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Temporal trends in concentrations and total serum burdens of organochlorine compounds from birth until adolescence and the role of breastfeeding

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ABSTRACT

Introduction: The aims of the present study are to assess the temporal trends of organochlorine compounds (OCs) concentrations and total serum burdens from birth until adolescence and the influence of breastfeeding in these temporal trends. *Methods*: In 1997 two birth cohort studies were set up in Ribera d'Ebre (N = 102) and the island of Menorca (N = 482), Spain. Concentrations (ng/mL) of OCs [pentachlorobenzene (PeCB), four isomers of hexachlorocyclohexane (HCH), hexachlorobenzene (HCB), dichlorodiphenyltrichloroethane (4,4′-DDT), dichlorodiphenyldichloroethylene (4,4′-DDE) and seven polychlorobiphenyl congeners (Σ_7PCBs)] were measured in cord blood and at the age of 4 and 14 years. The total serum burdens (ng) of these compounds were estimated based on the total blood volume (mL) of children at the different ages. We compared median concentrations and total serum burdens of these OCs at the different time-points of follow-up between children of Ribera d'Ebre and Menorca and between breastfed and non-breastfed children. *Results*: From birth until adolescence concentrations of all OCs drastically reduced. These reductions were mainly derived from the dilution of OCs, associated to an increase in total blood volume of children at the age of 4 and 14 years. Despite the reduction in OCs concentrations, the total serum burdens of 4,4′-DDE and Σ_7PCBs, were higher in adolescents than at birth. Increases in OCs total serum burden occurred both in breastfed and non-breastfed children, but were significantly higher in the first. *Conclusions*: Even after decades of banning OCs production and use, current young generations in westernized countries are still bioaccumulating these compounds. Given the potential health effects of OCs, especial attention should be paid in the control of secondary emissions in the environment and in the control of food production and contamination. In countries with endemic malaria it is important to work towards effective alternatives to the use of DDT.

1. Introduction

Organochlorine compounds (OCs) include a wide range of chemicals, such as polychlorobiphenyls (PCBs), dioxins, dichlorodiphenyldichloroethylene (DDE) or hexachlorobenzene (HCB). They are lipophilic synthetic chemicals and belong to the family of persistent organic pollutants (POPs) because they persist in the environment for years and bioaccumulate through the food chain in human and animal fatty tissues (Carpenter, 2011). Through the placenta, humans start being exposed to OCs during prenatal life. After birth, in the first months or years of life, mothers can transfer a certain amount of these compounds through breastfeeding because of the lipophilic properties of POPs

Abbreviations: 4,4′-DDE, dichlorodiphenyldichloroethylene; 4,4′-DDT, dichlorodiphenyltrichloroethane; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; OCs, organochlorine compounds; PeCB, pentachlorobenzene; PCBs, polychlorobiphenyls; POPs, persistent organic pollutants.

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(LaKind et al., 2004; Ribas-Fito et al., 2005). After breastfeeding, the child continues being exposed to OCs through diet, which currently is the most important source of exposure in the general population (Llop et al., 2010; Vrijheid et al., 2010). Because of their persistency and the health effects associated to OCs exposure, including neurotoxic, immunotoxic and endocrine and reproductive health effects, as well as cancer, the production and use of most OCs are currently banned in the majority of countries, which has led to a general reduction of the levels in the environment and human tissues (Carpenter, 2011). In Spain, these compounds were banned between the early 70s and the late 80s (Ribas-Fito et al., 2005). However, HCB has been unintentionally produced until now as a subproduct of industrial processes. This is the case of the chloro-alkali plant in the village of Flix, area of Ribera d'Ebre, Catalonia, Spain; in this village of around 5000 inhabitants, air and human serum samples collected in the early 90s had the highest levels of HCB ever reported worldwide (Grimalt et al., 1994; Sala et al., 1999, 2001), which made this case unique and particularly relevant at an international level (Ballester et al., 2000; Herrero et al., 1999; Ozalla et al., 2002; Ribas-Fito et al., 2003c; Sunyer et al., 2008). Furthermore, because of the high levels of HCB found in the area, a birth cohort study was set up in 1997 with the aim to study the health effects of prenatal and postnatal exposure to environmental pollutants, particularly OCs and mercury, in children (Guxens et al., 2012). In this same year, another birth cohort was set up in the island of Menorca, Spain, with the aim to study the effects of early life exposure to air-borne irritants and allergens on allergy and asthma (Guxens et al., 2012). In both sites OCs exposure was evaluated at birth and at the age of 4 years (Carrizo et al., 2007b, 2008; Sala et al., 2001) as well as the health effects associated (Ribas-Fito et al., 2002, 2003a,b, 2006a,b, 2007a,b). The inclusion of both birth cohorts in a common study was of interest because of the different exposure scenarios in each site: whereas Ribera d'Ebre was an industrial site with a high production of OCs, Menorca had a rural environment without industrials sites manufacturing this type of chemicals. Thus, children from the latter constituted an example of the background exposure to these pollutants in western countries (Carrizo et al., 2007b). In 2012, when children were around 14 years of age, a new follow-up with a common protocol was performed in both study areas and POPs were analyzed in serum samples of participant adolescents. To our knowledge, no other birth cohort study has assessed exposure to OCs at different ages from birth until adolescence and in two different settings with contrasted sources of exposure and levels of OCs. Thus, the aims of the present study are to assess 1) the current concentrations of OC exposure in adolescents of both birth cohort studies, 2) the temporal trends of OC concentrations and total serum burdens from birth until adolescence and 3) the influence of breastfeeding in these temporal trends. Because OC exposure concentrations at birth and at the age of 4 years and differences between the two birth cohorts were already assessed and discussed in a previous study (Carrizo et al., 2007b), in the present study we will focus on exposure concentrations at the age of 14 years and on the exposure temporal trends from birth up to adolescence.

2. Materials and methods

2.1. Study populations

A total of 102 singleton children born in the main hospital of the Ribera d'Ebre between 1997 and 1999 were included in the Ribera d'Ebre birth cohort study. OCs were measured at three different follow-ups: at birth (cord blood, N = 73), at the age of 4 years (serum, N = 58, years 2001–2003) and at the age of 14 years (serum, N = 36, year 2012). Additionally, at the age of 14 years, schoolmates of children of the original cohort were invited to participate in the study (all children attended the same high school in the village of Flix); 15 accepted to participate and to provide serum samples.

Between 1997 and 1998 the Menorca birth cohort study recruited all women presenting for antenatal care. In total, 482 children were enrolled and OCs were measured at three different follow-ups: at birth (cord blood, N = 405, years 1997–1998), at the age of 4 years of children (serum, N = 285, years 2001–2002) and at age 14 years (serum, N = 43, year 2012). Both birth cohort studies were approved by the ethical committee of the Institut Municipal d'Investigació Mèdica (IMIM, Barcelona) and the hospitals of each area.

2.2. Exposure assessment

OCs in serum samples were analyzed by gas chromatography (GC) with electron capture detection and GC coupled to chemical ionization negative-ion mass spectrometry. All of the analyses were carried out in the Department of Environmental Chemistry (IDAEA-CSIC). Details of the methodology have been reported elsewhere (Carrizo et al., 2006, 2007b; Ribas-Fito et al., 2003b). The limits of detection (LOD) and quantification (LOQ) ranged between 0.01 ng/mL and 0.05 ng/mL depending on the year of analysis and the compound analyzed. Compounds measured in all samples were pentachlorobenzene (PeCB), four isomers of hexachlorocyclohexanes (α-HCH, β-HCH, δ-HCH, γ-HCH), HCB, dichlorodiphenyltrichloroethane (4,4′-DDT), and its main metabolite 4,4′-DDE, and seven PCB congeners (28, 52, 101, 118, 138, 153 and 180), which were summed into one single exposure variable (Σ_7PCBs). The protocol and instruments used were the same in the three follow-ups, and the method performed satisfactorily in repeated international intercalibration exercises within the Arctic Monitoring and Assessment Program (Arctic Monitoring Assessment Programme, 2002).

At the age of 14 years, 23 children from Ribera d'Ebre (3 not belonging to the original cohort) and 43 from the Menorca birth cohort had information on total lipid serum levels. This information was used to calculate OC concentrations in ng/g lipid [based on the equation of (Phillips et al., 1989)] and compare these exposure concentrations with those of previous studies including adolescent population. However, because total lipid data was only available for some of the participants at the age of 14 years, the main results of the present study are based on non-lipid adjusted OC concentrations (ng/mL).

To calculate the total serum burden of OCs (ng) at each age, we estimated the total blood volume (mL) of each child and multiplied it by the concentrations of each OC (ng/mL). The total blood volume was estimated using the body weight and the gender of the child according to different references consulted (Booth; Green; Linderkamp et al., 1977; Stephen, 2011). At birth (cord blood) we estimated 85 mL of blood per kg of body weight, at age 4 years we estimated 75 mL per kg of body weight, and at age 14 years we estimated 65 mL per kg of body weight for girls and 70 mL per kg of body weight for boys.

2.3. Breastfeeding definition

At the age of 1 and 2 years of the child mothers were asked whether they had breastfed their child. In the present study, we classified children as breastfed children (any breastfeeding, independently of the duration) and non-breastfed children.

2.4. Data analysis

OCs exposure concentrations (ng/mL) at each follow-up were calculated for each study population separately (median and the 25th and 75th percentiles). Children of Ribera d'Ebre not belonging to the original cohort were treated separately in order to compare OC concentrations with those of the original cohort. We compared the total serum burden of OCs (median and the 25th and 75th percentiles) between birth cohort studies and between breastfed and not breastfed children. Statistical significant differences ($p \leq 0.05$) were tested with the Kruskal–Wallis test.

Two sensitivity analyses were performed. In one of them we compared the general results with those from children providing complete exposure information at all three ages: 61 children had complete information on OCs exposure concentrations (ng/mL) and 45 children additionally had complete information on total blood volume burden of OCs (ng). As changes in the amount of adipose tissue in the body can lead to significant changes in the serum OC concentrations (Porta et al., 2012), we conducted another sensitivity analysis including only children with a healthy weight at both the ages of 4 and 14 years. To classify children, we first calculated their body mass index (BMI) and used the male and female CDC growth charts to determine whether a child was underweight (<5th percentile), healthy weight (≥5th and <85th percentile), overweight (≥85th and <95th percentile) or obese (≥95th) (Centers for Disease Control, Prevention (CDC), 2000; Kuczmarski et al., 2002).

3. Results

3.1. Exposure concentrations

In children of Ribera d'Ebre, out of all OC compounds measured, HCB was the compound with the highest concentration at birth (median = 1.13 ng/mL), at age 4 years (0.98 ng/mL) and at age 14 years (0.16 ng/mL). At 14 years the sum of the seven PCB congeners (Σ_7PCBs) was 0.20 ng/mL, being PCB153 the congener present at higher concentrations (Table 1 and Table A). Concentrations of 4,4′-DDE and β-HCH in adolescents were of 0.12 ng/mL and 0.02 ng/mL, respectively (Table 1). At 14 years there were no significant differences in OC concentrations between children of the original cohort and their schoolmates joining the study in 2012, except for PeCB, δ-HCH and DDT (p-value for differences between study populations ≤0.05), but very few children had detectable concentrations and in general these were very low in both study populations (Table A). In the Menorca birth cohort, 4,4′-DDE was the compound with the highest concentrations at birth (median = 1.03 ng/mL), at age 4 years (0.81 ng/mL) and at age 14 years (0.33 ng/mL). In this birth cohort, the concentration of Σ_7PCBs measured at the age of 14 years was 0.31 ng/mL, being PCB153 the congener present at higher concentrations (Table 1 and Table B). Concentrations of HCB and β-HCH in the adolescents were 0.04 ng/mL and 0.02 ng/mL, respectively (Table 1). Concentrations of other OCs are shown in Table B.

At the age of 14 years, concentrations of all OCs significantly differed between the birth cohorts of Ribera d'Ebre and Menorca ($p \leq 0.05$; Fig. 1) except PCB153, for which no differences were observed (Table A and Table B). Children of Ribera d'Ebre had higher concentrations of HCB and children of Menorca had higher 4,4′-DDE and Σ_7PCBs concentrations. These results were the same with the inclusion or exclusion of children from Ribera d'Ebre not belonging to the original cohort (data not shown). In both study sites, temporal trends in concentrations from birth up to adolescence showed decreasing concentrations of all OCs (Table 1 and Fig. 1); only concentrations of Σ_7PCBs in adolescents

Table 1
Characteristics of the study populations [original birth cohort of Ribera d'Ebre and birth cohort of Menorca].

	Ribera d'Ebre (Initial N = 102)		Menorca (Initial N = 482)	
	N		N	
Age of the child (years) at each visit (mean, min–max)				
Visit 4 years	74	4.2 (3.4, 5.3)	422	4.4 (3.4, 4.8)
Visit 14 years	35	13.6 (11, 14.5)	327	14.6 (14.2, 15.7)
Female (%)	102	54.9	482	48.6
Breastfeeding (%)	91	75.8	482	82.4
OC concentrations (ng/mL) (median, 25th–75th)				
β-HCH				
Cord blood	70	0.54 (0.03, 1.07)	405	0.16 (0.16, 0.52)
Serum visit 4 years	58	0.31 (0.19, 0.48)	285	0.20 (0.11, 0.30)
Serum visit 14 years	36	0.02 (0.01, 0.04)	43	0.02 (0.01, 0.03)
HCB				
Cord blood	70	1.13 (0.80, 1.69)	405	0.68 (0.40, 1.02)
Serum visit 4 years	58	0.98 (0.66, 1.48)	285	0.31 (0.19, 0.50)
Serum visit 14 years	36	0.16 (0.10, 0.25)	43	0.04 (0.02, 0.06)
4,4′-DDE				
Cord blood	70	0.86 (0.50, 1.68)	405	1.03 (0.57, 1.94)
Serum visit 4 years	58	0.75 (0.38, 1.32)	285	0.81 (0.44, 1.77)
Serum visit 14 years	36	0.12 (0.09, 0.19)	43	0.33 (0.23, 0.58)
Σ_7PCBs				
Cord blood	70	0.14 (0.10, 0.47)	405	0.71 (0.53, 0.97)
Serum visit 4 years	58	0.81 (0.20, 1.21)	285	0.82 (0.58, 1.23)
Serum visit 14 years	36	0.20 (0.12, 0.28)	43	0.31 (0.24, 0.42)
OC total serum burdens (ng)[a] (median, 25th–75th)				
β-HCH				
Cord blood	70	152.0 (7.2, 290.4)	405	52.2 (42.7, 120.7)
Serum visit 4 years	49	460.0 (289.8, 667.0)	178	279.9 (165.0, 429.5)
Serum visit 14 years	31	53.7 (40.7, 133.0)	43	52.4 (28.1, 102.1)
HCB				
Cord blood	70	312.9 (219.6, 486.6)	405	182.7 (120.1, 273.5)
Serum visit 4 years	49	1439.3 (943.1, 2755.6)	178	414.0 (271.6, 706.1)
Serum visit 14 years	31	484.1 (229.6, 1065.3)	43	149.4 (75.1, 232.5)
4,4′-DDE				
Cord blood	70	232.3 (122.3, 434.0)	405	275.1 (161.9, 503.1)
Serum visit 4 years	49	1050.0 (642.2, 1632.0)	178	1291.0 (645.6, 2646.3)
Serum visit 14 years	31	410.1 (301.8, 687.0)	43	1342.1 (791.8, 2519.0)
Σ_7PCBs				
Cord blood	70	38.1 (28.4, 150.7)	405	191.2 (145.5, 266.5)
Serum visit 4 years	49	1047.6 (305.7, 1647.4)	178	1201.1 (828.1, 1750.8)
Serum visit 14 years	31	703.9 (503.8, 1070.3)	43	1117.6 (807.2, 1628.1)

[a] Estimated by multiplying the concentrations of OCs (ng/mL) by the total blood volume (mL) at each age, which was estimated from the weight of the child (see Section 2 Materials and methods).

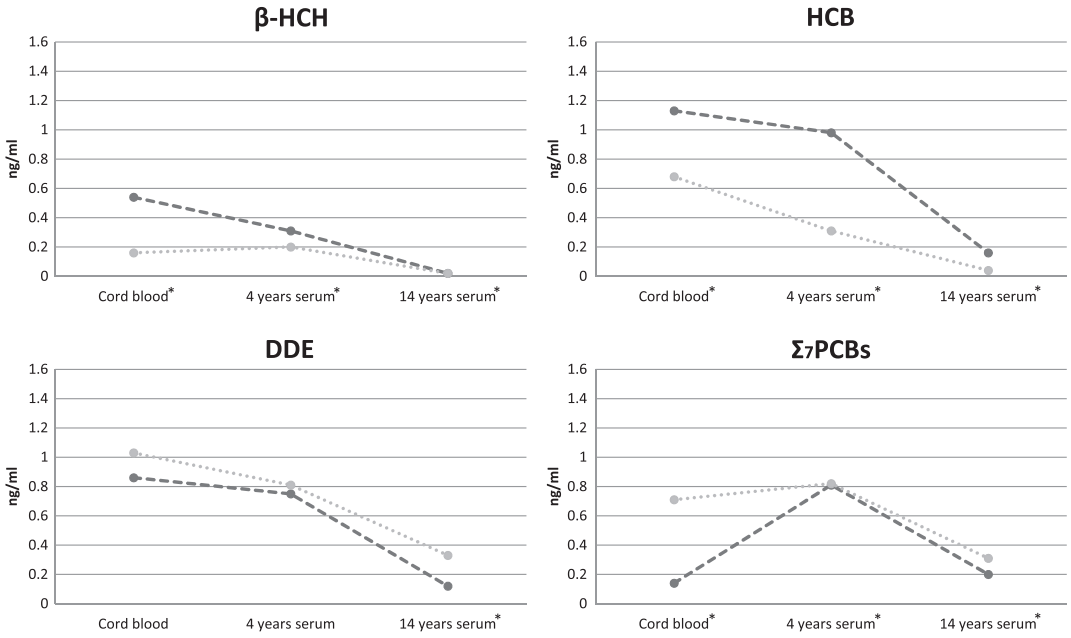

Fig. 1. Evolution of serum concentrations (ng/mL, 50th percentile) of β-HCH, HCB, 4,4′-DDE and Σ_7PCBs in the birth cohorts of Ribera d'Ebre (dark line) and Menorca (light line). Ribera d'Ebre N = 70 (cord blood serum), N = 58 (serum 4 years), N = 36 (serum 14 years) and Menorca N = 405 (cord blood serum), N = 285 (serum 4 years), N = 43 (serum 14 years). *Significant differences ($p \leq 0.05$) between children of the two birth cohorts.

of the Ribera d'Ebre increased a little compared to concentrations at birth.

3.2. OC's total serum burdens

We observed that in both study populations the total serum burdens of all OCs increased from birth to 14 years, with the exception of β-HCH in both birth cohorts and HCB in the Menorca birth cohort, which showed an opposite pattern (Table 1 and Fig. 2). The most important increases were observed at the age of 4 years, moment in which the total serum burdens of all OCs reached up to six times the total serum burdens at birth. In Ribera d'Ebre the Σ_7PCBs burden at the age of 4 years (1047.6 ng) was 27.6 times higher than at birth (38.1 ng) (Table 1 and Fig. 2). In this birth cohort, the most important total serum burdens at the age of 14 years were those of Σ_7PCBs (703.9 ng), followed by HCB (484.1 ng) and 4,4′-DDE (410.1 ng). In the Menorca birth cohort, the highest total serum burdens at 14 years were those of 4,4′-DDE (1342.1 ng), followed by Σ_7PCBs (1117.6 ng)

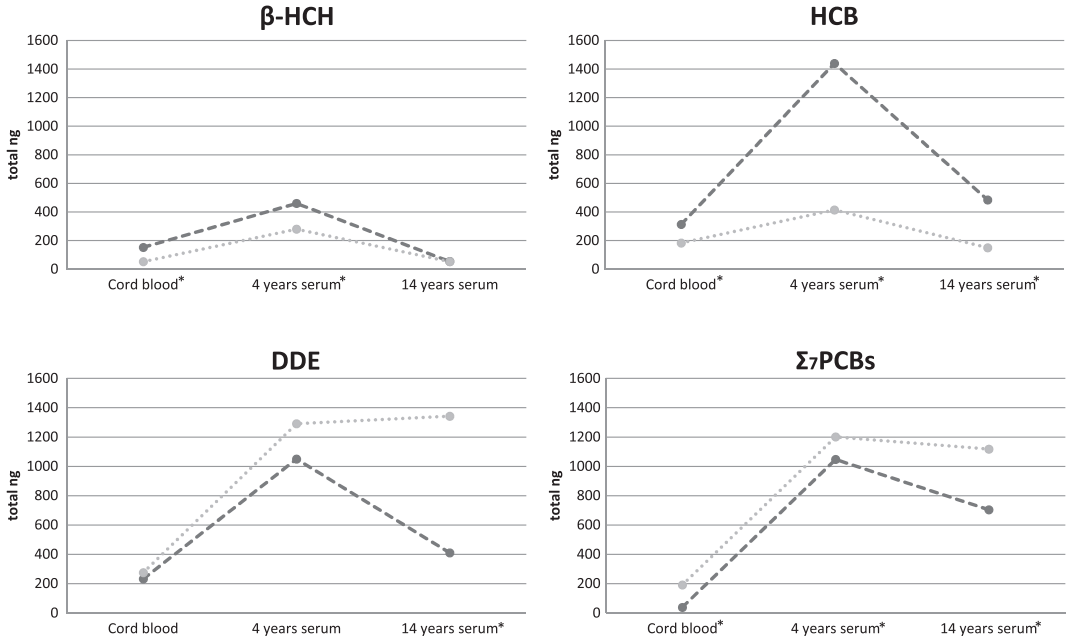

Fig. 2. Evolution of total serum burden (ng, 50th percentile) of β-HCH, HCB, 4,4′-DDE and Σ_7PCBs in the birth cohorts of Ribera d'Ebre (dark line) and Menorca (light line). Ribera d'Ebre N = 70 (cord blood serum), N = 49 (serum 4 years), N = 31 (serum 14 years) and Menorca N = 405 (cord blood serum), N = 178 (serum 4 years), N = 43 (serum 14 years). *Significant differences ($p \leq 0.05$) between children of the two birth cohorts.

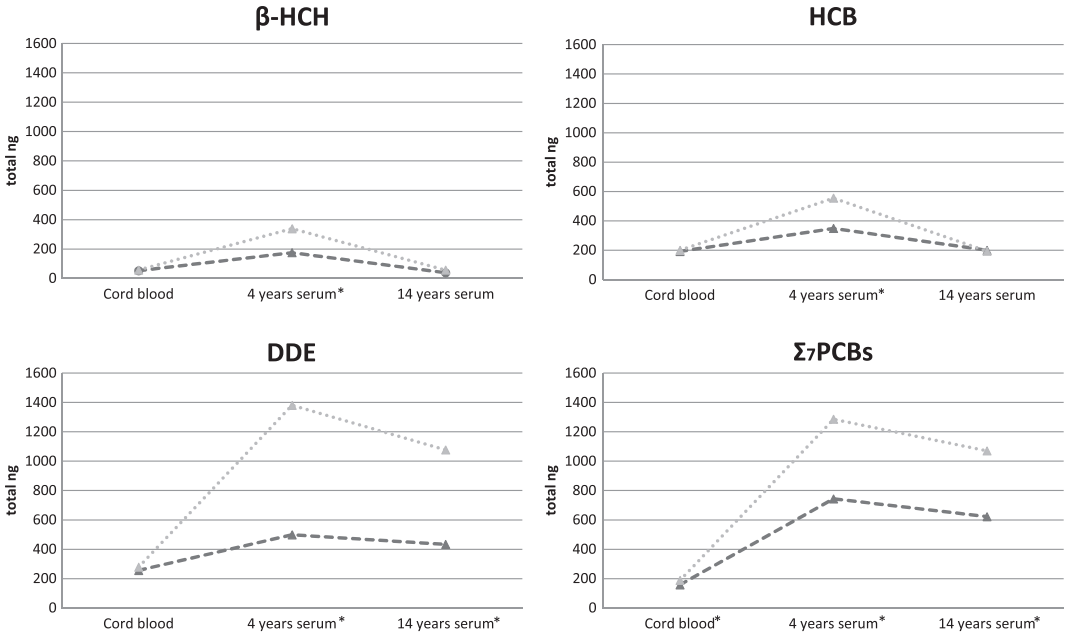

Fig. 3. Evolution of total serum burden (ng, 50th percentile) of β-HCH, HCB, 4,4′-DDE and Σ_7PCBs in breastfeeders (light line) and non-breastfeeders (dark line). Breastfeeders N = 383 (cord blood serum), N = 193 (serum 4 years), N = 60 (serum 14 years) and non-breastfeeders N = 85 (cord blood serum), N = 33 (serum 4 years), N = 12 (serum 14 years). *Significant differences ($p \leq 0.05$) between breastfeeders and non-breastfeeders.

and, much lower HCB (149.4 ng) (Table 1 and Fig. 2). While for 4,4′-DDE, Σ_7PCBs and HCB there were statistically significant differences between the two birth cohorts, no differences were observed for β-HCH (Table 1 and Fig. 2).

3.3. The role of breastfeeding

The total serum burdens of all OCs were increased with increasing age both in breastfed and non-breastfed children, however, the increase was more accentuated among the first (Fig. 3). At the age of 4 years there were statistically significant total serum burden differences between breastfeeders and non-breastfeeders for all OC compounds (Fig. 3). At the age of 14 years, the total serum burdens of β-HCH and HCB did not differ between breastfeeders and non-breastfeeders. Total serum burdens for 4,4′-DDE and Σ_7PCBs were higher among breastfeeders (1076.5 ng and 1070.2 ng, respectively) than among non-breastfeeders (433.5 ng and 622.3 ng) at this age (Fig. 3).

3.4. Sensitivity analyses

The observed trends in the main analysis did not change when only children with complete exposure information were included in the analyses (data not shown). The only differences involved an intensification of the maximum concentration at the age of 4 years for 4,4′-DDE and HCB in the Menorca and Ribera d'Ebre cohorts, respectively. For instance, the median total serum burdens of 4,4′-DDE in Menorca at age 4 years reached up to 2040 ng in the sensitivity analysis. We also obtained similar results when we only included children with a healthy weight at both the ages of 4 and 14 years in the analyses (N = 146 of the 245 children with complete information on BMI) (data not shown).

4. Discussion

Results of the present study show an important decrease in concentrations (ng/mL) of OCs from birth up to adolescence in two Spanish birth cohorts. Total serum burden calculations show, however, that the reduction in OC concentrations was mainly due to the increase in dilution of these compounds in the total blood volume with age. Indeed, at the age of 14 years the total serum burdens of 4,4′-DDE and Σ_7PCBs, especially in Menorca, were increased compared to total serum burdens at birth. In Ribera d'Ebre the total serum burden of HCB at age 14 years was also increased. These increases were more accentuated in breastfed children.

4.1. OC concentrations in adolescents

There are few studies assessing OCs exposure in adolescent subjects, and those available include study populations of a wide range of ages (between 7 and 20 years) and most of them were conducted more than ten years ago (Centers for Disease Control and Prevention, 2009; Cuadra et al., 2006; Linderholm et al., 2011; Newman et al., 2009; Santos Filho et al., 2003; Schettgen et al., 2011; Schroijen et al., 2008; Schulz et al., 2009) (Table 2). Compared to adolescents of European and North-American countries (Germany, Belgium, the US and Canada), participants of Ribera d'Ebre and Menorca have similar OCs exposure concentrations, with some exceptions (Table 2). For instance, HCB concentrations in Ribera d'Ebre were higher than in adolescents of other westernized countries (Centers for Disease Control and Prevention, 2009; Newman et al., 2009; Schettgen et al., 2011; Schroijen et al., 2008; Schulz et al., 2009). On the contrary, adolescents of the Menorca birth cohort showed the lowest HCB concentrations (Table 2). DDE concentrations in our study populations were similar to those reported in Germany (Schulz et al., 2009; Schettgen et al., 2011), but lower than those reported in Belgium or in the US (Centers for Disease Control and Prevention, 2009; Schroijen et al., 2008). Finally, PCB concentrations were similar to those reported in European countries (Schettgen et al., 2011; Schroijen et al., 2008; Schulz et al., 2009) but higher than those reported in the US (Centers for Disease Control and Prevention, 2009) (Table 2). In any case, differences among study populations of westernized countries are generally minimal for all the compounds. Compared to low-/middle-income countries, the most remarkable difference is in relation to DDT and DDE concentrations, which are much higher in countries like Bangladesh, Nicaragua or Brazil (Cuadra et al., 2006; Linderholm et al., 2011; Santos Filho et al., 2003) (Table 2). This is mainly due to the fact that in these countries a more recent (and intensive) use of this insecticide has taken place for agricultural purposes or to control the malaria vector, a practice still used in countries with endemic malaria (Bouwman et al., 2011; Gascon et al., 2012).

Table 2
Median OC concentrations (in ng/g lipid) found in serum of adolescents from different countries.

Location	Year of OCs assessment	n	Age	HCB	β-HCH	DDT	DDE	PCB118	PCB138	PCB153	PCB180	ΣPCBs[a]	Reference
Ribera d'Ebre	201	20[b]	11–15										
ng/mL				[0.18]	[0.01]	[0.003]	[0.12]	[0.01]	[0.04]	[0.11]	[0.04]	[0.22]	
ng/g lipid				42.0	3.0	0.6	27.1	1.4	9.0	24.5	8.5	46.5	
Menorca	2012	43	14–16										
ng/mL				[0.04]	[0.02]	[0.03]	[0.33]	[0.05]	[0.06]	[0.12]	[0.06]	[0.31]	
ng/g lipid				7.4	3.0	7.1	65.7	9.9	12.4	22.1	12.3	63.4	
Bangladesh[c]	2008	30	7–16	NA	32	326	1327	NA	8.5	7.1	3.2	NA	Linderholm et al. (2001)
Germany[d]	2003–2006	1079	7–14	[0.10]	[0.01]	NA	[0.18]	NA	[0.09]	[0.12]	[0.06]	[0.28]	Schulz et al. (2009)
Germany[d]	2003–2004	15	11–20	[0.15]	NA	NA	[0.34]	[0.02]	[0.12]	[0.15]	[0.10]	[0.40]	Schettgen et al. (2011)
Belgium	2003–2004	1679	14–15	21	NA	NA	94	NA	NA	NA	NA	66	Schroijen et al. (2008)
US	2003–2004	598	12–19	13.3	NA	ND	94	NA	4.6[e]	5.4	3.0	NA	CDC (2009)
Nicaragua[f]	2002	37	11–15	NA	NA	12	993	39	67	86	33	278	Cuadra et al. (2006)
US	2001–2002	758	12–19	13.3	NA	ND	113	NA	ND[e]	ND	ND	NA	CDC (2009)
US	1999–2000	686	12–19	13.3	NA	ND	108	NA	ND[e]	ND	ND	NA	CDC (2009)
Canada (Inuit)[g]	1995–2000	271	10–17	(0.03)	NA	NA	(0.35)	(0.06)	(0.07)[e]	(0.08)	(0.04)	NA	Newman et al. (2009)
Brazil[d,e,h]	NR	103	10–19	[2.5]	[1.3]	[0.3]	NA	NA	NA	NA	NA	NA	Santos Filho et al. (2003)

NA: Information not available (compound not analyzed or result not reported); ND: not detected.
[a] Sum of all congeners analyzed in each study.
[b] Only 20 children from the Ribera d'Ebre birth cohort had information on total lipids. Thus, results are presented for these 20 children only.
[c] Medians for the whole population were not available in the cited paper. The presented values have been calculated based on the weighted mean of the OC's median of the different groups reported.
[d] Values are expressed in [ng/mL].
[e] The reported value is the sum of PCB138 with other PCB congeners or all HCH congeners (in the case of β-HCH).
[f] Medians for the whole population were not available in the cited paper. The presented values have been calculated based on the weighted mean of the OC's median of the different groups reported (we excluded two groups of children working in a waste-disposal site).
[g] Values are expressed in parts per billion (ppb).
[h] Mean is reported instead of the median.

4.2. Temporal trends of OC concentrations and total serum burdens

The overall decrease of OC concentrations in our study populations are in line with results obtained in previous studies focused on temporal trends of OC concentrations in adults of westernized countries (Carpenter, 2011; Garí et al., 2014; Ribas-Fito et al., 2003c; Ryan and Rawn, 2014). For instance, already between 1994 and 1999 concentrations of HCB in women of Ribera d'Ebre significantly decreased because of improvements in the incineration processes in the chlor-alkali plant (Ribas-Fito et al., 2003c). This might lead to the conclusion that the reductions in OC concentrations in adolescents of our study population are due to a reduction of the environmental background levels. However, when the total blood volume is taken into account and we calculate the total serum burden of these compounds at each age, we observe an increase of the total serum burdens of all OCs at age 4 years. Compared to birth, at age 14 years total serum burdens of 4,4′-DDE and Σ_7PCBs remain increased, although there is a reduction compared to the total serum burdens at age 4 years. Thus, results indicate that there is not a reduction of OC exposure in our study populations. The big increase in total serum burdens from birth up to age 4 years is partly due to breastfeeding, as the results in Fig. 3 show. However, in non-breastfed children total serum burden increases also occurred, which indicates that breastfeeding is not the only exposure determinant and that diet, as already reported by previous studies in adults (Llop et al., 2010; Vrijheid et al., 2010), is probably the other main source of OCs exposure in our children. We see that from the age of 4 years up to the age of 14 years total serum burdens of all OCs reduced, probably because the effect of breastfeeding is not as strong as in the first 4 years of life and because in this period children eat less amount of food per kilogram of total serum weight than in the first 4 years of life (Nicklas and Johnson, 2004), thus, the ingestion of OCs is also proportionally less. The fact that at age 14 years the total serum burdens of some OCs remained increased compared to the initial total serum burdens at birth could be explained by the influence of the environmental background levels of these compounds, as is the case of HCB in Ribera d'Ebre, 4,4′-DDE in Menorca (maybe due to a more intense use of DDT in this rural site in the past), and PCBs in both study populations. Increases in PCBs exposure between 1994 and 1999 were already reported in adult women in Ribera d'Ebre (Ribas-Fito et al., 2003c), something also observed for the total serum burdens of PCBs in the present study. It is remarkable that although in Ribera d'Ebre HCB serum burdens reached similar levels to those reported for 4,4′-DDE and Σ_7PCBs at the age of 4 years, children were able to substantially reduce HCB exposure at the age of 4 years. However, reductions were less important for 4,4′-DDE and Σ_7PCBs. This indicates that it is possible to slowly eliminate these compounds from our bodies unless there is a continuous or constant exposure to them (i.e. through diet).

Overall, results of the present study indicate that breastfeeding in the first 4 years of life and diet along the whole study period have an important influence on the total serum burden of OCs. Results also indicate that local environmental background levels of OCs are still a key factor in the final total serum burdens of the studied subjects. We can also conclude that, since birth, reductions in OC concentrations (ng/mL) were mainly derived from the dilution of OCs, associated to an increase in the total blood volume of children at the age of 4 and 14 years. Although these compounds bioaccumulate, OCs total serum burdens in the present study did not keep increasing in children between the 4th and the 14th year of life due to different factors: less influence of breastfeeding in this period, reductions in food intake per kilogram of body weight and/or reductions of the environmental exposures in this second period of study. Because OCs accumulate in fatty tissue, changes in body weight and body fat could have also influenced OC concentrations over time (Porta et al., 2012). A sensitivity analysis using only children with a healthy BMI at 4 and 14 years did not show any difference with respect to the concentration trends of the whole study population. Thus, the observed trends in the present study do not depend on the presence of individuals with an unhealthy weight or with weight changes. In fact, in healthy weight children the percentage of fat remains constant along childhood (around 20%) whereas in obese children a gradual fat increase of about 10% along a period of 10 years is often observed (Knittle et al., 1979). The lack of dependence of the observed trends from children with an unhealthy weight or with weight changes supports that the concentration differences identified in the present study constitute a general feature of the OC accumulation in the first life years.

4.3. Strengths and limitations

To our knowledge, this is the first prospective study assessing the temporal trends of concentrations and total serum burdens of OCs from birth until adolescence (a study period of 14 years) and which also compares two sites with very different exposure scenarios. Based on previous studies (Llop et al., 2010; Vrijheid et al., 2010), in the present work we hypothesize that diet is one of the most influencing factors in the final OCs total serum burdens in Ribera d'Ebre and Menorca children. Unfortunately, we did not have accurate and complete diet information to assess the role of diet and particularly of different food items (fish, meat, dairy products or vegetables) in both study populations.

One aspect to be considered in this comparison of OC concentrations at different ages is the lower lipid content in cord blood serum compared to venous serum (Aylward et al., 2014; Vizcaino et al., 2014). The average lipid content in cord blood and the 4 years serum samples of the Menorca children is 2.6 and 8.2 g/L, respectively (Carrizo et al., 2007a), and the average lipid concentrations in the 14 years serum samples is 5.2 g/L. No data on lipid contents is available in children of the Ribera d'Ebre cohort for cord blood and 4 years serum samples. In the Menorca birth cohort, lipid normalization of cord blood serum concentrations can be done by multiplying the non-lipid adjusted concentrations by a factor of 2.58, obtained from the following formula: $(8.2 + 5.2) / (2 * 2.6)$. Thus, for comparative purposes, cord blood concentration values of Table 1 and Fig. 1 should be transformed into 0.41, 1.75, 2.66 and 1.83 ng/mL for β-HCH, HCB, 4,4′-DDE and Σ_7PCBs, respectively. Compared to non-lipid normalized values, these are also higher than those observed at the age of 4 and 14 years. These results indicate that, in qualitative terms, OC concentrations constitute a stronger potential chemical insult in the prenatal period than in the postnatal period. Likewise, lipid normalization of total serum burdens at birth (Table 1 and Fig. 2) provides amounts of 134.7, 471.4, 709.8 and 493.3 ng for β-HCH, HCB, 4,4′-DDE and Σ_7PCBs, respectively. These values obviously increase the total body burden serum at birth. However, with the exception of HCB, the serum burdens at ages 4 and 14 years are again higher than at birth. In this respect, it has to be outlined that whereas the burdens of β-HCH and HCB tend to decrease with age, those of 4,4′-DDE and Σ_7PCBs at 4 and 14 years of age are higher than at birth even after lipid correction.

Another limiting aspect of the present study is that the study population was small at the age of 14 years and that there was a small number of subjects with complete information on OCs exposure and total blood volume. However, and as shown, our results were robust and consistent in the different sensitivity analyses performed. It is important to note that in Ribera d'Ebre contact was lost with the families participating in the cohort since the follow-up in 2001–2003. This lack of contact could explain our capacity to encourage them to participate in the study of 2012. This is an important difference with the Menorca birth cohort, where additional follow-ups between 2001–2003 and 2012 have been performed. We limited OCs analysis to 43 children due to budget limitations but general participation in the follow-up was much higher ($N = 345$). Finally, as OC levels were assessed at all follow-ups in the same laboratory and using the same protocol and instruments, differences in levels cannot be explained by differences in laboratory techniques.

5. Conclusions

Even after decades of banning OCs production and use, current young generations in westernized countries are still bioaccumulating these compounds, with higher total serum burdens at adolescent ages than at birth for 4,4′-DDE and Σ_7PCBs. However, our results show that, in qualitative terms, the concentrations of OC in utero constitute a much strong dose in the prenatal than in the postnatal period, particularly after normalization to serum lipid content. In the present work, breastfeeding, diet and point-source secondary emissions had different degrees of influence in the final total serum burdens in each studied area. Given the bioaccumulation of OCs and their potential health effects, especial attention should be paid in the control of secondary emissions of these pollutants in the environment and in the control of food production and contamination. In countries with endemic malaria it is important to work towards effective alternatives to the use of DDT.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2014.10.010.

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