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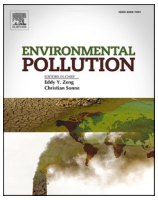

Postnatal exposure to organic pollutants in maternal milk in north-western Spain☆

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ABSTRACT

Evaluation of postnatal exposure to organic pollutants is especially important for suckling infants during breastfeeding, a crucial perinatal growth period when organs and hormonal systems develop. We determined levels of 60 pollutants, including organochlorine pesticides (OCPs), organophosphorus pesticides (OPPs), pyrethroids (PYRs), polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs), and polybrominated diphenyl ethers (PBDEs), in 81 breast milk samples from breastfeeding mothers from Santiago de Compostela (north-western Spain). For most detected organic pollutants, levels were correlated with the season of milk sampling, maternal age at delivery, and place of residence. Dietary consumption habits (eggs, molluscs, and vegetable oils) were also correlated with OCP, OPP, PCB, PBDE and PYR levels. We also assessed the risk to infant health of exposure to organic pollutants in breast milk. PAHs, OCPs, OPPs, and PYRs accounted for almost 95% of the targeted organic pollutants in the samples analysed.

1. Introduction

Human exposure to organic pollutants is a topic of growing concern, as even low concentrations of these substances can cause reproductive disorders, immune system defects, altered neurological behaviour, endocrine disturbances, genotoxic effects, and increased risk of cancer and congenital defects (World Health Organization (WHO), 2019). The presence of organic pollutants in breast milk may result in higher levels of exposure over shorter periods of time (Fernández-Cruz et al., 2017a). Human milk is considered one of the best matrices for biomonitoring of lipophilic pollutant exposure in both mothers and infants: it is abundant, can be sampled non-invasively, and has a high lipid content (Jensen and Slorach, 1991).

In the past, the most studied pollutants were the persistent organic pollutants (POPs) listed in the Stockholm Convention (SC) since 2001 (UNEP, 2001). Spain has developed and putted into effect a National Implementation Plan since 2008 to monitor the current pollution status and the effectiveness of SC's measurements for POPs elimination at a national scale (Muñoz-Arnanz et al., 2016; Roscales et al., 2018; Muñoz-Arnanz et al., 2018). The commonly encountered POPs were OCPs and PCBs, owing to their continued use (Table S1). Although OCPs are included in the annexes A (elimination) and B (restriction) of SC, DDT is still used as vector control in battle against malaria (Van den Berg et al., 2017) while lindane is used for control of ectoparasites on cattle and was earlier used against scabies and head lice earlier for humans (e.g. Africa, Mexico, Bangladesh, India and Iran) (Bouwman et al., 2006; Chávez-Almazán et al., 2016; Haque et al., 2017; Bawa et al., 2018; Shahmoradi et al., 2019). The highest concentration levels detected in Turkey (Eroğlu et al., 2018), China (Lu et al., 2015; Xu et al., 2015) or Russia (Mamontova et al., 2017) could be related with their historical

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use. The highest concentrations of PCBs (listed in the annexes A and C of SC) are often found in humans exposed during occupation, living close to vicinity of heavy industries, or in populations with high consume of marine mammals and marine fish. Consequently, the highest PCB levels in human milk have been reported in Turkey (Eroğlu et al., 2018) followed by China (Man et al., 2017) and in central European areas with heavy industry, including Russia, the Czech Republic, and Slovakia due to their unintentional production (Brajenović et al., 2018). The lowest PCB levels have been reported in Ghana (Asamoah et al., 2018) and Tanzania (Müller et al., 2017, 2019). Most of the aforementioned studies have demonstrated a marked decrease in recent years detecting lower concentrations than in the past (Asamoah et al., 2018; Bawa et al., 2018; Brajenović et al., 2018; Gómara et al., 2011; Mamontova et al., 2017; Schuhmacher et al., 2013; Zietz et al., 2008). PBDEs were included in the annexe A of SC since august 2009 and they have been also extensively studied in recent years. The highest concentrations were detected in the USA (Guo et al., 2016; Hartle et al., 2018; Marchitti et al., 2017) and in parts of China (Li et al., 2017; Chen et al., 2020), without regulation action on deca-PBDE in this country. The lowest concentrations have been reported Europe (Dimitriadou et al., 2016; Harrad and Abdallah, 2015; Iszatt et al., 2019), Asia (Chen et al., 2018; Kim et al., 2018; Li et al., 2017; Yang et al., 2016; Zhang et al., 2017), and Australia (Chen et al., 2015) (Table S1).

Far fewer studies have evaluated concentrations of PAHs in biological samples, and even fewer PYRs and OPPs. They are organic pollutants not included in the SC for now, although chlorpyrifos has been already proposed for listing. PAHs have been detected in breast milk in Africa (Loutfy et al., 2017; Asamoah et al., 2019; Hegazy et al., 2020), Asia (Wang et al., 2018), USA (Acharya et al., 2019; Torres-Moreno et al., 2022), and Europe (Pulkrabova et al., 2016; Santonicola et al., 2017; Oliveira et al., 2020). To the best of our knowledge, PYR and OPP concentrations have been only reported in South Africa (Bouwman and Kylin, 2009; Sereda et al., 2009), Iran (Brahmand et al., 2019), India (Sharma et al., 2014; Anand et al., 2021), Brazil, Colombia and Spain (Corcellas et al., 2012; Rovira et al., 2022), and the Netherlands (Čechová et al., 2017b). The highest PYR levels reported in human breast milk have been detected in Africa, owing to the extensive use of PYRs both for malaria control and agricultural activities (Bouwman et al., 2006; Bouwman and Kylin, 2009; Feo et al., 2012; Sereda et al., 2009) (Table S1).

Almost of the studies reported in Spain have been focused on the determination of POPs in breast milk (Garí et al., 2019; Gómara et al., 2011; Grimalt et al., 2022; Hernández et al., 2020; Luzardo et al., 2013; Rovira et al., 2022; Schuhmacher et al., 2013). Therefore, the objective of this study was to evaluate postnatal exposure to 60 organic pollutants, including OCPs, OPPs, PAHs, PBDEs, PCBs, and PYRs, in human breast milk samples. Greater monitoring of organic pollutants is warranted given the risks they pose to human health, and in particular their potential effects in children. Its outputs are meaningful not only for the scientific knowledge, but also for the health and environmental authorities.

2. Materials and methods

2.1. Sample collection and socio-demographic characteristics of mothers

During the period 2016–2018 at the University Clinical Hospital of Santiago de Compostela (CHUS) a total of 81 human breast milk samples ($\geq$50 mL) were collected from mothers in the Spanish region of Galicia (Fig. S1).

Fully mature breast milk samples were manually collected (50 mL) in uncontaminated plastic bottles within 8–24 weeks to reduce the likelihood of negatively impacting the already low breastfeeding rates. Collected samples were refrigerated during transfer to the laboratory or hospital and, once received, were frozen at −20 °C for subsequent analysis.

Participating mothers provided written informed consent and completed a questionnaire on their diet, lifestyle, and personal habits. Details about the donors are summarized in Table S2. The present study was approved by the Ethical Committee of Galicia (2014/410).

2.2. Sample preparation and organic pollutant determination

A list of the target organic pollutants and the labelled internal and surrogate standards including abbreviations, Chemical Abstracts Service (CAS) numbers, and supplier is provided in Tables S3 and S4, respectively. Details of analysis are described in supporting information (Appendix S2). In brief, milk samples were extracted using pressurized liquid extraction (PLE) after addition of surrogate standards. Clean-up was performed by dual layer EZ-POP SPE cartridges. Quantification of targeted compounds was performed by GC-QqQ-MS (Fernández-Cruz et al., 2017b; González-Gómez et al., 2018; Fernández-Cruz et al., 2022) (Table S5). Quality control has also been described in supporting information (Appendix S2).

2.3. Human risk assessment

The long-term health risk due to organic pollutant exposure in infants was estimated based on the estimated daily intake (EDI) exposure (equation S1) and the hazard quotient (HQ) (equation S2). To evaluate the acute/short-term risk, the International Estimation of Acute Intake (IESTI) (equation S3) and the acute reference dose (ARfD) were used to determine the acute consumer health risk (aHI) (equation S4). More details are described in supporting information (Appendix S3 and Table S6).

2.4. Statistical analysis

For statistical calculations, values > LOD were imputed as the LOD divided by the square root of 2. Preliminary descriptive analysis revealed skewing of some data, which were log-transformed to improve normality of residuals.

P values < 0.05 were considered significant for all tests. Multi-way ANOVA was used to assess associations between the log value of organic pollutants in breast milk and epidemiologic factors (Table S2). The quantitative variables age (<35 and >35 years), weight gain at delivery (<12.29 and >12.29 kg) and sample point (<8 and >8 weeks) were grouped in two categories to ensure sufficient degrees of freedom for data analysis.

Statgraphics Centurion 16.1 (Statpoint Technologies INC., Warrenton, VA, USA) and R software version 3.6.1 (R Core Team 2019) with R Commander (Fox, 2005) were used for statistical data analysis and regression procedures.

3. Results and discussion

3.1. Levels of targeted pollutants in human breast milk

Concentrations of the main pollutants (mean, maximum and minimum) in the studied breast milk are summarized in Table 1. The human breast milk fat content ranges from 0.96% to 6.9%.

3.1.1. PAHs

Total PAH levels (ΣPAHs) ranged from 0.88 to 1064 ng/g fat (equivalent to 0.033–37 ng/g milk), with a mean concentration of 54 ng/g fat (equivalent to 1.9 ng/g milk). ΣPAHs was in the range reported in previous studies. Pulkrabova et al. (2016) reported the lowest PAH breast milk concentrations in their study conducted in the Czech Republic (interquartile Range (IQR), 0.71–378 ng/g fat), with mean values of 32 ng/g fat in non-smoker mothers. Higher mean concentrations were reported in Italy (115 ng/g fat) (Santonicola et al. (2017) and Portugal (245 ng/g fat) (Oliveira et al. (2020). Torres-Moreno et al. (2022)

Table 1
Main contributing congeners in target OCPs, PYRs, PAHs, OPPs, PCBs, and PBDEs in human milk samples.

OPs	Mean[a] ± SD (detection rate)	Range[a] (median[a])	Main contributing congeners (%)
PYRs	18 ± 36 n = 60 (74%)	4.9–183 (12)	∑Permethrin (36%) Deltamethrin (33%) Cyfluthrin (23%) Cypermethrin (8.0%)
PAHs	54 ± 179 n = 63 (78%)	0.88–1064 (15)	Pyrene (48%) Fluoranthene (31%) BbF (8.8%) BaA (7.6%) BaP (1.5%) Others (3.1%)
OPPs	21 ± 42 n = 64 (77%)	0.56–187 (6.3)	Diazinon (57%) Paranthion (28%) Chlorpyrifos (14%) Others (1.0%)
OCPs	37 ± 24 n = 68 (82%)	0.74–268 (2.85)	HCB (40%) β-HCH (33%) *t*-Chlordane (12%) c-Chlordane (4.4%) ∑DDT (3.0%) Dieldrin (2.6%) Endrin (1.8%) Aldrin (1.2%) α-HCH (1.2%) Heptachlor (0.80%)
NDLPCBs	15 ± 40 n = 69 (83%)	0.59–276 (2.89)	PCB 153 (22%) PCB 138 (19%) PCB 180 (18%) PCB 11 (17%) PCB 28 (16%) PCB 52 (7.5%) Others (0.50%)
DLPCBs	0.70 ± 2.1 n = 64 (77%)	0.44–19 (0.52)	PCB 114 (31%) PCB 157 (20%) PCB 167 (8.0%) PCB 126 (7.0%) PCB 156 (5.5%) PCB 189 (5.3) PCB 105 (5.1) PCB 123 (5.2) PCB 77 (3.8) PCB 81 (3.3) PCB 118 (3.3) PCB 169 (2.5)
PBDEs	2.3 ± 4.5 n = 54 (65%)	0.29–27 (1.5)	PBDE 100 (21%) PBDE 154 (19%) PBDE 99 (17%) PBDE 153 (17%) PBDE 47 (16%) PBDE 28 (11%)

[a] ng/g fat; PYRs (pyrethroids); PAHs (polycyclic aromatic hydrocarbons); OPPs (organophosphorus pesticides); OCPs (organochlorine pesticides); NDLPCBs (non-dioxin like polychlorinated biphenyls); DLPCBs (dioxin like polychlorinated biphenyls); PBDEs (polybrominated diphenyl ethers).

reported mean concentrations of 187 ng/g fat in 3 Colombian cities with heavy industrial activity and urban traffic.

Of the 10 PAHs studied, pyrene was the most abundant (median, 26 ng/g fat; 2–80% of ΣPAHs), followed by fluoranthene (median, 17 ng/g fat; 1.5–77% of ΣPAHs), benzo(b)fluoranthene (median, 4.7 ng/g fat; 1.5–88% of ΣPAHs) and benzo(a)anthracene (median, 4.1 ng/g fat; 1.4–50% of ΣPAHs). Lower concentrations of other PAHs were detected, including indeno [1,2,3-c,d]pyrene (median, 0.39 ng/g fat; 0.50–64% of ΣPAHs), benzo(a)pyrene (median, 0.81 ng/g fat; 0.0–51% of ΣPAHs), and chrysene (median, 0.34 ng/g fat; 0.25–47% of ΣPAHs). Benzo(k) fluoranthene, dibenzo [a,h]anthracene, and benzo [g,h,i]perylene were detected in less than 35% of samples. Almost all previous studies have assessed concentrations of low molecular weight PAHs such as naphthalene, acenaphthylene, acenaphthene, fluorene, phenanthrene, and anthracene, and found that the most abundant PAHs were acenaphthene (Torres-Moreno et al., 2022), naphthalene (Oliveira et al., 2020), phenanthrene (Çok et al., 2012; Luzardo et al., 2013; Wang et al., 2018; Acharya et al., 2019; Oliveira et al., 2020; Torres-Moreno et al., 2022), pyrene (Luzardo et al., 2013; Acharya et al., 2019), and fluoranthene (Luzardo et al., 2013; Acharya et al., 2019; Torres-Moreno et al., 2022) (Table S1). In the aforementioned studies, PAHs with 2–3 rings (LMW) accounted for approximately 80% of total PAHs. In the present study only PAHs with 4–6 rings PAHs were included as these are only included as indicators by the EFSA. The EFSA established ΣPAH2 (Chr and B*a*P), ΣPAH4 (B*a*A, Chr, B*b*F and B*a*P), and ΣPAH8 (B*a*A, Chr, B*b*F, B*k*F, B*a*P, D*ah*A, Ind123-*cd*P and B*ghi*P) as indicators of occurrence and effect of the carcinogenic PAHs in food (EFSA- European Food Safety Authority, 2008). We detected median ΣPAH2, ΣPAH4, and ΣPAH8 concentrations of 1.2, 9.9, and 11 ng/g fat, corresponding to 0.041, 0.35, and 0.39 ng/g milk, respectively. The median ΣPAH4 concentration in breast milk was below the permissible limit of 1.0 ng/g established by European Regulation EC/835/2011 (EU European Union Commission, 2011). Nonetheless, this defined limit was exceeded in 11 samples. Similar concentrations were reported by Oliveira et al. (2020) in Portugal, although in that study the permissible limit was exceeded in only 1 sample. ΣPAH4 levels reported by Santonicola et al. (2017) in Italy were higher than those described here. Those authors found that the permissible limit was exceeded in 86% of samples (median concentration, 2.8 ng/g milk).

3.1.2. PCBs

The mean concentration of NDLPCBs was 15 ng/g fat, with a range of 0.59–276 ng/g fat (equivalent to 0.050–9.7 ng/g milk). Marker PCBs (PCB 28, 52, 101, 138, 153 and 180) were detected in 100% of human milk samples. The mean contribution of marker PCBs to total NDLPCBs was 76% (mean, 8.6 ng/g fat; range, 0.045–250 ng/g fat). PCB 11 accounted for 20% of total NDLPCBs (mean, 1.8 ng/g fat; range, 0.0012–36 ng/g fat), and PCB 209 only 5.0% (mean, 0.25 ng/g fat; range, 0.076–0.72 ng/g fat). Similar mean NDLPCB concentrations were reported by Gómara et al. (2011) (mean, 14 ng/g fat) in Spain and by Agus et al. (2022) (mean, 8.2 ng/g fat) in Turkey, and higher mean concentrations by Čechová et al. (2017a, 2017b) (Slovakia, 166 ng/g fat; the Netherlands, 43 ng/g fat; Norway, 74 ng/g fat), Guo et al. (2021) (mean, 101 ng/g fat; IQR, 62–145 ng/g fat) in China, and Fromme et al. (2022) in Germany (mean, 59 ng/g fat) (Table S1). Table 1 depicts the main NDLPCBs detected: PCB 153 > PCB 138 > PCB 180 > PCB 11 > PCB 28 > PCB 52. A similar trend was reported by Gómara et al. (2011), Schuhmacher et al. (2013), and Grimalt et al. (2022) in human milk samples in Spain, and by other authors in other countries (Chen et al., 2015; Klinčić et al., 2016; Čechová et al., 2017a, Matovu et al., 2021; Gyllenhammar et al., 2021; Fromme et al., 2022). PCB 138, 153 and 180 were also the PCB congeners found in the highest median concentrations (>180 ng/g fat) in adipose tissue samples of an adult cohort from Granada (Southern Spain). Moreover, they are the NDLPCBs with longest half-lives estimated in 9.2, 7.8 and 8.9 years, respectively by Esser et al. (2021) in plasma samples after occupational exposure in Germany.

Total DLPCB concentration ranged from 11 to 18,761 pg/g fat (mean, 700 pg/g fat) with a corresponding ΣWHO-TEQ$_{2005}$ of 0.0095–65 pg/g fat (mean, 5.7 pg TEQ/g fat). These levels are slightly higher than those reported by Schuhmacher et al. (2013) in Spain (mean, 2.2 pg TEQ/g fat), Lu et al. (2015) in China (mean, 2.2 pg TEQ/g fat), Hernández et al. (2020) in Spain (mean, 436 pg/g fat; IQR, 0.40–6108 pg/g fat), Matovu et al. (2021) in Uganda (median, 129 pg/g fat; IQR, 13–1297 pg/g fat), Hu et al. (2021) in China (mean, 3.1 pg TEQ/g fat), and Fromme et al. (2022) in Germany (mean, 2.7 pg TEQ/g fat). In the present study, *mono-ortho*-PCBs (PCB 105, 114, 118, 123, 156, 157, 167 and 189; mean, 578 ng/g fat) and *non-ortho*-PCBs (PCB 77, 81, 126 and 189; mean, 122 n/g fat) accounted for around 70% and 30% of DLPCBs and around 18% and 8.8% of total PCBs, respectively. PCB 114 (31%), 157 (20%) and 167 (8.0%) were the most abundant

mono-ortho-PCBs, whereas similar contributions were observed for *non-ortho*-(PCB 126 (7.0%), 189 (5.3%), 77 (3.8%) and 81 (3.3%)). Minor contributing *mono-ortho*-PCBs were PCB 156 (5.5%), PCB 123 (5.2%), PCB 118 (3.3%) and PCB 169 (2.5%).

3.1.3. OCPs

In the present study, we detected a total mean OCP concentration of 32 ng/g fat (range, 0.74–268 ng/g fat [equivalent to 0.054–9.5 ng/g milk]). Similar OCP levels were reported in Croatia by Klinčić et al. (2016) (median, 31 ng/g fat) and Jovanović et al. (2019) (mean, 37 ng/g fat); higher concentrations by Iszatt et al. (2019) in Norway (mean, 88 ng/g fat) and Antignac et al. (2016) in France (median, 106 ng/g fat); and much higher concentrations by Müller et al. (2019) in Tanzania (median, 141 ng/g fat), Bawa et al. (2018) in India (median, 528 ng/g fat), Chávez Almazán et al. (2018) in México (median, 834 ng/g fat), and Shahmoradi et al. (2019) in Iran (median, 5500 ng/g fat).

HCB (35%; mean, 13 ng/g fat; IQR, 0.71–266 ng/g fat), β-HCH (29%; mean, 11 ng/g fat; IQR, 0.81–88 ng/g fat), cis and trans-Chlord (15%; mean, 3.9 ng/g fat; IQR, 0.736–96 ng/g fat), and ΣDDTs (2.6%%; mean, 0.95 ng/g fat; IQR, 0.35–45 ng/g fat) were the predominant contributors. Although β-HCH is no longer intentionally produced following the regulation established by the Stockholm Convention (UNEP, 2001), this compound is the most persistent and bioaccumulative of all HCHs. Moreover, β-HCH is the main metabolite of Lindane (γ-HCH), which was still used in some countries up to March 2015 (Bawa et al., 2018). β-HCH and HCB have also been detected in France (Antignac et al., 2016), Greece (Dimitriadou et al., 2016), Croatia (Klinčić et al., 2016), India (Bawa et al., 2018), and Iran (Shahmoradi et al., 2019). Nevertheless, DDT metabolites (pp', op'-DDE and pp', op'-DDD) have been reported as the main contributors to OCPs (>50% ΣOCPs) in studies conducted in Europe (Eroğlu et al., 2018; Iszatt et al., 2019; Jovanović et al., 2019; Lenters et al., 2019; Gyllenhammar et al., 2021; Rovira et al., 2022); Bawa et al., 2018; Haque et al., 2017; Kao et al., 2019), Africa (Müller et al., 2019), America (Chávez-Almazán et al., 2018; 2016; Polanco Rodríguez et al., 2017), and Oceania (Du et al., 2017).

3.1.4. PYRs and OPPs

The targeted PYRs were detected in 85% of milk samples (permethrin, 58%; deltamethrin, 52%; cyfluthrin, 44%; cypermethrin, 32%) with a mean concentration range of 4.9–184 ng/g fat (equivalent to 0.27–6.49 ng/g milk), with major contributions by cypermethrin (35%; mean, 7.6 ng/g fat; IQR, 0.82–83 ng/g fat), permethrin (33%; mean, 7.5 ng/g fat; IQR, 0.06–75 ng/g fat), deltamethrin (22%; mean, 4.8 ng/g fat; IQR, 0.051–142 ng/g fat), and cyfluthrin (10%; mean, 2.3 ng/g fat; IQR, 0.023–46 ng/g fat).

Mean OPP levels ranged from 0.56 to 187 ng/g fat (mean, 21 ng/g fat), and OPPs were detected in 88% of milk samples (diazinon, 75%; parathion, 72%; fenthion, 46%; chlorpyr, 56%). Diazinon was the main contributor (57%; mean, 12 ng/g fat; IQR, 0.0020–5.8 ng/g fat), followed by parathion (29%; mean, 5.9 ng/g fat; IQR, 0.020–3.8 ng/g fat), chlorpyr (13%; mean, 2.8 ng/g fat; IQR, 0.0020–3.4 ng/g fat), and fenthion (1.0%; mean, 0.16 ng/g fat; IQR, 0.0020–0.0754 ng/g fat).

To the best of our knowledge, few studies have evaluated levels of pyrethroids and OPPs in milk samples, and results vary between countries. Permethrin (2579 ng/g fat) was the pyrethroid most frequently detected in breast milk samples from South Africa (Bouwman et al., 2006), followed by cyfluthrin (13,876 ng/g fat), cypermethrin (833 ng/g fat), and deltamethrin (2518 ng/g fat). Corcellas et al. (2012) detected PYRs in breast milk samples collected in Barcelona (Spain), Brazil, and Colombia, and reported concentrations ranging from 1.5 to 24 ng/g fat. Bifenthrin was the most abundant PYR in Brazilian samples, λ-cyhalothrin in Colombian samples, and permethrin in Spanish samples. Bifenthrin (96% of samples; IQR, not detected – 420 ng/g w/w) was also the most ubiquitously detected in India, followed by λ-cyhalothrin (IQR, not detected – 45 ng/g w/w) and permethrin (IQR, not detected – 54 ng/g w/w) (Anand et al., 2021). Pedersen et al. (2021) detected cypermethrin (25 ± 25 nM) and permethrin (20 ± 25 nM) in breast milk samples from American women in California.

As regards OPPs, Čechová et al. (2017a, 2017b) found chlorpyrifos in human breast milk samples from the Netherlands, and reported mean concentrations of 0.63 ng/g fat, as compared with 2.8 ng/g fat detected in the present study. Brahmand et al. (2019) detected chlorpyrifos in 71% of milk samples in Iran (mean concentration, 2.1 ± 1.4 μg/mL). Rovira et al. (2022) reported chlorpyrifos in 39% of milk samples from Catalonia (Spain) (mean concentration, 0.9 ± 1.7 ng/g fat).

3.1.5. PBDEs

PBDEs were the organic pollutants for which the lowest concentrations were detected. As shown in Table 2, the mean PBDE concentrations ranged from 0.29 to 27 ng/g fat (equivalent to 0.011–0.97 ng/g milk), with a mean concentration of 2.3 ng/g fat (median, 1.8 n/g fat). PBDE 100 (mean, 0.47 ng/g fat; IQR, 0.074–8.1 ng/g fat), 154 (mean, 0.42 ng/g fat; IQR, 0.074–5.0 ng/g fat), 99 (mean, 0.39 ng/g fat; IQR, 0.074–5.7 ng/g fat), 153 (mean, 0.36 ng/g fat; IQR, 0.14–8.6 ng/g fat), and 47 (mean, 0.35 ng/g fat; IQR, 0.14–6.7 ng/g fat) were the predominant congeners. PBDE levels were in the same range as reported by Schuhmacher et al. (2013) in Catalonia (mean PBDE levels, 1.3 ng/g fat), Dimitriadou et al. (2016) in Greece (1.5 ng/g fat), Matovu et al. (2019) in South Africa (median, 1.2 ng/g fat), and Zhao et al. (2021) in China (3.3 ng/g fat). Nevertheless, we observed some differences in our PBDE profile with respect to those reported in the aforementioned studies. PBDE 209 was the predominant congener in human milk samples collected in Madrid (Gómara et al., 2011), southern Taiwan (Chen et al., 2018), and Uganda (Matovu et al., 2019). Tetra/penta and hexa/hepta PBDE commercial mixtures were listed in the Stockholm Convention in 2009, while deca PBDE, used as a replacement for Penta/Octa PBDEs in several applications, was listed much later, in 2019. Shin et al. (2016) also collected house dust during the prenatal period and found that PBDE 47 and 99 were the predominant congeners in human breast milk and umbilical cord serum, but PBDE 209 in house dust. They found considerable associations between PBDE 47 and 99 in umbilical cord serum and PBDE 209 levels in house dust and they argued that PBDE 209 has a very short half-life and is rapidly transformed into less brominated congeners. PBDE 47 has been reported as the predominant PBDE, owing to its relatively long half-life (1.8 years) in humans (Gómara et al., 2011; Malarvannan et al., 2013; Dimitriadou et al., 2016; Guo et al., 2016; Shin et al., 2016). In the present study, PBDE 100 and PBDE 154 contributed most to mean ΣPBDEs, as also reported in other studies of human milk samples from Oceania (Chen et al., 2015) and Africa (Müller et al., 2019). Costa et al. (2016) also evaluated the associations between PBDE levels in serum and dietary habits, and found that PBDE 47 and 99 levels were positively correlated with shellfish and cephalopod consumption, PBDE 153 levels with a higher frequency of house cleaning, and PBDE 209 with foam mattress use. Carpets and plastic electronics materials like televisions have been also detected as sources of PBDE 209 (Young et al., 2021).

3.2. Health risk to exposed infants

Breast milk consumption could represent one of the main routes of suckling infant exposure to organic pollutants. Several approaches have been used in recent years to assess health risk to infants exposed to organic pollutants in their mother's breast milk as previously commented in section 2.3. TDI used values are provided in Table S7.

3.2.1. PAHs

In 2015, the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2015) proposed a BaP ADI >10 ng/kg$_{bw}$/day as the threshold for health risk. We found that median daily BaP intake of breastfeeding Spanish children was 6.2 ng/kg$_{bw}$/day (Table S7 and Fig. S2) using the EDI proposed in section 2.5, and the proposed B*a*P threshold was exceeded in 15% of samples, a much lower proportion than that

Table 2
Summary of the statistically significant factors and their interactions affecting organic pollutant levels in the selected samples.

OPs	Epidemiological Factors		Dietary habits	
	Factors	Interactions	Factors	Interactions
PAHs				
BaP				
ΣPAH2				
ΣPAH4; ΣPAH8	Sample time[1] (0.08094), (0.09661)	Smoker: Weight gain*		
OCPs				
ΣHCH				
Heptachl		Age:Place*; Parity:Place[1] (0.05068)	Eggs*	
ΣDDT				
Dield	Place*, Sample time[1] (0.05297)	Age:Place*	Mollusc*	
End				
OPPs				
Chlorpyr	Age[1] (0.0950)	Age:Pets*		
Diaz	Sample time[1] (0.09732)			
Fent		Age:Place*	Eggs*	
Parat				
NDLPCBs				
markerPCBs	Age[1] (0.0975)			Eggs:Meat**
PCB11				
PCB209			Eggs*, Molluscs[1]	
DLPCBs				
Mono_orthoPCBs			Molluscs*	
Non_orthoPCBs			Molluscs*	
PBDEs				
PBDE 28	Age*		Eggs**, Molluscs*	Eggs:Meat*, Fish: Molluscs*
PBDE 47			Molluscs*	Fish: Molluscs*
PBDE 99	Age*			Eggs:Meat*
PBDE 100	Age*		Eggs*	
PBDE 153	Age*		Eggs*	
PBDE 154				
PYRs				
Delt			Vegetable oils*	

**p < 0.010; *p < 0.050; [1]p < 0.10 (p value); PAHs (polycyclic aromatic hydrocarbons); BaP (Benzo[a]pyrene); ΣPAH2 (Chr (Chrysene) and BaP); ΣPAH4 (BaA (Benzo[a]anthracene), Chr, BbF (Benzo[b]fluoranthene) and BaP); ΣPAH8 (BaA, Chr, BbF, BkF (Benzo[k]fluoranthene), BaP, DahA (Dibenzo[a,h]anthracene), Ind123-cdP (Indene[1,2,3-cd]P) and BghiP (Benzo[ghi]perylene)); OCPs (organochlorine pesticides); Dield (Dieldrin); End (Endrin); ΣHCH (hexachlorocyclohexanes (α and β)); Heptachl (Heptachlor); ΣDDTs (1,1-Bis-(4-chlorphenyl)-2,2,2-trichelorethanes (mixture p,p' & o,p')); OPPs (organophosphorus pesticides); Chlorpy (Chlorpyrifos); Diaz (Diazinon); Fent (Fenthion); Parat (Parathion); NDLPCBs (non-dioxin like polychlorinated biphenyls); Marker PCBs (PCB 28, 52, 101, 138, 153 and 180); DLPCBs (dioxin like polychlorinated biphenyls); DLPCBs (dioxin like polychlorinated biphenyls); PBDEs (polybrominated diphenyl ethers).

reported by Santonicola et al. (2017) in southern Italy (53%). Median daily BaP intake values of 27 ng/kg$_{bw}$ and 59 ng/kg$_{bw}$ have been reported in breastfeeding American (Acharya et al., 2019) and Chinese (Wang et al., 2018) children, respectively. Oliveira et al. (2020) did not detect BaP in breastmilk from Portuguese woman. In the present study, we detected the following mean daily intake values (ng/kg$_{bw}$/day): PAH2, 8.5; PAH4, 54; PAH8, 62; ΣPAHs, 272. Overall, median daily PAH intake in breastfeeding Spanish children was lower than the values reported in Italy Santonicola et al. (2017), China (Wang et al., 2018), the USA (Acharya et al., 2019), and Portugal (Oliveira et al., 2020). Nonetheless, no ADI has been proposed for these compounds.

To calculate MOE_PAHs, we used the BMDL$_{10}$ value established for B*a*P (0.070 mg/kg), PAH2 (0.17 mg/kg), PAH4 (0.34 mg/kg), and PAH8 (0.49 mg/kg) in food (EFSA- European Food Safety Authority, 2008). Mean MOE_B*a*P, MOE_PAH2, MOE_PAH4, MOE_PAH8 values were 20, 861, 33,798, 37,213, and 33,327, respectively. However, our data revealed MOE values < 10,000 in 21%, 17%, 26%, and 22% of breast milk samples for BaP, PAH2, PAH4, and PAH8, respectively. To our knowledge, few authors have determined MOE values in human breast milk (Santonicola et al., 2017; Wang et al., 2018): existing data reveal a high percentage of breast milk samples with MOE values < 10,000 (BaP, 63%; PAH2, 60%; PAH4, 67%; PAH8, 90%).

3.2.2. PCBs

For total PCBs, the estimated mean EDI of infants was in a range of 4.8–850 ng/kg$_{bw}$/day, below the tolerable daily intake (TDI) of 1.0 μg/kg$_{bw}$/day proposed by The Canadian Guideline (Van Oostdam et al., 2005) and the provisional TDI proposed by FAO/WHO in (2008). Nevertheless, the TDI established by other international organizations (the Agency for Toxic Substances and Disease Registry (ASTDR), and the French Food Safety Agency (AFSSA)) was exceeded in some of the samples analysed in the present study. The threshold of 20 ng/kg$_{bw}$/day proposed by ASTDR in 2015 for cumulative levels of PCBs (Arochlor 1242, PCB 101, 118, 138, 153 and 180) was exceeded in 23% of samples. Previous studies also reported PCB concentrations >20 ng/kg$_{bw}$/day in human milk samples, including Dimitriadou et al. (2016) in Greece (85 of 87 samples) and Mamontova et al. (2017) in Eastern Siberia. The total EDI of PCB markers ranged from 1.1 to 550 ng/kg$_{bw}$/day (mean, 17 ng/kg$_{bw}$/day). PBC153, 138, and 180 accounted for 63% of the total daily intake of PCB markers (Fig. S2). These levels were lower than those reported by Hu et al. (2021) in China (mean, 47 ng/kg$_{bw}$). Nonetheless, in about 60% of milk samples TDI values for PCB markers were below 10 ng/kg$_{bw}$/day, the threshold proposed by AFSSA (AFSSA, 2019). Čechová et al. (2017a) also reported that the established level for PCB markers was exceeded in human milk samples in Norway (10 out of 388 samples) and Slovakia (6 out of 37 samples).

A revised tolerable weekly intake (TWI) of 2 pg TEQ kg$_{bw}$/day for PCDD/Fs and DLPCBs has been proposed (EFSA- European Food Safety Authority, 2021; Hu et al., 2021). This value is 7 times lower than the previous tolerable intake established by the European Commission's former Scientific Committee on Food in 2001. In the present study, we detected mean values of 29 pg TEQ kg$_{bw}$/day for DLPCBs (median, 0.80 pg TEQ kg$_{bw}$/day; IQR, 0.18–250 pg TEQ kg$_{bw}$/day). Several studies have reported that this TWI threshold is exceeded by 1 or 2 orders of magnitude (van den Berg et al., 2017). Hu et al. (2021) reported a value of 15 pg TEQ kg$_{bw}$/day for DLPCBs. Nonetheless, TWI should not be directly compared with DLPCB levels detected in breast milk.

3.2.3. OCPs

EDIs ranged from 3.2 to 1325 ng/kg$_{bw}$/day (mean, 160 ng/kg$_{bw}$/day; median, 16 ng/kg$_{bw}$/day) for total OCPs. Table S7 shows EDIs for all the target OCPs. These values are much lower than the ADI values proposed by the EFSA (EFSA- European Food Safety Authority, 2006; EFSA- European Food Safety Authority, 2021): 100 ng/kg$_{bw}$/day for heptachlor and dieldrin; 200 ng/kg$_{bw}$/day for endrin; 500 ng/kg$_{bw}$/day for total chlordane; and 10,000 ng/kg$_{bw}$/day for total DDTs. The ADI value for dieldrin exceeded 100 ng/kg$_{bw}$/day in only 1 sample. HQs for OCPs of interest are shown in Fig. S3.

Some studies have reported OCP levels that exceed the aforementioned TDI proposed by the EFSA. In their study conducted in China, Tsang et al. (2011) found that in 35% of breast milk samples analysed in Hong Kong total DDT levels exceeded the 20,000 ng/kg$_{bw}$/day limit

stipulated by the Canadian Guideline (Van Oostdam et al., 1999), while in 30% of samples levels ranged from 14,000 to 16,000 μg/kg_{bw}/day. They concluded that tighter restrictions should be imposed on the illegal use of DDT in some countries. Bouwman et al. (2006) and (2009) concluded that infants in areas with chemical malaria control programs are exposed to combinations of chemicals that could have deleterious effects if intake is sufficiently high.

3.2.4. PYRs and OPPs

We found that EDI values ranged from 24 to 908 ng/kg_{bw}/day (mean, 110 ng/kg_{bw}/day; median, 57 ng/kg_{bw}/day) for total pyrethroids. Table S7 shows EDIs for all target PYRs. For risk assessment of PYRs, ADI values established by WHO were considered (20, 50, 10 and 50 μg/kg_{bw}/day for cyfluthrin, cypermethrin, deltamethrin, and permethrin, respectively (FAO/WHO, 2005)). Values were one and two orders of magnitude lower than ADI values, indicating no appreciable risk.

For risk assessment of consumer exposure to OPPs in human breast milk, ARfD values (mg/kg_{bw}/day) (0.030 for Diaz, 0.010 for Part, 0.10 for chlorpyr, and 0.010 for Fent), as well as ADI values (mg/kg_{bw}/day) (0.0010 for Diaz, 0.010 for Part, 0.10 for chlorpyr, and 0.010 for Fent) from JMPR (Joint FAO/WHO Meeting on Pesticide Residues (FAO/WHO, 2019),) evaluations were used for IESTI and HQ calculations. The short and long-term risk assessment values established based on aHI (0.0090 for Diaz, 0.025 for Part, 0.0011 for chlorpyr, and 0.0099 for Fent) and HQ (0.42 for Diaz, 0.00027 for Part, 0.00013 for chlorpyr, and 0.0079 for Fent), respectively, indicated that the tested human milk samples posed negligible short or long-term risk. HQs for OCPs of interest are shown in Fig. S3.

3.2.5. PBDEs

For total PBDEs, EDIs ranged from 2.6 to 135 ng/kg_{bw}/day (mean, 13 ng/kg_{bw}/day; median, 10 ng/kg_{bw}/day) (Table S7 and Fig. S2). The RfD values established by USEPA for neurodevelopmental toxicity for BDE 47, 99, and 153 are 0.10, 0.10, and 0.20 μg/kg/day, respectively (US EPA, 2015). In the present study, EDI did not exceed these RfD values in any of the samples analysed.

3.3. Factors influencing organic pollutant concentrations

Multiple analysis of variance (MANOVA) revealed significant outcomes ($p < 0.05$) for selected epidemiological factors and consumption habits (Table 2).

Our results suggest that organic pollutant body burden increases with maternal age for most PBDEs ($p < 0.050$) and for chlorpyrifos and PCB markers ($p < 0.10$). Previous studies have reported similar findings for OCPs and PCBs in China (Man et al., 2014; Lu et al., 2015), PCBs in Greece (Dimitriadou et al., 2016), OCPs and PCBs in Eastern Siberia (Russia) (Mamontova et al., 2017), OCPs in India (Bawa et al., 2018), and PCBs in European countries (Brajenović et al., 2018). The graph in Fig. S3A plots mean concentrations of individual PBDEs as a function of maternal age, and shows that the congeners detected differed between older versus younger mothers. Ongoing exposure of younger mothers to penta-BDEs (PBDE 47 and PBDE 99) used in thermoplastics (electrical appliances) could account for these differences. Matovu et al. (2019) reported no significant association between PBDEs and maternal age, BMI, or infant birth weight, owing to the potential confounding effect of parameters such as parity, nursing history, and maternal educational level. Chao et al. (2010) concluded that positive and negative correlations between age and PBDE levels may be explained by occupational factors. Differences in PBDE levels between geographic regions could be explained by differences in environmental exposure (waste disposal sites, housekeeping frequency, and use of foam mattresses).

Sample time when the sample was collected was observed also as an important factor ($p < 0.10$) for ΣPAH4, ΣPAH8, Dield and Diaz (Fig. S4). The effect of the sampling time of breast milk samples on some organic compound levels has been demonstrated (Loverlady et al., 2002; LaKind et al., 2009; Harrad and Abdallah, 2015; Li et al., 2017). The WHO guidelines recommended sample collection within 3–8 weeks of delivery. Nevertheless, in our case sample collection was not possible within these weeks for all the samples and we decided to collect samples within 8–24 weeks to reduce the likelihood of negatively impacting the already low breastfeeding rates.

In contrast to previous reports (Asamoah et al., 2018; Müller et al., 2017; Miniero et al., 2018; Schuhmacher et al., 2013), we observed no correlation between PCB levels and place of residence. Most of these studies compared regions with differing levels of industrial activity. In our study, only samples from urban and rural areas were collected.

Interactions between factors are also presented in Table 2. Significant interactions were observed between maternal age and place of residence for some pesticides (heptachlor, dieldrin, and fenthion) (Fig. 1A). Significant interactions were also observed between smoking status and weight gain during pregnancy for PAHs, and between age and pet ownership for chlorpyrifos (Fig. 1B). As shown in Fig. 1B, PAH levels were higher in milk samples from mothers with lower weight gain during pregnancy. Smoking status has been previously correlated with PAH levels in biological samples (Fernández-Cruz et al., 2017b; Fernández-Cruz et al., 2020). Gestational weight gain has been proposed to influence levels of organobromine compounds in umbilical cord serum samples (Vizcaino et al., 2014). Recently, Grimalt et al. (2022) reported that lower gestational weight gain was associated with increased transfer of certain organic pollutants to infants during breastfeeding. Finally, in milk samples from younger mothers with pets we detected higher levels of chlorpyrifos (Fig. 1B), which is an active ingredient in veterinary antiparasitics for household pests.

Food consumption habits were also included our analysis. Egg consumption was significantly associated ($p < 0.050$) with levels of heptachlor, fenthion, PCB 209, PBDE 28, PBDE 100, and PBDE 153 in milk samples; mollusc consumption with levels of dieldrin, DLPCBs, PBDE 28 and PBDE 47; and oil consumption with levels of deltamethrin.

Food is the main exposure route for humans (EFSA- European Food Safety Authority, 2021). Previous studies have reported associations between organic pollutant concentrations and food consumption. Lu et al. (2015) described a moderate association between levels of PCB 77 in breast milk samples and frequency of fish consumption, and between DLPCB exposure and frequency of consumption of meat and meat products. Runkel et al. (2021) reported significant correlations between levels of PCB 153 and 180 in milk samples and higher levels of seafood consumption. Costa et al. (2016) found that one of the main sources of exposure to PBDE in Spain, especially PBDE 47 and 99, is fish and shellfish consumption. Matovu et al. (2019) found higher levels of PBDE 47 in milk from mothers with high versus low levels of fish consumption.

Runkel et al. (2021) also reported elevated levels of ΣDDT metabolites (*o,p'*-DDE and *p,p'*-DDTE) in milk samples from mothers who frequently consumed eggs. In our study, we found that egg consumption was significantly associated with concentrations of heptachlor, fenthion, PCB 209, and PBDE 28, 100 and 153. The characteristics of the feed used in commercial broiler chicken production could account for the higher organic pollutant levels detected in milk samples from mothers who frequently consume eggs. Frequent consumption of vegetable oils was also associated with significantly higher deltamethrin levels in breast milk ($p < 0.005$). Direct comparison with previous studies is not possible due to the paucity of studies that have evaluated pyrethroid levels in human milk. The presence of pesticide residues in oil crops is an important food safety concern, and could be one of the main source of human exposure to these pollutants.

The graphs in Fig. S6 depict the interactions between dietary habits and organic pollutant concentrations in breast milk.

4. Conclusions

To the best of our knowledge this study is the first to evaluate

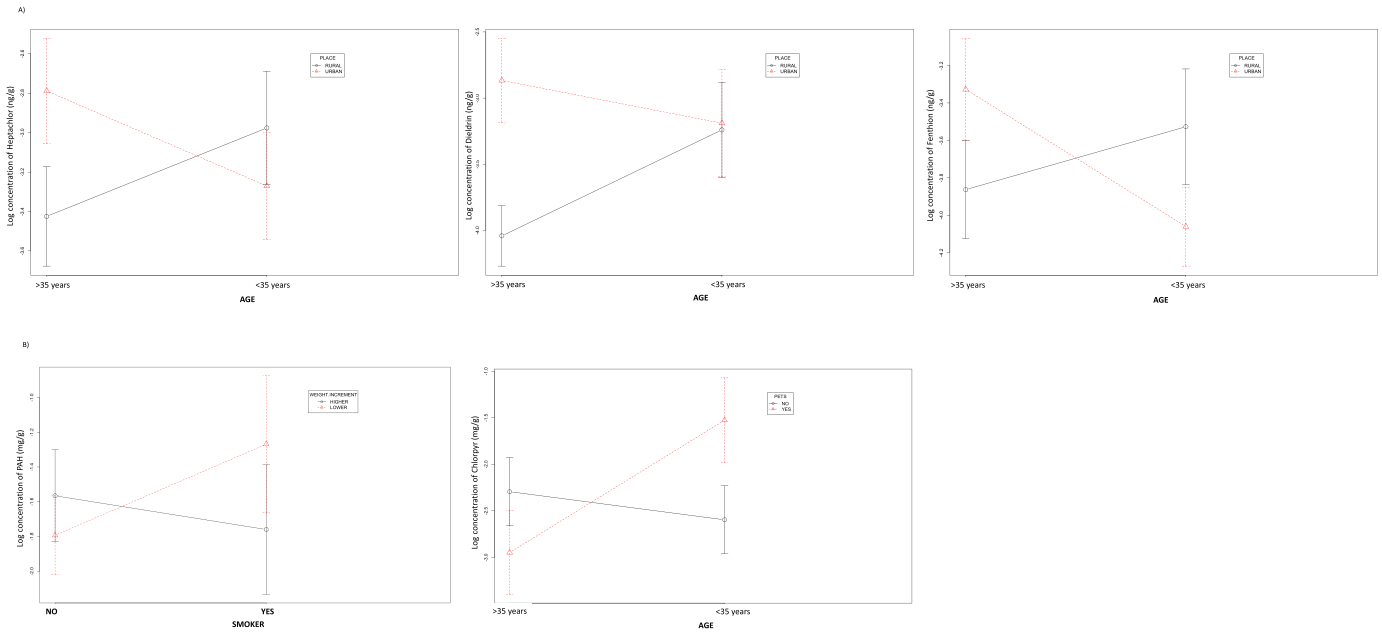

Fig. 1. Means plot showing significant interactions between: (A) maternal age and place of residence for specific pesticides (heptachlor, dieldrin, and fenthion); (B) weight gain and smoking status for PAHs and maternal age and pet ownership for chlorpyrifos.

postnatal exposure to organic pollutants in Galicia (north-western Spain). Most of the target pollutants were detected in human milk samples, with median concentrations in the following order: ΣPAHs (15 ng/g fat) > ΣPYRs (12 ng/g fat) > ΣOPPs (6.3 ng/g fat) > ΣNDLPCBs (2.89 ng/g fat) > ΣOCPs (2.85 ng/g fat) > ΣPBDEs (1.5 ng/g fat) > ΣDLPCBs (0.52 ng/g fat).

The sample time point of milk sampling, maternal age, and place of residence were identified as factors that may influence levels of most of the detected organic pollutants. We observed significant interactions with smoking status and weight gain for PAHs, place of residence, and season of milk sampling for some OCPs, maternal age and place of residence for fenthion, and maternal age and pet ownership for chlorpyrifos. Frequent consumption of eggs, molluscs, and vegetable oils was also associated with higher concentrations of some of the targeted organic pollutants.

In the absence of established TDI values with which to evaluate exposure to these toxic compounds in human milk samples, we calculated the EDI in order to assess the risk to infant health. Our results indicated that levels of targeted pollutants are below the TDI recommended for the EFSA, except in 15% samples with PAH levels higher than the threshold proposed by JECFA.

Author statement

Carolina López Sanguos: Investigation, Resources, Conceptualization. **Olalla López Suárez**: Investigation, Resources, Conceptualization. **Elena Martínez-Carballo**: Formal analysis, Supervision, Writing-Reviewing and Editing. **María Luz Couce**: Visualization, Supervision, Funding acquisition.

Declaration of competing interest

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

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2022.120903.

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