Changes of organochlorine compound concentrations in maternal serum during pregnancy and comparison to serum cord blood composition

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Abstract

The concentrations of organochlorine compounds (OCs), including pentachlorobenzene, hexachlorobenzene (HCB), hexachlorocyclohexanes (α-, β-, γ- and δ-HCH), polychlorobiphenyls (PCBs 28, 52, 101, 118, 138, 153 and 180), DDT and metabolites were measured in maternal serum samples collected at the first trimester of pregnancy, at delivery and in umbilical cord from a cohort of mother-newborn pairs from Tarragona (Spain) (n=50), representing general population of a Mediterranean area from Southern Europe. The observed concentrations were generally low in comparison with previous studies in other world areas.

Higher OC concentrations were observed in the maternal serum collected at delivery than in the first trimester and the cord blood concentrations were lower than the maternal levels. These results show for the first time a small but statistically significant increase in maternal venous concentration of OCs between the first trimester and delivery when measured in ng/ml.

HCB, β-HCH and the PCB congeners in cord blood were significantly correlated with the concentrations of these compounds in maternal venous blood and the coefficients were stronger for the samples collected at delivery which was consistent with OC transfer from mother to foetus. In the case of DDT compounds, only 4,4'-DDT showed maternal-cord blood correlation which documented the low metabolic capacity of newborns for OC transformation, e.g. DDT into DDE.

Maternal age was the most significant driver of the observed maternal venous OC concentrations in both periods, older ages involving higher concentrations. Higher body mass index was only significantly correlated with higher 4,4'-DDE concentrations in maternal venous blood and cord blood. In some cases, social class and education level were significantly correlated with OC concentrations, e.g. 4,4'-DDE in maternal venous blood from the first trimester and cord blood and PCB153 in maternal venous blood at delivery. In these cases, highest concentrations were found in the women with highest education level and most affluent social class.

Comparison of the maternal OC concentrations of this cohort with those observed in 2002 in population of the same geographic area and age range shows decreases between two and ten times over this fourteen-year period.

Keywords

Prenatal exposure; Maternal serum; Umbilical cord serum; Organochlorine compounds; Human biomonitoring; mother-to-foetus pollutant transfer

1. Introduction

Human exposure to organochlorine compounds (OCs) already begins at prenatal life because these compounds are able to pass through the placental barrier (Vizcaino et al., 2014a). OCs were used intensively in agriculture and industry for several decades. This class of compounds include polychlorobiphenyls (PCBs), dichlorodiphenyltrichloroethane (DDT) and its metabolites, hexachlorocyclohexanes (HCHs), hexachlorobenzene (HCB) and others. Their lipophilic nature and high chemical stability lead to their bioaccumulation in food chains and the human body (Junqué et al., 2017; 2018; Bravo et al., 2019). Due to their adverse effects in humans and the environment, their use was progressively banned in many countries since the 1970s and they were finally banned globally, with a few exceptions, by the Stockholm Convention in 2001 (Stockholm Convention on Persistent Organic Pollutants, 2005). Despite these regulations, OCs are still present in soils, water, air and organisms, involving a risk for the general population (Vizcaino et al., 2014a).

The maternal-to-foetal transfer of OCs was documented a few decades ago (Ando et al., 1986). Several studies reported concentrations of these chemicals in placenta, breastmilk, maternal, cord and newborn blood serum (Carrizo et al., 2006; Grimalt et al., 2010; Vizcaino et al., 2014a; Bravo et al., 2017). Foetuses and infants are more vulnerable to environmental pollutants than adults due to their greater exposure by high consumption of water, food and air in relation to their body weight, the immaturity and weakness of their metabolic system and longer lifetime to develop chronic diseases (Landrigan et al., 2011). In utero OC exposure has been associated with adverse outcomes including preterm birth (Longnecker et al., 2001), reduced birth weight (Wojtyniak, et al., 2010), smaller head circumference (Wolff et al., 2007), delayed neurodevelopment (Walkowiak et al., 2001) and depleted cognitive abilities (Patandin et al., 1999). These results have increased notably the interest of the scientific community on exposure to these compounds during gestation and the incidence of these disturbances is a matter of public health concern.

However, examination of previous work evidences major difficulties for assessment of the maternal-fetal transfer patterns (Jakobsson et al. 2012). There is still limited experimental evidence based on analytical studies to evaluate the distributions and partition ratios of OCs between cord and maternal serum (Needham et al. 2011; Barr et al., 2005). One aspect to be considered concerns the changes on OC concentrations in maternal blood during pregnancy. This is obviously an important factor as the maternal blood circulation system drives the transfer of these pollutants into foetus.

The present study is aimed to give insight into these OC processes based on the study of a population exposed to baseline levels of these pollutants and examination of maternal and foetal distributions in mother-child pairs. A cohort from Reus (Camp de Tarragona region) that is representative of general population has been selected as test case. This region of 2,703 km^2 is located in the Mediterranean coast of Southern Europe. It contains two petrochemical sites, intensive agriculture and urban cities (total population 516,988 inhabitants). Maternal blood samples were collected at the first trimester of pregnancy and at delivery as well as umbilical cord. OCs were analyzed and the distributions and correlation patterns of the concentrations of these pollutants in mothers and foetus were studied. Parity, maternal age, body mass index as well as lifestyle and demographic factors of the mothers were evaluated for the possible influence on the maternal and newborn OC concentrations (Zhang et al., 2018). This study contributes to broader the understanding on the maternal variables and compound properties that have influence on the accumulation of OCs during pregnancy and after birth.

2. Materials and methods

2.1. *Population and study design*

The study population is based on a cohort of 50 pregnant women and 33 offsprings born in the Hospital Universitari Sant Joan de Reus (Tarragona, Catalonia, Spain). Recruitment of pregnant mothers started in March 2016 and ended in October 2017. Maternal blood samples were collected at the first trimester of pregnancy and at delivery. Umbilical cord blood was also collected. All mothers were interviewed by trained personnel using a standardized questionnaire to request information on age, body mass index (BMI), parity, education level, social class and tobacco consumption. The age of the mothers ranged between 26 and 45 years (arithmetic mean 34 years). The study protocol was approved by the Ethical Committee of Clinical Research of the Hospital Universitari Sant Joan de Reus and written informed consent was obtained from each participant.

2.2. *Analytical methods*

Nineteen OCs were analysed: pentachlorobenzene (PeCB), HCB, four HCHs, α-, β-, γ- and δ-HCH, the DDT group, 2,4′-DDT, 4,4′-DDT, 4,4′-DDE, 2,4′-DDE, 4,4′-DDD and 2,4′-DDD, and seven PCB congeners, 28, 52, 101, 118, 138, 153 and 180.

One mL of serum was introduced into 10 mL centrifuge tubes. A standard solution of tribromobenzene and PCB-209 (50 ng/mL; 25 µL) followed by 3 mL of n-hexane and 3 mL of conc. H_2SO_4 were also added to these tubes. After vigorous stirring in a vortex (ca. 1500 rpm, 30 s), the mixture was centrifuged (ca. 3500 rpm, 10 min) and the supernatant n-hexane layer was transferred into a second centrifuge tube. Further n-hexane (2 mL) was added to the first tube containing the acid layer, and the mixture was stirred, centrifuged and transferred. This clean-up was repeated again and all the n-hexane extracts were combined. The n-hexane solution was further purified by addition of 3 mL concentrated H_2SO_4. The suspension was then mixed (vortex, 1500 rpm, 90 s), centrifuged (3500 rpm, 10 min), transferred and the n-hexane layer was eluted through a Pasteur pipette. Further H_2SO_4 (2 mL) was added again followed by mixing, centrifuging and transferring once more. Then, the supernatant n-hexane was eluted through a column packed with 1 g of sodium sulphate. The extracts were reduced to near dryness under a gentle stream of nitrogen and transferred to vials using 75 µL of isooctane. Before instrumental analysis, the samples were evaporated to nearly dryness under gentle nitrogen flows and a solution of PCB 142 was added as internal standard (10 ng/mL; 100 µL).

The instrumental OC analyses were performed by gas chromatography with electron capture detection (GC-ECD, Agilent Technologies 7890 A, Palo Alto, California, USA). The instrument was equipped with a HP-5MS capillary column (60 m length, 0.25 mm internal diameter, 0.25 µm film thickness; J&W Scientific) protected with a retention gap. Two µL were injected in splitless mode. Injector and detector temperatures were 250°C and 320°C, respectively. The oven temperature started at 90°C (holding 2 min), increased to 130°C at 15°C/min and finally to 290°C at 4°C/min, keeping the final temperature for 15 min. Ultrapure helium was the carrier gas (1.5 mL/min) and nitrogen was used as a make-up gas (60 mL/min).

Structural confirmations were performed by GC coupled to mass spectrometry (MS, Agilent Technologies 5975 C, Agilent Palo Alto, USA) operating in negative chemical ionization mode (GC-NICI-MS; Junqué et al., 2018).

One procedural blank was included in each batch of samples. Method detection and quantification limits were determined from the average signals of the procedural blank plus three and five times the standard deviation, respectively. Detection limits ranged between 0.001 and 0.0079 ng/ml, depending on the OCs. Method validation was performed by analysis of testing materials from the Arctic Monitoring and Assessment Program (AMAP Ring Test, 2014).

2.3. *Data analysis*

Statistical analysis and graphics were performed using the software R package (R Development Core Team, 2018). Statistics was focused on the compounds above limit of detection in more than 30% of the samples: HCB, β-HCH, 4,4'-DDT, 4,4'-DDE, PCB138, PCB153 and PCB180. The concentrations were expressed in ng/mL.

Statistical differences between OCs levels in umbilical cord serum and maternal serum collected at the first trimester of pregnancy and delivery were tested for significance using the Kruskal-Wallis and Mann Whitney tests.

Linear multivariate models were used to assess the dependences of maternal and umbilical cord serum OC concentrations with age, body mass index (BMI), parity, education level, social class and tobacco consumption as follows: log (OCs) = $\alpha + \beta_1$ (age) + β_2 (BMI_before_pregnancy) + β_3 (parity) + β_4 (education level) + β_5 (social class) + β_6 (tobacco consumption). Before model calculation, the observed OC concentrations were standardized and transformed to natural logarithms.

3. Results and discussion

3.1. Sociodemographic characteristics

The mean maternal age of the cohort participants was 34 years (ranging between 26-45 years old; Table 1). Most cohort mothers (57%) had body mass index (BMI) within normal range (18.5–25 kg/m^2) and the remaining 43% were overweight (≥25 kg/m^2). Most mothers (62%) were multiparous. Concerning education, more than half received higher education than primary school (74%) and a large proportion of them had a university degree (41%). About half of the families from the cohort belonged to the general social class (53%). Most women had no active tobacco smoking before or during pregnancy (71% and 20%, respectively). Fifty-seven percent of the newborns were girls (Table 1).

3.2. Organochlorine compound concentrations

Table 2 shows the geometric means (GMs) with the 95% confidence intervals (CIs), medians, minimum and maximum values of each of the analyzed OCs in the maternal venous blood serum in the first trimester of pregnancy, at delivery and in cord blood serum. 4,4'-DDE was the most abundant OC in all cases (medians 0.47, 0.62 and 0.26 ng/mL, respectively) followed by PCB153 (medians 0.11, 0.21 and 0.033 ng/mL, respectively).

Concerning the DDT compounds, 4,4’-DDE and 4,4'-DDT were found in all matrices while 4,4'-DDD was only above limit of detection in maternal serum at delivery. The remaining DDT metabolites were not found above limits of detection. The 4,4’-DDE and 4,4’-DDT concentrations found in the present study were much lower than those reported in venous maternal blood or cord blood serum of Shanghai and Huaihe River Basin (China; Zhang et al.,2018; Luo et al., 2016; Cao et al., 2011), Crete (Vafeiadi et al., 2014), Michalovce and Svidnik (Slovakia; Park et al., 2008), Algarve (Lopez et al., 2014), Rio Grande do Sul (Mohr et al., 2015), Menorca (Carrizo et al., 2016), Granada (Mariscal-Arcas et al., 2010), Valencia (Vizcaino et al., 2010), Ribera d’Ebre (Sala et al., 2001) and Antwerp (Covaci et al., 2002). In contrast, they were higher than those from cohorts in Ushuaia (Bravo et al., 2017) and Al-Kharj (Saudi Arabia; Al-Saleh et al., 2012) and similar to those observed in Brescia (Bergonzi et al., 2009), the average European Union (Govarts et al., 2012) and Canadian Northwest Territories and Nunavut areas (Butler Walker et al., 2003) (Table 3).

Concerning the PCB distributions, congener 153 was the most prevalent in all matrices followed by PCB180 and PCB138. Similar patterns are found in both venous maternal and cord serum of other locations, e.g. Algarve (Lopes et al., 2014), Michalovce and Svidnik (Slovakia; Park et al., 2008), Ribera d’Ebre (Sala et al., 2001), Menorca (Carrizo et al., 2006) and Valencia (Vizcaino et al., 2010), which correspond to the group of most hydrophobic PCB congeners (octanol-water coefficients, logKow > 6.9) and bioaccumulation potential.

The PCB concentrations found in this Tarragona cohort are lower than those described in most previous studies such as cord blood serum from Rio Grande do Sul (Mohr et al., 2015), Algarve (Lopes et al., 2014), Crete (Vareiadi et al., 2014), Menorca (Carrizo et al., 2006), European Union average (Govarts et al., 2012), Shanghai (Cao et al., 2011), Valencia (Vizcaino et al., 2010), Michalovce and Svidnik (Slovakia; Park et al., 2008), Canadian Northwest Territories and Nunavut areas (Butler Walker et al., 2003), Antwerp (Covaci et al., 2002) and Ribera d’Ebre (Sala et al., 2001) and venous maternal blood serum from Algarve (Lopes et al., 2014), Canadian Northwest Territories and Nunavut areas (Butler Walker et al., 2003), Antwerp (Covaci et al., 2001) and Ribera d’Ebre (Sala et al., 2001) (Table 3). Conversely, the maternal serum concentrations from Tarragona are similar to those found in Crete (Vafeiadi et al., 2014) and higher than those in Ushuaia (Bravo et al., 2017).

The maternal and cord blood serum concentrations of HCB observed in this Tarragona cohort are lower than those reported in Ushuaia (Bravo et al., 2017), Shanghai (Zhang et al., 2018; Cao et al., 2011), Crete (Vafeiadi et al., 2014), Menorca (Carrizo et al., 2006), Granada (Mariscal Arcas et al., 2010), Valencia (Vizcaino et al., 2010), Brescia (Bergonzi et al., 2009), Canadian Northwest Territories and Nunavut areas (Butler Walker et al., 2003), Antwerp (Covaci et al., 2002) and Ribera d'Ebre (Sala et al., 2001) (Table 3).

The distributions of HCHs were predominated by β-HCH. The other HCH isomers were only found in less than 5% of the samples. Again, the concentrations of β-HCH in venous maternal blood and cord blood serum from the cohort of Tarragona were lower than those described in studies from Ushuaia (Bravo et al., 2017), Shanghai (Zhang et al., 2018; Cao et al., 2011), Canadian Northwest Territories and Nunavut areas (Butler Walker et al., 2003) and Ribera d'Ebre (Sala et al., 2001) (Table 3).

3.3. Changes in maternal venous concentrations

The concentration changes of HCB, β-HCH, 4,4-DDT, 4,4'-DDE, PCB118, PCB153 and PCB180 in maternal venous serum from the first trimester of pregnancy to delivery are shown in Figure 1. In general, the geometric mean concentrations were higher at the time of delivery. Statistically significant differences in the Mann Whitney's test of these two concentration series were found for HCB ($p<0.05$), β-HCH ($p<0.05$), 4,4'-DDT ($p<0.001$), PCB153 ($p<0.001$) and PCB180 ($p<0.05$). Some previous studies considered OC changes during pre and post-pregnancy but they essentially compared maternal serum with umbilical cord serum (Park et al., 2008; Nashua et al., 2009; Herrero-Mercado et al., 2011; Monteagudo et al., 2016; Choi et al., 2018) or placenta (Bergonzi et al., 2009; Dewan et al., 2013). To the best of our knowledge, this is the first case considering maternal venous OC concentrations during different pregnancy stages. The observed differences may result from the mobilization of fat stores and blood volume increases during pregnancy (Verner et al., 2008; Vizcaino et al., 2014b; Gentry et al., 2002; 2003). The former tend to increase blood concentrations of chemically stable pollutants stored in fat and the latter may involve dilution when the concentrations are expressed in ng/ml. The results from the present cohort shows that there is a small but statistically significant increase in maternal venous concentrations between the first trimester and delivery (Figure 1).

3.4. Correlations between maternal and cord blood serum concentrations

All analytes showed statistically significantly lower concentrations in cord blood than in maternal venous blood at delivery ($p<0.01$ for 4,4'-DDE and $p<0.001$ for the other compounds; Figure 1). Statistically significant differences were also found between the concentrations of HCB, PCB153 and PCB180 in umbilical cord and maternal venous blood at the first trimester of pregnancy ($p<0.05$, 0.001 and 0.001, respectively).

Based on the linear regression models, the umbilical cord levels of HCB, β-HCH and PCBs were significantly correlated with the maternal venous concentrations (Table 4). The β coefficients were higher for the correlations with the maternal concentrations at delivery, 0.42-0.80, than in the first trimester, 0.28-0.80, which is consistent with the lower time difference between sample collection in the former than in the latter cases.

The concentrations of 4,4'-DDT and 4,4'-DDE in cord blood and maternal venous blood only showed significantly correlation for maternal 4,4'-DDT at delivery. The lack of correlation of 4,4'-DDE may reflect higher immaturity of the newborn's enzymatic system (Gentry et al., 2002; 2003) which is unable to transform 4,4'-DDT into 4,4'-DDE efficiently. Thus, comparison of the geometric mean concentrations of 4,4'-DDE and 4,4'-DDT in maternal venous and cord blood shows 4,4'-DDT/(4,4'-DDT + 4,4'-DDE) ratios of 0.023, 0.038 and 0.037 for maternal blood in the first trimester, at delivery and in cord blood, respectively. The same ratio of the latter two is consistent with the low capacity of newborns to metabolize 4,4'-DDT.

The significant correlation between concentrations of cord blood and maternal venous blood at delivery only for 4,4'-DDT ($p < 0.001$; Table 4) is also consistent with low capacity of metabolizing this insecticide in newborns. The survival of 4,4'-DDT in the transfer from mothers to foetuses was also observed in a cohort study involving maternal venous blood, placenta and cord blood (Vizcaino et al., 2014a). In this Tarragona cohort, correlation of summed DDT metabolites shows a significant coefficient only for cord blood and maternal blood at delivery ($p < 0.05$; Table 4) which is again consistent with the low capacity of newborns for metabolizing 4,4'-DDT.

3.5. Factors influencing the concentrations of OCs

Multivariate linear regression models of the maternal socio-demographic characteristics and OCs concentrations were built to assess the possible role of these determinants on the concentrations of these pollutants (Table 5). The GMs and CIs of the OC concentrations of each class are shown in Figure 2.

Age was the most significant driver of the observed maternal venous OC concentrations in the first trimester and at delivery, older ages involving higher concentrations (Table 5; Figure 2). These correlations with age were not observed for the OC cord blood concentrations except in the case of 4,4'-DDE ($p < 0.01$). The increase of OC concentrations with age has been observed in serum from general population (Porta et al., 2010; Hassine et al., 2014) and serum from maternal cohorts (Patayová et al., 2013; Veyhe et al., 2015; Bravo et al., 2017; 2019). It has also been observed in other human matrices such as breastfeeding (Harris et al., 2000) and cord blood (Carrizo et al., 2006; Vizcaino et al., 2010; Patayová et al., 2013). Higher concentrations of these compounds with age are consistent with their chemical stability and hydrophobic properties which tend to their bioaccumulation in human tissues.

Higher body mass index was significantly correlated with higher concentrations of 4,4'-DDE in maternal venous blood and cord blood serum (Table 5) but not in the case of the other pollutants. The observed correlation is consistent with the above mentioned physical-chemical properties of 4,4'-DDE such as chemical persistence and hydrophobicity. However, despite most of the OC have the same properties, significant correlations are only observed for this compound. Results from previous studies do not show a robust correspondence between OC concentrations and BMI. Positive significant associations were reported between most OCs and blood serum concentrations in adults (Glynn et al., 2003; Porta et al., 2010; Vizcaino et al., 2014b). These correlations were very strong for HCHs in the study of a Chinese cohort (Zang et al., 2018). In the study of two cohorts of French women higher BMI were also correlated with higher concentrations of 4,4'-DDT in venous serum but a significant negative correlation between BMI and PCBs was observed. In Menorca, associations between higher maternal BMI and cord blood concentrations were only observed for HCB, 4,4'-DDE and 4,4'-DDT (Carrizo et al., 2006). Other studies on serum from general population from Bolivia (Arrebola et al., 2012) and Tunisia (Hassine et al., 2014) did not show significant correlations between BMI and OC concentrations.

Parity is also a factor influencing the concentrations of OCs in women since they transfer these pollutants to the foetus during pregnancy. In the Tarragona cohort an inverse significant correlation between parity and HCB concentrations was observed in the maternal venous blood serum collected in the first trimester of pregnancy but not in the other cases (Table 5). Inverse correlations between parity and concentrations of diverse OCs in adult venous serum (Bravo et al., 2019; Veyhe et al., 2015), breast milk (Manaca et al., 2011) and cord blood serum (Manaca et al., 2013) have been observed. However, no significant correlation was found in other studies, e.g. maternal cohort of Valencia (Vizcaino et al., 2010).

Social class and educational level are often related as people from the most affluent social groups are those with higher education. In the present cohort, the correlations between these two variables and OC concentrations were not strong. However, there were several statistically significant correlations between the most affluent social class and higher concentrations of 4,4'-DDE in maternal venous blood collected at the first trimester of pregnancy and cord blood and PCB138 in maternal venous blood at delivery (Table 5). The cohort participants with higher educational level also showed higher cord blood concentrations of 4,4'-DDE (Table 5; Figure 2). Despite these results only concern a few significant cases, they consistently show that the most affluent women with highest education level are those more exposed to some of these OCs. This higher exposure could respond to distinct dietary habits (Tarasuk et al., 2010) since these groups tend to have a higher proportion of fish and seafood in the diet and fish has been shown to be a preferred source of incorporation of these pollutants in Mediterranean cohorts (Junque et al., 2018). However, in the specific case of Tarragona, examination of the food consumption habits did not show any significant trend in relation to OC incorporation except for the positive association of organic food consumption and the concentration of PCB138 in the maternal serum collected in the first trimester and at delivery. The concentrations of PCB153 and PCB180 in serum collected at delivery also showed positive associations with the organic food consumption.

In contrast, there are also studies showing higher educational level and lower OC concentrations (Cerrilo et al., 2006; Cao et al., 2011) or lack of correlation between social class and OC concentrations also in Mediterranean cohorts (Porta et al., 2010). Studies on the influence of socio-economic status and OC exposure in pregnant women attributed only 1-5% of the concentration variability to this factor (Vrijheid et al., 2012). These estimates suggest that higher numbers of cases are needed for a more grounded statistical assessment of the relevance of socioeconomic status and food consumption habits on OC exposure.

No significant association was found between tobacco consumption by family members and OC concentrations in the maternal venous blood or in cord blood.

3.6. Changes in OC concentrations through time

A previous study of serum OC concentrations encompassing a representative sample of the population of Catalonia performed on samples collected in 2002 also encompassed individuals from the Tarragona area (Porta et al., 2010). Selection of the results belonging to these individuals of the age interval between 26-45 years in this previous study (n = 110) affords a comparison with the 2016 results observed in the present one (n = 45).

Calculation of the means and standard deviations of both groups shows strong statistically significant decreases ($p < 0.001$) for most compounds, between two and ten times (Table 6). In the case of hexachlorobenzene even a decrease of 22 times is observed. 4,4'-DDT is also showing a strong drop, nearly 11 times.

The Stockholm convention was implemented in 2001 (Stockholm Convention, 2005), one year before the extensive sampling survey in Catalonia (Porta et al., 2010). The strong decreases observed in this fourteen-year interval is consistent with an efficient removal of OC sources in the studied area after implementation of this international agreement.

4. Conclusions

The concentrations of OCs found in serum of maternal venous blood and cord blood of the Tarragona cohort are generally lower than those previously described in other cohorts from diverse world areas.

Higher OC concentrations were observed in the maternal serum collected at delivery than in the first trimester of pregnancy, and the differences were statistically significant for most compounds. All OCs in cord blood showed statistically significant lower concentrations than in maternal venous blood. HCB, β-HCH and the PCB congeners in cord blood were significantly correlated with the concentrations of these compounds in the maternal venous blood and the coefficients were stronger for the samples collected at delivery. These correlations are consistent with an OC transfer from mother to foetus. However, for the DDT compounds only 4,4'-DDT showed correlation between maternal venous blood at delivery and cord blood. No significant correlations were observed for the other individual metabolites, e.g. 4,4'-DDE. These differences document the low metabolic capacity of newborns for OC transformation, e.g. DDT into DDE.

Maternal age was the most significant driver of the observed maternal venous OC concentrations collected in the first trimester and at delivery, older ages involving higher concentrations. Higher BMI was only significantly correlated with higher concentrations of 4,4'-DDE in maternal venous blood and cord blood. Social class and education level were significantly correlated with the OC concentrations in some cases, such as 4,4'-DDE in maternal venous blood collected at the first trimester and cord blood and PCB138 in maternal venous blood at delivery. In all these cases, the highest concentrations were observed for the women with highest education and most affluent social class.

Comparison of the maternal OC concentrations with those observed in population of the same geographic area and age range collected in 2002 shows decreases between two and ten times over this fourteen-year period.

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Table 1 Socio-demographic characteristics of the Tarragona cohort.

	N	%
Mothers	Mean: 34	
Age (years)	Range: 26–45	
≤ 30	14	28
31–35	15	31
≥ 36	20	41
Body mass index (kg/m²)	Mean: 25 Range: 16-44	
Normal weight (18.5–25)	28	57
Overweight (≥25)	21	43
Parity		
Primiparous	19	38
Multiparous	31	62
Education level		
Primary school	13	26
Secondary school	16	33
University	20	41
Social class		
I (most affluent)	10	20
II	26	53
III (least affluent)	13	27
Tobacco consumption		
Never	35	71
Not during pregnancy	10	20
Also during pregnancy	4	8
Infants		
Sex		
Male	13	43
Female	17	57

Table 2 Descriptive statistics of the OC serum concentrations (ng/mL) of the Tarragona cohort.

Contaminants	Maternal venous serum in the first trimester (n=45)				Maternal venous serum at delivery (n=39)				Cord blood serum (n=33)			
	% detection	GM (95%CI)	50th	Range (Min-Max)	% detection	GM (95%CI)	50th	Range (Min-Max)	% detection	GM (95%CI)	50th	Range (Min-Max)
PeCB	4	0.032 (0.0029-0.0034)	0.0030	0.0030-0.0019	0	<LOD	–	–	0	<LOD	–	–
HCB	29	0.024 (0.018-0.031)	0.014	0.014-0.49	64	0.044 (0.030-0.062)	0.045	0.014-0.96	6	0.015 (0.013-0.017)	0.014	0.014-0.13
α-HCH	4	0.0073 (0.0068-0.0079)	0.0070	0.0070-0.038	3	0.0071 (0.0069-0.0072)	0.0070	0.0070-0.010	0	<LOD	–	–
β-HCH	16	0.0081 (0.0055-0.011)	0.0050	0.0050-1.202	36	0.015 (0.0087-0.026)	0.0050	0.0050-1.2	3	0.0055 (0.0045-0.0066)	0.0050	0.0050-0.10
γ-HCH	2	0.0073 (0.0067-0.0080)	0.0070	0.0070-0.054	3	0.0072 (0.0069-0.0074)	0.0070	0.0070-0.11	0	<LOD	–	–
δ-HCH	0	<LOD	–	–	0	<LOD	–	–	0	<LOD	–	–
4,4'-DDT	40	0.011 (0.0093-0.013)	0.0080	0.0080-0.070	72	0.022 (0.016-0.030)	0.027	0.0080-0.12	33	0.011 (0.0089-0.014)	0.0080	0.0080-0.069
2,4'-DDT	0	<LOD	–	–	0	<LOD	–	–	0	<LOD	–	–
4,4'-DDE	98	0.47 (0.21-0.72)	0.47	0.045-4.1	100	0.55 (0.40-0.77)	0.62	0.069-5.0	94	0.29 (0.19-0.44)	0.26	0.045-4.92
2,4'-DDE	0	<LOD	–	–	0	<LOD	–	–	0	<LOD	–	–
4,4'-DDD	0	<LOD	–	–	5	0.0030 (0.0030-0.0031)	0.0030	0.0030-0.0040	0	<LOD	–	–
2,4'-DDD	0	<LOD	–	–	0	<LOD	–	–	0	<LOD	–	–
PCB28	0	<LOD	–	–	0	<LOD	–	–	3	0.010 (0.0098-0.010)	0.010	0.010-0.015
PCB52	4	0.0056 (0.0048-0.0065)	0.0050	0.0050-0.072	3	0.0050 (0.0050-0.0051)	0.0050	0.0050-0.0070	0	<LOD	–	–
PCB101	2	0.0011 (0.00093-0.0013)	0.0010	0.0010-0.029	8	0.0012 (0.00096-0.0016)	0.0010	0.0010-0.037	12	0.0016 (0.0010-0.0025)	0.0010	0.0010-0.075
PCB118	0	<LOD	–	–	0	<LOD	–	–	0	<LOD	–	–
PCB138	11	0.054 (0.048-0.061)	0.048	0.048-0.29	56	0.094 (0.072-0.12)	0.060	0.048-0.68	0	<LOD	–	–
PCB153	67	0.084 (0.066-0.11)	0.11	0.033-0.59	85	0.17 (0.13-0.24)	0.21	0.033-1.3	12	0.036 (0.032-0.040)	0.033	0.033-0.12
PCB180	73	0.057 (0.041-0.080)	0.073	0.011-0.49	90	0.10 (0.072-0.15)	0.13	0.011-0.98	12	0.013 (0.011-0.015)	0.011	0.011-0.064

GM (95%CI): Geometric mean with 95% confidence intervals.

Table 3 Median OC concentrations (ng/ml) in maternal and umbilical cord serum in other populations worldwide.

Location	Year	Type of sample	N	HCB	β-HCH	4,4'-DDT	4,4'-DDE	PCB138	PCB153	PCB180	References
Tarragona (Spain)	2016	Maternal serum (first trimester)	45	0.014 [0.024]	0.0050 [0.0081]	0.0080 [0.011]	0.47 [0.47]	0.048 [0.054]	0.11 [0.084]	0.073 [0.057]	Present study
		Maternal serum (delivery)	39	0.045 [0.044]	0.0050 [0.015]	0.027 [0.022]	0.62 [0.55]	0.060 [0.094]	0.21 [0.17]	0.13 [0.10]	
		Cord serum	33	0.014 [0.015]	0.0050 [0.0055]	0.0080 [0.011]	0.26 [0.29]	<LOD <LOD	0.033 [0.036]	0.011 [0.013]	
Ushuaia (Argentina)	2011-2012	Maternal serum (delivery)	199	0.067	0.57	0.022	0.22	0.046	0.064	0.0055	Bravo et al., 2017
Shanghai (China)	2003-2004	Maternal serum	102	0.40	1.1	<LOD	3.23				Zhang et a., 2018
		Cord serum	102	0.16	0.27	<LOD	0.71				
Huaihe River Basin (China)	2013-2014	Cord serum	972		<LOD	2.5	1.5				Luo et al., 2016
Rio Grande do Sul (Brazil)	2006	Cord serum	148					0.94	0.55	0.73	Mohr et al., 2015
Algarve (Portugal)	2010-2011	Maternal serum	68				0.93 [0.92]	0.14 [0.14]	1.0 [0.98]	0.42 [0.39]	Lopes et al., 2014
		Cord serum	68				0.71 [0.70]	0.11 [0.10]	0.94 [0.96]	0.37 [0.34]	
Crete (Greece)	2007	Maternal serum (first trimester)	1117	[0.089]		[0.043]	[2.1]	[0.062]	[0.12]	[0.062]	Vafeiadi et al., 2014
Menora (Spain)	1997-1988	Cord serum	344	[0.67]		[0.08]	[1.06]	[0.14]	[0.18]	[0.13]	Carrizo et al., 2006
European Union average	1999-2008	Cord serum	7530				0.53		0.14		Govarts et al., 2012
Al-Kharj (Saudi Arabia)	2005-2006	Cord serum	1536			0	0				Al-Saleh et al., 2012
		Maternal serum (delivery)	1518			0	0.05				
Shanghai (China)	2008-2009	Cord serum	1438	0.42	0.45	0.11	1.9	0.040	0.18		Cao et al., 2011
Granada (Spain)	2000-2002	Cord serum	318	2.2		2.56	2.6				Mariscal-Arcas et al., 2010
Valencia (Spain)	2004-2006	Cord serum	499	[0.19]	[0.050]	[0.020]	[0.50]	[0.070]	[0.10]	[0.070]	Vizcaino et al., 2010
Brescia (Italy)	2006	Maternal serum	70	0.16 [0.18]			0.96 [1.1]				Bergonzi et al., 2009
		Cord serum	70	0.05 [0.05]			0.25 [0.25]				
Michalovce and Svidnik districts (Slovakia)	2002-2004	Maternal serum	1087					0.95	1.5	1.3	Park et al., 2008
		Cord serum	1087					0.22	0.30	0.25	
Northwest Territories and Nunavut areas (Canada)	1994-1999	Maternal serum (third trimester)	385	[0.22]	[0.080]	[0.060]	[1.1]	[0.16]	[0.24]	[0.12]	Butler Walker et al., 2003
		Cord serum	400	[0.070]	[0.030]	[0.030]	[0.34]	[0.040]	[0.060]	[0.030]	
Antwerp (Belgium)	1999	Maternal serum (delivery)	44	0.18			1.6	0.42	0.58	0.31	Covaci et al., 2002
		Cord serum	44	0.070			0.49	0.095	0.15	0.060	
Ribera d'Ebre (Spain)	1997-1999	Cord serum	69	[1.1]	[0.26]		[0.83]	[0.080]	[0.060]	[0.070]	Sala et al., 2001
		Maternal serum (delivery)	72	[3.2]	[1.1]		[2.2]	[0.44]	[0.48]	[0.46]	

[a] Geometric mean in [].

Table 4 Results of the regression models showing the associations between the OCs concentrations in cord blood serum and maternal venous serum (at the first trimester and delivery).

Contaminants	First trimester		Delivery	
	[a]β	p	[a]β	p
HCB	0.48	p<0.001	0.66	p<0.001
β-HCH	0.28	p<0.05	0.42	p<0.001
4,4'-DDT	0.12		0.44	p<0.001
4,4'-DDE	0.20		0.19	
[b]ΣDDT	0.19		0.24	p<0.05
PCB153	0.60	p<0.001	0.72	p<0.001
PCB180	0.80	p<0.001	0.80	p<0.001

[a]β coefficients of the multivariate regression models after standardizing all the variables. [b]ΣDDT = 2,4’-DDT + 4,4’-DDT + 2,4’-DDE + 4,4’-DDE + 2,4’-DDD + 4,4’-DDD
OCs concentrations in both maternal serum matrices were adjusted by age, BMI, parity, education level, social class and tobacco consumption.

Table 5 Main socio-demographic predictors of serum OC concentrations in maternal and umbilical cord blood after adjustment for BMI before pregnancy.

Contaminants		First trimester		Delivery		Umbilical cord	
	Variable	Std. β	P	Std. β	P	Std. β	P
HCB	Age	0.043	p<0.001	0.055	p<0.01	0.011	0.13
	BMI	0.012	0.25	0.0084	0.68	0.00040	0.95
	Parity	0.25	p<0.05	0.075	0.64	0.056	0.44
	Education level	-0.022	0.78	0.18	0.15	-0.086	0.12
	Social class	0.18	0.061	0.057	0.67	0.035	0.55
	Tobacco consumption	-0.048	0.62	-0.083	0.56	-0.0095	0.88
β-HCH	Age	-0.0061	0.76	0.073	p<0.05	0.015	0.14
	BMI	-0.029	0.11	-0.012	0.73	-0.000016	1.0
	Parity	0.029	0.89	0.16	0.54	0.066	0.50
	Education level	-0.21	0.17	-0.098	0.63	-0.12	0.10
	Social class	-0.050	0.77	0.34	0.14	0.038	0.64
	Tobacco consumption	0.10	0.57	-0.15	0.52	-0.016	0.85
4,4'-DDT	Age	0.013	0.14	0.013	0.34	0.014	0.24
	BMI	0.0023	0.77	0.012	0.49	0.015	0.19
	Parity	0.11	0.21	0.19	0.18	0.10	0.38
	Education level	0.025	0.69	0.0058	0.96	0.047	0.58
	Social class	0.020	0.81	-0.075	0.52	0.0097	0.92
	Tobacco consumption	0.059	0.45	-0.022	0.86	0.018	0.86
4,4'-DDE	Age	0.037	p<0.01	0.046	p<0.01	0.053	p<0.01
	BMI	0.015	0.21	0.042	p<0.05	0.060	p<0.001
	Parity	0.11	0.43	0.13	0.35	-0.020	0.90
	Education level	0.13	0.17	0.22	0.052	0.24	p<0.05
	Social class	-0.25	p<0.05	-0.22	0.074	-0.29	p<0.05
	Tobacco consumption	0.072	0.54	-0.076	0.55	-0.25	0.080
PCB138	Age	0.012	p<0.05	0.040	p<0.01	–	–
	BMI	-0.0047	0.38	0.0030	0.84	–	–
	Parity	-0.015	0.80	-0.023	0.84	–	–
	Education level	0.020	0.64	0.086	0.33	–	–
	Social class	-0.072	0.15	-0.22	p<0.05	–	–
	Tobacco consumption	0.032	0.54	-0.0030	0.98	–	–
PCB153	Age	0.050	p<0.001	0.047	p<0.01	0.0092	0.10
	BMI	-0.0018	0.85	0.0021	0.91	-0.0022	0.67
	Parity	0.11	0.29	0.0053	0.97	0.049	0.35
	Education level	0.049	0.50	0.16	0.16	-0.026	0.50
	Social class	-0.11	0.22	-0.098	0.42	-0.0061	0.89
	Tobacco consumption	-0.054	0.55	0.0099	0.94	-0.0030	0.95
PCB180	Age	0.060	p<0.001	0.060	p<0.001	0.011	0.21
	BMI	-0.0045	0.71	0.0013	0.95	-0.0065	0.44
	Parity	0.057	0.67	-0.030	0.85	0.045	0.60
	Education level	0.025	0.80	0.10	0.38	-0.052	0.41
	Social class	0.038	0.74	-0.0015	0.99	0.012	0.86
	Tobacco consumption	-0.0018	0.90	-0.021	0.87	0.023	0.76

β: regression coefficient.
p: p-value of each category of the variable.
All regression models adjusted by BMI before pregnancy.

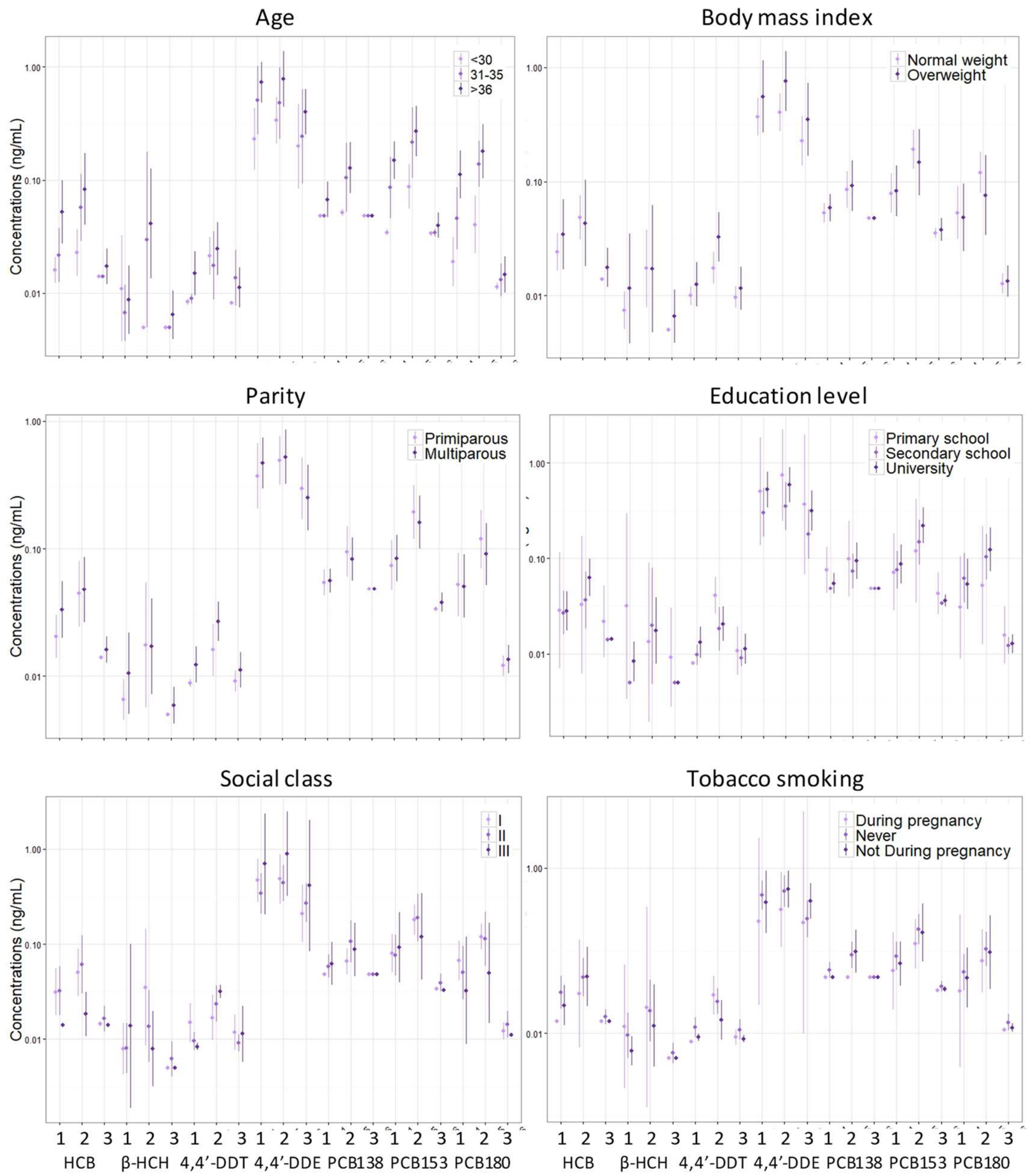
Table 6. Comparison of the average concentrations and standard deviations of the simples collected in the present study (2016) with those collected in the same area in 2002. Age range 26-45 years in both cases.

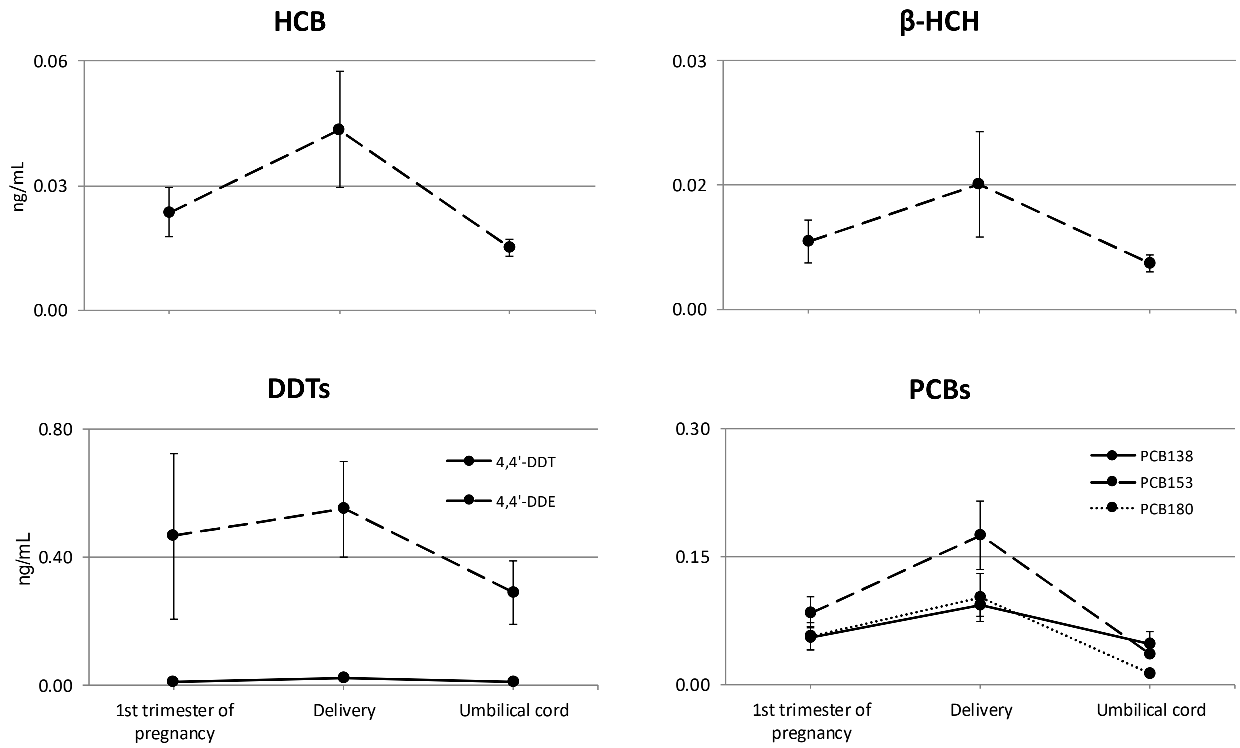
Compoud	**2002[a]**	**2016b**	**2016/2002**	***p***
PeCB	0.014 (0.016)	0.0034 (0.0024)	0.24	<0.001
HCB	0.96 (0.90)	0.042 (0.076)	0.044	<0.001
α-HCH	0.014 (0.010)	0.0078 (0.0046)	0.56	<0.001
β-HCH	0.50 (0.44)	0.059 (0.21)	0.12	<0.001
γ-HCH	0.029 (0.035)	0.0080 (0.0070)	0.28	<0.001
4,4'-DDT	0.15 (0.18)	0.014 (0.012)	0.093	<0.001
4,4'-DDE	2.11 (1.9)	0.76 (0.88)	0.36	<0.001
PCB52	0.0076 (0.031)	0.0075 (0.012)	0.99	<0.001
PCB101	0.0030 (0.0086)	0.0016 (0.0042)	0.53	<0.001
PCB138	0.39 (0.33)	0.061 (0.045)	0.16	<0.001
PCB153	0.60 (0.51)	0.12 (0.10)	0.2	<0.001
PCB180	0.58 (0.46)	0.093 (0.091)	0.16	<0.001

[a]Samples collected in 2002 (Porta et al., 2010). [b]Samples collected in 2016 (this study)

Figure 1 Changes of serum concentrations of HCB, β-HCH, 4,4'-DDT, 4,4'-DDE, PCB138, PCB153 and PCB180 during the first trimester of pregnancy, at delivery and in umbilical cord in mothers from the Tarragona cohort. Results in ng/mL, geometric mean.

Figure 2 Influence of the maternal socio-demographic characteristics on the organochlorine compound concentrations (ng/mL; geometric means and 95% confidence intervals) of the maternal venous and cord blood serum. 1: mothers at first trimester, 2: mothers at delivery, 3: newborn umbilical cord. Age and body mass index refer to the first trimester of pregnancy. Social classes: I and III the most and least affluent, respectively.





HCB
β-HCH
DDTs
PCBs
ng/mL
0.06
0.03
0.00
0.03
0.02
0.00
0.80
0.40
0.00
0.30
0.15
0.00
4,4'-DDT
4,4'-DDE
PCB138
PCB153
PCB180
1st trimester of pregnancy
Delivery
Umbilical cord