# Discussion on the research paper

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## Bayesian evaluation of a physiologically based pharmacokinetic (PBPK) model for perfluorooctane sulfonate (PFOS) to characterize the interspecies uncertainty between mice, rats, monkeys, and humans: Development and performance verification

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ABSTRACT

A challenge in the risk assessment of perfluorooctane sulfonate (PFOS) is the large interspecies differences in its toxicokinetics that results in substantial uncertainty in the dosimetry and toxicity extrapolation from animals to humans. To address this challenge, the objective of this study was to develop an open-source physiologically based pharmacokinetic (PBPK) model accounting for species-specific toxicokinetic parameters of PFOS. Considering available knowledge about the toxicokinetic properties of PFOS, a PBPK model for PFOS in mice, rats, monkeys, and humans after intravenous and oral administrations was created. Available species-specific toxicokinetic data were used for model calibration and optimization, and independent datasets were used for model evaluation. Bayesian statistical analysis using Markov chain Monte Carlo (MCMC) simulation was performed to optimize the model and to characterize the uncertainty and interspecies variability of chemical-specific parameters. The model predictions well correlated with the majority of datasets for all four species, and the model was validated with independent data in rats, monkeys, and humans. The model was applied to predict human equivalent doses (HEDs) based on reported points of departure in selected critical toxicity studies in rats and monkeys following U.S. EPA's guidelines. The lower bounds of the model-derived HEDs were overall lower than the HEDs estimated by U.S. EPA (e.g., 0.2 vs. 1.3 μg/kg/day based on the rat plasma data). This integrated and comparative analysis provides an important step towards improving interspecies extrapolation and quantitative risk assessment of PFOS, and this open-source model provides a foundation for developing models for other perfluoroalkyl substances.

### 1. Introduction

Perfluorooctane sulfonate (PFOS) is a persistent organic pollutant that is used in a wide variety of consumer products, including cookware, furniture, household cleaners, and clothing; and it has been found to be ubiquitous in the environment (ATSDR, 2018). Due to its long half-life in humans (Olsen et al., 2007), environmental persistence, confirmed human environmental and occupational exposures (Calafat et al., 2006; Calafat et al., 2007; Olsen et al., 2003b; Olsen et al., 2008), as well as reported mammalian toxicity (Elcombe et al., 2012a; Seacat et al., 2003; Seacat et al., 2002), the potential risk of PFOS has become a public health concern. However, because of its substantial interspecies differences in toxicokinetics, its risk assessment and dosimetry extrapolation between animals and humans are difficult and of high uncertainty, which can be addressed through a physiologically based pharmacokinetic (PBPK) model that is validated in multiple species.

PFOS is known to be well absorbed in the gastrointestinal tract following oral exposure (Chang et al., 2012), minimally metabolized,

*Abbreviations:* ASC, average serum concentration; AUC, area under the curve; HED, human equivalent dose; EFSA, European Food Safety Authority; IV, intravenous; MCMC, Markov chain Monte Carlo; MOA, Mode of action; NOAEL, no-observed-adverse-effect-level; OATs, organic anion transporters; PBPK, physiologically based pharmacokinetic; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; POD, point of departure; PTCs, proximal tubule cells; RfD, reference dose; TK, toxicokinetic; U.S. EPA, United States Environmental Protection Agency; WHO, World Health Organization

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# Perfluorooctane sulfonate (PFOS)

- Persistent organic pollutant used in variety of products and found ubiquitous in the environment
  - Long half-life in humans, environmental persistence and mammalian toxicity
    - Potential risks require assessment
  - Substantial interspecies differences in toxicokinetics
    - Risk assessment is difficult
- Current study introduces physiologically-based pharmacokinetic model that is validated through several species