Prenatal exposure to PFOS and PFOA in a pregnant women cohort of Catalonia, Spain

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ABSTRACT

This study was aimed at assessing the prenatal exposure to perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) in a cohort of pregnant women living in Reus (Tarragona County, Catalonia, Spain). These chemicals were biomonitored in maternal plasma during the first trimester of pregnancy, at delivery, and in cord blood. The dietary exposure of PFOS and PFOA was estimated by using questionnaires of food frequency and water intake, as well as data on food levels previously reported in the same area. In addition, the exposure through air inhalation and indoor dust ingestion was also calculated. Finally, a physiologically-based pharmacokinetic (PBPK) model was applied in order to establish the prenatal exposure of the fetus/child and to adjust exposure assessment vs. biomonitoring results. Probabilistic calculations of fetal exposure were performed by forward internal dosimetry and Monte-Carlo simulation. Mean plasma levels of PFOA were 0.45, 0.13 and 0.12 ng/mL at the first trimester, at delivery and in cord plasma, while those of PFOS were 2.93, 2.21, and 1.17 ng/mL, respectively. Traces of PFOS were found in all samples in the trimester and at delivery, and almost in all cord blood samples. Transplacental transfers of PFOS and PFOA were estimated to be around 70% and 60%, respectively. A temporal decrease trend in plasma levels of PFOS and PFOA was noticed, when comparing current values with data obtained 10 years ago in the same area. In agreement with many other studies, dietary intake was the main route of exposure to PFOS and PFOA in our cohort of pregnant women. It is an important issue to establish the exposure in critical windows periods such as fetal development to perfluoroalkylated substances, but also to other endocrine disrupting chemicals.

Key words: PFOS, PFOA, prenatal exposure, PBPK modeling, cord blood, plasma, dietary intake

Highlights

- PFOS was detected in most of the samples of mother plasma and cord blood.
- Transplacental transfers of PFOS and PFOA were around 70% and 60%, respectively.
- The dietary intake was the main exposure pathway to PFOS and PFOA.
- The estimated dietary intake of PFOS exceeded the EFSA tolerable weekly intake.
- Modeled PFOS levels adjusted well to biomonitoring data, validating the PBPK model.

1. Introduction

Perfluoroalkylated substances (PFASs) are a group of synthetic chemicals, which include perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA). They share a common structure, as they own a long hydrophobic carbon chain saturated with fluorine atoms with a hydrophilic functional group at the end. This structure gives oil and water repellence, chemical stability and reduces surface tension (OECD, 2002). Since 1940s, these substances have been used in a wide range of industrial and commercial proposes, such as textiles, cosmetics, adhesives, electronic and photographic devices, cleaning agents, fire-fighting foams, paper, board, cookware and food packing materials, among others (Domingo and Nadal, 2017; Hekster et al., 2001).

Due to the high volume of production, demand and consumption of these products, PFASs have been detected in a number of environmental matrices, including air, dust and water (Fromme et al., 2009). Moreover, they have been also found in remote areas of the planet, such as the Tibetan Plateau and the Arctic (Cai et al., 2012; Shi et al., 2010; Shoeib et al., 2006). In addition, PFASs are highly resistant to degradation in the environment and tend to bioaccumulate in living organisms (Suja et al., 2009). As a result of this occurrence, traces of PFASs have been largely detected not only in wildlife but also in humans (Butt et al, 2010; Kannan et al., 2004; Kärrman et al., 2010; Letcher et al., 2010; Morales et al., 2015).

The food chain, as well as the water and indoor environments, are polluted with PFASs, meaning a worldwide health problem (Arrebola et al., 2018; Islam et al., 2018). The ingestion of contaminated food or the migration of these substances from food packaging or cookware have been identified as key sources of human exposure to PFASs (Begley et al., 2005; Domingo, 2012; Ericson et al., 2012; Fromme et al., 2009). In an exhaustive study performed in Tarragona County (Catalonia, Spain), it was established that the dietary intake is the main exposure pathway to PFOS and PFOA, followed by the consumption of drinking water (Ericson et al., 2008). In contrast, the indoor environment (dust and air) has a minor contribution, with less than 1% and 2% for PFOS and PFOA, respectively (Ericson et al., 2012). Among food, fish and seafood was pointed out as the most important contributor to total dietary intake of both chemicals, while high levels of PFOS and PFOA were also found in eggs and meat, respectively (Domingo and Nadal, 2017; Sungur, 2018).

Concerning the exposure of pregnant women, the placental barrier is not impermeable to the passage of PFOS and PFOA (Liu et al., 2011; Kim et al., 2011). Furthermore, these toxic substances can be also transferred from mother to child during breastfeeding (Kärrman et al., 2010; Motas Guzmàn et al., 2016). PFOS and PFOA have been recognized as endocrine disrupting chemicals (WHO, 2013). Moreover, prenatal and early exposure to PFASs is associated with a decreased birth weight and gestational age (Meng et al., 2018), developmental problems (Chen et al., 2013), reproductive system problems (Lyngsø et al., 2014), and increased susceptibility to disease in adulthood (Tsai et al., 2015; Zhang et al., 2018). However, some controversy exists in the association between PFASs and decrease in

birth weight. A meta-analysis (Steenland et al, 2018) showed little or no association with decreased birthweight when PFASs were measured during early pregnancy where potential confounding exposure by the glomerular filtration rate would be minimal. However, Meng et al. (2018) study performed in early pregnancy, not included in this meta-analysis, found association between PFASs and a decrease of birth weight (Verner et al., 2015).

This study aimed at assessing the prenatal exposure to PFOA and PFOS from a cohort of pregnant women in Tarragona County (Catalonia, Spain). To achieve this goal, PFOA and PFOS were biomonitored in maternal blood during the first trimester of pregnancy, at delivery and in cord blood. In addition, the intake of PFOS and PFOA though food and drinking water consumption for this cohort was also estimated, while the potential contribution of indoor dust ingestion and air inhalation were also calculated according to the activity profile of these pregnant women.

2. Materials and methods

2.1. Subjects

The study population comprised a cohort of pregnant women and an ongoing birth cohort. Pregnant women were recruited during the first trimester of pregnancy as part of the HEALS European project. The recruitment of pregnant women started in March 2016 and ended in September 2017 and, in the present survey, 50 mother-child pairs from Reus (Tarragona, Spain) were included. Women were informed about the investigation during their first visit (12^{th} gestational week (GW)) to the University Hospital "Sant Joan" in Reus (Catalonia, NE Spain). Women were eligible to participate according to the following inclusion criteria: ≥16 years old, intention to deliver at the reference hospital, and no problems with the communication language. This study was approved by the Ethical Committee of Clinical Research of the Hospital and a written informed consent was obtained from the participants. A description of the characteristics of the study population is shown in Table 1.

2.2. Questionnaires for data acquisition and sampling

Face-to-face and personal interviews were used in order to determine the pregnant women's dietary intake of PFOS and PFOA. Dietary factors were assessed using food frequency questionnaires (FFQs), which were originally designed to evaluate the average dietary intake in two phases: the 1^{st} FFQ covered the year before pregnancy, and the 2^{nd} FFQ covered the whole pregnancy including the last period until birth. Food items were classified into 9 general groups: a) grains and grain-based products (cereals, pasta, rice, and bread), b) milk and dairy products (milk, yogurt, hard cheese, and fresh cheese), c) meat (chicken, turkey, beef, pork, lamb, and minced meat), d) fish and seafood (white fish, blue fish and seafood), e) fruits and vegetables (salad, green beans, Swiss chard, spinach, and garnish

vegetables), f) legumes and potatoes (lentils, chickpeas, white beans, and potatoes), g) eggs, h) sugar and confectionary (cupcakes, biscuits, stuffed cookies, donuts, sweets, cream or chocolate cakes, chocolate, and ice cream), and i) drinking water (tap water and bottle water). As well as dietary factors, the questionnaires also included information on other non-dietary sources such as smoking, lifestyle, time spent outdoors/indoors, and occupational risk. Therefore, based on this information, dietary (food) and non-dietary (inhalation and dust ingestion) values of exposure were estimated individually. Blood samples were collected at the end of the first trimester (around the 12th GW), at delivery, as well as from the umbilical cord. Blood was centrifuged at 3500 rpm for 15 minutes to separate the plasma. The aliquots of plasma (2 mL) were stored at -80°C until the determination of PFOS and PFOA.

2.3. Analysis of PFOS and PFOA

PFOA and PFOS analyses were performed as previously described (Vassiliadou et al., 2010). Briefly, 2 mL of blood plasma, 200 µL of the internal standard working solution (containing 100 ng/mL of $^{13}C_4$-labelled PFOS and 100 ng/mL of $^{13}C_4$-labelled PFOA in methanol) and 20 mL of acetonitrile were added and vortex-mixed for 1 min. The sample was centrifuged at 4000 rpm for 5 min to clarify the supernatant. The organic phase was evaporated until dryness in a flash evaporator and the residue obtained was dissolved in 5 mL of phosphate buffer solution 0.05 M, pH = 7.8. A solid-phase extraction was performed conditioning a C18 cartridge with 2.5 mL of methanol and 5 mL of water. The sample was passed through, and then the cartridge was washed with 5 mL of water. Finally, PFOS and PFOA were eluted from the cartridge with 5 mL of methanol. The flow rate of the cartridge was approximately 1–2 drops per second. The organic phase was evaporated until dryness in a flash evaporator and re-suspended in 200 µL of methanol:ammonium acetate (5 mM) (20:80, v/v).

Sample extracts were analyzed by liquid chromatography–tandem mass spectrometry (LC-MS/MS) with electrospray ionization (ESI) operating in negative mode. The method was validated for accuracy, repeatability, robustness, recovery and sensitivity with spiked samples at three different levels (n = 3) of 1, 5 and 10 ng/mL. The limits of detection (LoD) and quantification (LoQ) were determined as signal/noise (S/N) ratio of 3 and 10, respectively. For both, PFOS and PFOA, the LoD was calculated at 0.1 ng/mL.

2.4. Exposure assessment

Pregnant women exposure to PFOA and PFOS was assessed at the 12th and 32nd gestational weeks (GW) in a probabilistic way using a Monte Carlo simulation. Equations, data and parameters were adapted and described elsewhere (Martínez et al., 2017, 2018). The total exposure to PFOS and PFOA for pregnant women was considered as the sum of dietary intake (DI), dust ingestion ($Dust_{Ing}$) and inhalation (Inh), being calculated by applying the following equations:

$$DI = \sum(C_{PFOA/PFOS}(i) \cdot F_r(i) \cdot F_f(i)) / BW / 7 \quad \text{Eq. (1)}$$

$$Dust_{ing} = (C_{PFOA/PFOS}dust \cdot Ir) / BW \quad \text{Eq. (2)}$$

$$Inh = (C_{PFOA/PFOS}air \cdot Ihr) / BW \quad \text{Eq. (3)}$$

Where DI is the total dietary intake of PFOA or PFOS (in µg/kg bw/day); $C_{PFOA/PFOS}$ (i) is the concentration of PFOS or PFOA in the food category *i* (in µg/kg); $F_r(i)$ is the food ingestion rate of food category *i* (in kg/ration); $F_f(i)$ is the food consumption frequency of category i (in rate/week); BW is the body weight (in kg); $C_{PFOA/PFOS}dust$ is the level of PFOS or PFOA in homes dust (in µg/kg); Ir is the Ingestion rate (in kg/day); $C_{PFOA/PFOS}air$ is the concentration of PFOA or PFOS in air (in $\mu g/m^3$); and Ihr is the inhalation rate (in m^3/day).

The concentration levels of PFOS and PFOA in different food items, in dust and in air were taken from the literature, applying as preference rule, data from Tarragona County > Catalonia > Europe. To deal with the variability and uncertainty of parameters, the dietary and non-dietary (dust ingestion and inhalation) exposure was estimated in a probabilistic way. Monte-Carlo simulation is a common approach used to incorporate variability and uncertainty of the parameters used into the estimation of human health exposure (Linares et al., 2010; Nadal et al., 2004; Rovira et al., 2016). The Monte-Carlo simulation was carried out by Oracle Crystal Ball© software. Exposures were calculated based on the propagation of variability and uncertainty given by each parameter probability function until 100,000 iterations. Data and probabilistic distributions used to assess total exposure of PFOA and PFOS are shown in the supplementary material (Table S1, Supplementary Information). To calculate the exposure, levels below the LoD were assumed to be zero.

2.5. Physiologically-based pharmacokinetic (PBPK) modelling

The PBPK model of PFASs was adapted from previously published studies (Fàbrega et al., 2014, 2015; Sharma et al. 2018a). It comprises plasma, fat, brain, lung, gut, liver, kidneys, filtrate, mammary gland, bone marrow, placenta, and the rest of the body. As the target population was pregnant women, a fetal compartment was included. Furthermore, a renal resorption process was inserted in the model. In the filtrate compartment, chemicals are reabsorbed back in the plasma comportment by a saturable process (Andersen et al., 2006; Tan et al., 2008). The fetal compartment was subcategorized again into liver, kidney, brain, and plasma. All the physiological parameters during pregnancy were considered as dynamic, so they changed due to the growth of maternal organs (Abduljalil et al., 2012; Gentry et al., 2003; Loccisano et al., 2013). The source of exposure to fetuses was via a free fraction of chemicals into mother's placenta, considering that fetuses' exposure is directly related to mother's exposure. In the plasma compartment, more than 90% of PFOA and PFOS is bound to albumin, and only less than 10% is free to move to other tissues (Han et al., 2003). Detailed

descriptions of standard and pregnancy-specific model equations were adapted from those published by Sharma et al. (2018b). Metabolic kinetic parameters for both mothers and fetuses were previously estimated from *in vitro* studies.

2.6. Statistical analysis

For statistical analysis, the software package IBM SPSS Statistics (version 25.0) was used. To elucidate whether data presented a parametric distribution, a Levene test was performed. Subsequently, Student's t-test, ANOVA (parametric data) or Kruskal-Wallis (non-parametric data) test were applied. A significance level of 0.05 (p<0.05) was established.

3. Results and discussion

3.1. Levels of PFOS and PFOA

Plasma levels of PFOS and PFOA in maternal blood at the first trimester, at delivery and in cord blood are depicted in Fig. 1. PFOA mean values were 0.45, 0.13 and 0.12 ng/mL, respectively, with only four samples above the LOD (0.1 ng/mL) in maternal plasma at delivery. Plasma levels in the first trimester were significantly higher than those at delivery, and in cord blood ($p<0.001$). PFOS presented higher levels than PFOA, with mean concentrations of 2.93, 2.21, and 1.17 ng/mL at the first trimester, at delivery and in cord plasma, respectively. PFOS was detected in all plasma samples, except in a single sample of cord blood. Furthermore, significant concentrations ($p<0.001$) were found according to the pregnancy period, with a decreasing trend with time. High positive Pearson's correlations were found in PFOS levels when comparing the values of the first trimester and those at delivery (0.855), between the first trimester and in cord blood (0.720), and between those at delivery and in cord blood (0.708). Regarding PFOA levels, no significant correlations were found due to the low ratio of detected samples in cord blood, and especially in mother plasma at delivery. Finally, a low but significant ($p< 0.05$) Pearson's correlation coefficient was found between PFOS and PFOA levels during the first trimester (0.349) (Table S2, Supplementary Information).

Decreases of 69% and 25% in PFOA and PFOS plasma levels, respectively, between the first trimester and at delivery were registered. Our results are in agreement with others from the scientific literature, where a decreasing trend during pregnancy has been also reported. Reduction rates of PFOS in plasma have been observed to range 11-30%, while those of PFOA are even higher (16-30%) (Glynn et al. 2012; Kato et al. 2014). This fact could be due to both a placental transfer and a dilution process caused by the increase of blood plasma volume (Mitro et al., 2015; Glynn et al. 2012). Moreover, Caserta et al. (2018) also observed the occurrence of transplacental transfer of PFOS and PFOA. In this study, around 70% and 60% of maternal plasma levels in the first trimester were found in cord blood for PFOA and PFOS, respectively. Similar trends have been observed, especially for PFOS,

in several studies worldwide (Buck et al. 2018; Cariou et al., 2015; Han et al., 2018; Kim et al., 2011).

The levels of PFOS and PFOA in blood of pregnant women and in cord blood in several studies performed around the world are summarized in Table 2. Plasma concentrations of both chemicals in pregnant women living in Reus (Spain) were notably lower compared to other studies in Germany, Denmark, USA, as well as in some Asian countries (e.g., China, Korea, and Japan). They are also slightly lower but in the same order of magnitude as those found in other residential areas in Spain (Valencia, Sabadell, and Gipuzkoa) (Matilla-Santander et al., 2017). On the other hand, our findings were in line with levels found in studies from France (Cariou et al., 2015; Dereumeaux et al., 2016), Italy (Caserta et al., 2018), Australia (Callan et al., 2016), and USA (Morello-Frosch et al. 2016). In the latter studies, samples were collected more recently, being this an important issue to be considered when comparing different studies. Decreasing temporal trends in PFOS and PFOA blood levels were found in pregnant women in Sweden from 1996 to 2010 (Glynn et al., 2012), in Australia between 2002 and 2011 (Toms et al., 2014), and in an adult population of USA between 2000 to 2015 (Olsen et al., 2017). In 2006, our group performed a biomonitoring study of PFASs in an adult female population in the same area (Tarragona County). PFOS and PFOA levels in blood were 6.81 and 1.57 ng/mL, respectively (Ericson et al., 2007). This means that in 10 years (from 2006 to 2016/17), plasma levels of PFASs have decreased to about one third in this area, being reduced from 6.81 to 2.93 ng/mL, for PFOS, and from 1.57 to 0.45 ng/mL, for PFOA. It should be finally remarked that only in some specific studies from China, PFOA levels are higher than PFOS levels in maternal and cord blood (Tian et al., 2018; Han et al., 2018).

Table 3 shows the levels of PFOA and PFOS in maternal plasma at the first trimester, at delivery and cord blood plasma according to maternal characteristics. Only few significant ($p<0.05$) differences were noted. PFOS levels in cord blood and PFOA levels in the first trimester of pregnancy were significantly higher ($p<0.05$) in primiparous than multiparous women. Underweight in pre-pregnancy (BMI<18.5 kg/m^2) and medium-high annual income (>19,000 €) is associated with higher levels ($p<0.05$) of PFOA at the first trimester of pregnancy. In contrast, a lower annual income (<9,000-19,000 €) is associated with higher ($p<0.05$) levels of PFOS at the first trimester and at delivery, but not in cord blood. Despite not reaching levels of significance ($p<0.05$), an increasing trend of PFOS and PFOA plasma levels was detected with the increase of maternal age. This fact has been largely reported elsewhere (Tsai et al. 2018; Manzano-Salgado et al., 2016). Significantly ($p<0.05$) higher PFOA levels were found in Spanish mothers. In an investigation of pregnant women conducted in Spain, Manzano-Salgado et al. (2016) pointed out that maternal PFAS concentrations during pregnancy were mainly associated with maternal country of birth (higher in Spanish mothers), parity (decreasing trend of PFAS levels with number of children) and age (lower levels in younger mothers).

Regarding the food intake, Table 4 summarizes the levels of PFOS and PFOA in maternal plasma at the first trimester, at delivery and in cord blood plasma in relation to food

frequency intakes. The chosen food groups were selected to be relevant to PFAS exposure according to levels found in Catalonia and international previous studies (Ericson et al., 2008; Domingo and Nadal, 2017; Sungur, 2018). Concerning mother characteristics, few differences were found between groups. Significant differences ($p<0.05$) in PFOS levels at the first trimester and in cord blood were found only between groups reporting high milk consumption (>1 serving/day) and medium consumption (1 serving/day). Higher levels of PFOA at the first trimester were also found in the group reporting high egg consumption (>7 servings/week). Despite that no significant differences ($p>0.05$) were found between high- and medium-fish and seafood consumer groups, an increasing trend in PFOS and PFOA was noted when the consumption edible marine species increases. The same tendency was pointed out in PFOA levels, especially in the first trimester, when milk consumption increased. Manzano-Salgado et al. (2016) found that fish and shellfish consumption was the main factor associated with higher PFAS levels in a Spanish cohort.

3.2. Exposure assessment

The total exposure to PFOS and PFOA, as well as the contribution of each pathway (dietary intake, inhalation and dust ingestion), are depicted in Fig. 2. The global dietary intake of PFOA and PFOS, including drinking water, at the first trimester of pregnancy was estimated in $1.3 \cdot 10^{-4}$ (CI 95%: $1.1 \cdot 10^{-4}$; $1.7 \cdot 10^{-4}$) and $3.3 \cdot 10^{-3}$ µg/(kg·day) (CI 95%: $1.7 \cdot 10^{-3}$; $6.6 \cdot 10^{-3}$), respectively. In the 32nd GW, the global dietary intake of PFOA and PFOS was calculated in $9.8 \cdot 10^{-5}$ (CI 95%: $8.2 \cdot 10^{-5}$; $1.2 \cdot 10^{-4}$) and $2.5 \cdot 10^{-3}$ µg/(kg·day) (CI 95%: $1.4 \cdot 10^{-3}$; $4.6 \cdot 10^{-3}$), respectively. The slight decrease in both, PFOS and PFOA, exposure levels between 12th and 32nd GW was due to an increase of the body weight, while no significant changes in the dietary intake patterns were reported. The global mean inhalation exposure at the 12th GW for PFOA and PFOS was $2.2 \cdot 10^{-6}$ (CI 95%: $9.0 \cdot 10^{-7}$; $4.3 \cdot 10^{-6}$) and $5.0 \cdot 10^{-6}$ (CI 95%: $4.6 \cdot 10^{-7}$; $1.6 \cdot 10^{-5}$) µg/(kg·day), respectively. Finally, the mean dust ingestion at 12th GW of PFOA and PFOS was estimated in $2.0 \cdot 10^{-6}$ (CI 95%: $6.2 \cdot 10^{-7}$; $4.9 \cdot 10^{-6}$) and $1.9 \cdot 10^{-6}$ (CI 95%: $6.2 \cdot 10^{-7}$; $4.8 \cdot 10^{-6}$) µg/(kg·day), respectively.

Recently, the European Food Safety Authority (EFSA) published its scientific opinion on the risk of the presence of PFOA and PFOS in food (EFSA, 2018). EFSA estimated a dietary exposure for the adult population between 0.22 and 3.28 ng/(kg·day) for PFOA and between 0.29 and 4.08 ng/(kg·day) for PFOS. In a previous study conducted in Catalonia, the adult female dietary ingestion was estimated to be $2.3 \cdot 10^{-3}$ and $2.2 \cdot 10^{-3}$ µg/(kg·day) for PFOA and PFOS, respectively (Domingo et al., 2012b). Furthermore, when analyzing the role of inhalation as a contributive exposure pathway of PFOA and PFOS for the Catalan population (Ericson et al., 2012), an estimated exposure of $5.7 \cdot 10^{-4}$ µg/(kg·day) for PFOA and $1.4 \cdot 10^{-3}$ µg/(kg·day) for PFOS was reported, with a contribution of <1% for inhalation and dust ingestion (Ericson et al., 2012). In Latvia, very similar exposure levels were obtained in a cohort of pregnant women, with dietary exposure levels of 0.32 (P95: 0.62) and 0.43 (P95: 0.99) ng/(kg·day) for PFOA and PFOS, respectively (EFSA, 2018).

In 2008, EFSA set a provisional tolerable dietary intake (TDI) for PFOA and PFOS at 1.5 and 0.15 μg/(kg·day), respectively (EFSA, 2008). These values were well above the current levels for the population here assessed. However recently, EFSA (2018) updated the values regarding the provisional tolerable weekly intake (TWI) of PFOA at 6 ng/(kg·week) ($8.6 \cdot 10^{-4}$ μg/(kg·day)) and of PFOS at 13 ng/(kg·week) ($1.86 \cdot 10^{-3}$ μg/(kg·day)). Taking into account these new provisional tolerable intake limits, which are almost 1000-fold lower than the previous ones, the dietary exposure of PFOS for most pregnant women in the studied cohort would be higher than the provisional TWI. In addition, the PFOA exposure would be close to the provisional threshold. It must be highlighted that the current provisional TWI is based on epidemiological studies that have shown an increase in serum total cholesterol for PFOA and increased serum total cholesterol (adults) and decreased antibody response (children) for PFOS (EFSA, 2018). However, some recent findings, involving humans in a phase 1 clinical trial with PFOA (Convertino et al., 2018), genetically engineered "humanized" mice fed with PFOA (Pouwer et al., 2019) and a six-month feeding study of primates with PFOS (Chang et al., 2017), disagree with the results of the epidemiologic studies considered by EFSA in its opinion. This means an important issue of discussion before the publication of EFSA final report. In any case, despite TWIs are still provisional, it is important to state the current position of the regulatory body.

Fish and seafood showed the highest contribution in the total dietary intake for PFOS (86%) and the second highest for PFOA (42%), after milk and dairy products (48%) (Fig. 2). According to EFSA (2012), fish and other seafood is the highest contributor to PFOS (50-80%), while fruits and fruit products (8-27%), as well as meat and meat products (5-8%) have also some importance. With respect to PFOA, the food categories that mostly contribute to the total exposure are fruit and vegetables (18-39%), followed by fish and seafood (8-27%), eggs and eggs products (10-15%), and meat and meat products (2-11%).

3.3. Fetal exposure (PBPK modelling)

Pregnancy PBPK models of PFOA and PFOS were applied for individual participants with their respective physiology, age and exposure dose. We assumed that lifetime exposure of PFOA and PFOS was constant for each subject. The estimated mean plasma concentrations for the mother in the first trimester of pregnancy of PFOA and PFOS were 0.34 (CI 95%: 0.29; 0.38) and 3.14 ng/mL (CI 95%: 2.83; 3.46), respectively. Estimated mean plasma concentrations for the fetus during the first trimester of pregnancy (6-12th GW) were 0.33 (CI 95%: 0.28; 0.38) and 1.39 ng/mL (CI 95%: 1.25; 1.53) for PFOA and PFOS, respectively. At the time of delivery (38-39th GW), the estimated mean plasma concentrations of PFOA and PFOS for the mother were 0.33 ng/mL (CI 95%: 0.28; 0.38) and 2.99 ng/mL (CI 95%: 2.71; 3.27), respectively. For the fetus (38-39th GW), they were 0.32 ng/mL (CI 95%: 0.27; 0.37) and 1.34 ng/mL (CI 95%: 1.22; 1.47), respectively (Fig. 3).

The model simulation results obtained for plasma were mostly in line with results from biomonitoring in samples for both PFOS and PFOA, excepting for plasma concentration of

PFOA in the mother at delivery. In general terms, modelled levels were higher than those obtained by biomonitoring. This could be due to the fact that data used for exposure assessment were obtained from studies performed in the study area some years ago (Ericson 2008a,b, Domingo et al. 2012a). It is well known that levels of PFOS and PFOA have decreased in food during the last years (Johansson et al. 2014). In addition, the use of FFQ results and food ratios from the literature instead of food models could underestimate the real intake during pregnancy.

The amount of total PFOA and PFOS in the fetal body, in terms of body burden, significantly increased by the time of delivery. However, the relative concentrations of both chemicals showed a slight decrease due to the increased body weight of the fetus. In comparison to previous biomonitoring studies in the same area (Pérez et al. 2013; Fàbrega et al, 2016), a significantly lower concentration of PFOA has been observed in the present study.

4. Conclusions

Perfluoroalkylated substances are ubiquitous pollutants, especially PFOS, which were found in all plasma samples in the first trimester and at delivery, and in most cord blood samples. Mean plasma levels were 0.45, 0.13 and 0.12 ng/mL for PFOA and 2.93, 2.21, and 1.17 ng/mL for PFOS at the first trimester, at delivery and in cord blood, respectively. A transplacental transfer of PFOS and PFOA of around 70% and 60%, respectively, was observed. A decreasing trend of PFOS and PFOA in plasma was found when data from the current study are compared with values obtained in the past for the same adult population. The dietary intake was the main route of exposure to PFOS (>99%) and PFOA (>96%) for pregnant women in Tarragona County. In addition, the consumption of fish and seafood was the main contributor to PFOS intake (86%), and the second contributor to PFOA (42%), after milk and dairy products (48%). The results of PFAS dietary intakes are in line with other national and international studies, including a recently published assessment conducted by EFSA. Dietary exposures of PFOA in our study were close to, but below, the provisional TWI set by EFSA (6 ng/(kg·week)). In turn, the dietary intake of PFOS was calculated to be well above the most updated provisional TWI (13 ng/(kg·week)). Pregnancy PBPK models of PFOA and PFOS were adapted and used to simulate mother and fetus internal exposure. Even with a small cohort population, models were able to validate analytical data from biomonitoring samples. However, assumptions for exposure scenarios and intake assessment were simplistic with high uncertainty, meaning this issue needs a clear improvement. Moreover, the performance of the PBPK model can be further improved by introducing temporal dynamics of exposure concentration and physiological parameters for long-term exposure.

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Table 1

Characteristics of the participants in the study: 50 pregnant women living in Reus (Catalonia, Spain).

Maternal age at delivery (years)		**Water consumption**	
<20	0%	<1 L	6%
20–29	15%	1–2 L	87%
30–39	71%	>2 L	7%
>40	14%	**Type of water consumed**	-
Twin pregnancy	7%	Tap water	6%
Number of children		Bottled water	77%
Primiparous	35%	Both	17%
1	48%	**Fish and seafood consumption in pre-pregnancy**	
2	15%	<2 servings/week	19%
>2	2%	2 to 4 servings/week	53%
Maternal pre-pregnancy BMI		>4 servings/week	28%
Underweight (< 19 kg/m^2)	6%	**Fish and seafood consumption during pregnancy**	
Normal (19–25 kg/m^2)	50%	<2 servings/week	27%
Overweight (>25-30 kg/m^2)	28%	2 to 4 servings/week	55%
Obese (>30 kg/m^2)	19%	>4 servings/week	18%
Maternal pregnancy (32 GW) BMI		**Milk consumption in pre-pregnancy**	
Underweight (<24 kg/m^2)	13%	<1 serving/day	25%
Normal (24–28 kg/m^2)	31%	1 to 2 servings/day	64%
Overweight (>28-32 kg/m^2)	35%	>2 servings/day	11%
Obese (>32 kg/m^2)	21%	**Milk consumption during pregnancy**	
Maternal education		<1 serving/day	24%
Primary	23%	1 to 2 servings/day	60%
Secondary	29%	>2 servings/day	16%
University	48%	**Eat Fast-food in pre-pregnancy**	
Social economic status (€/year)		Never	38%
Low level (<9000)	10%	≤ 1 serving/week	52%
Mid-Low level (9000-19,000)	41%	> 1 serving/week	10%
Mid-High level (>19,000-35,000)	20%	**Eat Fast-food during pregnancy**	
High level (>35,000)	29%	Never	66%
Maternal country of origin		≤ 1 serving/week	31%
Spain	69%	>1 serving/week	3%
Other	31%	**Eat organic products in pre-pregnancy**	
Marital Status		Never	49%
Living with the father	98%	Sometimes	29%
Not living with the father	2%	Frequently	18%
Smoking 1 year before pregnancy		Almost daily	4%
Non-smoker	71%	**Eat organic products during pregnancy**	
Active smoker	29%	Never	48%
1-5 cigarettes/day	20%	Sometimes	36%
6-10 cigarettes/day	4%	Frequently	10%
>10 cigarettes/day	5%	Almost daily	6%

[a] BMI: Body mass index; GW: gestational week

Table 2

PFOA and PFOS levels in maternal and cord blood recently published in the scientific literature.

				PFOA (ng/mL)				PFOS (ng/mL)			
				Maternal		Cord		Maternal		Cord	
	Country	Year	Sampling	n	Mean (P 95%)	n	Mean (P 95%)	n	Mean (P 95%)	n	Mean (P 95%)
Europe											
Present study	Spain	2016/17	T1 At del.	44 39	0.45 (P95: 1.08) 0.14 (P95: 0.93)	40	0.12 (0.45)	44 39	2.93 (P95: 5.48) 2.20 (P95: 4.23)	40	1.17 (P95: 2.03)
Caserta et al., 2018	Italy	2016	At del.	29	1.05 [0.45-1.9][a]	29	0.98 [0.30-2.50] [a]	29	1.54 [0.02-4.7][a]	29	1.75 [0.02-6.00][a]
Dereumeaux et al., 2016	France	2011	T3	277	1.49 (1.39, 1.59)[b]	-	-	277	3.07 (2.87, 3.27)[b]	-	-
Cariou et al., 2015	France	2010/13	At del.	100	1.22 [0.31-7.31][a]	94	0.92 [0.31-7.06][a]	100	3.67 [0.32-24.5][a]	94	1.28 [<LD-8.04][a]
Glynn et al., 2012	Sweden	2009/10	After del.	pool	[1.39-2.40] ng/g[c]	-	-	pool	[5.11-8.89] ng/g[c]	-	-
Matilla-Santander et al., 2017	Spain	2003/08	T1	1240	2.31 (P95: 5.23)	-	-	1240	5.77 (P95: 11.4)	-	-
Wilhelm et al. 2015	Germany	2000/02	T3	81	2.69 (P95: 5.09)	104	1.02 (P95: 2.09)	81	9.01 (P95: 15.4)	104	1.74 (P95: 3.10)
Meng et al. 2018	Denmark	1996/02	T1/T2	3535	4.6 (3.3-6.0)[d]	-	-	3535	30.1 (22.9-39.0) [d]	-	-
Impinen et al. 2018	Norway	1992/93	-	-	-	641	1.8 [0.1-11][a]	-	-	641	5.6 [0.5-21][a]
Asia											
Han et al., 2018	China	2010/13	At del.	369	39.3 (P95: 144)	369	31.8 (P95: 110)	369	4.25 (P95: 10.1)	369	1.33 (P95: 3.30)
Tian et al., 2018	China	2012	T2	981	19.6 (P95: 25.4)	-	-	981	10.8 (P95: 26.8)	-	-
Tsai et al., 2018	Japan	2003/12	T3	2123	2.06 [0.25-24.9][e]	-	-	2123	4.96 [0.81-30.3][e]	-	-
Kim et al., 2011	Korea	2008/09	T3.	44	1.46 (1.15-1.91) [d]	43	1.15 (0.95-1.86)[d]	44	2.93 (2.08-4.36) [d]	43	1.26 (0.81-1.82)[d]
America											
Morello-Frosch et al. 2016	USA	2010/11	T2/T3	77	0.47 (P95: 2.14)	64	<LD (P95: 1.68)	77	2.55 (P95 7.25)	64	2.27 (P95: 4.35)
Buck et al. 2018	USA	2003/06	T1 At del.	71	T1: 4.91(4.32, 5.59)[d] Del: 3.43(3.01-3.90)[d]	71	2.85 (2.51, 3.24)[d]	71	T1: 11.57(9.90, 13.53)[d] Del: 8.20(7.01-9.58)[d]	71	3.32 (2.84, 3.89)[d]
Woodruff et al. 2011	USA	2003/04	T1 to T3	76	2.39 (P95: 5.6)	-	-	-	12.3 (P95: 21.8)	-	-
Africa and Oceania											
Callan et al., 2016	Australia	2008/11	T3	98	1.00 [0.21-3.1]	-	-	98	2.32 [0.45-8.1]	-	-
Hanssen et al. 2010	South Africa	2005/06	At delivery	71	1.3 [0.17-8.5][e]	58	1.3 [<LD-10.5][e]	71	1.6 [<LD-15.9][e]	58	0.7 [<LD-10.8][e]

T1, T2, and T3: first, second, and third trimester of pregnancy, respectively. At del.: at delivery. NA: Not available.

[a] mean [Range]; [b] geometric mean (95% confidence interval); [c] [Range] in ng/g; [d] median (Interquartile range (IQR)); [e] median [Range].

Table 3

PFOA and PFOS plasma levels (in ng/mL*)* according to mother and pregnancy characteristics. Data given as mean (standard deviation).

	PFOA			PFOS		
	First trimester	**At delivery**	**Cord**	**First trimester**	**At delivery**	**Cord**
Mothers age						
<30 years old	0.32(0.26)	<0.10	<0.10	2.40(1.11)	1.63(0.90)	1.17(0.39)
30-35 years old	0.44(0.46)	0.12(0.31)	0.15(0.18)	2.81(1.26)	2.17(0.88)	1.16(0.48)
>35 years old	0.51(0.27)	0.18(0.30)	0.13(0.14)	3.19(1.41)	2.37(1.54)	1.16(0.46)
Body mass index (pre-pregnancy)						
<18.5 kg/m^2	0.84(0.27)^{a}	<0.10	0.16(0.19)	3.86(1.48)	1.86(1.00)	1.11(0.51)
18.5-25 kg/m^2	0.44(0.40)^{ab}	0.16(0.34)	0.15(0.18)	2.65(1.07)	2.02(0.76)	1.11(0.42)
>25 kg/m^2	0.38(0.29)^{b}	0.12(0.22)	0.10(0.11)	3.09(1.49)	2.48(1.58)	1.20(0.50)
Nationality						
Spanish	0.52(0.38)^{a}	0.15(0.31)	0.14(0.16)	3.08(1.28)	2.24(1.21)	1.21(0.46)
Other	0.26(0.20)^{b}	<0.10	0.07(0.06)	2.53(1.30)	2.03(1.19)	0.89(0.30)
Education						
Primary	0.32(0.32)	0.10(0.14)	<0.10	3.26(1.60)	2.89(2.03)	1.37(0.62)
Secondary	0.41(0.31)	0.17(0.32)	0.10(0.12)	2.48(1.33)	1.81(0.66)	0.97(0.43)
University	0.55(0.42)	0.13(0.32)	0.19(0.19)	3.06(1.02)	2.17(0.80)	1.22(0.33)
Annual income						
<9.000-19.000€	0.24(0.20)^{a}	0.10(0.15)	<0.10	3.53(1.56)^{a}	3.24(2.05)^{a}	1.40(0.59)
19.001-35.000€	0.43(0.26)^{b}	0.19(0.39)	0.16(0.20)	2.39(1.07)^{a}	1.76(0.81)^{b}	1.03(0.42)
>35.000€	0.66(0.50)^{b}	0.12(0.24)	0.14(0.12)	3.27(1.17)^{ab}	2.21(0.53)^{ab}	1.20(0.43)
Parity						
Primiparous	0.61(0.42)^{a}	0.08(0.12)	0.10(0.12)	3.16(1.22)	2.27(0.92)	1.38(0.52)^{a}
1	0.35(0.23)^{b}	0.18(0.37)	0.17(0.19)	2.83(1.38)	2.36(1.60)	1.08(0.46)^{b}
≥2	0.26(0.32)^{b}	0.18(0.33)	0.08(0.07)	2.38(1.13)	1.88(0.84)	0.93(0.13)^{b}
Breastfeeding last child						
Yes	0.34(0.27)	0.23(0.43)	0.13(0.19)	2.89(1.40)	2.60(1.72)	0.97(0.38)
No	0.32(0.27)	0.14(0.27)	0.19(0.16)	2.48(1.24)	1.87(0.88)	1.14(0.44)
Years form last child						
No previous child	0.61(0.42)	0.08(0.12)	0.10(0.12)	3.16(1.22)	2.27(0.92)	1.38(0.52)
≤ 3 years	0.37(0.28)	0.23(0.42)	0.17(0.21)	2.64(1.23)	2.14(0.86)	1.10(0.43)
>3 to 10 years	0.25(0.12)	0.16(0.31)	0.13(0.13)	2.49(1.12)	1.66(0.86)	0.95(0.40)
>10 years	0.51(0.65)	<0.10	0.13(0.16)	2.55(0.24)	2.22(0.39)	1.00(0.13)
Smoking						
Never	0.41(0.29)	0.18(0.33)	0.14(0.17)	3.04(1.38)	2.44(1.30)	1.15(0.47)
Not during pregnancy	0.57(0.52)	<0.10	0.09(0.11)	2.74(1.06)	1.68(0.79)	1.22(0.50)
Yes	0.40(0.50)	<0.10	0.13(0.15)	2.17(1.01)	1.68(0.63)	1.00(0.14)

Different superscripts indicate significant differences at 0.05 level.

Table 4

PFOA and PFOS plasma levels (in ng/mL) according to the mother's food frequency. Data given as mean (standard deviation).

	PFOA			PFOS		
	first trimester	**At delivery**	**Cord**	**first trimester**	**At delivery**	**Cord**
Fish and seafood consumption						
<2 times/week	0.38(0.21)	<0.10	0.15(0.15)	3.05(1.16)	2.04(1.11)	1.17(0.53)
2 to 4 times/week	0.41(0.32)	0.21 (0.37)	0.13(0.16)	2.76(1.17)	2.10(0.80)	1.14(0.44)
>4 times/week	0.54(0.51)	<0.10	0.08(0.09)	3.20(1.73)	2.56(1.86)	1.18(0.43)
Meat consumption						
<7 times/week	0.34(0.30)	0.08(0.11)	0.09(0.09)	3.45(1.49)	2.65(1.72)	1.26(0.53)
7 to 14 times/week	0.52(0.40)	0.20(0.37)	0.14(0.18)	2.84(1.14)	2.04(0.79)	1.11(0.39)
>14 times/week	0.35(0.23)	<0.10	0.12(0.11)	2.01(0.98)	1.79(0.72)	1.16(0.54)
Eggs consumption						
<2 times/week	0.34(0.29)[a]	0.24(0.43)	0.14(0.21)	2.85(1.35)	2.40(1.07)	1.16(0.61)
2 times/week	0.38(0.26)[a]	0.15(0.28)	0.12(0.12)	2.89(1.46)	2.23(1.51)	1.09(0.30)
>2 times/week	0.62(0.48)[b]	<0.10	0.13(0.15)	3.05(1.14)	2.05(0.82)	1.23(0.48)
Milk consumption						
<1 time a day	0.48(0.31)	0.26(0.46)	0.21(0.24)	3.47(1.12)[a]	2.36(0.80)	1.30(0.41)[a]
1 time a day	0.37(0.25)	0.09(0.18)	0.11(0.11)	2.57(1.16)[b]	2.07(1.34)	1.04(0.38)[b]
>1 time a day	0.73(0.78)	0.13(0.19)	0.05(0.01)	3.81(1.87)[a]	2.58(1.21)	1.46(0.67)[a]
Cheese consumption						
<3 times/week	0.30(0.29)	0.17(0.29)	0.13(0.13)	2.91(1.43)	2.13(0.99)	1.21(0.51)
3 to 7 times/week	0.48(0.42)	0.09(0.18)	0.11(0.12)	2.85(1.39)	2.22(1.35)	1.13(0.46)
>7 times/week	0.50(0.23)	0.26(0.52)	0.16(0.26)	3.17(0.98)	2.28(1.02)	1.16(0.36)
Fast food consumption						
0 times a week	0.43(0.27)	0.26(0.46)	0.14(0.21)	2.60(1.11)	1.99(0.95)	1.12(0.55)
1 time/week	0.51(0.43)	<0.10	0.11(0.12)	3.23(1.26)	2.54(1.42)	1.17(0.34)
>1 time/week	0.40(0.32)	0.16(0.30)	0.19(0.16)	2.72(1.33)	1.88(0.60)	1.05(0.41)
Water consumption						
≤1 litter /day	0.47(0.46)	0.12(0.22)	0.10(0.10)	2.77(1.16)	2.12(0.80)	1.21(0.52)
>1 litter/day	0.42(0.27)	0.15(0.33)	0.14(0.18)	3.05(1.43)	2.28(1.47)	1.11(0.37)

Different superscripts indicate significant differences at 0.05 level.

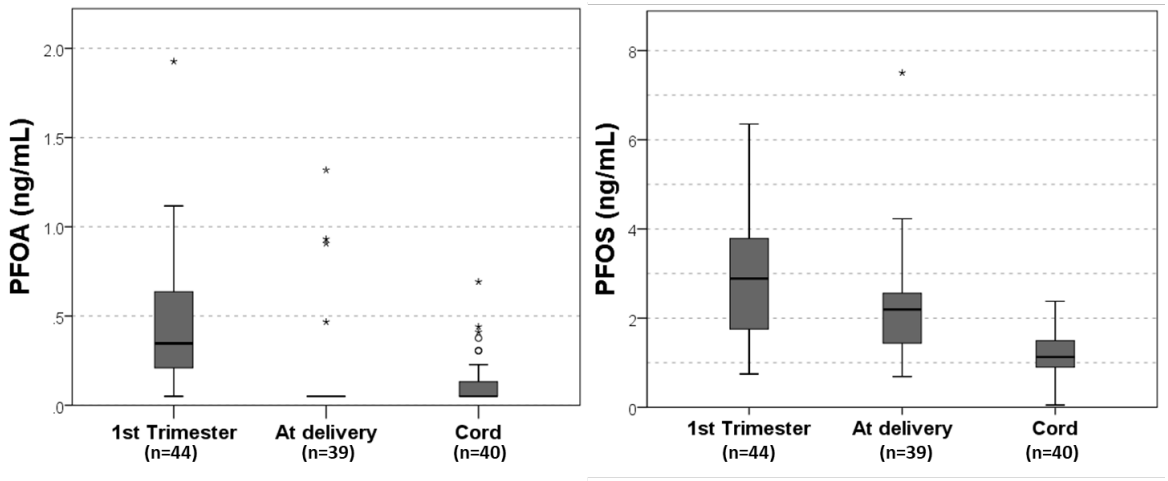

Fig. 1. PFOA and PFOS levels in plasma of pregnant women during the first trimester, at delivery and in cord blood.

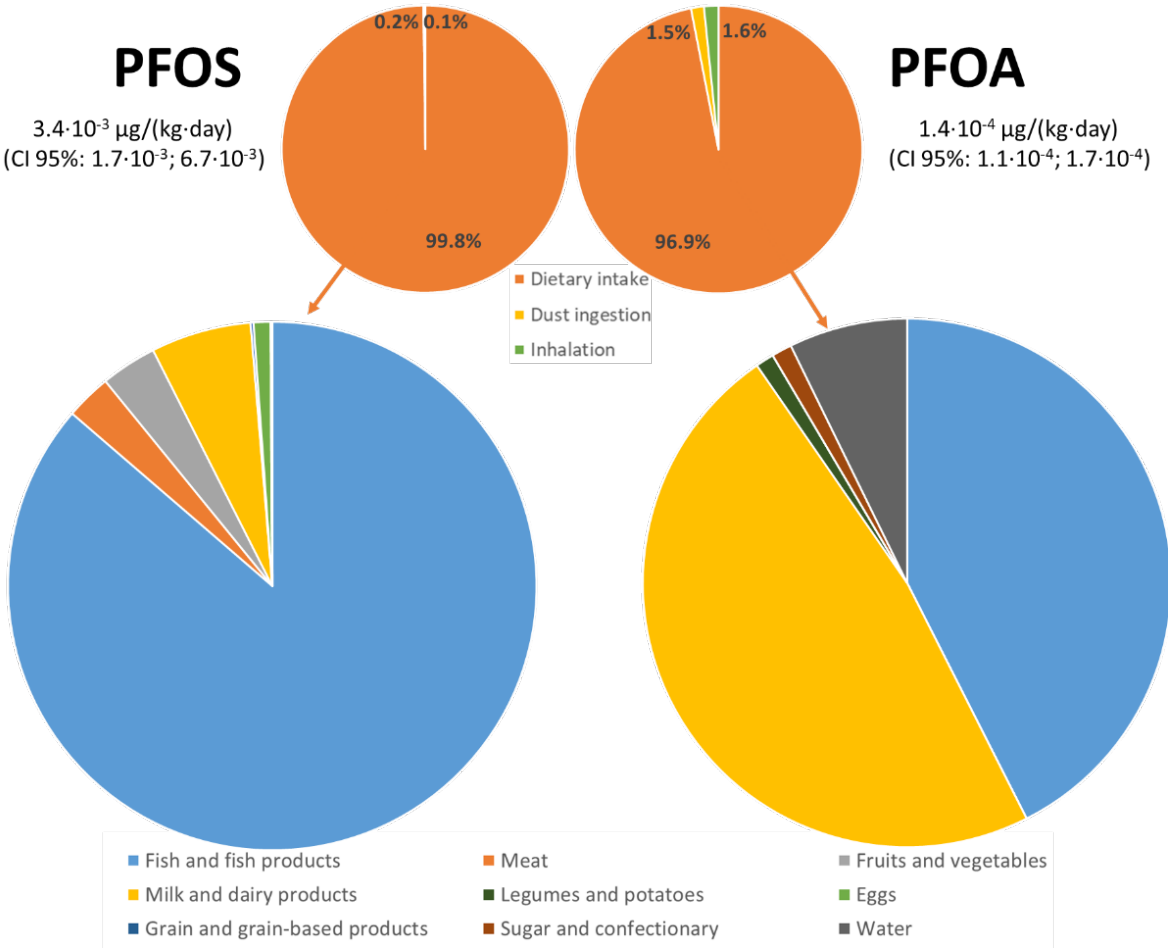

Fig. 2. Total PFOS and PFOA exposure: Main pathways (dietary intake, dust ingestion, and air inhalation) and contribution of each food category to the dietary intake.

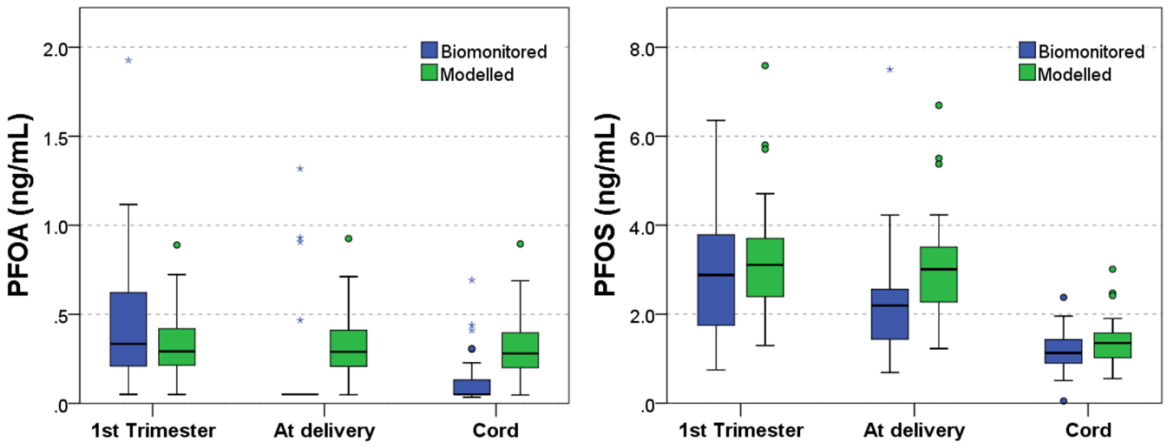

Fig. 3. Modelled and biomonitored levels of PFOA and PFOS in plasma of pregnant women at the first trimester, at delivery and in cord blood.