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Toxicokinetics of perfluorooctane sulfonate in rabbits under environmentally realistic exposure conditions and comparative assessment between mammals and birds.

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HIGHLIGHTS

- PFOS rabbit toxicokinetics at realistic exposure, 0.085 μg/kg per day, is described.
- The model is defined by full assimilation and a dissipation half-life of 88 days.
- Rabbits have higher assimilation and faster elimination of PFOS than chickens.
- Differences in mammals *vs.* birds kinetic affects terrestrial top predators exposure.

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ABSTRACT

This article describes the toxicokinetics of perfluorooctane sulfonate (PFOS) in rabbits under low repeated dosing, equivalent to 0.085 μg/kg per day, and the observed differences between rabbits and chickens. The best fitting for both species was provided by a simple pseudo monocompartmental first-order kinetics model, regulated by two rates, and accounting for real elimination as well as binding of PFOS to non-exchangeable structures. Elimination was more rapid in rabbits, with a pseudo first-order dissipation half-life of 88 days compared to the 230 days observed for chickens. By contrast, the calculated assimilation efficiency for rabbits was almost 1, very close to full absorption, significantly higher than the 0.66 with confidence intervals of 0.64 and 0.68 observed for chickens. The results confirm a very different kinetics than that observed in single-dose experiments confirming clear dose-related differences in apparent elimination rates in rabbits, as previously described for humans and other mammals; suggesting the role of a capacity-limited saturable process resulting in different kinetic behaviours for PFOS in high dose versus environmentally relevant low dose exposure conditions. The model calculations confirmed that the measured maximum concentrations were still far from the steady state situation, and that the different kinetics between birds and mammals should may play a significant role in the biomagnifications assessment and potential exposure for humans and predators. For the same dose regime, the steady state concentration was estimated at about 36 μg PFOS/L serum for rabbits, slightly above one-half of the 65 μg PFOS/L serum estimated for chickens. The toxicokinetic parameters presented here can be used for higher-tier bioaccumulation estimations of PFOS in rabbits and chickens as starting point for human health exposure assessments and as surrogate values for modeling PFOS kinetics in wild mammals and bird in exposure assessment of predatory species.

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1. Introduction

PFOS is a fully fluorinated anion having the following molecular formula: $C_8F_{17}SO_2Y$, where Y represents an OH group, a metal or other salt, halide, amide or other derivatives including polymers. PFOS is a representative model for the perfluoroalkyl sulfonate substances, which constitute a new category of Persistent Organic Pollutants (POPs). In 2009, the UN Stockholm Convention listed PFOS under Annex B (Restriction for not essential uses).

Despite the voluntary and world-wide regulatory efforts to reduce PFOS emissions, environmental levels are still increasing in large areas of the planet (Filipovic et al., 2013). The environmental fate of PFOS is characterized by its persistence and bioaccumulation, but with a very different mechanism. Regardless of some transformation within the family, the perfluorinated moiety is extremely stable even under high-temperature and strong acid or basic conditions, and are not degraded under environmentally relevant conditions (Buck et al., 2011). Models, such as the fugacity-based multimedia mass balance unit-world model, have been proposed for calculating the environmental fate and long-range transport potential of PFOS and related substances based on parameters such as the overall persistence (P_{OV}), the characteristic travel distance (CTD), and the transfer efficiency (TE) in percent of the P_{OV} describes the overall lifetime of a chemical in a multi-compartment environment consisting of air, water, and soil (Gomis et al., 2015).

PFOS and other perfluorinated substances with long carbon chains are surface-active agents and have physical-chemical properties, water soluble with very low volatility and extremely high persistency, resulting in a different environmental fate than the hydrophobic POPs (Rayne and Forest, 2009; Zareitalabad et al., 2013). The bioaccumulation potential is not related to lipophilicity but attributed to the strong binding potential of this anion to proteins; slow renal clearance and enterohepatic circulation (Conder et al., 2008; Zhao et al., 2015), therefore, toxicokinetic based models are essential for assessing this potential in humans and top predators (Loccisano et al., 2011, 2012a,b; Tarazona et al., 2015).

Physiologically-based pharmacokinetic (PBPK) models have been developed for studying the kinetics of PFOS in humans (Loccisano et al., 2011, 2013; Fàbrega et al., 2014), monkeys (Loccisano et al., 2011), rats (Loccisano et al., 2012a), cows (vanAsselt et al., 2013) and polar bears (Sonne et al., 2009; Dietz et al., 2015). In a previous paper, we have demonstrated that a simple pseudo monocompartmental first-order kinetics model is sufficient for a proper kinetic prediction, provided that the experimental conditions are conducted at low realistic doses (Tarazona et al., 2015). This paper presents the results of a long-tem, hundred days, and realistic low-dose, less than 0.1 μg/kg per day, kinetic study. The selected dose, 0.2 μg/kg bw three days a week equivalent to 0.085 μg/kg per day, is within the average long-term exposure level estimated for several species including humans (Trudel et al., 2008); and below the TDI for humans proposed by the European Food Safety Authority (EFSA CONTAM Panel, 2008). The toxicokinetic data obtained for rabbits are compared with the results conducted on chickens under the same dose patterns, allowing a comparison of the toxicokinetic profile in mammals and birds. At the best of our knowledge this is the first study on the toxicokinetics of PFOS in rabbits. The species was selected to complement our previous study on chickens, using identical exposure patterns for a mammal of equivalent size, daily weight increase, performance efficiency for food production (FAO, 1997) and trophic status. The selection complements the previous mammalians studies which cover rodents, ruminants and primates including humans. In addition, due to the high dose levels used in the rodent studies, generating data on small mammals at repeated realistic low doses is essential for further modelling PFOS transfer through food chains.

2. Materials and methods

2.1. Test substance

The study was conducted with a single batch of potassium perfluorooctanesulfonate (Lot number LPFOS1207) manufactured by Techno Spec from Wellington Laboratories (Canada). Purity was determined to be >98% by liquid chromatography/mass spectrometry. The material was stored at 4–7 °C and protected from the light.

2.2. Animals

The study was conducted on clinically healthy white new Zealand female rabbits obtained from the institution Fundación Premio Arcein Spain. At the time of the first dosing, rabbits were twelve weeks old and the weight (3.54 ± 0.29, $n = 15$) was uniform with a variation not exceeding 20% of the mean weight by dose group. The animal holding room was maintained at 20–25 °C, with controlled humidity and air exchange systems and artificial illumination with12 h light/dark cycle. Variations from these conditions were documented and were considered to have no effect on the outcome of the study. Animals were housed and provided with feed and water*ad libitum*.

2.3. Experimental design

Following an acclimatizing period of 15 days, animals were randomly assigned to either control ($n = 3$) or treatment ($n = 12$) group. Rabbits were observed daily for abnormal behavior, mortality, morbidity, and signs of toxicity. At least once weekly, each animal was removed from its cage and a detailed examination was performed. Body weights were measured at test initiation, during 15 weeks on alternated days and weekly until day 231 when the rabbits were euthanized.

The test substance was dissolved in water (1 μg/mL) and the PFOS was administered by oral gavage at a dose of 0.2 μg/kg bw three days a week (Monday, Wednesday and Friday), equivalent to a daily dose of 0085 μg/kg bw/day, during 102 days, followed by 129 d of depuration.

Two milliliter blood samples were collected through a sterile needle, every week after administration, from the lateral ear vein. The samples were centrifuged at 1800 g for 20 min, within 30 min after collection. Serum aliquots were frozen (−80 °C) until assayed (analyses were performed within 4 weeks after sample collection). The study was approved by the Animal Experimentation Ethics Committee of the School of Veterinary Medicine at the Universidad Complutense de Madrid.

2.4. PFOS serum analysis

PFOS analysis in blood was performed using the method described by Powley et al. (2005, 2008) for biota tissues with slight modifications. About 0.3 g of blood were weighted and transferred into a PP-centrifuge tube and spiked with a 1 ppm M-PFOS (^{13}C-PFOS) solution. Tubes were capped, shaken for a few seconds and let for some minutes. 3 g of ACN (Acetonitrile) were added to the tubes and mixed by shaking and vortex for 30 s. Tubes were extracted during 15 min with the help of an ultrasonic bath, and centrifuge (2000 rpm, 5 min) for sedimentation. Supernatant extracts were transferred to a concentration tube, and the final volume was reduced to 0.5 mL under a gentle N_2 stream.