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Toxicokinetics of perfluorooctane sulfonate in birds under environmentally realistic exposure conditions and development of a kinetic predictive model

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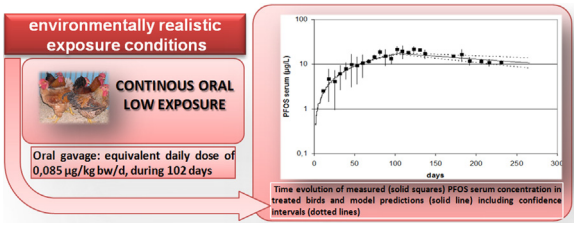
HIGHLIGHTS

- We measured PFOS kinetics in birds under realistic continuous oral low exposure.
- The results suggest much longer half-life, 230 days, than that observed at high doses.
- The best fitting was a simple pseudo monocompartmental first-order kinetics model.
- The model can estimate the expected internal dose following dietary exposure.

GRAPHICAL ABSTRACT



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ABSTRACT

This article describes the toxicokinetics of perfluorooctane sulfonate (PFOS) in birds under low repeated dosing, equivalent to 0.085 µg/kg per day, representing environmentally realistic exposure conditions. The best fitting was provided by a simple pseudo monocompartmental first-order kinetics model, regulated by two rates, with a pseudo first-order dissipation half-life of 230 days, accounting for real elimination as well as binding of PFOS to non-exchangeable structures. The calculated assimilation efficiency was 0.66 with confidence intervals of 0.64 and 0.68. The model calculations confirmed that the measured maximum concentrations were still far from the steady state situation, which for this dose regime, was estimated at a value of about 65 µg PFOS/L serum achieved after a theoretical 210 weeks continuous exposure. The results confirm a very different kinetics than that observed in single-dose experiments confirming clear dose-related differences in apparent elimination rates in birds, as described for humans and monkeys; suggesting that a capacity-limited saturable process should also be considered in the kinetic behavior of PFOS in birds. Pseudo first-order kinetic models are highly convenient and frequently used for predicting bioaccumulation of chemicals in livestock and wildlife; the study suggests that previous bioaccumulation models using half-lives obtained at high doses are

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expected to underestimate the biomagnification potential of PFOS. The toxicokinetic parameters presented here can be used for higher-tier bioaccumulation estimations of PFOS in chickens and as surrogate values for modeling PFOS kinetics in wild bird species.

1. Introduction

Perfluoroalkyl sulfonate substances and particularly, PFOS constitute a new category of Persistent Organic Pollutants (POPs) with increasing concern, as despite efforts to reduce emissions, environmental levels are still increasing in large areas of the planet (Filipovic et al., 2013). PFOS is a fully fluorinated anion having the following molecular formula: $C_8F_{17}SO_2Y$, where Y = OH, metal or other salt, halide, amide and other derivatives including polymers. Such as the other POPs, the environmental fate of PFOS is characterized by its persistence and bioaccumulation, but with a very different mechanism. Despite 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). The bioaccumulation potential is not related to lipophilicity but to its potential for binding to proteins (Conder et al., 2008). They have a non linear sorption potential governed by entropy-driven exclusion of PFOA and PFOS from the aqueous phase towards organic, as well as mineral, surfaces (Zareitalabad et al., 2013), and physical–chemical properties conferring a particular environmental fate (Rayne and Forest, 2009).

Perfluorinated substances with long carbon chains, including perfluorooctane sulfonate, are surface-active agents repelling both water and lipids and have been used various applications. The UN Stockholm Convention reported a wide variety of applications e.g., in textiles and leather products; metal plating; food packaging; fire fighting foams; floor polishes; denture cleansers; shampoos; coatings and coating additives; in the photographic and photo-lithographic industry; and in hydraulic fluids in the aviation industry. In 2009, the Conference of the Parties listed PFOS under Annex B (Restriction for not essential uses) of the Convention, limiting the use of Perfluorooctane sulfonic acid (PFOS), its salts and perfluorooctane sulfonyl fluoride (PFOS-F) to a set of acceptable purposes and setting specific exemptions.

Bioaccumulation and biomagnification modelling in different species is essential for a proper understanding and prediction of exposure levels in humans and top predators. Simplistic approaches, e.g., mono-compartment first order kinetic are usually sufficient for modelling standard lipophilic substances (Alonso et al., 2008). However, the bioaccumulation of PFOS is related to the strong binding potential of this anion to proteins; and lower tier toxicokinetic assumptions, are not appropriate. The use of PBPK (Physiologically Based Pharmacokinetics) models for studying PFOS kinetics has received significant attention in mammals (Loccisano et al., 2011, 2012a,b) in order to understand human kinetics, and have confirmed the complexity of PFOS toxicokinetics (Loccisano et al., 2013); the more recent studies focus on placental and milk transfer, and therefore are only relevant for mammals.

Only few studies on the kinetics of PFOS in birds have been published. The studies cover mallards, *Anas platyrhynchos* L., Northern bobwhite quail, *Colinus virginianus* L., and juvenile chickens, *Gallus gallus* L., (Newsted et al., 2006; Yeung et al., 2009; Yoo et al., 2009); but the exposure patterns did not reflected the long-term and low-dose combination which in our opinion are essential for a real understanding of the bioaccumulation and biomagnification potential of PFOS in the real environment.

Single dose or short-term toxicokinetic studies at relatively high doses, derived from the standard toxicokinetic may provide highly valuable information for understanding the toxicity of these substances. However, more realistic exposure conditions are required for understanding the long-term bioaccumulation of PFOS like substances as demonstrated by the few kinetic studies comparing single/short-term with repeated PFOS administrations (Harris and Barton 2008; Benskin et al., 2009; De Silva et al., 2009).

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, was three orders of magnitude lower than the "low dose" employed in the three weeks chicken study by Yeung et al., 2009 and is within the average long-term exposure level estimated for several species including humans (Trudel et al., 2008). The toxicokinetic data were then used for developing a predictive model of PFOS serum concentrations covering continuous and intermittent exposures.

2. Matherials 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 male chickens (*Gallus gallus domesticus*) breed "Rubio label *campero*" obtained from a commercial farm "Avícola Grau" in Spain. At the time of the first dosing, birds were eight weeks of age and the weight variation did not exceed 20% of the mean weight by dose group. Environmental controls for the animal room were set to maintain a temperature of 20–25 °C, humidity and air exchange systems controlled and animal rooms were artificially illuminated on a 12 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 ($n = 6$) group. Birds 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 chicken 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 tarsal vein. The