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Risk Assessment of Perfluorooctane Sulfonate (PFOS) using Dynamic Age Dependent Physiologically based Pharmacokinetic Model (PBPK) across Human Lifetime

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ABSTRACT

The widespread use of Perfluorooctane sulfonate (PFOS) in everyday life, its long half-life, and the lipophilicity that makes it easily accumulate in the body, raises the question of its safe exposure among different population groups. There are currently enough epidemiological studies showing evidence of PFOS exposure and its associated adverse effects on humans. Moreover, it is already known that physiological changes along with age e.g. organ volume, renal blood flow, cardiac output and albumin concentrations affect chemicals body burden. Human biomonitoring cohort studies have reported PFOS concentrations in blood and autopsy tissue data with PFOS present in sensitive organs across all human lifespan. However, to interpret such biomonitoring data in the context of chemical risk assessment, it is necessary to have a mechanistic framework that explains show the physiological changes across age affects the concentration of chemical inside different tissues of the human body. PBPK model is widely and successfully used in the field of risk assessment. The objective of this manuscript is to develop a dynamic age-dependent PBPK model as an extension of the previously published adult PFOS model and utilize this model to predict and compare the PFOS tissue distribution and plasma concentration across different age groups. Different cohort study data were used for exposure dose reconstruction and evaluation of time-dependent concentration in sensitive organs. Predicted plasma concentration followed trends observed in biomonitoring data and model predictions showed the increased disposition of PFOS in the geriatric population. PFOS model is sensitive to parameters governing renal resorption and elimination across all ages, which is related to PFOS half-life in humans. This model provides an effective framework for improving the quantitative risk assessment of PFOS throughout the human lifetime, particularly in susceptible age groups. The dynamic age-dependent PBPK model provides a step forward for developing such kind of dynamic model for other perfluoroalkyl substances.

1. Introduction

PFOS (perfluoro octane sulfonate) is a fluorinated organic compound having a sulfonated functional group and eight carbon backbone with a wide variety of use in industrial and consumer applications (Abraham et al., 2020; Roberts et al., 2016; Tan et al., 2008). It is widely used in consumer products like furniture, household cleaners, clothing, and due to its resistance to environmental and metabolic degradation, it was also categorized as persistent organic pollutants (POPs) in 2009 under the Stockholm Convention (Chou and Lin, 2019; Domazet et al., 2020; Dourson et al., 2019; Roberts et al., 2016; Zhang et al., 2011). Due to its high bioaccumulation potential, PFOS is detected in many human tissues and biological samples in both occupational and non-occupation people across the human lifespan. Because of its widespread persistence in the environment, human exposure to this emerging pollutant occurs through multiple pathways and multiple sources, including the food chain, dust ingestion, air inhalation, and municipal drinking water (Augustsson et al., 2021; Ericson et al., 2009; Grandjean et al., 2017; Rovira et al., 2019; Tian et al., 2016). Biomonitoring studies have found that dietary intake is the major exposure pathway for PFOS followed by other sources of exposure like drinking water and dust ingestion (Černá et al., 2020; Domingo and Nadal, 2019; Ehresman et al., 2007; Rovira et al., 2019). Different cohort studies have reported variation in exposure pathways based on different variables like age groups, gender, and

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body weight. For instance, Ericson et al. showed that children of 4–8 years showed the highest daily intake values and geriatric people (>65 years old) corresponded to the lowest daily intake (Ericson et al., 2009). Another study by Zhang et al. showed estimated daily intake on a bodyweight basis for PFOS to be higher in toddlers than in adolescent groups (Zhang et al., 2011). However, in most of these studies, only dietary intake has been considered and the source of other exposure has not been characterized. Exposure in different age groups especially pediatric can be via multiple pathways apart from dietary intake like ingestion of house dust, contact with specific consumer products etc. leading to high body weight normalized estimated daily intakes (Winkens et al., 2017). There are no experimental studies that have measured the exposure associated with direct contact of consumer products in the pediatric population or external exposure by indoor environment after breastfeeding till adulthood. The limited data regarding multiple exposure pathways for the pediatric and other populations need for pharmacokinetic models for reconstructed exposure and assess the risk in different organs considering the variation in kinetics and toxicological activity of PFOS with changes in physiological and biochemical parameters.

In recent years tremendous research has been done on kinetics and toxicity study for PFOS in the human, in-vitro and in-vivo (Butenhoff et al., 2012; Cui et al., 2009; Li et al., 2017; Loccisano et al., 2012; Luebker et al., 2005; Tan et al., 2008; Yu et al., 2009; Zeng et al., 2019). Pharmacokinetic studies from humans and animal data demonstrated that PFOS is readily absorbed and distributed inside the human body after binding to plasma proteins (Thibodeaux et al., 2003). Human serum albumin (HSA) is considered the most abundant protein in plasma. HSA is the main carrier for PFOS in human beings with a binding ratio of 1:1 (Luo et al., 2012). Plasma proteins like HSA and alpha 1 acid glycoprotein tend to be less in children than in adults which may account for varying unbound fractions in children (Edginton et al., 2006). In the case of the geriatric population, HSA declines by almost 1.5% in each age decade leading to hypoalbuminemia in some patients (Mene-Afejuku et al., 2019; Stader et al., 2019). This shows the need for the proper scaling of absorption and distribution factors in the different age groups. In relation to the elimination, PFOS studies carried out in adults showed a biological half-life of approx. between 3.1 and 7.4 years. In a study conducted with retired production workers, a half-life of up to 8–9 years was reported (Conway et al., 2018; Olsen et al., 2007; Thibodeaux et al., 2003). One explanation for the long-half life in humans may be due to saturable resorption from kidneys and enterohepatic recycling of PFOS. In the case of pediatric & geriatric populations, PFOS clearance may vary leading to different elimination half-life. The clearance mechanism is immature from birth to several months until the adult clearance is achieved (Hayton, 2000). This question becomes more prominent in renally eliminated chemicals with a long biological half-life (PFOS, PFOA, etc.). Extrapolation for renal clearance from adults to pediatric and geriatric should be approached taking into account the half-life, the fraction unbound for specific chemicals, and the variation in glomerular filtration rate. Also, some other physiological factors like body weight, height, body mass index (BMI) play a major role in the kinetics of the xenobiotics. Interspecies, gender, physiological and age-wise difference in toxicokinetic makes the risk assessment challenging which can only be addressed through the aid of the PBPK model. PBPK model can be a valuable tool for risk assessment in PFOS and other related compounds to address the concerns of age-related sensitivity across the human lifespan (Sharma et al., 2018; Schuhmacher et al., 2014). PBPK model for PFOS has been developed for rats, monkeys, and humans (adult, pregnant female and fetus, lactation) (Chou and Lin, 2019, 2020; Sharma et al., 2017; Fàbrega et al., 2014, 2016; Loccisano et al., 2011, 2013). Different authors developed the PFOS pregnancy PBPK model for estimating risk in the maternal and fetal population (Loccisano et al., 2013; Rovira et al., 2019). However, to date, there is not a PBPK model for PFOS that considers the risk assessment across the human lifespan (from pediatrics, adults to the geriatric population). To the best of our knowledge, although for different chemicals, PBPK models have been developed for different life stages, it does not exist for the whole lifespan in case of long acting chemicals like perfluoroalkyl substances (PFAS).. For instance, Sharma et al. has developed dynamic pregnancy PBPK for BPA to predict the toxicokinetic profile of BPA in the fetus during gestational growth (Sharma et al., 2018). Song et al. developed an age-specific PBPK model for pyrethroids in rats for risk assessment in early age population (Song et al., 2019). Recently, Mallick et al. (2019) has developed a whole life-stage PBPK model for evaluating age-related differences in internal target tissue exposure and pharmacokinetics for pyrethroids in humans (Mallick et al., 2019). The widespread use, bioaccumulative nature, and observed health effects in humans for PFOS by epidemiologists call for the dynamic age-dependent PBPK model for assessing risk across the human life span. This PBPK model, which includes the entire lifespan, can be used to assess individual risk, or for a specific age group (with their anthropometric, physiological, and pharmacokinetic parameters). This can help to assess risk in a high-risk population (Loccisano et al., 2013; Zheng et al., 2019).

The objective of this manuscript is to develop and evaluate a dynamic age-dependent PBPK model to understand pharmacokinetic and assess the potential risk across different age groups (Fig. 1). Age kinetic equations were developed considering the changes in the organ's physiology, and biochemical parameters were scaled to incorporate them in the PBPK model. Already published adult model and autopsy tissue data across age groups from Spain was used for validation. Biomonitoring data from three countries (China, Norway, and Australia) was used for model evaluation. Sensitivity analysis was performed to assess the impact of uncertainty/variability in anthropometric, physiological and biochemical parameters with the context of changes in the accumulation of PFOS in different organs across age. The use of dynamic age-dependent PBPK may aid in understanding how the physiological changes along the age affect the tissue distribution of this compound in pediatrics, adult and geriatrics, thus improving the life stage-specific risk assessment for PFOS. It also helps in defining the reconstructed exposure in a sensitive population (pediatrics and geriatrics). Further, this model can be extended to other PFAS chemicals and examine the specific risks (neurotoxicity, reproductive effects, etc.) in the population based on the pharmacokinetic (Sharma et al., 2017).

2. Methods

2.1. PBPK model structure

The structure of proposed dynamic age-dependent PBPK model is shown in Fig. 1. Previously developed adult model for PFOS has been described in earlier published papers (Fàbrega et al., 2014, 2016). The structural changes made to the model were addition of bone marrow and skin as two new compartments. This model was further extended to incorporate physiological and physicochemical parameters for the pediatric & geriatric population along with dynamic age growth. This model includes the pediatric, teenagers, adult, and geriatric module together with demography (height, weight, body surface area), physiology (organ volume, organ blood flow, cardiac output), and biochemistry (unbound fractions, renal elimination) for simulation of PK profile across different age groups. From four different countries i.e. China, Australia, Spain & Norway biomonitoring data were used to check the performance of the model. The model was built and analyzed in MCSIM version 5.6.6 (Bois, 2009) along with the R studio.

2.2. Age-dependent scaling (parameterization of the model)

2.2.1. Physiological parameters

Age-specific human anatomical and physiological parameters; like height, body weight, organ weight (or volumes), cardiac output, and blood flows were scaled across human lifetime considering the available

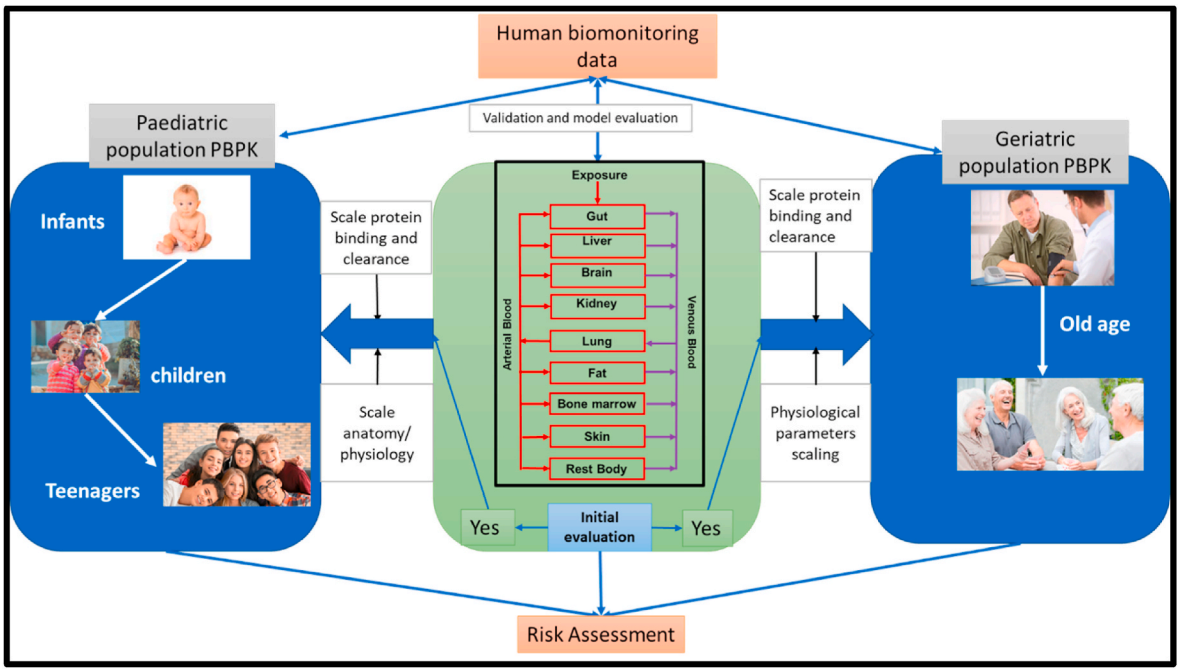

Fig. 1. Model building framework for dynamic age dependent PBPK model. Already published adult model was evaluated and extended to pediatric and aged people. Physiological and biochemical parameters were scaled using different approaches for prediction of risk across human lifespan.

human biomonitoring data (Clewell et al., 2004; Haddad et al., 2001; Mallick et al., 2019; Ogiu et al., 1997; Stader et al., 2019; Valentin and Streffer, 2002). Changes in body weight and height along with age were incorporated to generate equations for organ growth in pediatrics, adults, and geriatric population from 0 to 90 years. Based on the trends observed in the data, the linear regression equations, polynomial equations of second, third, or fourth degree were considered. These regression equations were made in R studio which included the variability for 0–90 years and distribution was done for 1000 virtual population (Table 1 in Supplementary file). Observed data from ICRP 89, Stader et al. and Hermanussen et al. was used to verify the simulated data from different regression equations for organ volume (Haddad et al., 2001; Heinemann et al., 1999; Hermanussen et al., 2012; Johnson et al., 2005; Mallick et al., 2019; Noda et al., 1997; Stader et al., 2019; Valentin and Streffer, 2002; Ogiu et al., 1997; Dekaban and Sadowsky, 1978).

Data on cardiac output were taken from ICRP 89 and Stader et al. which collected data from 12 studies with 645 subjects (Valentin and Streffer, 2002; Stader et al., 2019). The surface area was calculated using equations from Du Bois et al. corresponding to body weight and height for both males and females (D. Du Bois and E. Du Bois, 1989). Due to lack of data for blood flow and unavailability of standard equations in different organs in children, allometric scaling was done considering the adult blood flow of 25 years from ICRP 89 as the standard value. For validating and verifying the physiological equations, data from several authors were taken to make a robust equation with incorporated variability (supplementary file 1) (Clewell et al., 2004; Haddad et al., 2001; Johnson et al., 2005; Ogiu et al., 1997; Price et al., 2003; Stader et al., 2019; Valentin and Streffer, 2002).

2.2.2. *Physicochemical parameters*

Tissue: plasma partition coefficient parameters for dynamic age-dependent PBPK model were taken from the earlier published model (Fàbrega et al., 2016). Other parameters like fraction unbound, elimination rate constant & renal resorption were calculated based on available data or scaled using the standard approach. In this model, the fraction absorbed from stomach to liver is considered as one. All the values of parameters were reported in Table 1.

Table 1
Compound-specific parameter value for PFOS PBPK Model.

Parameters	Values	Reference
Molecular weight (g/mol)	500.13	(PubChem Compound Summary for CID 74483, Perfluorooctanesulfonic acid)
Unbound fraction in plasma (fu, age ≤ 3)	0.031	(McNamara and Alcorn, 2002; Meistelman et al., 1990; Zheng et al., 2019)
Unbound fraction in plasma (fu, age ≤ 10)	0.027	(McNamara and Alcorn, 2002; Meistelman et al., 1990; Zheng et al., 2019)
Unbound fraction in plasma (fu, age ≤ 71)	0.025	(Meistelman et al., 1990); b (Zheng et al., 2019); c (McNamara and Alcorn, 2002); d (Fàbrega et al., 2016); e (Rovira et al., 2019)
Unbound fraction in plasma (fu, age ≤ 89)	0.026	(McNamara and Alcorn, 2002; Meistelman et al., 1990; Zheng et al., 2019)
Unbound fraction in plasma (fu, age ≥ 90)	0.028	(McNamara and Alcorn, 2002; Meistelman et al., 1990; Zheng et al., 2019)
Tmc[a]	3.5–5.5	(Fàbrega et al., 2016; Rovira et al., 2019)
Tissue: Plasma partition coefficient		
Liver	2.56	(Fàbrega et al., 2016; Loccisano et al., 2013; Rovira et al., 2019)
Gut	0.05	(Fàbrega et al., 2016; Loccisano et al., 2013; Rovira et al., 2019)
Brain	0.35	(Fàbrega et al., 2016; Loccisano et al., 2013; Rovira et al., 2019)
Kidney	1.21	(Fàbrega et al., 2016; Loccisano et al., 2013; Rovira et al., 2019)
Adipose Tissue	0.32	(Fàbrega et al., 2016; Loccisano et al., 2013; Rovira et al., 2019)
Lung	8.70	(Fàbrega et al., 2016; Loccisano et al., 2013; Rovira et al., 2019)
Bone marrow	17.94	(Fàbrega et al., 2016; Loccisano et al., 2013; Rovira et al., 2019)
Skin	0.11	(Fàbrega et al., 2016; Loccisano et al., 2013; Rovira et al., 2019)

[a] Tmc refers to resorption maximum constant (ug/h/kg$^{0.75}$).

2.2.3. Unbound fraction

Plasma protein binding levels are lower in children and geriatrics than in adults especially newborn and old age. For PFOS, the binding affinity is higher for HSA than any other plasma protein. Fraction unbound for PFOS was calculated based on equation (1) for all age groups considering the variation in their albumin levels (McNamara and Alcorn, 2002). Unbound fraction was calculated based on the binding characteristic of PFOS in adults and ontogeny for binding protein factor as shown in equation (1).

$$fu_{child} = \frac{1}{1 + OSF * \frac{(1 - fu_{adult})}{fu_{adult}}} \quad (1)$$

Here, fu_{child} represents unbound fraction of PFOS in child, fu_{adult} represents unbound fraction in adults, OSF is age dependent ontogeny scaling factor calculated based on human serum albumin levels (McNamara and Alcorn, 2002; Meistelman et al., 1990; Zheng et al., 2019).

2.2.4. Renal resorption

Long half-lives of PFOS suggest that renal resorption is the main driving factor that has been considered by resorption maximum (Tm) and affinity constant (Kt) in the model. Values of Tm and Kt for adults were taken from an already published adult model (Table 1) (Fàbrega et al., 2014, 2016; Rovira et al., 2019). Scaling up these parameters in the pediatric and geriatric population is somewhat complicated due to the lack of renal data in these population groups; therefore, dynamic allometric scaling was used. For renal resorption, the value of adult resorption maximum constant (Tmc) was used and the scaling was done with respect to the fraction of BW in different age groups (BW_{AG}) and adult body weight (BW_{adult}) (equation (2)). Value of urinary elimination rate constant (KurineC) was taken from adult model to calculate urinary elimination rate and then scaled based on $BW^{-0.25}$ (equation (3)).

$$Tm = Tmc * \left(\frac{BW_{AG}}{BW_{adult}}\right)^{0.75} \quad (2)$$

$$\text{Kurine} = \text{KurineC} * (\text{BW})^{-0.25} \quad (3)$$

2.3. Adult model simulation

Firstly, the dynamic age-dependent PBPK model was evaluated at the adult age as a reference by doing simulation from 25 to 35 years, and results were verified against the data obtained by simulating the same age group using the already published model (Fàbrega et al., 2014, 2016; Rovira et al., 2019). Model predictions were evaluated using the Pearson correlation test. It provided the correlation coefficient to establish the relationship (goodness of fit) for results from both the models using a statistical level of significance (p-value). Statistical analysis and data processing were done in R studio using a correlation package (corr) (Makowski et al., 2020).

2.4. Exposure reconstruction

Very limited experimental or modeling studies have measured or estimated external exposure in pediatric and geriatric populations considering the different exposure routes. Dynamic PBPK model was used to estimate the external exposure for different age groups through internal plasma concentration from human biomonitoring data. The daily intakes were estimated for different age groups using the Bayesian framework and a uniform prior distribution using Markov Chain Monte Carlo (MCMC) distribution. Bayesian framework along with MCMC distribution helps in optimizing the model and evaluating the uncertainty and variability of model parameters (Chou and Lin, 2020). For the autopsy data in different organs from Perez et al. the liver data was used for reconstructed exposure using MCMC distribution. Reconstructed exposure was needed as there was no available data about daily exposure from multiple pathways in different age groups. Then the reconstructed exposure was used to simulate the concentration of chemicals in other organs (brain, kidney, lungs, and liver) at specific ages. Different biomonitoring studies from three countries were available with the reported concentration in plasma, serum, or blood at varying ages (Haug et al., 2009; Kärrman et al., 2006; Zhang et al., 2010). Raw data was not available from these studies and reported data was with wide age groups. In order to cover all the exposure range for observed biomonitoring plasma samples, which could be due to random sample at any specific year or variability in the subjects, the dynamic distribution for external exposure was simulated.

2.5. Biomonitoring data and model simulation

For evaluating accumulation of PFOS in different body compartments with age, human biomonitoring data of PFOS in autopsy tissues of liver, brain, lung, and kidney from subjects who had been living in Spain (Tarragona, Catalonia) was used (Pérez et al., 2013). Samples were collected in 2008 within the first 24 h of the death of the patient and 21 PFAS were analyzed in 99 samples. Subject ages ranged from 28 to 86 years. This data was used for model evaluation covering different age groups. Another biomonitoring Data from China contains 245 human blood samples with age-related differences (Zhang et al., 2010). PFC concentrations were characterized in human blood from infants, toddlers, children, and adolescents in China (Table 1 in supplementary file). Another study by Haug et al. analyzed serum samples at different years (from 1976 to 2007) in Norwegian residents covering age groups (0–59 years) (Haug et al., 2009). An Australian study by Kärrman et al. (2006) reported pooled serum samples from 3802 Australian residents with people from 5 different age groups (0–80 years). Serum samples were collected from rural and urban regions of Australia. Data was divided into pools for each specific region with 2 pools in each stratum (Table 1 in supplementary file).

Different model simulations were carried out to obtain the plasma concentration as a function of age and these data were compared with the biomonitoring results. Monte Carlo simulation was performed taking into account the parameter distribution representing interindividual variations. Agreement of the model results with biomonitoring data was examined graphically and statistically using the correlation plot with the Pearson correlation coefficient.

2.6. Sensitivity analysis

Global sensitivity analysis (GSA) was performed on the dynamic age-dependent model across ages through the pksensi R package. A global sensitivity analysis was performed instead of local sensitivity analysis because it allows all input factors to be varied simultaneously and quantifies the importance of model input and their interaction with respect to model output. The analysis was performed considering the system at a steady state similar to the realistic scenario. Variance-based GSA method is based on the Sobol sensitivity index (SI) and calculates the sensitivity with the effect of specific parameters on organs (Hsieh et al. 2018a, 2018b. All the parameters were varied 1% to compute the effect on model output (plasma, liver, kidney, bone marrow, lung, and fat compartment). Sometimes, due to smaller sample size, SI is not stable showing high variability, random phase shift approach was used for replicating samples across random points to test the robustness and convergence of the sensitivity index. If the model is built under $y = f(x_i)$, the sampling scheme can be described as

$$x_i = \frac{1}{2} + \frac{1}{\pi}\arcsin(\sin(w_i s + \varphi_i)) \quad \text{(Hsieh et al. 2018a)} \quad (4)$$

where x_i refers to the nominal value of the i_{th} parameter, w_i is a vector giving the set of frequencies, one frequency for each parameter, and s is a random phase-shift coefficient ranged from 0 to 2 one frequency for each

parameter, and φ_i is a random phase-shift coefficient ranged from 0 to 2 π. Extended Fourier amplitude sensitivity testing (eFAST), a variance-based sensitivity analysis method helps in determining influential parameters by randomly generating the sequence. Further, heat map visualization was performed to distinguish between influential and non-influential parameters with a cut-off point. If the cut-off is more than 0.1, it was considered as a highly influential parameter and less than 0.05 was considered as non-influential parameters indicating these parameters would not contribute to a major change in the output. Results were analyzed to detect sensitive parameters at different age groups (Figs. 1–3 in supplementary file).

3. Results

Growth and gender variations in anthropometric and physiological parameters across the human lifetime are shown in Table S2 in the supplementary file. The equations cover the physiological growth of a complete human lifetime along with variability in parameters. Initially, dynamic age-dependent PBPK model at adult age was compared with the results from the published PBPK model at the same age. Then this model was used to simulate organ concentration over a human lifetime and validated with autopsy data. Further, the model was used to simulate plasma concentration across a human lifetime and evaluated with data from 3 different cohorts. Across age groups, sensitive parameters were evaluated for the sensitivity of different organs with PFOS exposure.

3.1. Adult model evaluation

To evaluate the dynamic age-dependent PBPK model, first, this model was run at an adult age for plasma concentration. For comparison, results from an already published adult model from Fàbrega et al. was used to evaluate the plasma concentration with the same exposure level (Fàbrega et al., 2014, 2016). Concentration in plasma from the dynamic adult model was in good agreement with the concentration in plasma from the published model (Fig. 12 in Supplementary file). The relationship (goodness of fit) between results from concentration in plasma from both models using linear regression (Pearson correlation coefficient) showed a good correlation with p-value less than 0.001 and correlation coefficient approximately equal to 1.

3.2. Model predictions for autopsy data

Next, we evaluated the dynamic age-dependent PBPK model across different age groups by simulating PFOS tissue distribution with the autopsy data of the population living in Tarragona. First, individual exposure was reconstructed utilizing the liver PFOS concentration and then the estimated reconstructed exposure was used to predict the concentration in different organs (brain, kidney, liver, lungs) (Fig. 2). As indicated in Fig. 2, simulation results were within the range of autopsy data in liver, brain, and kidney except for the lung. In kidney few data points were outside the simulated range but within 2-fold of simulated concentration. However, in the lungs, the model overpredicted the results in comparison to autopsy data which may be due to variation in partition coefficient. From autopsy data, it is noticed that PFOS accumulation is lowest in the brain from age 20–85 years and the same trend can be seen in the simulation results from PBPK (Fig. 2).

3.3. Model evaluation using different cohorts

Dynamic age-dependent PBPK model was used to simulate plasma concentration over the human lifespan and biomonitoring data from the

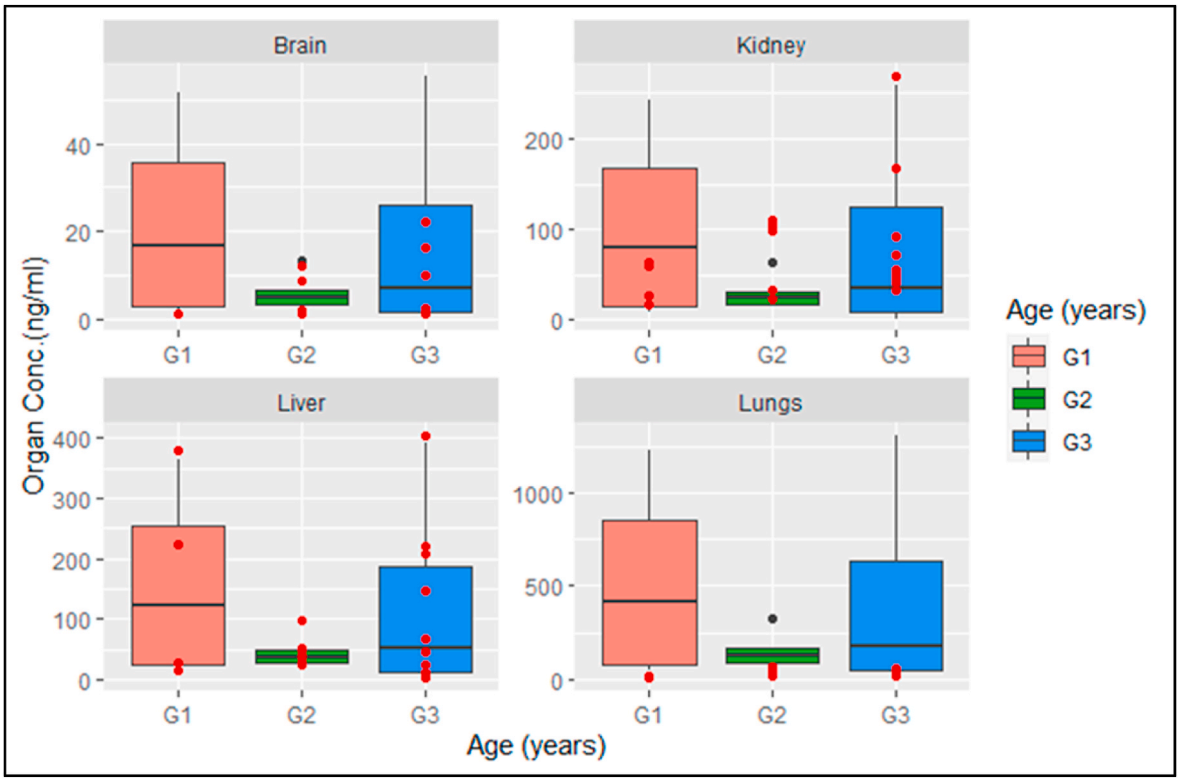

Fig. 2. PFOS concentrations in brain, kidney, liver and lungs of human at different ages simulated individually using PBPK model. G1 refers to the age group 25–35 years, G2 for 36–60 years and G3 for 61–86 years. Red dot represents the autopsy data obtained from postmortem samples of different human tissues in Tarragona region (Catalonia, Spain). Upper whiskers show the percentile 95 and lower whisker presents the percentile 5 of the simulated organ concentration. More detailed description about the data can be obtained from (Pérez et al., 2013). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

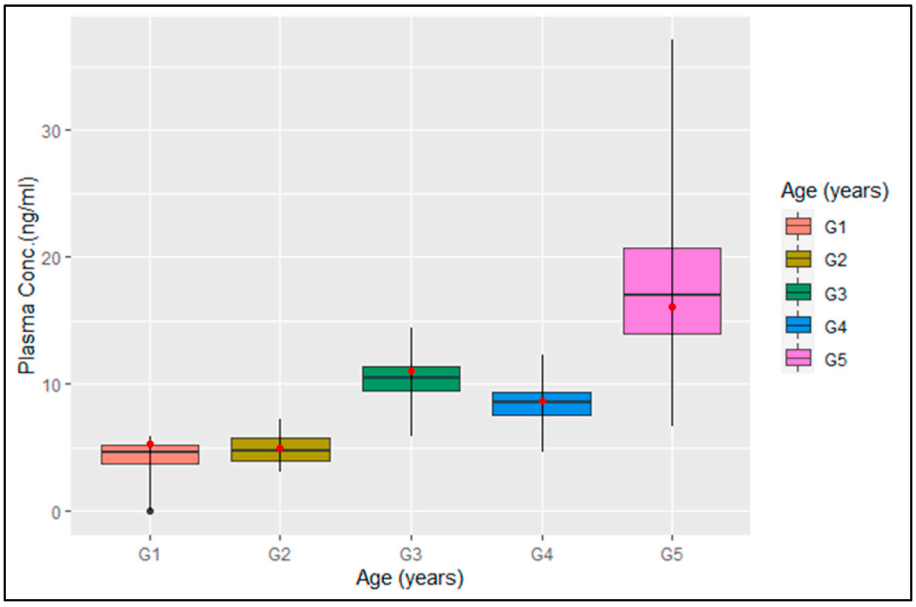

Fig. 3. Time course concentration of PFOS in plasma with age in infants (G1: 0–1 years), toddlers (G2: 1–5 years), children (G3: 5–10 years), adolescents (G4: 10–18 years) and adults (G5:18–90 years). Biomonitoring data was from China from year 2009 across all age group (0–90 years) presented by red circles. Upper whisker represents 95 percentile and lower whisker represents 5 percentiles of PFOS distribution in plasma. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

different cohort was used for comparing the results. Fig. 3 compares the observed and predicted plasma concentration from China (ages ranging from 0 to 90 years). The PFOS biomonitoring data from Zhang et al. for different age groups showed that the concentrations increase slightly with age. This same trend was observed in simulated data (Zhang et al., 2010). Fig. 4 represents the plasma concentration of the Norwegian population from 1976 to 2007. To capture the downfall trend after 2000, dynamic exposure was used considering the reduction in daily exposure. This was due to the phase-out of PFOS production in many countries and reduced emission in European countries after 2000 (Nøst et al., 2014; Sun et al., 2020). Comparison of model-predicted plasma PFOS concentration versus Australian biomonitoring data from 2007 to 2008 (range from 0 to 85 years) was in good agreement for all pools based on region and age groups (Fig. 5). Simulated results from this study indicate that PFOS accumulation increase with age. Similar results were obtained from a biomonitoring study by Kärrman et al. (2006) with elevated PFOS accumulation at age <16 years and >60 years. The reason behind this may be elimination, chemical half-life with age, physiological factors and exposure to the chemical Kärrman et al. (2006).

To better illustrate the plasma concentration, a goodness-of-fit plot was used for predicted and observed plasma concentration as shown in Fig. 6. This figure shows that most of the predicted concentrations fall within the two-fold error range of observed concentrations which meets the WHO model precision criteria (Project and No, 2010). Thus, based on these studies, we can validate that the developed PBPK model can reasonably predict the concentration of PFOS inside human body for different age groups.

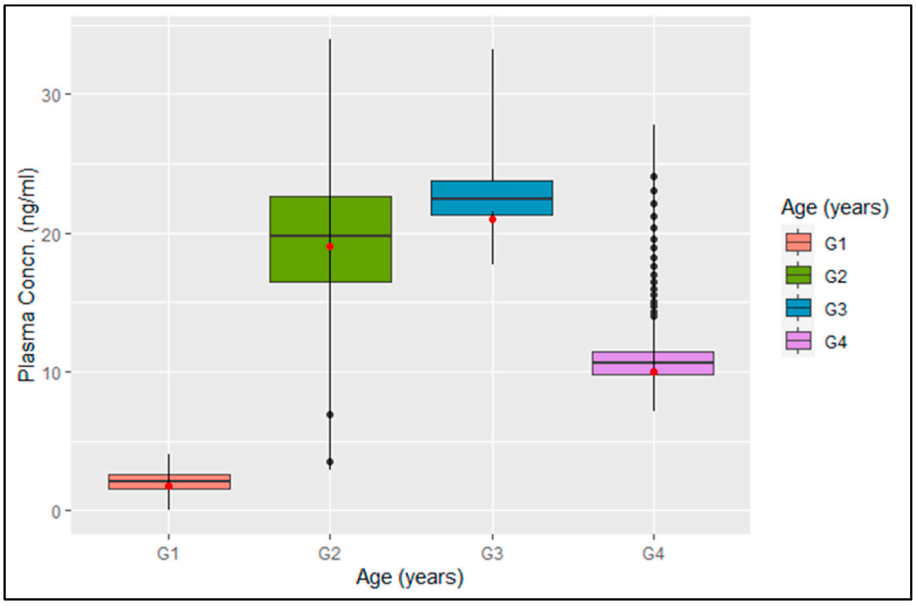

Fig. 4. Concentration of PFOS (ng/ml) in plasma sample of Norwegian population. G1 represents age 0–4 years, G2 for 5–14 years, G3 for 15–24 years and G4 for 25–59 years. Red dot represents biomonitoring data from 1976 to 2007 covering population from 0 to 59 years. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

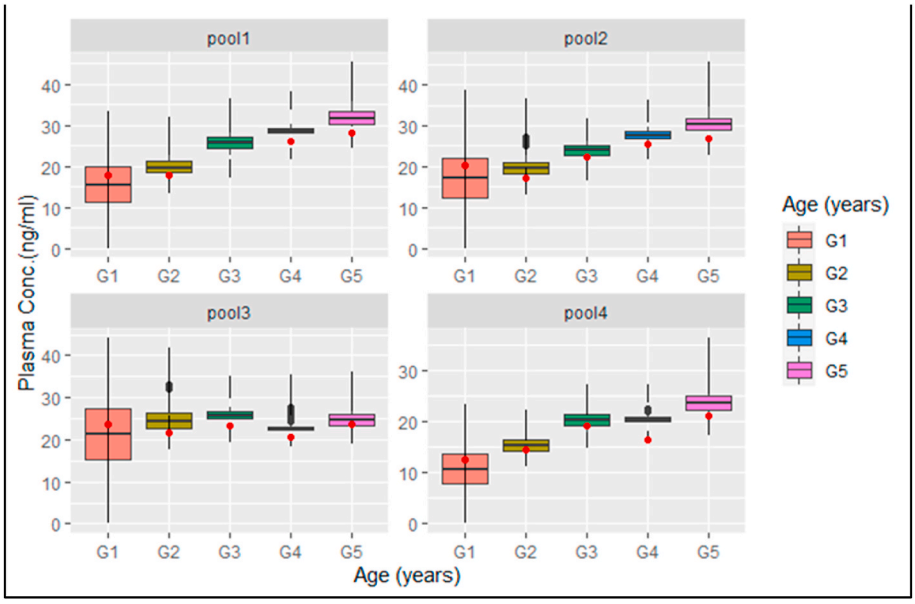

Fig. 5. Concentration of PFOS in Australian population with each pool having serum samples divided based on age and region. G1 refers to 0–16 years, G2 for 16–30 years, G3: 31–45 years, G4: 46–60 years, G5: 61–80 years and red dot represents biomonitoring data in specific age groups. Pool 1 and pool 2 represents the rural region where pool 3 and pool 4 represents the urban region. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

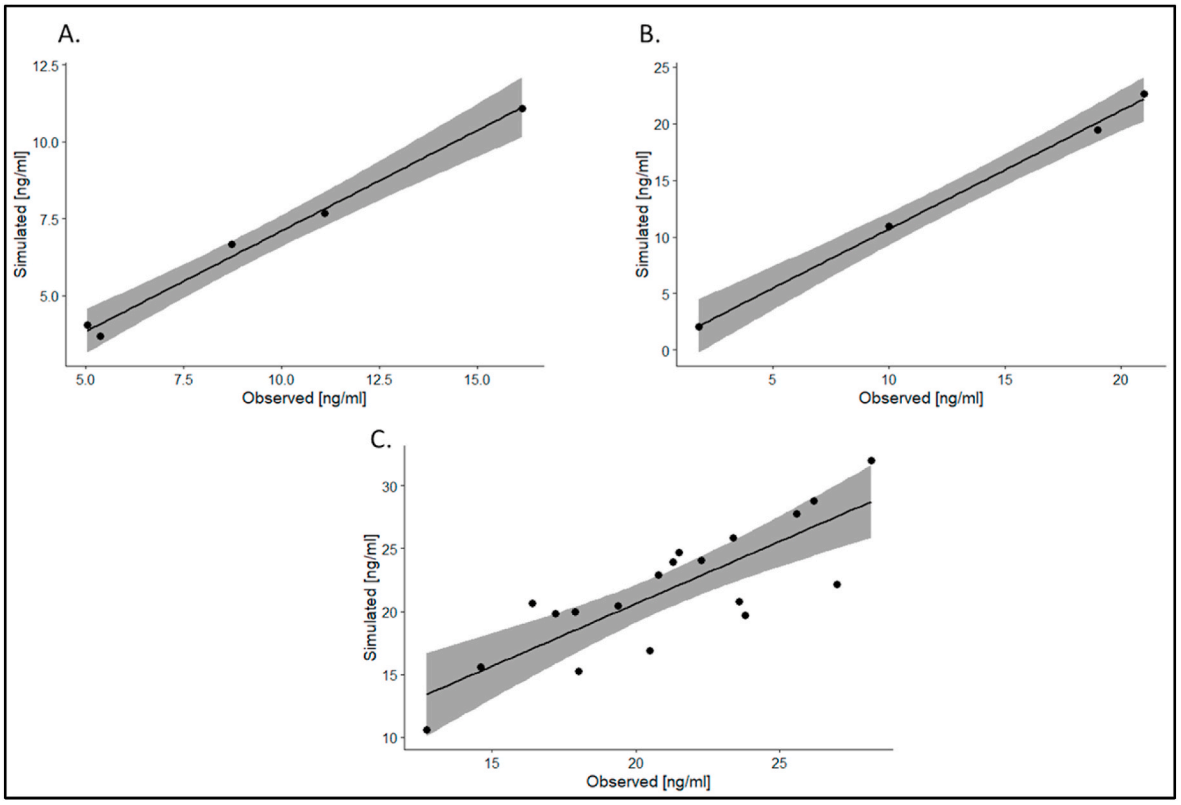

Fig. 6. Comparison of simulated (y-axis) and observed (x-axis) plasma concentration with goodness of model fit with correlation plot from 3 different cohorts. In the plot, A represents biomonitoring data from China, B represents the biomonitoring data from Norway and C represents biomonitoring data from Australia.

3.4. Sensitivity analysis

A global sensitivity analysis was performed for a total of 33 anthropometric, physiological and biochemical parameters to determine the most influential parameters for concentrations of PFOS in 5 organs (plasma, fat, liver, kidney and bone marrow) in the human (Figs. 1–3 in supplementary file). Results of the GSA were based on a 1% variation in parameter values. The results indicated that in the physiological parameters, body weight, bone marrow volume, liver volume, blood flow to the kidney, GFR were most sensitive across all ages (Fig. 2 in supplementary file). Other physiological parameters were reported to have low sensitivity and showed variation with age (Fig. 7). Another sensitivity analysis was carried out for partition coefficient across all ages for 5 compartments (Fig. 1). Partitioning for liver and bone marrow is highly sensitive across all ages (Fig. 1 in supplementary file). The sensitivity analysis for biochemical parameters (Fig. 3 in supplementary file) in which affinity constant, renal reabsorption, and fraction unbound are the highly sensitive parameter for all age groups. The

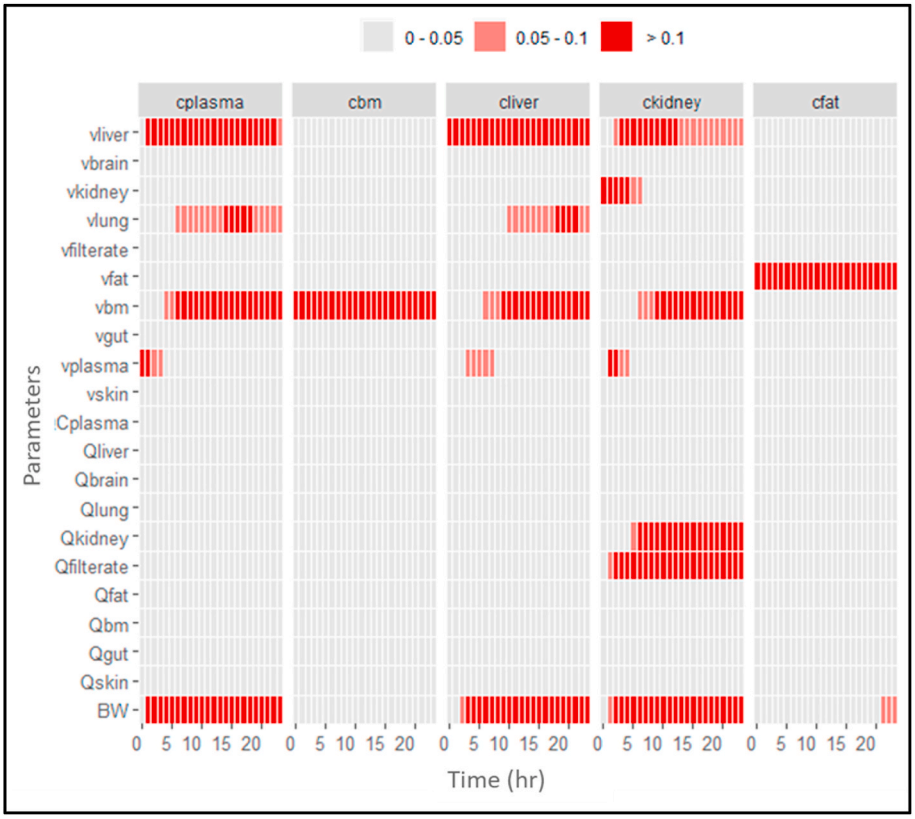

Fig. 7. Heat map representing sensitive physiological parameters to the different body organs at adult age. Here, cplasma refers to concentration in plasma, cbm refers to concentration in bone marrow, cliver refers to concentration in liver, ckidney to concentration in kidney and cfat to concentration in adipose tissue, vliver-volume of liver, vbrain-volume of brain, vkidney-volume of kidney, vlung-volume of lungs, vfiltrate-filtrate compartment volume, vfat-volume of adipose tissue, vbm-volume of bone marrow, vgut-volume of gut, vplasma-volume of plasma, vskin-volume of skin, QCplasma – cardiac output, Qliver-liver blood flow, Qbrain-brain blood flow, Qlung-lung blood flow, Qkidney-kidney blood flow, Qfilterate-glomerular filtration rate, Qfat-adipose tissue blood flow, Qbm-bone marrow blood flow, Qgut-gut blood flow, Qskin-skin blood flow and BW- Body weight.

sensitivity of some parameters changing with age shows that the risk factor changes with the age. This behavior has also been noted in autopsy data from Tarragona where accumulation in different organs changes with age. As renal clearance decreases with age, the half-life of these chemicals in the human body may increase more in geriatrics than adults.

4. Discussion

Adult PBPK model for PFOS had been developed by several researchers (Brochot et al., 2019; Chou and Lin, 2020; Fàbrega et al., 2014; Loccisano et al., 2012, 2013; Rovira et al., 2019) for describing the kinetics of PFOS in human but risk varies across human lifespan raising the need for robust dynamic age-dependent PBPK model. For PFOS risk assessment, a dynamic age-specific PBPK model was developed incorporating physiological and biochemical changes with age and their impact on the disposition of chemicals inside the human body. This is the first dynamic age-specific PBPK model for PFOS and provides a framework for understanding PFOS behavior in pediatrics, adults, and geriatric populations. The analysis was performed with the Monte Carlo simulation technique considering the uncertainty and variability of the anthropometric, physiological, and biochemical model parameters. This model was used for reconstructed exposure and to provide estimates in sensitive populations with high susceptibility to risk. Limited data are available on internal dose in human and this PBPK model serves as an important tool for improving the accuracy of quantitative risk assessment of chemicals like PFOS in sensitive population.

4.1. Biochemical parameters

Biochemical parameters are hybrid parameters that represent both the physiology and the chemical characteristics, thus these parameters become very important to investigate for the age-specific dynamic model taking into account both the uncertainty and variability. Free fraction is generally determined mostly by the level of the albumin which varies depending on the age group and this was emulated in the current model based on Edginton et al., (2006), (Forsthuber et al., 2020). As the level of albumin determine the extent of PFOS binding to plasma proteins and hence affecting the kinetics of PFOS as only the unbound fraction is subjected to clearance (Mallick et al., 2019). Renal clearance of PFOS is also being impacted by reabsorption from the proximal tubule back to the renal blood and this process follows saturation kinetics (Loccisano et al., 2012). This process could be responsible for varying plasma half-life of PFOS in young population and other sensitive age groups. Being the dynamically scaled age-dependent PBPK model, the clearance and reabsorption process were made dynamic based on the two biochemical parameters i.e. transporter maximum (Tmc) (refer equation (2)) and affinity constant (Kt). Both the dynamic changes in binding and elimination accounts for describing the pharmacokinetics of PFOS with age, hence giving a better perspective of quantitative risk assessment.

4.2. Model evaluation

Initially, the adult PBPK model was validated with the published model from Fabrega et al. (Fàbrega et al., 2014). The agreement between the predicted and observed concentration of PFOS in adult human plasma was good with an R-square value of more than 0.95. Next, the biomonitoring data from the Tarragona autopsy study was used for validating the model which include PFOS concentrations in various organs i.e. liver, kidney, brain, and lungs. First, the reconstructed external exposure was estimated utilizing the liver concentration data for various age groups separately (20–85 years) and then the estimated exposure was used to simulate the individual internal exposure for kidney, lungs, and brain along with the liver. The simulated data from the Tarragona autopsy study was in good correlation with the observed results from the dynamic PBPK model all within a factor of 2 (Fig. 2). In Fabrega et al. study, simulated concentrations were much less than experimental data,

but the dynamic PBPK model developed was able to capture the biomonitoring data. However, in the case of lung tissue, the model overpredicted the concentration compared to the autopsy results. This indicates there might be some additional mechanisms or it could be just the volume of distribution for lungs is different. This could compensate easily by recalibrating the partition coefficient between lungs to plasma. To confirm this further a detailed inhalational PBPK model along with some control experimental data might be required.

Reconstructed exposure was used for simulating plasma concentration with 3 independent cohorts from different countries. In China, the data covered all the age groups from 0 to 90 years and the trend shown by biomonitoring data was comparatively increased concentration of PFOS with age. Simulated data also showed the increased PFOS concentration in plasma with old age. The possible reason behind this could be PFOS is a long-acting chemical and as with the age, the organs like bone marrow and adipose tissue matures leading to higher disposition inside the body. Also, a positive correlation of PFOS with age may be due to increased dietary intake including seafood and fish having high PFOS levels in China (Zhang et al., 2010). In another study by Gulkowska et al. PFOS has been detected in all the seafood samples with a higher concentration in fish and crab (Gulkowska et al., 2006). However, in the case of the geriatric population, the dietary intake is low but decreased kidney elimination, reduced GFR capacity, decreased bone marrow volume, and increase in adipose tissue, leading to deposition of this lipophilic chemical inside human tissues. In general, accumulative, lipophilic nature and continuous exposure of PFOS may be responsible for an increase in PFOS concentration with age. Even in sensitivity analysis, the blood flow to the kidney, GFR, and volume of bone marrow and adipose tissue were parameters highly sensitive for PFOS. Gracia et al. showed the ability of PFOS to accumulate in adipocyte cells almost comparable to reference compounds (cationic amphiphilic drugs) (Sanchez Garcia et al., 2018). Another study by Xu et al. showed that PFOS promotes adipogenesis and lipid accumulation by Nrf2 signaling activation and PPAR alpha induction leading to adverse effects (Xu et al., 2016). These studies indicate that the sensitivity of adipose tissue towards PFOS could be linked with both its kinetic and dynamic aspects. Further experimental studies need to be done for explaining the sensitivity and accumulation potential of PFOS in the geriatric population. Another study by Kärrman et al. has shown that PFOS disposition increase from 16 to 60 years in the rural and urban population which is in sync with biomonitoring results from Zhang et al. suggesting that the geriatric population is more susceptible to PFOS risk as compared to adults (Kärrman et al., 2006; Zhang et al., 2010) (Fig. 5). Also, comparatively, higher reconstructed exposure and plasma concentration in children with age group 5–10 years was observed. This is in line with the other study where it has been showed that children's outdoor PFOS exposure involves more dust particles, dermal contact with PFOS or PFOS treated products, and multiple other sources, this may be responsible for comparatively higher plasma concentration in children (Winkens et al., 2017). In case of infant age (0–1), exposure from the mother is present by breastfeeding and other contacts which can lead to increased PFOS in plasma compared to other groups as has been seen in Fig. 3 (Liew et al., 2018). Another study from Haug et al. was used for model evaluation where they had pooled data for PFOS serum from 1976 to 2007 in different age groups from 0 to 59 years (Haug et al., 2009). Simulated and observed plasma concentration showed a drastic decrease in the 2007-year age group (Fig. 4) due to dynamic exposure. The possible reason for this decline may be due to i) after 2000, major producers like 3M announced the phase-out production of perfluoro compounds and ii) PFOS inclusion in the Stockholm convention in 2009. These global efforts and strict adherence to POPs regulations have led to reduced exposure of PFOS in the Norwegian population (Nøst et al., 2014).

4.3. Sensitivity analysis

To analyze the influential parameters across age, a global sensitivity analysis was performed for all physiological and biochemical parameters. The sensitivity analysis results suggest that the free fraction (fu), transporter maximum constant (Tmc), and affinity constant (Kt) are influential biochemical parameters at all ages. Several studies for PFOS by different authors have reported these parameters as the most influential which are consistent with our findings (Chou and Lin, 2019; Fàbrega et al., 2016). Tmc and Kt affect the renal reabsorption process thus lowering the renal clearance causing PFOS to accumulate inside the human body. The free fraction of PFOS is available to move and potential to accumulate and eliminate respectively in and from the different organs. Physiological parameters such as liver and bone marrow volume, kidney blood flow, GFR, and partition coefficient for liver, bone marrow, and kidney are highly sensitive across the human lifespan. These results support the finding of previously published studies that the kidney is the main organ for elimination in PFOS and contributes to predicted PFOS concentration in plasma and other organs (Chou and Lin, 2020; Loccisano et al., 2013; Tan et al., 2008). Liver volume is shown to be sensitive for all the organs as the liver is the primary highly exposed organ that receives the xenobiotics, via portal vein from the intestine before it gets distributed to plasma and then other organs (Fig. 2 in supplementary file). Exposure of PFOS to liver is higher in the human body from childhood and it starts accumulating in the organ. Even in Tarragona autopsy data (Fig. 2), the liver showed the highest accumulation across ages. The volume of bone marrow is more sensitive during childhood than adult. This may be due to immature bone marrow during early life stages. Also, the PFOS exposure is higher in bone marrow due to a higher partition coefficient. Kidney plays an important part in the elimination of PFOS making it a sensitive parameter especially for renal resorption which is affected by GFR. Autopsy data from Tarragona showed PFOS concentration in the kidney with an increased level in the geriatric population as compared to adults.

4.4. Dosimetry and risk assessment

One application of this dynamic age-dependent PBPK model is to estimate the human daily exposure from observed plasma/blood/serum concentration from biomonitoring studies. Because in a real-life scenario, it is very difficult to accurately estimate the contribution from various sources (diet, dust, water, soil, indoor exposure, and other sources), the currently developed PBPK model serves as an excellent tool for finding exposure at different age groups. For PFOS, the estimated reconstructed exposure varied from $1.4e^{-5}$ to $1.25e^{-4}$ μg/g body weight per day (Table S3 in supplementary file). The higher exposure was noticed in children than teenagers and adults in all the 3 cohorts which may be due to higher relative uptake by food consumption and hand-to-mouth transfer from carpets and dust ingestion (Trudel et al., 2008). Another reason behind high exposure can be the changes in physiology (varied distribution and elimination capabilities) in children than adults. The high exposure indicates that children may be more susceptible to health effects than adults from exposure to PFOS as they are in the development stage. The exposure in the geriatric population is less than in other age groups, still it poses a major challenge. With age, the kidney loses its nephrons and a corresponding decrease in GFR leading to decreased capability for the elimination of xenobiotics. Also, epidemiological studies have linked PFOS exposure to lower eGFR and chronic kidney disease further increasing the risk even with relatively lower exposure.

Due to variation in toxicokinetic across the human lifespan, higher external exposure may result in different internal dosimetry in humans. The varied concentration of PFOS in different organs increase the risk for toxicity in sensitive population. Currently, there are many mechanisms of actions (MOA) being evaluated by different researchers linked to toxicity in the liver, kidney, adipose tissue, and other organs

(hepatocellular hypertrophy, liver, and kidney cancer, decreased triglyceride levels, increased cholesterol levels and decreased GFR) (Deepika et al., 2020; Huang et al., 2020). Continuous exposure to PFOS inside the human body like kidney and liver for longer times pauses risk to sensitive population (Fig. 2) and gives insights into the association of PFOS with liver damage and kidney cancer (Saikat et al., 2013; Sunderland et al., 2019). A study by Gong et al. showed PFOS exposure increases kidney injury by impaired metabolism of purines and amino acids and increased oxidative stress in rat mesangial cells (Gong et al., 2019). Also, different epidemiological studies point towards associations between PFAS exposure and lower kidney functions. PFAS exposure alters different pathways like the peroxisome proliferator-activated receptor (PPAR) pathway, NF-E2 related factor 2 pathway, oxidative stress pathway, and increased endothelial permeability through actin filament modeling linking PFAS to kidney disease. PFOS was linked to liver toxicity by interfering with mitochondrial beta-oxidation of fatty acids and affecting the transcriptional activity of PPAR alpha in the liver (Martin et al., 2007; Wan et al., 2012; Wang et al., 2014). Such kind of associations can be explained indirectly by a dynamic PBPK model across ages through a simulated concentration in the liver, kidney, and other sensitive organs. Further, the dynamic age-dependent PBPK model can be linked to the pharmacodynamic and systems biology model to explain the effects of toxicity through mechanistic pathways at cellular and molecular levels.

5. Conclusion

The present study provided a dynamic age-dependent PBPK model for PFOS in different age groups from pediatrics, adult to geriatrics. By incorporating physiological and physicochemical parameters at different age groups, the model can describe the kinetics of PFOS in sensitive populations and different organs where biomonitoring data are limited or difficult to measure. The simulated results show that the geriatric populations have relatively higher PFOS concentration even with lower exposure than children making them more prone to risk. The presence of PFOS in different organs with age points towards adverse effects and increased vulnerability to PFOS linked adverse outcomes. The dynamic age-dependent PBPK model can be used to support risk assessment in a susceptible population like pediatrics and geriatric population and can be used to assess the exposure at different age groups. Further, this framework can be extended to predict the risk for the coming generation by introducing exposure for the next generation through pregnancy and lactation.

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.

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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.2021.111287.

CRediT author statement

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