Risk tools for ready-to-use modeling of PFAS transfer from contaminated feed into foods of animal origin

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Introduction

Mathematical models have a long tradition in both risk assessment and all branches of science. Toxicokinetic models in particular allow simulation of the transfer of chemical substances and contaminants from animal feedstuffs and drinking water into food products and processed foods of animal origin. These toxicokinetic models for farm animals are fitted using experimental results from expensive animal experiments and/or more cost-effective in-vitro methods.

The proliferation of toxicokinetic models has drawn interest not just from the scientific community but also from the regulators and practitioners of risk management. The ability to quickly obtain estimations and data with a reasonable degree of flexibility at much lower cost than experiments is a big asset to cost-constrained authorities dealing with food chain contaminants. At the same time, the personnel capacity in natural sciences, mathematics and computer science within authorities is limited to actually gain benefit from toxicokinetic models published by the scientific community. Usually, such models are printed as algorithms and parameters in a journal and demand serious effort, specialized software, additional data and often corrections to actually be implemented for calculations. An important effort to alleviate such problems are publicly available food safety model repositories such as openFSMR [1].

A crisis with PFAS contamination in North Rhine-Westphalia, Germany in 2006, where industrial waste was mixed with fertilizer and polluted agricultural lands used to produce feed crops sparked a series of experimental and theoretical efforts at the German Federal Institute for Risk Assessment (BfR). As risk assessors, we recognized the need for digital tools to facilitate the work of risk managers. In 2006, few data were available for the transfer of PFAS from feed to farm animal products, so we proceeded to perform A) the animal experiments and B) the corresponding mathematical modeling [2][3]. However, these two steps result only in scientific publications and reports useful only for a very specialized community. In this paper we present the details on a following step C) Risk tool programming, where the model is programmed into an easy-to-use software tool. This step entails adding a user-interface as well as sometimes expanding the model to include a wider variety of life stages for the farm animals as needed in practice.

Here, we present two examples of transforming contaminant transfer models into software tools guided by the actual needs of risk management authorities. The tools are designed to simulate absorption, accumulation and excretion of several perfluoroalkyl acids (PFAAs) in farm animals. Both programs employ a published two compartment model to calculate the toxicokinetics [4] combined with a physiological growth model and boundary conditions. RITOPS (Risk tool for estimation of PFAA concentration in swine) is a software tool to calculate the transfer of seven short- and long-chain perfluoroalkyl acids (PFAAs) from the feed and drinking water into various edible tissues such as muscle, fat, blood, liver and kidney based on model [2]. PFAAs are representatives and final degradation products of many poly- und perfluoroalkyl substances (PFAS). A second separate tool called PERCOW (Perfluoroalkyl Acids in Cow's Milk Calculator) was created to calculate the transfer of PFAAs from feed and drinking water into cow's milk and is based on model [3]. The framework of PERCOW is designed to be updated to incorporate new experimental data as they become available.

Materials and methods

RITOPS is based on an open two-compartment model, consisting of a central and a peripheral compartment, as well as influx (feeding and water intake) and outflux (excretion). The central compartment represents the blood plasma, in which the PFAAs are absorbed during digestion. It acts as main distribution system, linked to the peripheral compartment, which represents the summary of tissues (muscle, kidney, liver, fat). PFAAs are not metabolized by pigs, so their kinetics are a function of absorption, distribution and excretion only. The kinetics for each of the PFAAs are summarized in Equations S1a and S1b (Supporting Information) of [2]. These

equations describe the dynamic behavior independently of the growth of the pigs. Changes in the size of the system (i.e. physiological growth) do not influence the dynamics of the system. This enables RITOPS to use well-described physiological data and equations for fattening pigs to model the system size and combine that with the toxicokinetic model. The parameters of the simulated pig, like body weight and the weight of the different tissues or the required daily feed mass, are calculated from a set of equations with parameters fitted to physiological data [4-7]. Note that some of the physiological equations differ in comparison to [2] to extend the simulation range to adult pigs. For example, the function to describe the body weight was changed from a power function with offset to a logistic function (equation 1).

Equation 1:

$$body\ weight = \frac{body\ weight_{end}}{1 + e^{-\alpha \cdot t}(body\ weight_{end}/body\ weight_{birth} - 1)}$$

with $\alpha = 0.0112\ \left[\frac{1}{t}\right], body\ weight_{birth} = 18.7\ [kg], body\ weight_{end} = 262.1\ [kg]$ based on [5].

Due to the high degree of genetic homogeneity of fattening pigs, we were able to link all parameters to the age of the pig, making it the only parameter needed to determine the physiological condition. Thus, the only input RITOPS requires, is the intended age of slaughter or body weight by slaughter (interchangeably) and the mean concentration of the selected PFAAS in the feed and drinking water as well as some information about the timeframe in which the contamination occurs. To address the latter, we included two scenarios to choose from.

Scenario 1 features a short-term contamination in which the pigs are fed with PFAA-contaminated feed and/or drinking water for a limited time. The user specifies the start and duration of the contaminated period as well as the mean PFAA concentration in the feed and drinking water, assumed to be constant over the time period. An example of a situation that can be simulated is where a single lot of tainted feed enters the supply chain, resulting in a time-limited contamination.

Scenario 2 is intended to simulate a background contamination by ubiquitous PFAA and the uptake routes focusing on feed and drinking water. This background contamination is typically characterized by relatively low concentrations. However, this scenario could also be used to simulate an accidental life-long, highly concentrated uptake of PFAA from drinking water and/or feed.

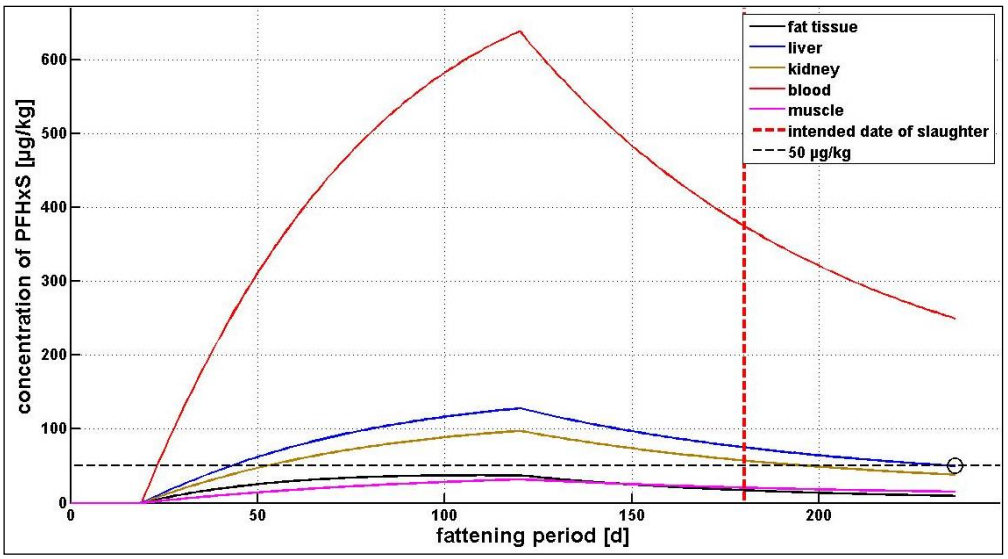
Given a maximum level for a given edible tissue (fat tissue, liver, kidney, muscle or blood plasma), RITOPS can estimate whether the concentration of the PFAA in the chosen tissue will be exceeded by the intended time of slaughter, and if not, how many extra days would be needed. This information can be used to decide whether the animal products are expected to be marketable.

Besides text output, RITOPS generates a figure, including a plot of time curves of the PFAA concentrations in each included tissue. The intended date of slaughter (vertical line) and an optional maximum level (horizontal dashed line) are marked on the plot (see figure 1 for an example).

PERCOW is a separate software tool for performing similar PFAA kinetics estimations in cow's milk. It is based on model [3] featuring milk as an additional pathway of excretion for PFAAs. While currently only supporting PFOS, the modules are ready to accommodate further PFAAs as data becomes available.

Figure 1: Example for a typical output generated by RITOPS

Time course of the perfluorohexanesulfonic acid (PFHxS) concentration in several tissues (fat, liver, kidney, blood plasma and muscle). The intended date of slaughter (180 days after weaning) is marked with a vertical red dashed line. This plot features a pig which received PFHxS contaminated feed from day 20 to day 120 after weaning. Although the PFHxS concentration in the feed is constant at 20 µg/kg over time, the amount of the daily feed intake increases (as customary in a fattening pig), resulting in an increasing daily absolute dose. At the same time, the gain of body weight causes dilution. After the contaminated feeding stops at day 120, a depuration occurs. As an example, the input uses a (fictional) legal maximum level of PFHxS in the liver of 50 µg/kg (black horizontal dashed line). The tool estimated a violation of that maximum level at the intended age of slaughter and automatically prolonged the simulation time until that maximum level is reached (here day 236, marked by a black circle).



Results and discussion

The need for practical tools for risk managers dealing with contamination events was again made clear when more than 400 hectares of farmland as well as some aquifers were found to be contaminated with PFAS in south Germany starting in 2014 [8]. Similar cases have been reported in many countries, usually in smaller scales. Software tools such as PERCOW and RITOPS can assist in managing the risks from using agricultural resources from polluted farmlands in a quantitative fashion. The European Food Safety Authority (EFSA) has established tolerable daily intake values (TDI) for PFOS and PFOA [9] in 2008. The EFSA is expected to revise the TDIs for PFOS and PFOA in 2017. TDIs for other PFAS are likewise expected to be published. The TDI is valid for the lifetime of an individual across all exposure pathways. However, no maximum level for any PFAS exists for individual food products (like those available for dioxins and dl-PCBs). Some risk managers circumvent this problem by working with locally valid "assessment values" seeking to minimize risk using observed values for agrifood products. These assessment values, or any other future established maximum levels, can be used as input in RITOPS and PERCOW to assist risk managers in the complex task of handling contaminated farmlands.

As for caveats, the tool needs to be validated with field data independent from the experiment it was fitted upon. As the tools depend heavily on assumptions for their physiological equations, RITOPS and PERCOW currently provide only time-dependent deterministic results without confidence intervals. This should be interpreted as an educated guess as these biological systems are not free from error and natural variability. The next versions of the program aim to visually include confidence intervals to better inform the risk managers about the expected variability. We expect RITOPS and PERCOW to become valuable helpers for risk managers and experts in their disciplines without the need for them to delve into programming or differential equations.

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