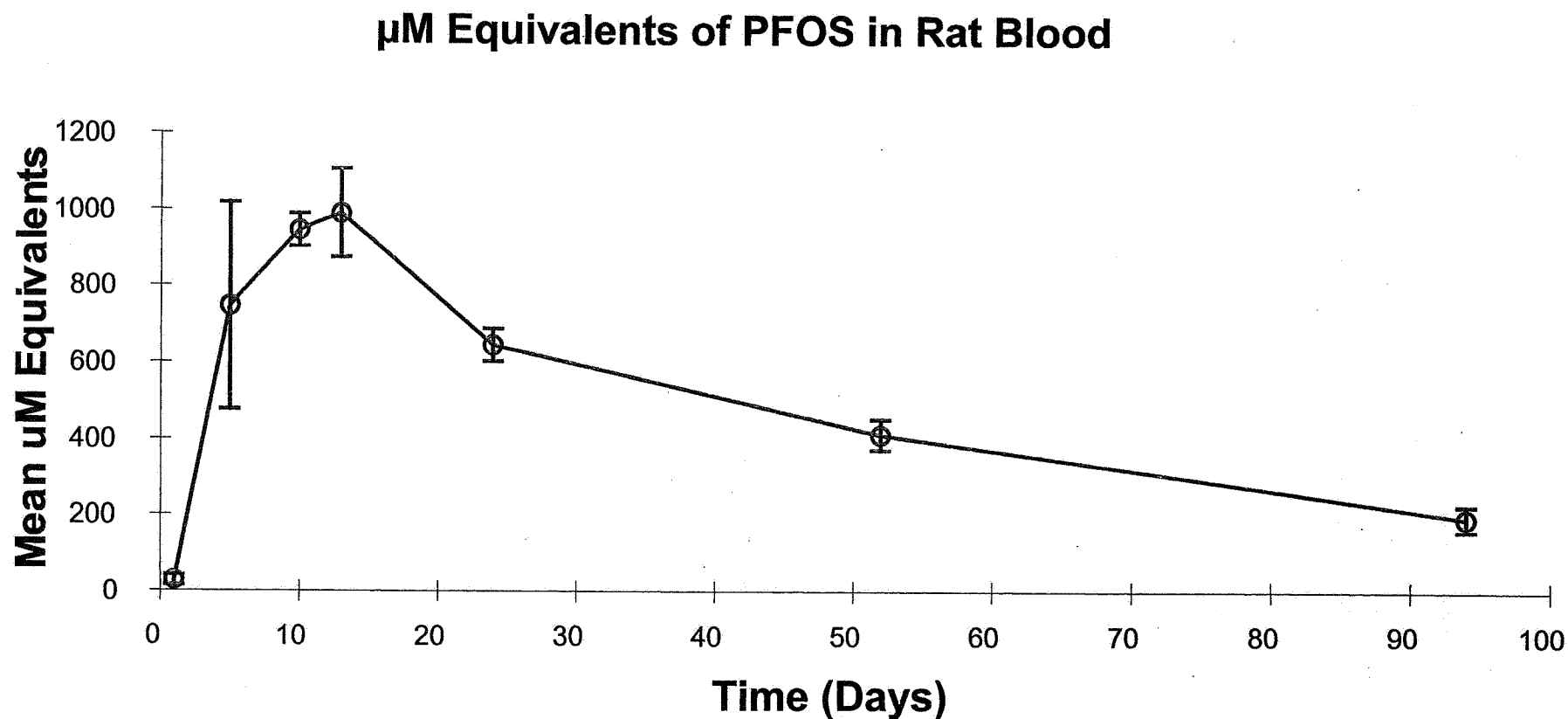
WinNonlin software provided a means of computing derived pharmacokinetic parameters from data files including area under the curve (AUC), C_{max} and terminal half-life (T_{1/2}). The AUC (concentration x time) represents the area under the blood concentration curve from the time of dosing extrapolated to infinity. The points included in determination of the terminal half-life were selected manually and given in units of time. Since the dosages and fluorine content for each positive control and the test material varied, all doses were normalized to 0.1 mmol/kg for comparative purposes. The background was set at 0.2 ppm fluorine because of variability and limited sensitivity of the analytical method. Since 0.2 ppm was the fluoride concentration limit of quantitation, any values listed as less than 0.2 ppm were excluded from further treatment.



Results

The PFOS normalized μM equivalents in rat blood continued to rise throughout the dosing period and may not have reached steady-state (Figure 1). The C_{max} for PFOS was 989.85 ± 116.90 ppm (Mean $\pm$ SD) with a terminal half-life of 40.5 days (Figure 2). The PFOA normalized μM equivalents in rat blood peaked after 5 days of dosing and then decreased throughout the dosing period (Figure 3). The C_{max} for PFOA was 518.12 ± 44.89 ppm (Mean $\pm$ SD) with a terminal half-life of 8.3 days (Figure 4). For each of the test materials, blood was sampled at seven time points throughout the study; with only four of them occurring post-dose. The small sample size and analytical variability should be taken into account when using the derived terminal half-life for comparative purposes. The total internal exposure resulting from a normalized dose was described by AUC and was the basis for comparison between the test compounds. The AUC for the fluorine component was 566,479.1 and 70,789.6 for PFOS and PFOA, respectively (Figure 5).

Figure 1



Micromolar (μ m) Equivalents of PFOS in Male Rat Blood Resulting from a 10-day Oral Exposure to a Normalized Dose of 0.1 mmol/Kg. Values shown are Mean $\pm$ SD.

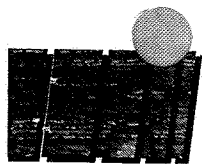
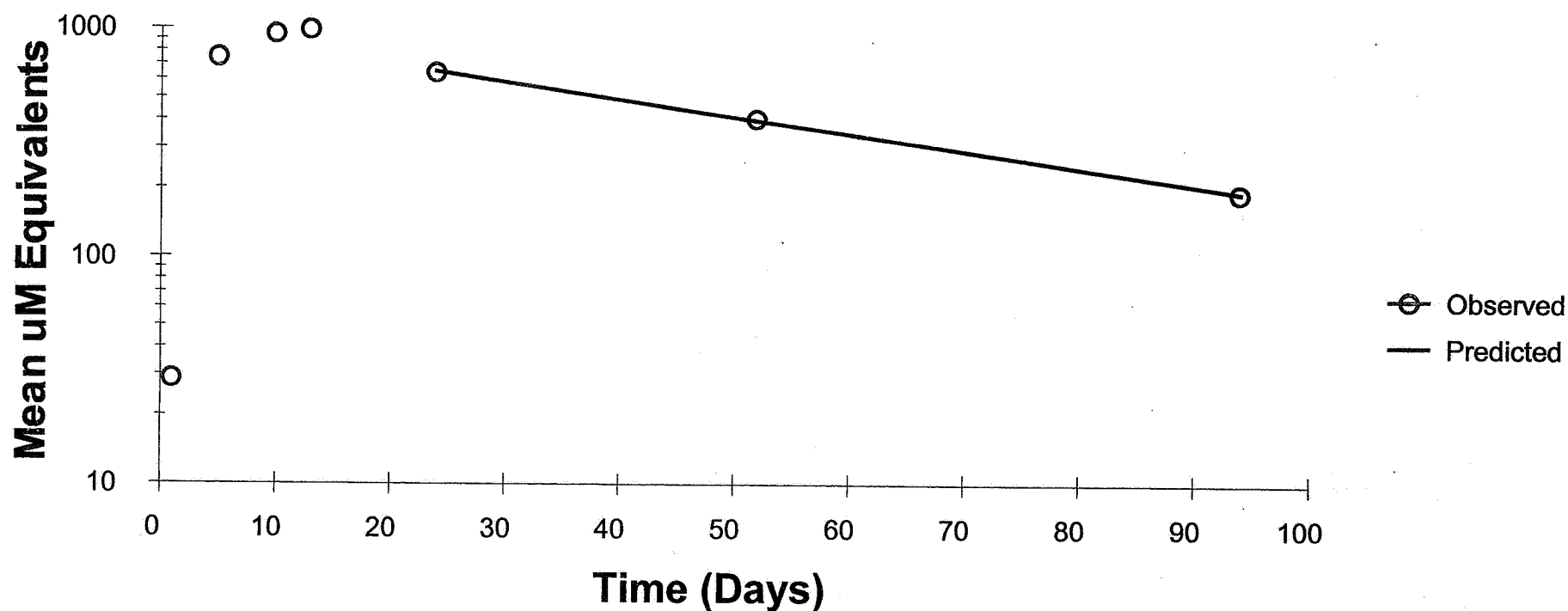


Figure 2

Half-life Estimation Using μM Equivalents of PFOS Rat Blood



Half-life Estimation Using Micromolar (μM) Equivalents of PFOS in Male Rat Blood Resulting from a 10-day Oral Exposure to a Normalized Dose of 0.1 mmol/Kg.

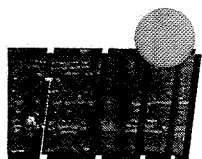
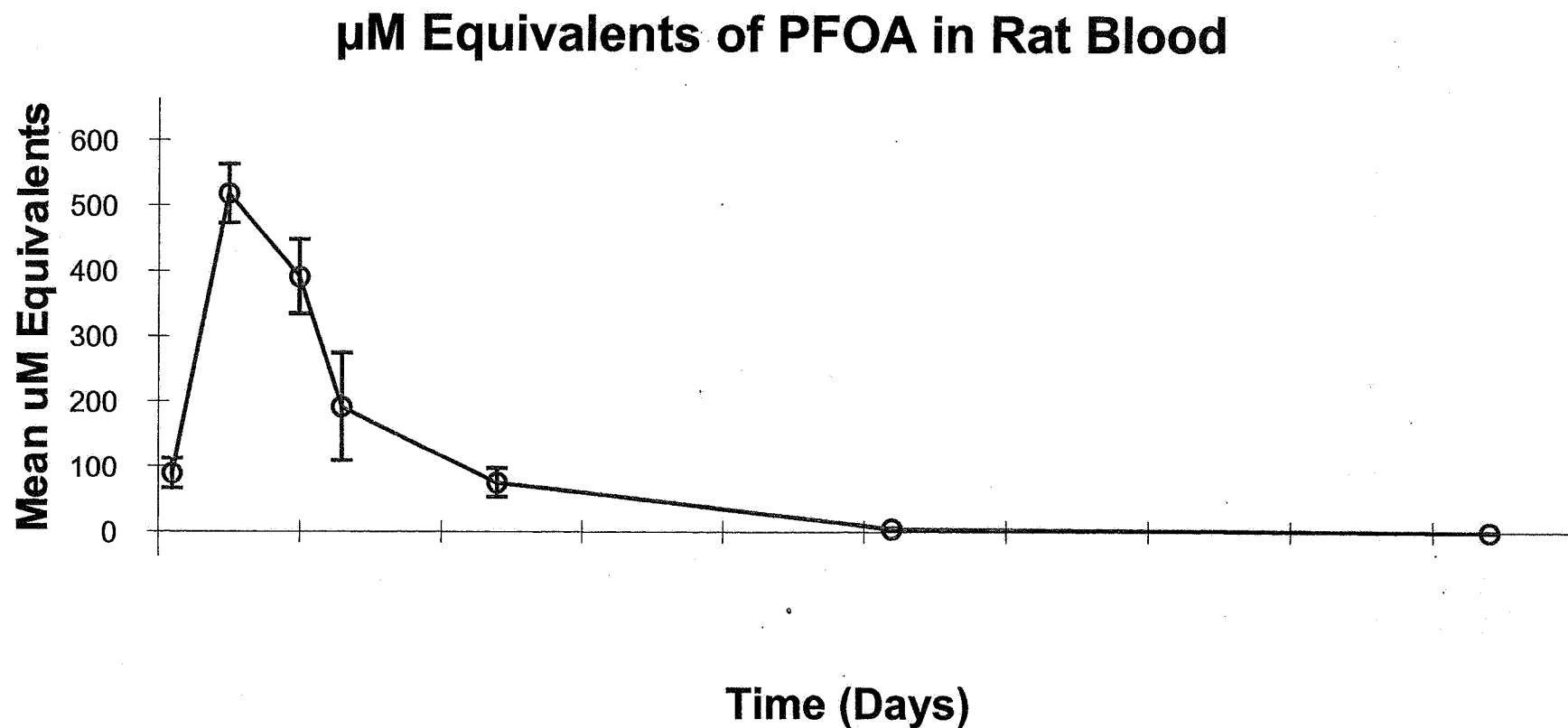
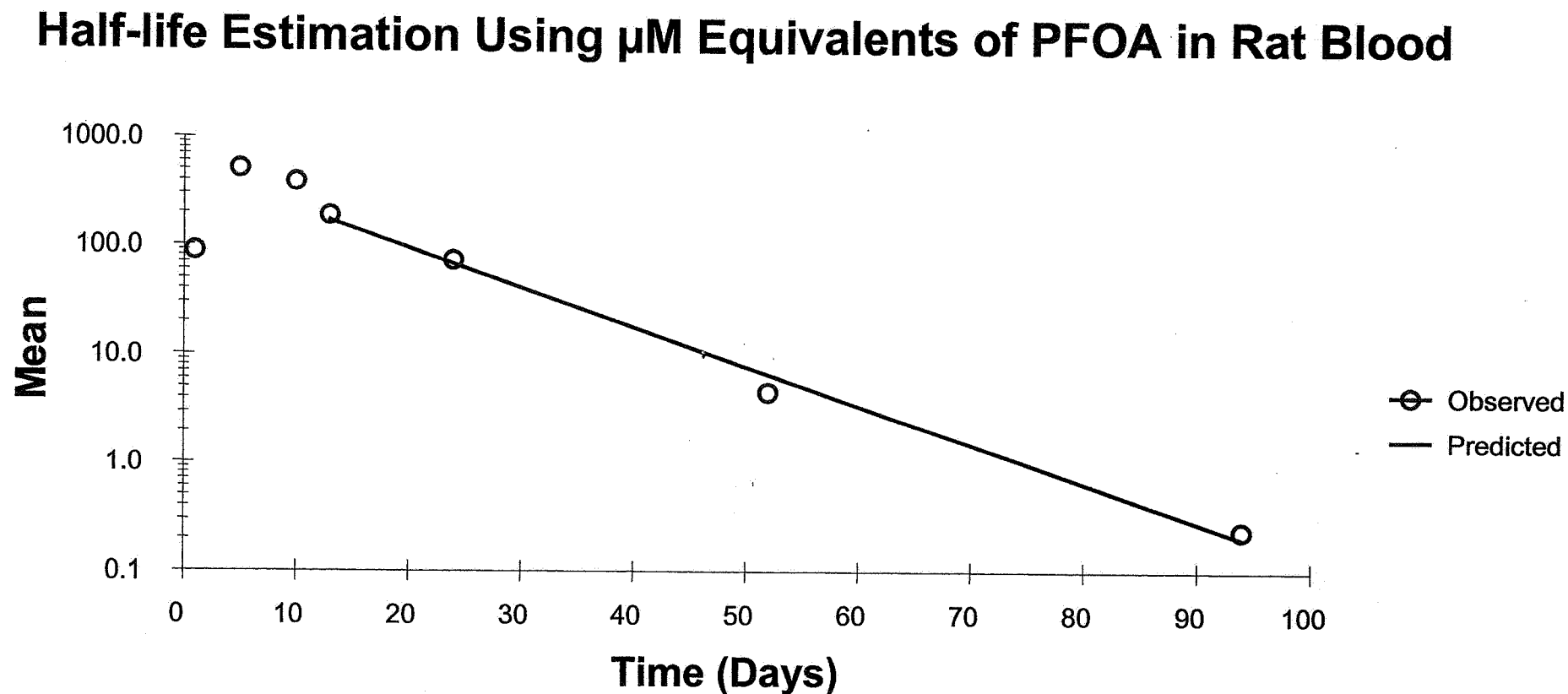


Figure 3



Micromolar (μ m) Equivalents of PFOA in Male Rat Blood Resulting from a 10-day Oral Exposure to a Normalized Dose of 0.1 mmol/Kg. Values shown are Mean $\pm$ SD.

Figure 4



Half-life Estimation Using Micromolar (μM) Equivalents of PFOA in Male Rat Blood Resulting from a 10-day Oral Exposure to a Normalized Dose of 0.1 mmol/Kg.

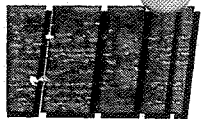
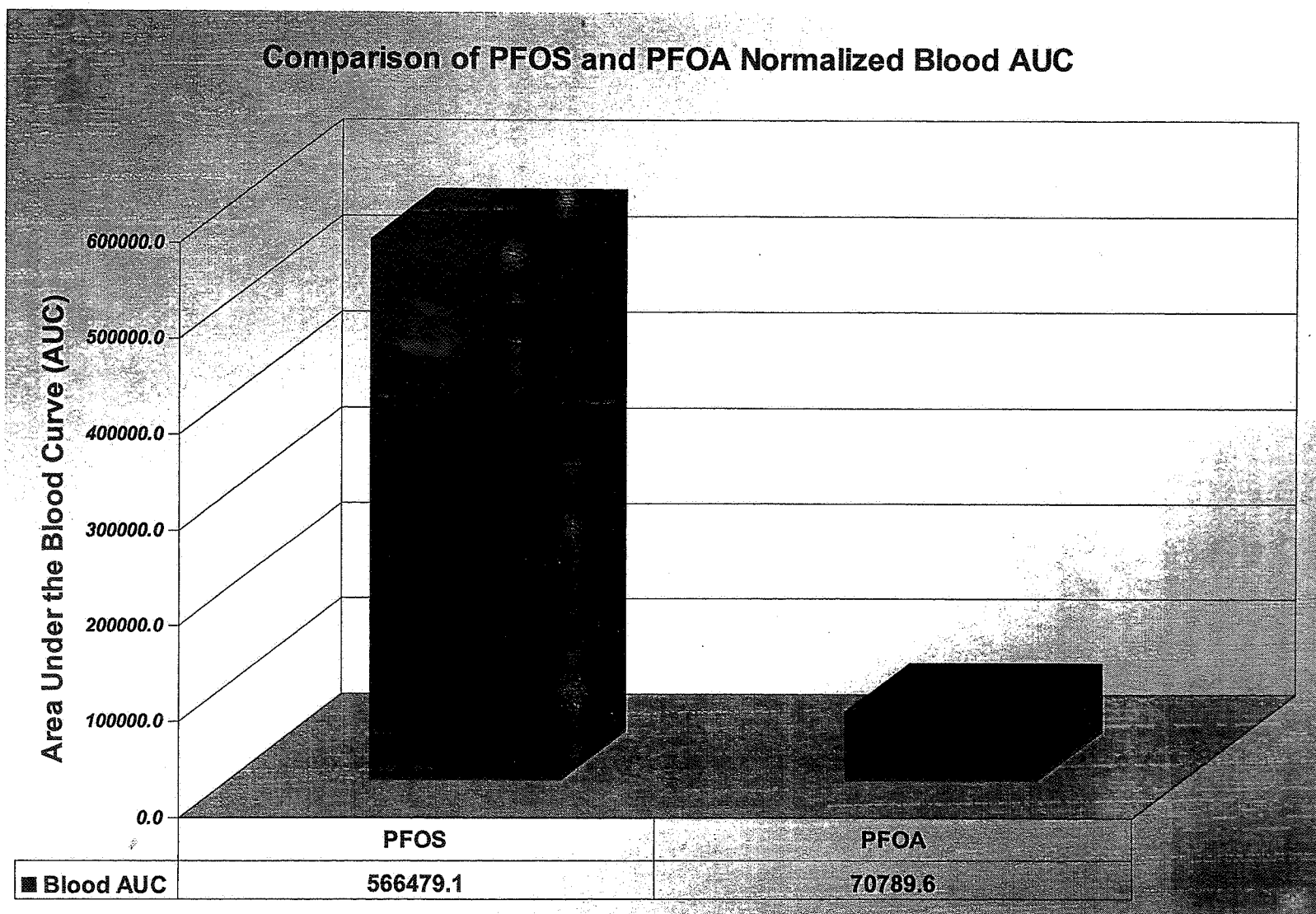


Figure 5



Comparison of PFOS and PFOA AUCs in Male Rat Blood Resulting from a 10-day Oral Exposure to a Normalized Dose of 0.1 mmol/Kg.

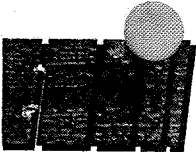
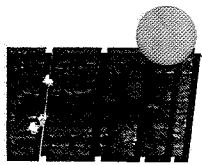


Table 1

Comparison of PFOS and PFOA Behavior in Male Rat Blood

	PFOS	PFOA
Terminal Half-life (Days)	4.05	8.3
Cmax (ppm)	989.8	518.1
AUC Normalized Dose	566479.1	70789.6



Conclusions

- PFOS is absorbed at a faster rate and to a greater extent than PFOA
- PFOS is eliminated from the blood at a slower rate than PFOA
- For an equivalent dose, the Blood AUC is approximately 8x higher for PFOS as compared to PFOA.