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Comparison of aggregated exposure to perfluorooctanoic acid (PFOA) from diet and personal care products with concentrations in blood using a PBPK model – Results from the Norwegian biomonitoring study in EuroMix

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ABSTRACT

Background: Per- and polyfluoroalkyl substances (PFAS) constitute a large group of compounds that are water, stain, and oil repellent. Numerous sources contribute to the blood levels of PFAS in the European population. The main contributor for perfluorooctanoic acid (PFOA) is food, house dust, consumer products and personal care products (PCPs).
Objectives: The purpose of the present work is to calculate the dietary and dermal external exposure to PFOA, estimate the aggregated internal exposure from diet and PCPs using a PBPK model, and compare estimates with measured concentrations.
Methods: Detailed information on diet and PCP use from the EuroMix study is combined with concentration data of PFOA in food and PCPs in a probabilistic exposure assessment. A physiologically based pharmacokinetic model (PBPK) was further refined by incorporating a dermal exposure pathway, and changes in the kidney and faecal excretion.
Results: The aggregated internal exposure using the PBPK model shows that the major contributor to the internal exposure is diet for both males and females. The estimated internal exposure of PFOA for the EuroMix population was in the same range but lower than the measured blood concentrations using the lower bound (LB) external exposure estimates, showing that the LB estimates are underestimations. For seven females the internal exposure of PFOA were higher from PCPs than from diet.
Conclusion: PCPs and diet contributed in the same range to the internal PFOA exposure for several women participating in EuroMix. This calls for additional studies on exposure to PFOA and possibly other PFAS from PCPs, especially for women. Overall, PBPK modelling was shown as valuable tool in understanding the sources of PFOA exposure and in guiding risk assessments and regulatory decisions.

Credit autor statement

Husøy T: Conceptualization, Methodology, Software, Formal analysis, Writing – original draft, Caspersen IH: Validation, Writing – review & editing, Thépaut E: Data curation, Writing – review & editing: Writing – review & editing, Haug LS: Writing – review & editing, Andreassen M: Resources, Writing – review & editing, Gkrillas A: Data curation, Writing – review & editing, Lindeman B: Writing – review & editing, Thomsen C: Writing – review & editing, Herzke D: Writing – review & editing, Dirven H: Resources, Writing – review & editing, Wojewodzic MW: Validation, Software, Writing – review & editing

1. Introduction

Per- and polyfluoroalkyl substances (PFAS) constitute a large group of widely used chemically synthesized compounds with water-, stain,- and oil repellent-properties. These characteristics can be ascribed to their partly or fully fluorinated hydrophobic carbon chain and a hydrophilic end group. Due to the strong covalent C–F bonds PFAS are

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Abbreviations(as footnote)

BM	Biomonitoring
bw	body weight
kfil	clearance from kidney to filtrate compartment
EPA	Environmental Protection Agency
EFSA	European Food Safety Authority
KBS	food and nutrient calculation system
FFQ	food frequency questionnaire
Free	free fraction of PFOA in serum
GSA	global SA
LOD	limit of detection
LOQ	limit of quantification
LS	literature search
LB	Lower bound
MB	medium bound
NIPH	Norwegian Institute of Public Health
MoBa	Norwegian Mother, Father and Child Cohort Study
OAT	one-at-a-time
ODEs	ordinary differential equations ()
PFASs	Per- and polyfluoroalkyl substances
PFHxS	perfluorohexane sulfonic acid
PFNA	perfluorononanoic acid
PFOS	perfluorooctane sulphonic acid
PFOA	perfluorooctanoic acid
PCPs	personal care products
PBPK	Physiologically based pharmacokinetic modelling
Tm	resorption maximum
SI	sensitivity index
Vplas	serum volume
SA	sensitivity analyses
VSk	skin volume
SD	standard deviation
TWI	tolerable weekly intake
Kt	transport affinity constant
UB	upper bound
VL	volume of the liver

highly persistent, and several accumulate in the food chain and have a long half-life in humans (Conder et al., 2008).

Recently the European Food Safety Authority (EFSA) set a tolerable weekly intake (TWI) of 4.4 ng/kg of body weight (bw) per week for the sum of the four PFAS perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorohexane sulfonic acid (PFHxS) and perfluorooctane sulphonic acid (PFOS) (EFSA, 2020). These four PFAS bioaccumulate and are the most prevailing PFAS compounds in human blood in Europe (EFSA, 2020). Because the estimated dietary exposures exceed the TWI in parts of the European population, EFSA concluded that the current level of exposure indicate a health concern (EFSA, 2020). The European Commission has in 2023 proposed a total restriction for PFAS for non-essential use in Europe.

Although the composition of PFAS compounds measured in blood varies, PFOS is usually the most abundant and contributing with approximately 60% to the sum concentration of the PFAS regularly detected in adults. PFOA is often the second most abundant PFAS in blood in adults, contributing with approximately 15%. Of note, in children, PFOA and PFOS most often contribute approximately equally to the sum; PFOA 35% and PFOS 37% (EFSA, 2020). The health effects of PFOA and PFOS in humans are still being studied, but current evidence suggests that exposure to these substances may be associated with a range of potential health effects, including developmental and reproductive toxicity (Li et al., 2018; Song et al., 2018) and immune system effects (Pachkowski et al., 2019).

There are numerous exposure sources that contribute to the observed blood levels of PFAS in the European population and the relative contribution of different sources can have large intra-individual variations (Haug et al., 2011; Poothong et al., 2020; Trudel et al., 2008; Vestergren and Cousins, 2009). PFOA and PFOA-precursors are present in outdoor and indoor air as well as house dust at varying concentrations. For PFOA, the main contributor in the general population is food and beverages, but the exposure from house dust (Eriksson and Karrman, 2015; Harrad et al., 2010; Haug et al., 2011) and contact with PFOA containing consumer products (Gluge et al., 2020; Herzke et al., 2012) can be substantial. Dermal exposure by use of personal care products (PCPs) can also contribute to the internal exposure (Abraham and Monien, 2022; Thepaut et al., 2021).

Biomonitoring studies are pertinent to measure the total exposure to PFAS as it integrates the contribution from all different sources. However, the knowledge about relative contribution from different external sources and routes of exposure is necessary for implementing efficient measures to reduce **exposure**. Physiologically based pharmacokinetic modelling (PBPK) is a powerful tool to disentangle the relative contribution from different exposure pathways to the internal (measured) concentration in blood, and other body fluids or tissues.

Several PBPK models for PFOA have been reported, but most of them are a further development from the model published by Loccisano et al. (2011), with exception of the model published by Worley et al. (2017).

The PBPK model published by Loccisano et al., (2011) was first developed for monkey. It contained compartments for blood, gut, liver, kidney, filtrate, fat, skin, and a lumped compartment for remaining body tissues. The model included oral and intravenous exposure. In this model, the plasma and liver were the primary target tissues for PFOA with possible involvement of enterohepatic circulation. The monkey PBPK model aligned with the existing pharmacokinetic (PK) data for monkeys. Subsequently, authors extended the monkey model to predict human outcomes and effectively replicated the observed data from residents in two communities exposed to PFOA through drinking water.

The model by Worley et al., (2017) has fewer compartments (plasma, liver, a lumped compartment representing the rest of the body, a three-compartment kidney and gastrointestinal tract) and with oral exposure only. The model for PFOA and PFOS by Loccisano and co-workers was developed in monkeys and was extrapolated to humans (Loccisano et al., 2011). This model was modified and applied by EFSA, but only the oral exposure route was included (EFSA, 2020). Human biomonitoring studies have indicated a positive association between the use of specific cosmetic products and the presence of certain PFAS in the body. Furthermore, an in vivo transdermal study has supported this observation by demonstrating that PFAS can indeed be absorbed through the skin. These findings underscore the urgent necessity of refining the skin absorption model. In this paper, the model published by EFSA was further developed to include additional uptake- and excretion routes.

The purpose of the present work is to; 1) estimate the dietary and dermal external exposure to PFOA, and 2) study the aggregated internal exposure to PFOA from diet and PCPs, by further refining the PBPK model by Loccisano and co-workers by including the dermal exposure- and faecal excretion.

The importance of the different pathways of internal PFOA exposure are estimated. Individual data from the EuroMix biomonitoring study are used for aggregated exposure assessment, and the internal doses obtained through the PBPK model are compared to measured concentrations in the blood.

2. Materials and methods

2.1. Study population, registration, and sample collection

The Norwegian EuroMix biomonitoring (BM) study is a part of the "European Test and Risk Assessment Strategies for Mixtures" project (EuroMix, 633,172–2) which was funded by the Horizon 2020 (H2020) program. The study was previously described in detail in the paper by Husoy et al. (2019).

In short, the EuroMix BM study investigated the exposure to chemical mixtures from foods and PCPs for two non-consecutive days (with 2–3 weeks in between). The study recruited 144 participants: 44 men (25–72 years old, mean = 43.3, SD = 11.6) and 100 women (24–72 years old, mean = 42.2, SD = 12.3). Participants were recruited from governmental institutes and universities in the counties of Oslo and Akershus in Norway between September 2016 and November 2017. All the participants completed the first day of the study, while 140 participants completed the second day (43 men and 97 women). The participants recorded their weighed food consumption and their use of PCPs for the two days in a diary. They also completed a validated food frequency questionnaire (FFQ) that covered the total diet the previous year, and a questionnaire on socio-demographic and lifestyle characteristics, including sex, education, age, weight, height, and smoking habits. The FFQ has been thoroughly validated in a sub-group of pregnant women in the Norwegian Mother, Father and Child Cohort Study (MoBa), and was found to be a valid tool for ranking participants according to high and low intakes of foods, energy, and nutrients (Birgisdottir et al., 2013; Brantsæter et al., 2008). The FFQ and the diaries of the food consumption were registered and coded by a dietician into the food and nutrient calculation system (KBS) (Rimestad et al., 2000) at the University of Oslo. For the use of PCPs, participants had to record the type of products used (e.g. shampoo, cosmetics, perfume), the time of use of these products and their brand. Participants collected each urine void in separate containers during the 24-h periods of recording and marked these with time and date. Blood (in total 70 ml per participant per study day) was collected at the end of each 24-h period at the Norwegian Institute of Public Health (NIPH), to obtain serum, plasma, white and red blood cells, as well as RNA/DNA extracted from total blood, which were immediately stored at −80 °C. For the blood samples, 2 and 3 subjects did not donate blood samples on day 1 and 2, respectively. The study was approved by the Regional Committees for Medical and Health Research Ethics (REK ID no 2015/1868) and all the participants provided their written informed consent. Data were anonymised by destroying the ID key at the end of the collection.

2.2. Scope of the exposure modelling

External exposure to PFOA was modelled using individual data from the EuroMix BM study (Husøy et al., 2019). The exposure from foods and PCPs were modelled probabilistically and independently from each other by considering all individual-based data available in the same 24-h period. A probabilistic exposure estimate was performed for PFOA from foods and PCPs by Monte Carlo simulations for each individual with 1000 iterations using the software R version 3.6.2. The R code for the exposure modeling is available (https://github.com/TrineHusoy/PBPK_PFOA).

2.3. Estimation of external exposure from the diet

Two estimations of dietary exposure were performed, the first based on the individual data by averaging the weighed consumption from the food diaries of both days and the second based on the reported habitual consumption during the last year from the FFQ of the EuroMix BM study. The consumption data were combined with the PFAS concentration database first presented by Papadopoulou et al. (2017), which is composed of mainly Norwegian data but also some data from other European countries when data for Norway was lacking. A detailed description of the PFAS concentrations in foods were presented in the Supplementary Material of Papadopoulou et al. (2017). Lower bound (LB), medium bound (MB) and upper bound (UB) for PFOA concentrations were calculated by imputing data below the limit of detection (LOD) with 0, ½ LOD and LOD respectively (Table S2). The concentration data of PFOA in foods were grouped into broad food categories, except for fish. Fish was subdivided into fish types due to a larger number of available concentration measurements (Table S2). The concentration of PFOA in flat fish was excluded in the exposure assessment from the diaries, since no participants reported consumption of flat fish. No other food categories were excluded. The distributions of the concentration data in each of the food categories were examined and were found to fit the lognormal distribution. The mean and standard deviation (SD) of the LB, MB and UB concentrations were used to calculate the location and shape parameters which defined a lognormal distribution of the concentrations for each food category, by using the rlnorm function from stats package in R. Daily dietary intakes of PFOA were estimated by combining the consumption data and the PFOA concentrations in foods, using a probabilistic approach and the following equation *1*.

$$Oral\ Exposure = \left(\sum_{food=1}^{foods} C_{food} \times \sum_{day=1}^{days} x_{day}^{food} \right) \Big/ \ days \ \left[\frac{pg}{day} \right] \qquad 1$$

Where $\boldsymbol{C}$ is the concentration of PFOA in a given food item (pg/g); $\boldsymbol{foods}$ is the number of food items consumed; $\boldsymbol{x}$ is amount of a given food eaten on a specific day (g) as reported in the diary or FFQ. For the diary, the average gram of food eaten on study day 1 and 2 was used for each individual.

2.4. Estimation of external exposure from PCP

2.4.1. Identification of concentration data

A literature search (LS) in electronic databases MEDLINE (Ovid) and ISI Web of Science was performed in August 2020 to retrieve data on concentration of PFAS in PCPs. A research librarian at NIPH was involved in the search strategy and conducted the search. For search terms and search strategy see Table S1. Only relevant papers published after 2005 were included, to capture only the recent changes in the use and the regulation of PFAS. The concentrations data used for PFOA exposure was limited to the data found for Scandinavia.

The publication selection was done by one reviewer. The extracted papers were transferred to EndNote and duplications were removed. First title and abstract of 6916 records were screened and then 52 full-text articles were assessed. Only five articles were found to include concentrations of PFAS in PCP's, facial moisturiser/cleanser, body lotion, foundation, eye make-up, rouge and powder and shaving products (Fig. S1, Table S3).

2.4.2. Estimation of dermal exposure of PFOA

Exposure estimates for PFOA from PCPs were based on the frequency of use reported in the diaries (Husoy et al., 2019). Since the concentration database from the SLS was limited and a full distribution could not be defined for each PCP category, summary data based on the individual data (Table S3) were used to define the concentration distributions for the LB, MB and UB of exposure. A triangular distribution was used due to limited data availability. Some values were below the LOD (non-detects, ND) for specific PFAS, and were thus replaced with a concentration of 0 ng/g for the LB calculations, ½ LOD for the MB calculations and the LOD for the UB calculations. The Danish EPA (Miljøstyrelsen, 2018) did not specify the LOD of any compound, so an assumptive LOD of 0.5 ng/g was made since no sample had a reported concentration of PFAS below 0.5 ng/g. PCPs that were used by participants in the EuroMix study but for which no concentration data from Scandinavia were available, were not included in the exposure estimate.

Both user amounts per application for each PCP and retention factors for rinse-off products presented by Karrer et al. (2020) were used.

Estimation of the dermal exposure was performed using a probabilistic approach with Monte-Carlo simulation, to include the individual variability and uncertainty of all parameters used.

The individual PFOA exposure from PCP was calculated according to equation *2*.

$$Dermal\ exposure = \sum_{PCP=1}^{m} C_{PCP} * fr_{PCP} * a_{PCP} * Rf_{PCP} \quad \left[\frac{ng}{day}\right] \qquad 2$$

where ***C*** is the PFOA concentration in each PCPs (ng/g); ***m*** is number of PCPs used, ***fr*** is the frequency of application (application per day); a is the amount per application (g per application); ***Rf*** is the retention factor for rinse-off products (non-dimensional), and day is the study day 1 of the EuroMix BM study.

Table S3 shows the PFOA concentrations in PCPs and other factors used to assess the dermal exposure. The R code for the exposure modeling is available (https://github.com/TrineHusoy/PBPK_PFOA).

2.5. Estimation of internal exposure using the physiological based pharmacokinetic model

2.5.1. Model description

The PBPK model for PFOA used as a basis for this paper was first described by Loccisano et al. (2011), and was further developed by EFSA in 2018 (EFSA et al., 2018) and 2020 (EFSA, 2020). In this paper the model described by EFSA was upgraded with inclusion of dermal absorption, faecal excretion and the change in the urinary compartments as justified below. The purpose was to estimate the blood concentration of PFOA in Norwegian adults based on exposure from foods and PCPs. PFOA has been found in many PCPs (Miljøstyrelsen, 2018; Naturskyddsföreningen, 2017; Schultes et al., 2018) and the dermal absorption was recently found to be significantly higher than previously reported (Abraham and Monien, 2022). The model was therefore further extended with the dermal exposure to PFOA from PCPs. Although the majority of PFOA is reabsorbed from the GI tract, faecal excretion has been described to be an important pathway of PFOA excretion (Fasano et al., 2006) justifying the inclusion of faecal excretion of PFOA. The kidney compartment was also modified, as the Qfil (flow rate) was included as a blood flow by Loccisano et al. (2011) and by EFSA 2020; EFSA, 2020), but stated to be a clearance directly from the serum to the filtrate compartment. This is modified in the present PBPK model where the Qfil was changed to a kfil together with the other clearance parameters, such as kurine and kbiliary, and is described as a clearance from the kidney to the filtrate compartment.

The final PBPK model comprises nine compartments: serum, gut, liver, fat, skin, kidney, filtrate compartment of urine, storage compartment of urine, and a compartment for the rest of the body (Fig. 1). The absorption of PFOA from the GI-tract is assumed to be 100%, giving an absorption fraction of 1, and is therefore not included in the model (Pizzurro et al., 2019). The R code for the PBPK model is available on GitHub (https://github.com/TrineHusoy/PBPK_PFOA).

The equations and abbreviations used in the model are shown in Tables S4 and S5. The chemical specific parameters used in the model are shown in Table S6, and the physiological parameters are presented in Table S7.

2.6. Sensitivity analyses

Several sensitivity analyses (SA) were performed to evaluate the influence of variability of used model parameters on the model output. SA methods are generally divided into two categories: local one-at-a-time (OAT) method and global SA (GSA) method. OAT is highly efficient but may yield misleading results by disregarding input parameter interactions and simultaneous variation. A workflow for GSA for PBPK models has been suggested by both McNally et al. (2011) and Hsieh et al. (2018). A new R tool for global sensitivity analyses, pksensi, was recently published (Hsieh et al., 2020). This package enables simultaneous uncertainty and sensitivity analysis for multiple parameters, helping to distinguish between the influential and non-influential parameters in the PBPK model. We utilized the pksensi to assess uncertainty and sensitivity in the PFOA model and integrated it with the deSolve package for solving the ordinary differential equations (ODEs) in our PBPK model. The volume and plasma flow parameters were scaled for the total changes in the sensitivity analysis. This was done to avoid mass balance problems during changing parameters in the sensitivity analysis.

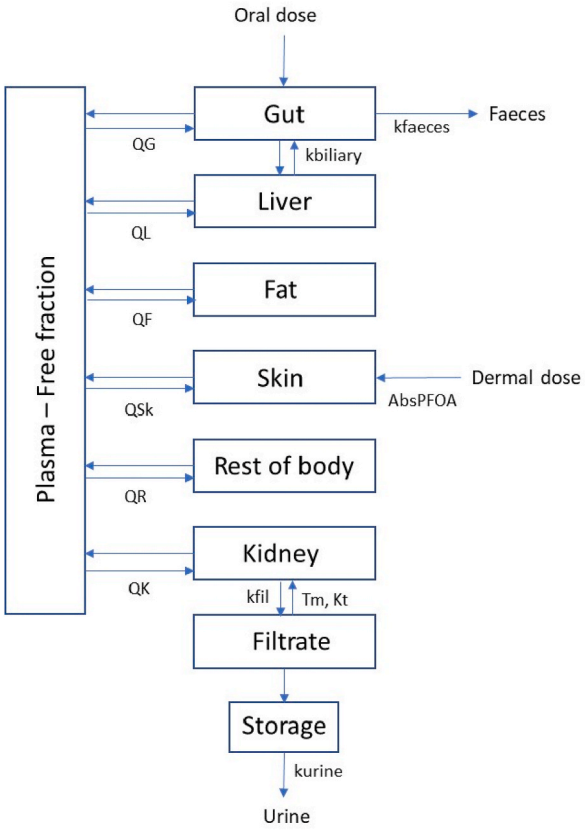

Fig. 1. An overview of the PBPK model of PFOA including nine tissue compartments, oral and dermal exposure pathways, and excretion via urine and faeces. The QG, QL, QF, QSk, QR and QK are the blood flows partitioning of the respective tissue compartments. AbsPFOA is the dermal absorption fraction of PFOA, Tm is the transport maximum, Kt is the resorption affinity, kbiliary is the biliary clearance, kfaeces is the faecal clearance, and kurine is the urinary clearance. The absorption of PFOA from the gastrointestinal tract is set to 100%, giving an absorption fraction of 1, and therefore not included in the model.

2.7. Biomonitoring data

The determination of PFOA in serum of the EuroMix participants has been described previously (Thepaut et al., 2021), together with the results of 24 other PFAS. High throughput online solid phase extraction ultra-high-performance liquid chromatography tandem mass spectrometry (UHPLC–MS/MS) method was used as described by Poothong et al. (2017). The LOD and limit of quantification (LOQ) for PFOA were 0.018 ng/ml and 0.06 ng/ml, respectively.

3. Results

3.1. External exposure from foods and cosmetics

The exposure estimates of PFOA based on consumption data from the FFQ were 3–4 times higher than the exposure based on the 2-days average consumption estimated from the food diaries (Table 1, Table S8 (ng/day), Table S9 and Table S10 (ng/day)). The mean exposure of PFOA from the food diaries (LB) was 0.092 ng/kw bw/day for males and 0.106 ng/kg bw/day for females, while the mean exposure from the FFQ were 0.24 ng/kg bw/day for males and 0.30 ng/kg bw/day for females (Table S9). The differences between the estimated exposures from diaries and FFQs were smaller at the MB and UB. Due to the high percentage of data below LOD for the food concentration data, imputation of these non-detects with LOD or ½ LOD for UB and MB, respectively, affected the exposure estimate considerably, as shown by the cumulative probability curves based on the diaries (Fig. 2), and on the FFQ's (Fig. S2). Seafood had the highest percentage of data below LOD and contributed most to the difference.

The external exposure estimates from PCPs are highly skewed, with some high exposure estimates having a significant impact on the mean (see Table 2 and Table S11). The exposure estimates from PCP (Table 2) are considerably lower than those from foods (as shown in Table 1). While a larger number of concentration data points were above the LOD for PCPs than for food, the differences between the LB and MB are smaller for PCP exposure compared to food exposure, as demonstrated by the cumulative probability in Fig. 3.

Many of the participants in the EuroMix biomonitoring study did not use the PCPs for which we have PFOA concentrations, or they only used PCPs for which the PFOA concentrations were low. Therefore, these participants have exposure values of PFOA from PCPs close to zero. The cumulative probability curves (Fig. 3) show that approximately 40% of the males will approach zero contribution of PFOA from PCPs, while for females the probability of having close to zero contribution of PFOA from PCPs is very low.

The contribution from food categories (both broad food categories and fish categories separately) to the estimated external exposure to PFOA (LB) based on the food diaries (Fig. S3) and for FFQ (Fig. S4) show that all parts of the diet contribute to the external exposure to PFOA from foods. The external exposure to PFOA from PCPs was higher for females than for males because females use a larger number of different PCPs than males. The major source of PFOA exposure from PCPs in females were foundation, body lotion, and rouge and powder, while for males the major single source of PCP was body lotion (Fig. S5).

3.2. The PBPK model

The PBPK model utilized in this study builds upon the model developed by the European Food Safety Authority (EFSA) in 2018 (EFSA et al., 2018) and 2020 (EFSA, 2020), which in turn was a modification of the Loccisano et al. (2011) model. We implemented this model with further improvements into R code for use in this work.

Table 1
Summary data on exposure to PFOA for males and females (LB = lower bound, MB = medium bound and UB = upper bound) based on probabilistic exposure estimates and using the average food consumption from the diaries of the two study days (ng/kg bw/day) in the EuroMix BM study. The summery data mean, geometrical mean (GM), percentiles 5 (P5), 50 (P50) and 95 (P95) are presented.

			Mean	GM	P5	P50	P95
PFOA	Males	LB	0.092	0.071	0.023	0.070	0.23
		MB	0.45	0.21	0.048	0.17	1.6
		UB	0.79	0.29	0.059	0.22	3.0
	Females	LB	0.11	0.080	0.024	0.078	0.28
		MB	0.66	0.29	0.051	0.23	2.6
		UB	1.2	0.42	0.061	0.29	5.1

3.2.1. Uncertainty and sensitivity analysis

Five of the EuroMix participants were used to examine the uncertainty and sensitivity of the PBPK model in pksensi. The output from the analyses for one of the participants is exemplified in Figs. 4 and 5. The uncertainty evaluation shows that the 90th percentile and 10th percentile of the plasma concentration of PFOA is approximately 2 μg/ml and 1.25 μg/ml, respectively, for the typical participant shown in Fig. 6.

To perform the sensitivity analysis, we selected 16 model parameters that are considered critical for the PBPK model outcome, as identified in previous literature. The pksensi package was employed to provide time-dependent sensitivity measurements for each parameter, as well as for possible parameter interactions. This is expressed by the sensitivity index (SI) over time. The results from sensitivity analyses for the five participants showed similar results, except for variations in PFOA exposure from PCPs. Whereas some participants had zero exposure from PCPs, for other participants the exposure from PCPs was considerable. The uncertainty index was, however, in the same range for all five analysed participants. The five parameters found to have most impact on the model output were ***free fraction of PFOA in serum (Free)***, ***clearance from kidney to filtrate compartment (kfil), BW*** and ***transport affinity constant (Kt)*** (Fig. 5). The parameters from the kidney compartment seems to have increasing importance with higher PFOA exposure (not shown).

3.3. Choice of exposure estimates

Twenty of the EuroMix participants were used to compare the different exposure estimates with the measured data to decide which exposure estimates are most relevant to use. These twenty selected participants did not differ in characteristics (i.e., sex, age, smoking habits) from the rest of the study sample. The model was run using the LB and the MB from the exposure estimates from the diaries, the FFQs and the PCPs. Using the mean LB exposure estimate showed a serum concentration closer to the measured concentrations than the mean MB estimate for both the food diary and the FFQ (not shown). The MB was a clear overestimate of the exposure. Also, the LB exposure estimates from the FFQs showed an overestimation of the serum concentration compared to the measured values (Fig. S6). The exposure estimates based on the average food consumption from the diaries of the two study days gave the best agreement to the measured serum concentrations (Fig. S6). The exposure estimates using LB concentrations from food and PCPs and the diaries were therefore used for validation of the model (Fig. S7). The concentration profile in serum, liver, kidney, and urine is shown for one individual in Fig. S8.

3.4. Comparison of modelled and measured internal exposure

The PFOA exposure from drinking water in a highly polluted water system of Little Hocking was used by both Loccisano et al. (2011) and EFSA (2020) to validate the PFOA models. For comparison, we estimated the PFOA intake from tap water (Table S6) for the population around Little Hocking based on the number of glasses with water (2 dl per glass of water) consumed from Table 5 in Emmett et al. (2006). This intake was fed into the PBPK model to estimate the serum concentration and compared with the measured serum concentration from Emmett et al. (2006). The estimated and measured serum concentrations were in the same range, especially for the lower exposure of PFOA represented by drinking 1–4 glasses of tap water a day (Table S12). For the higher PFOA exposure of 5 to >8 glasses of tap water (1–1.6 L), the PBPK model overestimate the exposure in serum.

The remaining 123 participants from the EuroMix study were used for validation of the PBPK model. PFOA serum concentrations were estimated from PCPs and food separately, as well as from aggregated exposure including both sources, using the PBPK model (Fig. 6). The estimated serum PFOA concentration from food ranged from 0.32 to

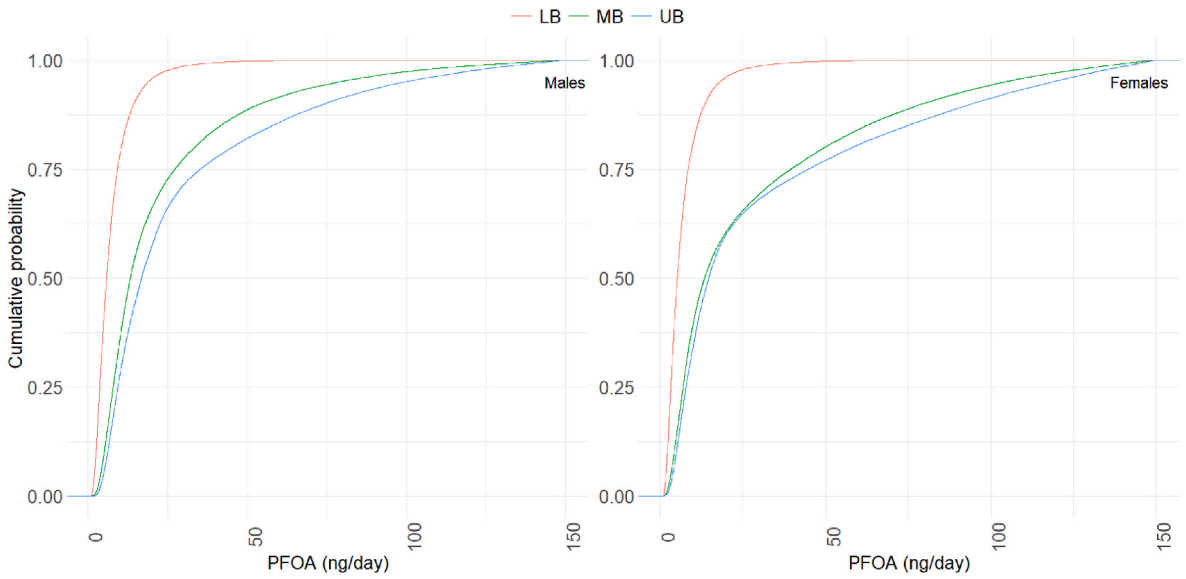

Fig. 2. Cumulative external exposure of PFOA from foods (LB = lower bound, MB = medium bound and UB = upper bound) based on probabilistic exposure estimates using the average food consumption from the diaries of the two study days.

Table 2
Summary data on dermal exposure to PFOA from PCPs based on probabilistic exposure estimates and data from the PCP diaries (ng/kg bw/day). The summery data mean, geometrical mean (GM), percentiles 5 (P5), 50 (P50) and 95 (P95) are presented.

			Mean	GM	P5	P50	P95
PFOA	Males	LB	0.086	0.16	0.0	0.0	0.64
		MB	0.088	0.16	0.0	0.0	0.65
		UB	0.09	0.17	0.0	0.0	0.65
	Females	LB	1.88	2.77	0.0	0.25	8.33
		MB	1.92	2.79	0.0	0.35	8.38
		UB	1.99	2.84	0.0	0.50	8.49

2.92 ng/ml, while the estimated serum concentration from cosmetics ranged from 0 to 1.40 ng/ml. The estimated aggregated serum concentrations by dietary and PCP exposure ranged from 0.32 to 3.53 ng/ml in serum.

The resulting high exposure of PFOA from PCPs is in the same range or a slightly higher than the low exposure from food, indicating that for some individuals, PFOA exposure from PCPs could be an important source. Out of the participants, 23 had an estimated PFOA concentration in serum calculated from food intake that was less than 2-fold higher than the estimated serum concentration of PFOA from PCP. For 7 of these participants, however, the estimated serum concentration of PFOA from PCP was higher than from the diet. All these participants, except one, were females. The exposure estimate using the LB concentrations from foods clearly underestimates the exposure when compared with the measured serum concentrations, especially for the participants with

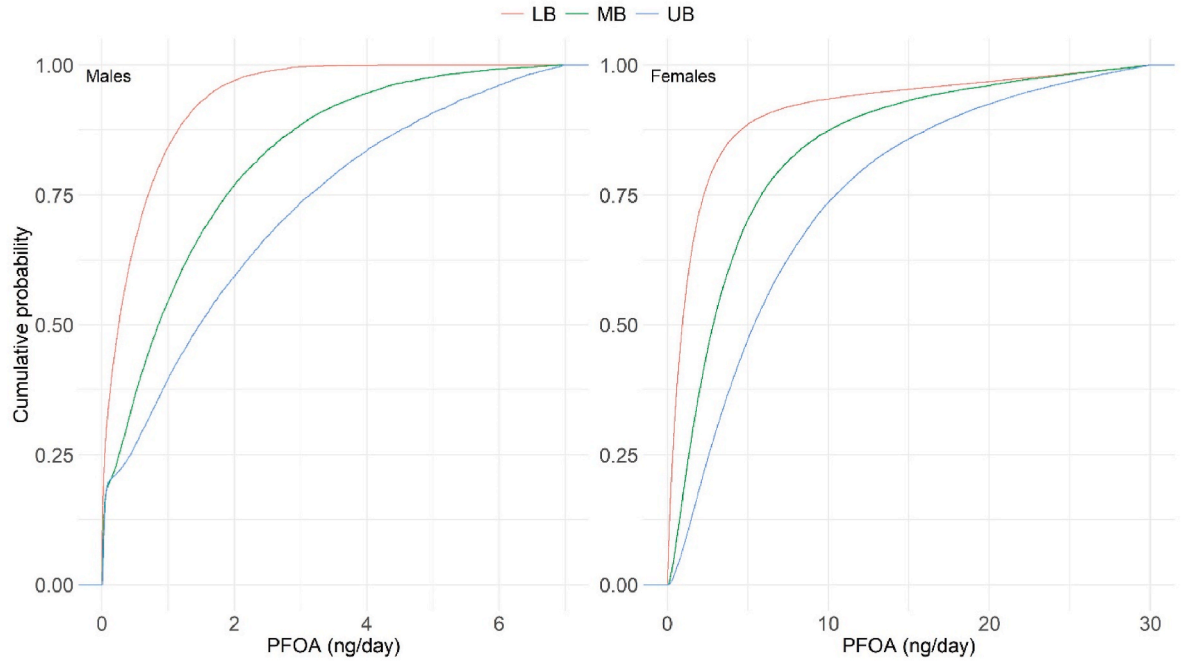

Fig. 3. Cumulative external dermal exposure of PFOA (LB = lower bound, MB = medium bound and UB = upper bound) based on the PCP diaries.

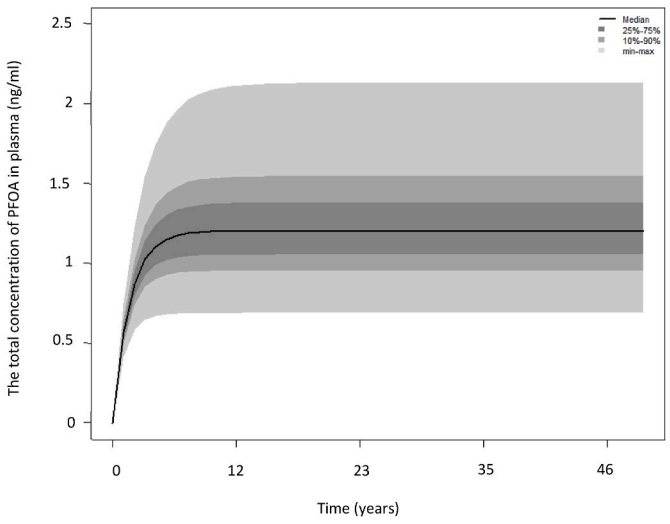

Fig. 4. The uncertainty evaluation of the total amount of PFOA in serum from one of the typical (random) participant in the EuroMix study with exposure both from foods and PCPs using the mean of LB exposure estimate from diet and PCPs.

high measured serum concentrations.

In Fig. 7, the mean of the estimated aggregated exposure is compared to the measured PFOA in serum for each individual by plotting against the differences between the same two measurements. The midline shows the bias between the estimated and the measured PFOA concentration in serum. The zero difference between the measurement and estimation lies within the standard deviation of the mean of the differences, which shows that the bias of the measured and estimated PFOA concentrations is not significant. In addition, there was no differences in males and females. The plot shows a proportional bias between the measurements when the difference between the measurement is increasing as a function of the average. Only five observations are located outside the two lines representing ±1.95 SD, which indicates good agreement between the estimated and the measured PFOA in serum. The data suggest that on average the estimated serum concentrations based on aggregated exposure by dietary and dermal (Loccisano et al., 2011) exposure for PFOA in serum is 0.7 ng/ml lower than the measured PFOA concentrations.

4. Discussion

We have refined the human PBPK model for PFOA published by Loccisano et al. (2011), and used the EuroMix biomonitoring data to compare estimated and measured serum concentrations, in order to validate the PBPK model using human data.

4.1. Exposure estimates and imputation of data

Estimated exposure of PFOA from the diet and from PCPs using the EuroMix study were used as input to the PBPK model. Due to detailed information on diet and PCP use as basis for exposure assessment and ample amounts of biological materials for internal dose measurements, the EuroMix study is well suited for this purpose. The uncertainty in the exposure estimates for individuals will affect the estimated internal doses and the correlation between the estimated internal doses and the measured serum concentrations of PFOA. In addition, the size of the EuroMix study adds uncertainty to the exposure estimate, as well as the contribution from diet and PCPs, and should be translated to the general population in Norway with caution. A large amount of concentration data on PFOA in food and PCPs used in the exposure assessment were below the LOD, especially for the analyses of foods. This is mostly due to a high LOD for PFAS in data from the early 2000s. The values below LOD were imputed and the value used for imputation had considerable impact on the external exposure estimates. The estimated internal serum concentrations for MB, using ½ LOD, were clearly overestimations when compared to the measured serum concentrations in EuroMix. The internal exposure estimate using the LB was closer (although it was underestimated) to the measured PFOA serum concentrations. The same was concluded by EFSA in their assessment, in which 92% of the analyses of PFAS in foods were below LOD, resulting in an UB dietary intake that was unrealistically high. Therefore the LB intake was used in the final exposure estimates (EFSA, 2020). The method of imputation of measurements below LOD has been criticized due to its arbitrary nature, introduction of artificial pattern in the data and its large impact on the exposure estimate when the number of imputed data is large (Helsel, 2010).

4.2. Probabilistic versus deterministic approaches

Traditional exposure assessment estimates chemical exposure using single values for each food/PCP, while probabilistic exposure estimates use distributions as inputs to estimate exposure. The latter approach is preferred for a comprehensive assessment, but its accuracy is limited by input data quality. The major benefit of using a probabilistic approach is that all available data are used as an input, and the uncertainty and sensitivity in the final estimate can easily be estimated. There are no standard recommendations regarding when to choose a deterministic or probabilistic approach, but the Environmental Protection Agency (EPA) have indicated that the deterministic approach is highly valuable for screening purposes and when the risk from the chemical is considered low (EPA, 2023). In the EuroMix study, a probabilistic approach was chosen due to limited data, although some categories had less than 10 concentration data and were associated with higher uncertainty. The central estimates, such as mean and median, of a deterministic and probabilistic exposure assessment will usually be very similar. The largest difference will occur in the high exposure scenario, as shown for the exposure assessment of deoxynivalenol (Gallardo et al., 2022). The probabilistic approach will give a better estimate for the highly exposed part of the population.

The number of concentration data for each food category differed considerably, with many hundred measurements in Norwegian fish, but much fewer concentrations in other food categories. This introduces larger uncertainty in the exposure assessment for the non-fish food categories. The available concentration data for PFOA in PCPs is even less for some categories. EFSA published in 2010 a scientific report where they studied the impact on few concentration data and left-censored data on the exposure assessment (EFSA, 2010). The result in this report showed that the number of samples had relatively limited impact on accuracy and precision of estimates for sample size higher than twenty, but the degree of censoring had a large effect also when the sample size was high (EFSA, 2010). However, our sample size was lower than 10 for some categories and therefore would probably impact the exposure assessment. In addition, concentration data was only available for some of the PCPs categories reported used in EuroMix. A significant association between mouth wash and PFOA serum concentrations was observed in EuroMix (Thepaut et al., 2021), but no concentration data was found for mouth wash. Lack of concentration data for several PCP categories is likely to result in an underestimation of PFOA exposure from PCPs. Therefore, the exposure estimates from PCPs are likely more uncertain than the exposure estimates from foods, although the food concentration data have higher degree of left censoring.

4.3. External exposure estimates

The average external exposure of PFOA in the EuroMix population was higher from PCP than for food for LB for females, while for males the average external exposure from foods were higher. The reason for this

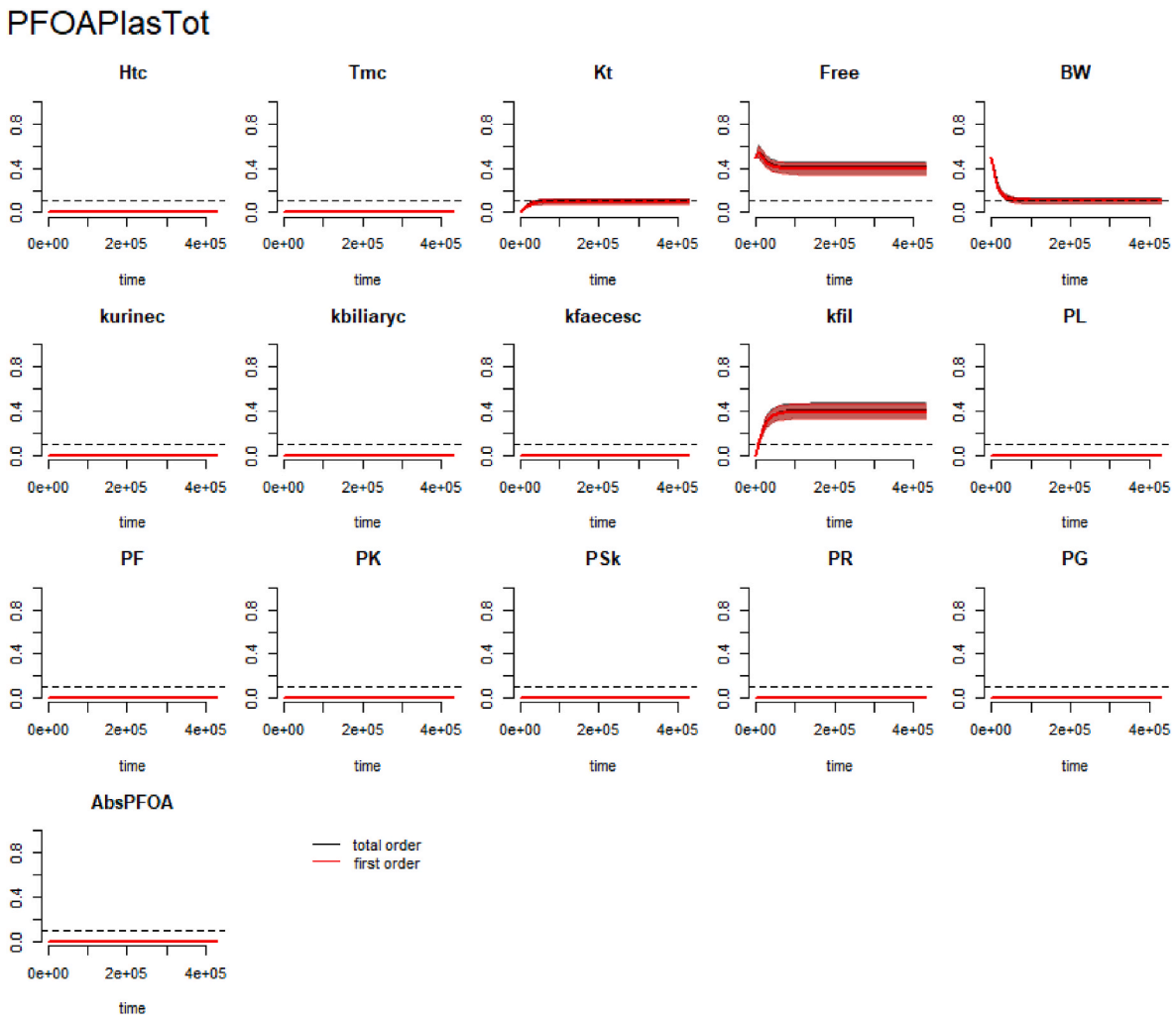

Fig. 5. The sensitivity analysis of 16 parameters for the total serum levels of PFOA (ng/ml) in the PBPK model over 50 years (time is given in hours) using the pksensi package in R. The parameters were varied by 10% in either direction. The figure shown is for one of the participants of the EuroMix study with exposure from both food and PCPs and using the mean of LB exposure estimate from diet and PCPs. The parameters included are hematocrit (Htc), resorption maximum constant (Tmc), affinity constant (Kt), Free fraction of chemical in serum (Free), body weight (BW), urinary clearance (kurinec), biliary clearance (kbiliaryc), faecal clearance (kfaecesc), clearance from kidney to the filtrate compartment (kfil), liver:serum partition coefficient (PL), fat:serum partition coefficient (PF), kidney:serum partition coefficient (PK), skin:serum partition coefficient (PSk), rest of body:serum partition coefficient (PR), gut:serum partition coefficient (PG), dermal absorption of PFOA (absPFOA).

discrepancy is probably explained by the PCP use, which was considerably higher for females than for males in the EuroMix study. PFAS has been found is several cosmetic products, such as cream and lotion, foundation, make up and shaving products (Framtiden-i-våre-hender, 2018; Fujii et al., 2013; Miljøstyrelsen, 2018; Naturskyddsföreningen, 2017; Schultes et al., 2018), with the highest concentrations in foundation. The PFAS are intentionally added to some PCPs as emulsifier and viscosity agent and to increase water resistance, but contamination from packaging and manufacturing can also occur (Harris et al., 2022). To our knowledge no papers have been published where exposure of PFOA from PCPs was assessed, however dermal exposure of PFOA measured in hand wipes was reported by Poothong et al. (2019). The measured concentration of PFOA in hand wipes were 0.18 and 2.8 ng for the mean and maximum respectively. This is considerably less than our estimated LB mean and 95th-percentile PFOA exposure from PCPs of 120 and 535 ng/day for females, respectively. The surface area of hands is reported to be approximately 2.4% of the total surface area of the body for females (Lee et al., 2007), and assuming that the daily dose are spread evenly out on the body the total daily exposure in our study of 2.88 and 12.8 ng could be allocate to the hands. This is in the same range of PFOA exposure as reported by Poothong et al. (2019). However, the uncertainty in the exposure estimate is high since the concentration data in PCPs are limited, and some PCP sources might be missed. Especially, several PFAS was previously found to be associated with the use of oral PCPs, such as toothpaste and mouth wash (Thepaut et al., 2021).

The external exposure of PFOA from diet has been estimated previously, and was reported from the A-team study in Norway by Poothong et al. (2020) using the same concentration database from foods and for several European studies by EFSA (EFSA, 2020)(Table 3). The estimated external dietary exposure of PFOA from the EuroMix study is in line with the reported exposure in Norway and EU (EFSA, 2020; Poothong et al., 2020; VKM, 2022). However, the EuroMix PFOA dietary exposure estimated from the diaries seems to be a bit lower or in the lower range of the reported exposure estimates, while the exposure estimates from the FFQ is in line with the exposure estimates by Poothong et al. (2020) and the upper range of the exposure estimates reported by EFSA. Overall, the exposure estimates from the EuroMix study were in agreement with previous reported estimates (Table 3).

4.4. PBPK model and internal exposure to PFOA

This paper developed a PBPK model for PFOA by including a dermal

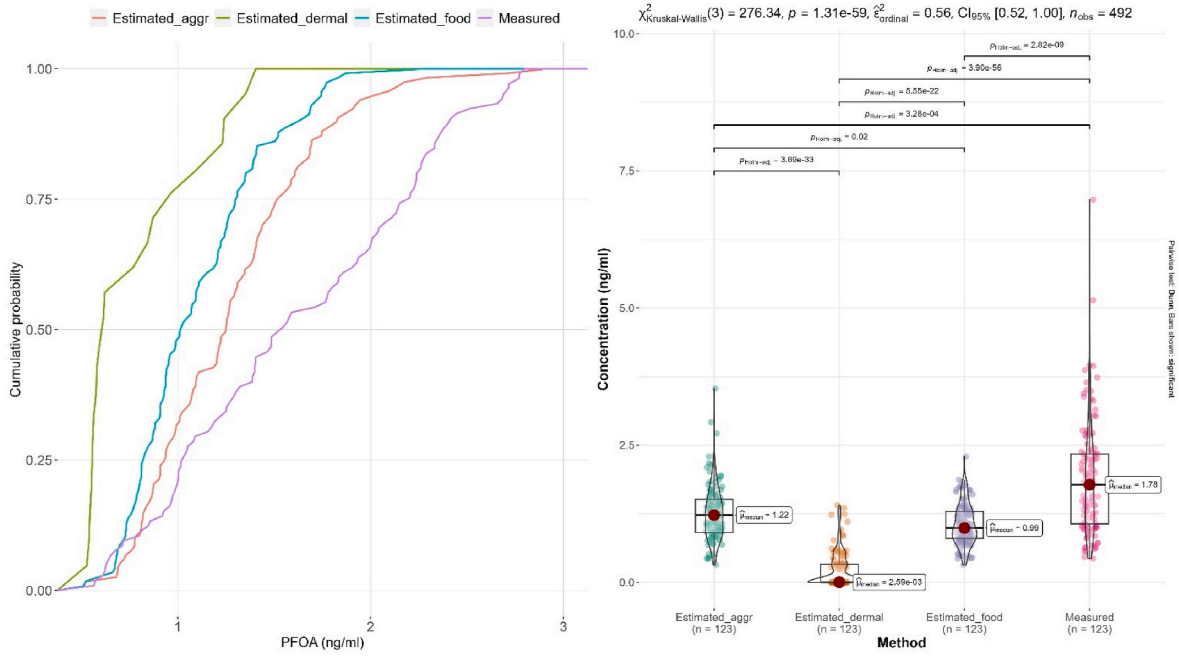

Fig. 6. Cumulative probability of estimated serum concentration from food, PCPs and aggregated, and measured total PFOA concentration in serum of the remaining 123 individuals of the EuroMix BM study using the mean of the LB probabilistic exposure estimate (left panel). The estimated concentrations were based on the average consumption from the food diaries of both study days. Violin plots of the estimated aggregated and measured total PFOA concentration in serum (right panel). The output of the Kruskal–Wallis nonparametric test is shown above the violin plots.

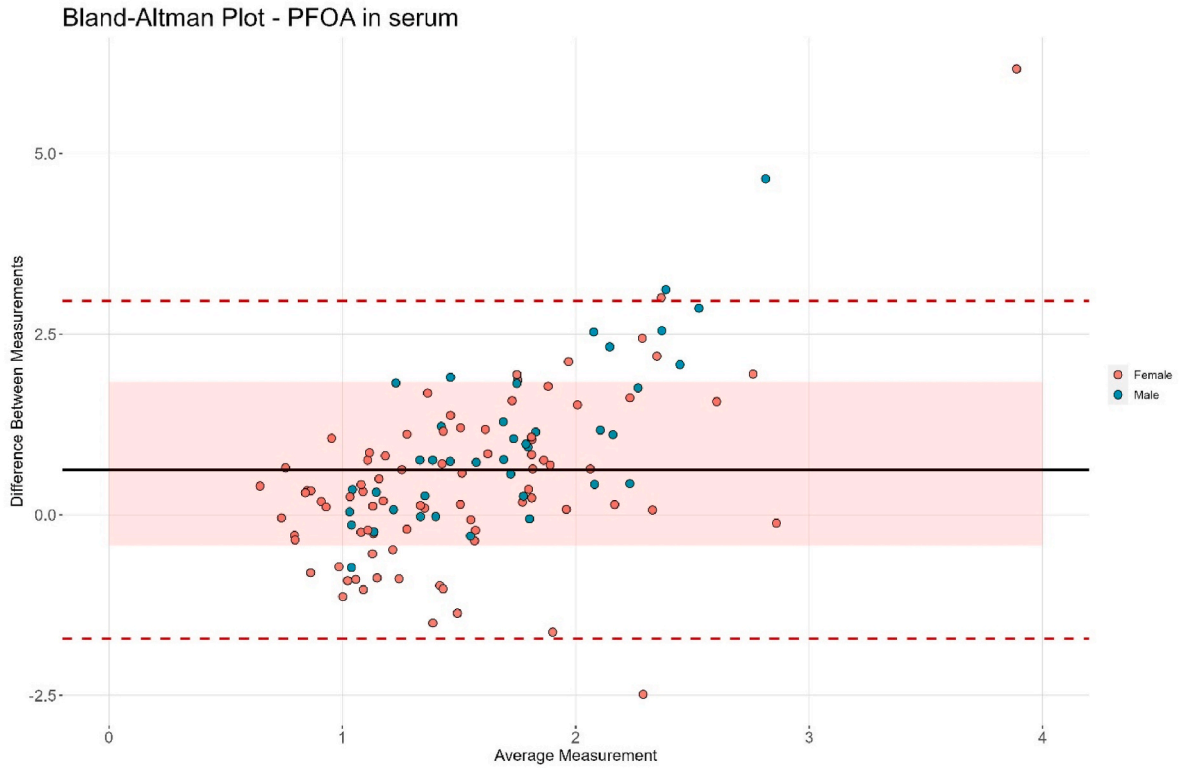

Fig. 7. Bland-Altman plot of the aggregated exposure estimate of PFOA in serum based on the LB correlated with the measured serum concentration of PFOA. The difference between measurements (y-axis) were calculated by subtracting the estimated from the measured concentration in serum. Lower and upper limits of agreements (mean of difference ± 1.96x SD) are shown with dash red lines. Mean of difference is shown as a black line, and the red shaded area is the standard deviation around the mean of differences.

Table 3
Estimated external exposure of PFOA in Norway and in EU (ng/kg bw/day).

Study	Sex		Mean	P50	P95
Poothong et al (2020)	M/F	–	0.269	0.248	0.519
EFSA opinion 2020*	M/F	LB	0.18–0.28	–	0.32–0.59
VKM opinion 2022	M/F	LB	0.234	0.220	0.41
Euromix study (FFQ)	M	LB	0.243	0.185	0.612
	F	LB	0.302	0.230	0.765
EuroMix study (diary)	M	LB	0.092	0.070	0.23
	F	LB	0.106	0.078	0.28

M = males, F = females, *a range of studies across EU.

exposure route from PCPs due to the discovery of high PFAS concentrations in several PCPs (Framtiden-i-våre-hender, 2018; Fujii et al., 2013; Harris et al., 2022; Naturskyddsföreningen, 2017; Schultes et al., 2018), and the new study indicating high absorption of PFOA through skin (Abraham and Monien, 2022).

Two additional improvements were done to the PBPK model for PFOA, including changing the kidney compartment and extending it by including biliary and fecal excretion of PFOA. Firstly, the kidney compartment was changed by redefining the QfilC to a clearance (kfil) from the kidney to the filtrate compartment. It is in line with the simple toxicokinetic model for monkeys described in Andersen et al. (2006). Clearance parameters in a model are always chemical specific and should therefore be carefully defined considering the chemical specific properties. Although the kfil parameter is one of the most important parameters in the model, the change in coding had only a minor impact on the model output. Secondly, our PBPK model was extended by including biliary and faecal excretion of PFOA as this was previously reported to be an important route of excretion for PFOA in rats (Fasano et al., 2006). This modification could potentially contribute to an increased half-life of PFOA in the body through enterohepatic circulation. However, the sensitivity analysis did not indicate that biliary and faecal excretion had a large impact on the model output.

The most sensitive and uncertain parameters in the model were the free fraction of PFOA in serum, clearance from kidney to filtrate compartment, body weight and transport affinity constant. The fraction of free PFOA is a sensitive parameter and was estimated based on serum concentrations from a study in monkeys. This is appropriate as monkeys were shown to be most similar to humans with respect to the half-life of PFOA (Andersen et al., 2006). In addition, the kidney was the most important compartment of the model with several sensitive parameters. This is supported by increase importance of the kidney parameter when increasing the dose (data not shown), which was also previously reported by Loccisano et al. (2011). The kidney parameters are also connected with highest uncertainty. The fact that some of the most sensitive parameters of the PBPK model of PFOA are also the most uncertain parameters, warrant a parameter estimation and updating of the model if new data become available in humans.

The estimated serum concentration of PFOA for the EuroMix population was lower than the measured PFOA concentration in serum due to the use of LB external exposure as an input to the PBPK model. Previous published studies from Norway where external exposures were compared with internal concentrations using single compartment toxicokinetic model showed comparable (Poothong et al., 2020) or higher (Haug et al., 2011) estimated internal concentration compared to the measured concentrations. Other sources of PFOA may also contribute to the internal exposure that was not included in this study, such as inhalation and dust (Haug et al., 2011; Poothong et al., 2020).

The contribution of PFOA from PCPs to the internal exposure was considerable for some participants with high use of PCPs. This was particularly due to the new data on dermal absorption published by Abraham and Monien (2022), which reported an absorption of 1.6% of the applied PFOA in creme in one human. This is considerably higher than previously reported data from Franko et al. (2012) (divided by 1000 since PFOA is ionized) and the absorption of the ammonium salt of PFOA in Fasano et al. (2005). Since the in vitro studies have some limitations, such as the application of solvent and the form of PFOA that was applied, we regard the human absorption study as more reliable although it is tested on only one human. The resulting high internal exposure of PFOA from PCPs is in the same range or a slightly higher than the low exposure from food. For seven female individuals the contribution of PFOA from PCP higher than the contribution from the diet indicate a need to create awareness among PCP users, especially women. Overall, the PBPK model estimated that the major contributor to internal exposure was diet for both males and females.

5. Conclusion

We have demonstrated that PBPK modelling is a powerful tool to estimate the internal dose of PFOA when also comparing two major exposure pathways (diet and PCP). Additionally, PBPK modelling helped to identify the key factors that influence the accumulation and elimination of PFOA in the human body. For instance, our work showed that women are more exposed to PFOA via PCP products than men, and that the contribution of PFOA from PCPs can be higher than from the diet for some individuals. Our work demonstrates the importance of collecting data on PCP use, and furthermore the need to create awareness of among PCP users, especially women, on the potential PFAS exposure from PCPs. In addition, producers should work on reducing the concentrations of PFAS's in PCPs.

In this work, we indirectly shine light on other individual characteristics such as the influence of kidney function. Future work could address how sensitive groups with compromised kidney function accumulate PFOA. Future research should also place greater emphasis on investigating PFOA as a substrate for transporters. Additionally, it would be valuable to explore the potential interactions between PFOA and long-term use of medications that share the same transporters as substrates.

Overall, PCPs and diet contributed in the same range to the internal PFOA exposure for several women participating in EuroMix. PBPK modelling including external exposure estimates was shown here to be a powerful tool to understand main sources of PFOA exposure and in guiding risk assessments and regulatory decisions. This pharmacokinetics simulations supplement large epidemiological studies as a less costly approach, also as an alternative for populations where biological PFOA data are unavailable.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The individual data in Euromix cannot be shared openly due to GDPR. I have made dummy data available from EuroMix on github. Data

sharing from EuroMix need a collaboration agreement.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2023.117341. The R code for the exposure assessment and the PBPK model is available on GitHub (https://github.com/TrineHusoy/PBPK_PFOA).

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