

Toxicology and Toxicokinetics

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D18-124 A physiologically-based toxicokinetic model of the fate of perfluorooctansulfonic acid (PFOS) in growing lambs

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Introduction

Perfluorooctansulfonic acid (PFOS) shows high bioaccumulative potential, making foods of animal origin important contributors to human exposure (EFSA, 2020). It is therefore essential to understand and quantify the fate of PFOS in farm animal species. Physiologically-based toxicokinetic (PBTk) models are useful tools for quantifying ADME (Mi and Lin, 2025). Ruminant PBTk models for PFOS have been developed for cattle (e.g. Mikkonen et al., 2023), but, as far as we are aware, none have been published for sheep. This study aimed to develop, optimize and evaluate a PBTk model that describes the transfer of PFOS from the oral intake to meat and offal of growing lambs.

Materials and Methods

A PBTk model was developed based on the toxicokinetic study on growing lambs from Abhoff et al. (2026). Data of ten growing lambs orally exposed to nine PFAS, including linear (n-) and branched (br-) PFOS, for 10 weeks (EXP10, n = 4), 20 weeks (EXP20, n = 3), or for 10 weeks followed by 10 weeks of depuration (DEP10, n = 3) were available. For PFAS analysis, blood plasma was harvested at 12 (EXP10), 18 (EXP20) or 22 (DEP10) time points, as well as longissimus thoracis muscle and liver after euthanasia at 10 (EXP10) or 20 (EXP20 and DEP10) weeks. The PBTk model consists of seven interconnected compartments, one excretion route (lumps faeces and urine), with no metabolic elimination (Lupton et al., 2014). In order to capture the experimentally observed kinetic asymmetry between blood plasma, muscle and liver, the blood plasma was divided into superficial and deep sub-compartments (50% each of total plasma volume) with a diffusion limited transfer in-between. Absorption from intestines (fixed to 100%, Lupton et al., 2014), distribution to muscles and rest of the body (i.e. other tissues), and excretion were connected to the superficial-compartment, whereas distribution to liver was connected to the deep-compartment. Four ADME parameters (plasma sub-compartment diffusion, muscle- and liver-to-plasma partitions, and excretion rate) were optimized against EXP10 and DEP10 lamb data (PayOff procedure, Vensim v.10.3.2). EXP20 lamb data served as evaluation set.

Results

At the optimization step, the model achieved satisfactory goodness-of-fit (mean absolute percentage error [MAPE] = 23% and 34%, $R^2 = 0.92$ and 0.86 , relative RMSE = 31% and 42%), which was confirmed at the evaluation step (MAPE = 11% and 29%, $R^2 = 0.99$ and 0.99 , relative RMSE = 17% and 47% for n-PFOS and br-PFOS, respectively). The optimized excretion rate was numerically higher for n-PFOS (0.08 d⁻¹) than for br-PFOS (0.05 d⁻¹), in accordance with the lower biotransfer factors, and shorter depuration half-life recorded experimentally (Abhoff et al., 2026).

Discussion and Conclusion

The ADME sub-model was further coupled to a physiological sub-model that describes in detail the feeding and physiology of the lamb. This allows the description of a wide variety of sheep farming systems (extensive suckling lamb to intensive fattening lamb) and the effects of physiological traits on PFOS toxicokinetics.

As an outlook, the model optimization is being pursued for the other eight PFAS from the experiment. An additional phase of external evaluation of the model performances is planned, involving a new experiment on lambs. This will allow the routine use of the lamb PBTk model and enable the exploration of complex scenarios of PFAS exposure and depuration for decision support.

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References

1. Abhoff et al., 2026. *Env. Poll.*, 396, 127845; EFSA, 2020. *EFSA Journal*, 18, e06223; Lupton et al., 2014. *J. Agric. Food Chem.*, 62, 1167-1173; Mi and Lin, 2025. *Env. Int.*, 198, 109372; Mikkonen et al., 2023. *Env. Int.*, 180, 108218.