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Placental docosahexaenoic and arachidonic acids correlate weakly with placental polychlorinated dibenzofurans (PCDF) and are uncorrelated with polychlorinated dibenzo-*p*-dioxins (PCDD) or polychlorinated biphenyls (PCB) at delivery: A pilot study

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ABSTRACT

Long chain polyunsaturated fatty acids (LC-PUFA), ARA (arachidonic acid, 20:4$n-6$) and DHA (docosahexaenoic acid, 22:6$n-3$) have positive effects and environment pollutants, polychlorinated dibenzo-*p*-dioxins/dibenzofurans(PCDD/F) and polychlorinated biphenyls (PCB) have negative effects on neural development during early life. Placental dioxin/PCB serves as markers for cumulative exposure to fetus. Fatty acid composition of placenta depends on nutrient supply during pregnancy, serving as indicators for fetal ARA and DHA accretion. This study investigated correlation between placental PCDD/F and PCB toxic equivalent (TEQ) and LC-PUFA in 34 pregnant women from Taiwan. Placental PCDF TEQ were inversely correlated with placental ARA ($p = 0.020$), C20:3$n-6$ ($p = 0.01$), C22:4$n-6$ ($p = 0.04$), C22:5$n-6$ ($p < 0.01$) and with DHA ($p = 0.03$), but ARA and DHA did not vary with PCDD, dioxin-like and indicator PCB. After adjustment for age and body mass index, a one-unit PCDF TEQ increase was associated with 1.021%w/w and 0.312%w/w decreases in ARA ($\beta = -1.021$, $p = 0.03$) and DHA ($\beta = -0.312$, $p = 0.03$). Since ARA and DHA were unrelated to three classes of toxins, and a weak negative association was found with PCDF, these data provide no basis for discouraging marine fish consumption during pregnancy for Taiwan women on the basis of these organics. Pregnant women should consume fish for its unique package of nutrients while avoiding few species with high organic pollutant or mercury contamination.

1. Introduction

Two of the $n-6$ and $n-3$ long chain polyunsaturated fatty acids (LC-PUFA), arachidonic acid (20:4$n-6$, ARA) and docosahexaenoic acid (22:6$n-3$, DHA), make up more than 25% of the total fatty acids in the central nervous system (Diau et al., 2005). ARA, which plays an important role normal growth (Carlson et al., 1993), is an upstream metabolite of adrenic acid (22:4$n-6$). Adrenic acid is the third most abundant brain LC-PUFA and may be essential to the development of myelin during the early postnatal period in infants (Martinez and Mougan, 1998; O'Brien and Sampson, 1965; Wijendran et al., 2002). DHA is essential to neural and retinal development (Uauy et al., 2000) and $n-3$ LC-PUFA supplementation has been reported to effectively promote the early development of visual system (SanGiovanni et al., 2000). The most rapid period of human brain growth occurs from the last trimester *in utero* and continues up to the second year of postnatal life (Martinez, 1992). During the fetal period, developing human infants have a limited ability to synthesize $n-6$ and $n-3$

Abbreviations: ARA, arachidonic acid; DHA, docoxahexenoic acid; LA, linoleic acid; LCPUFA, Long chain polyunsaturated fatty acids; LNA, linolenic acid; PCDDF, polychlorinated dibenzo-*p*-dioxins; PCDF, Polychlorinated and dibenzofurans; PCB, polychlorinated biphenyls; TEQ, toxic equivalents.

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LC-PUFA, and therefore obtain the ARA and DHA they need mostly through placental transfer (Carnielli et al., 1996; Greiner et al., 1997; Salem et al., 1996; Su et al., 2001). After delivery, their sources of LC-PUFA include human milk, formula enriched with LC-PUFA, and foods such as marine fish, egg and meat as well as self-synthesis of the 18 carbon precursor (Koletzko et al., 2008). The placenta requires substantial amounts of LCPUFA, both DHA and ARA, from body stores or diet during the rapid growth of the fetus which occurs during the first trimester of gestation (Haggarty, 2004). DHA and ARA are channeled much faster through placenta than other fatty acids including their respective 18 carbon polyunsaturates (PUFA) precursors, linoleic acid (LA, 18:2$n-6$) and linolenic acid (LNA, 18:3$n-3$) (Haggarty et al., 1999). This preferential transfer is due to the importance of these two LC-PUFA to fetal development (Dutta-Roy, 2000; Brenna and Lapillonne, 2009). Thus, the placenta is of pivotal importance for the selective channeling of ARA and DHA from the maternal diet and body stores of the two fatty acids to the fetus.

Polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/F), or dioxins, are a group of polyhalogenated and lipophilic pollutants derived from a variety of industrial and combustion sources. Polychlorinated biphenyls (PCB), which exert dioxin-like properties, were widely used for many industrial applications in Taiwan prior to 1976, when their use was banned. Perinatal exposure to dioxin and PCB results in low birth weight and retarded postnatal growth (Fein et al., 1984), delayed psychomotor development (Koopman-Esseboom et al., 1996; Weisglas-Kuperus et al., 1995), altered neurological development (Huisman et al., 1995; Jacobson and Jacobson, 1996) and intellectual development (Jacobson and Jacobson, 1996). These toxic organochlorines are resistant to biodegradation and are mainly bioaccumulated through the food chain (Smith and Gangolli, 2002). Approximately 90% of human exposure to these toxins is reported to occur through diet, with foods of animal origin including meat, fish and dairy products (Fiedler et al., 1997; Huang et al., 2007; Liem et al., 2000). Because 90–95% of exposure to dioxins are derived from food (Liem et al., 2000) and fetus is almost completely dependent on the placenta for nourishment (Haggarty, 2004), placental dioxin and PCB levels may represent fetal exposure. Blood dioxin levels are generally used to estimate exposure of dioxins/PCB above background levels. Schecter et al. (1998) and Chao et al. (2004) have reported that dioxin levels in maternal blood and breast milk can represent human body burden and postnatal exposure. Placenta levels of this pollutant are linearly correlated with the level in the maternal blood, human milk, and cord blood in 20 Taiwanese women who provided the four specimens (Wang et al., 2004). Pearson correlation coefficient between placental tissue and maternal blood is 0.74 for PCDD/DF, and 0.84 for Dioxin-like PCB. Therefore, placental levels of dioxin and PCB can also serve as an indicator of cumulative fetal exposure to these toxins (Schecter et al., 1998).

ARA can be obtained from the conversion of the 18C precursor, LA (Mohrhauer and Holman, 1963) or from foods containing preformed ARA including meat, daries, eggs and fish (Anderson et al., 1975; Mann et al., 1995; Posati et al., 1975). Similarly, DHA can also be obtained from consumption of marine fish or other types of seafood, which generally contain ample amounts of this fatty acid and other $n-3$ LC-PUFA.

Because of the similar chemical properties and origins of food sources, it is possible that delivery of these $n-3$ and $n-6$ LC-PUFA to the fetus may also expose the fetus to lipophilic organo-chlorines. To date, there has been no study analyzing the relationship between placental dioxins and PCB and placental LC-PUFA including ARA and DHA in women of childbearing age. This study analyzed placental PCDD/F and PCB toxic equivalent (TEQ) levels in relation to concentrations of $n-6/n-3$ LC-PUFA in 34 pregnant women from Taiwan.

2. Materials and methods

2.1. Participants characters

This cohort study was originally established in year of 2001. Pregnant women who had no clinical complications but visiting for regular pregnancy check-ups were recruited from the Obstetrics Department of a medical center in Taichung, a city located on the western coast of central Taiwan. These participants, aged 25–34 years old, gave birth in the same hospital between December 1, 2000 and November 2001. Very recently, we reported on the relationships between diet and placental TEQ levels of PCDD/F or PCBs among the 109 pregnant women recruited from this cohort (Huang et al., 2007). In this pilot study, we randomly selected 34 placental tissues from the 109 pregnant women and further examined relations between placental levels of dioxin/PCBs and fatty acids. Participants were interviewed by professional research nurses at which time they completed questionnaires related to demographic characters, reproductive and medical history. The body mass index (BMI) was recorded as pre-pregnancy BMI. The Human Ethical Committee of the National Health Research Institutes in Taiwan approved protocol for this study. All participants participating in this study provided informed consent.

2.2. Analysis of placental PCDD/F or PCB by gas chromatography and high resolution mass spectrometry

Placental tissues were collected during delivery, washed in saline, and frozen at −80 °C as reported previously (Wang et al., 2004). These specimens were placed in chemically clean containers and shipped on dry ice to the ERGO Laboratory in Germany for analysis. Concentrations of 17 specific congeners of 2,3,7,8-substituted PCDD/F, 12 dioxin-like PCB and six indicator-PCB were analyzed using gas chromatography and high resolution mass spectrometry (HP 5890 series II/VG-autoSpec) as described previously (Chao et al., 2007). The methods used to perform the analysis have been validated previously by international quality-control studies (WHOROE, 1995). Low, mid and high levels of PCDD/F or PCB were classified as 33.3 and 66.6 percentiles for PCDD, PCDF, total indicator PCB and dioxin-like PCB.

Placental lipid content was analyzed using a gravimetrical method. The detection limits for PCDD/F ranged from 0.1 to 20 pg/g lipid, and those for dioxin-like PCB ranged from 0.2 to 150 pg/g lipid. The coefficient of variation for concentrations of two blinded samples was less than 15% for most of the congeners except for OCDD (24%) and 1, 2, 3, 4, 6, 7, 8-HpCDF (22%). While all 17 congeners as well as 12 dioxin-like PCB have the same mode of action, they have different binding affinity to aryl hydrocarbon receptor (AhR) and subsequently result in various toxic potencies. AhR is a cytosolic receptor protein present in most vertebrate tissues with the highest affinity for 2,3,7,8-tertrachlorodibenzodioxin (TCDD) with TEF of 1.0" (Safe, 1986). We calculated the toxic equivalents (TEQ) of PCDD/F and PCB based on toxic equivalent factors (TEF) reported by the World Health Organization (WHO) (Van den Berg et al., 1998) by multiplying the concentration of each congener by the specific WHO-TEF, and reporting as pg WHO-TEQ/g lipids.

In a recent study examining the blood levels of dioxins and PCB in a general population in Taiwan, comparisons have been made between TEQ levels based on 1998 WHO-TEF (Van den Berg et al., 1998) and the latest 2005 WHO-TEF (Van den Berg et al., 2006; Hsu et al., 2009); conclusions were unchanged using 2005 WHO-TEF version.

2.3. Analysis of placental fatty acids using gas chromatography-flame ionization detection

Frozen placental tissues were stored at −80 °C until fatty acid analysis. Placental tissue lipids were extracted by a previously reported method (Bligh and Dyer, 1959) and were derivatized to fatty acid methyl esters using boron trifluoride–methanol. Fatty acid methyl esters were extracted by hexane and then separated using Hewlett–Packard GC 6890 series II equipped with a DB225 fused silica capillary column (60 m × 0.32 mm inner diameter × 0.25 μm film) and N_2 was employed as a carrier gas. The temperature for injector was set at 250 °C, and the flow rate for carrier gas was set at 25 ml/s. The oven temperature was programmed to start at 60 °C, increased at 10 °C/min to 180 °C and maintained for 5 min. It was then ramped at 3 °C/min to 220 °C and held for 29 min. Instrumental response factors were generated by running an equal weight Fatty acid methyl ester mixture (68A, Nu-Chek, Elysian, MN, USA) along with samples. The C17:0 was added to calculate quantitative profiles of placental fatty acids.

2.4. Statistical analysis

More than 87% PCDD/F of congener measurements were found to be above the lower limit of detection (LLOD). Measurement values below the LLOD were recorded as zero. Correlations between various fatty acids across low, medium and high levels of PCDD/F and PCB were determined. We examined the assumption of normality for the dioxins and the PCBs, and fatty acids levels using Shapiro–Wilks test. We analyzed data that fit the assumption of normality by Pearson correlation, and data that did not by Spearmen correlation. Multiple linear regression analysis

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was performed to examine the independent association between PCDD/F or PCB and various fatty acids after adjusting for the possible confounders age and BMI. However, considering some fatty acid levels might not fit the assumption of normality, we examined the associations using rank-transformed fatty acid levels in multiple linear regression to avoid the normal distribution assumption (Mitchell et al., 1994). All statistical operations were performed using SPSS version 17.0.

3. Results

3.1. Characteristics of study population

As can be seen in Table 1, a summary of demographic characteristics, the participants had a mean age (±SD) of 29.3 (±4.2) years, a pre-pregnant BMI (±SD) of 27.0 (±4.6) and education (±SD) of 13.3 (±1.7) years.

Table 1
Demographic characters of pregnant women in this study.

Characteristics	Mean	SD
Age	29.3	4.2
Body mass index (kg/m^2)	27.0	4.6
Education years	13.3	1.7
PCDDs (TEQ)[b]	5.9	2.1
PCDFs (TEQ)[b]	4.8	1.9
PCDD/Fs (TEQ)[b]	10.6	3.9
Dioxin-like PCBs (TEQ)[b]	2.9	1.3
Indicator PCBs (TEQ)[b,c]	26.9	18.3
Docosahexaenoic Acid (DHA,% of total fatty acids)	3.9	1.3
Arachidonic Acid (ARA,% of total fatty acids)	15.5	4.0

Q3 [a]Data is expressed as mean ± SD.
[b] Abbreviations: PCDD, polychlorinated dibenzo-*para*-dioxins; PCDF, polychlorinated dibenzofurans; PCB, polychlorinated biphenyls; indicator PCB, IUPAC 28,52,101,138, 153,180; dioxin-like PCBs, IUPAC77,81,126,169,105,114,118,123, 156,157,167,189.
[c] Indicator PCBs (TEQ)/1000.

3.2. Fatty acid profiles among different levels of PCDD/F or PCB

Saturated fatty acids: Profiles of total saturated fatty acids were similar among low, mid and high groups of PCDD, PCDF, dioxin-like PCB or total indicator PCB ($p > 0.05$) (Tables 2 and 3).

Monounsaturated fatty acids: Total monounsaturates were linearly increased across low, medium and high levels of PCDD/F. These correlations were, however, marginal (Table 2). Profile of total monounsaturates was similar across three levels of PCB (dioxin-like PCB and indicator PCB) and (Tables 2 and 3).*$n-6$ and $n-3$ PUFA:* Correlations between TEQ levels of PCDD/F or PCB and PUFA are presented in Tables 2 and 3. For $n-6$ LC-PUFA, ARA concentrations were 16.84% (±2.86%), 15.02% (±4.69%) and 14.54% (±4.16%) in low, mid and high TEQ levels of PCDF, respectively. We observed negative associations between placental ARA and PCDF ($p = 0.02$) (Table 2). Similarly, PCDF concentrations were significantly and negatively associated with other $n-6$ PUFA, including C20:3 $n-6$ ($p = 0.01$) and C22:5$n-6$ ($p = 0.003$); the magnitude of decreases in C20:3$n-6$ and C22:5$n-6$ were 15.2–25.8% in the high level of PCDF compared to the the low level. The mean DHA concentrations were 4.18% (±0.83%), 3.97% (±1.62%) and 3.48% (±1.19%) in low, mid and high TEQ levels of PCDF, demonstrating that DHA levels decreased as PCDF levels increased ($p = 0.03$) (Table 2). This correlation was weak with a magnitude of reduction of 5% in the median level and 16.7% in the high level compared to the low level of PCDF. All other $n-3$ PUFA including, 18:3, 20:5 and C22:5, did not vary with the three levels of PCDF.

No specific trends were noted between different concentrations of PCDD and $n-6$ or $n-3$ PUFA, except that there was a marginal and positive correlation between PCDD and 18:3$n-3$ ($p = 0.06$).

There were trends of increases in C18:3$n-3$ ($p = 0.01$) and C20:5$n-3$ ($p = 0.01$) as levels of dioxin-like PCB increased ($p = 0.01$). The correlations between dioxin-like PCB and C20:5$n-3$

Table 2
Placental fatty acid profiles among pregnant women with different TEQ levels of PCDD/F[a,b,c].

	PCDD				PCDF			
	% of total fatty acids by weight (wt.%)							
	Low	Medium	High	P[b]	Low	Medium	High	P[b]
Total SFA	43.23 ± 4.40 (42.89)	45.66 ± 7.56 (44.55)	43.85 ± 5.84 (42.18)	0.90	43.42 ± 4.13 (42.73)	45.49 ± 7.75 (44.96)	43.86 ± 5.83 (42.18)	0.93
Total MUFA	12.26 ± 2.79 (11.33)	13.05 ± 1.67 (12.64)	13.27 ± 2.02 (12.54)	0.06	12.00 ± 1.20 (12.00)	13.09 ± 2.85 (12.35)	13.48 ± 1.97 (13.77)	0.06
Total $n-6$ PUFA	36.76 ± 5.04 (37.40)	33.81 ± 7.01 (34.48)	35.31 ± 6.09 (37.13)	0.53	36.83 ± 4.21 (37.40)	33.99 ± 7.64 (33.40)	35.03 ± 5.92 (37.13)	0.43
C18:2	13.55 ± 1.47 (13.37)	12.99 ± 2.14 (13.25)	14.94 ± 2.03 (14.31)	0.13	13.32 ± 1.21 (13.32)	13.24 ± 2.32 (13.73)	14.89 ± 2.06 (14.31)	0.05
C20:3	4.55 ± 0.99 (4.81)	4.21 ± 0.96 (4.27)	4.07 ± 1.30 (4.33)	0.05	4.71 ± 0.74 (4.85)	4.14 ± 1.11 (4.31)	3.99 ± 1.26 (4.30)	0.01
C20:4	16.80 ± 3.74 (17.70)	14.94 ± 3.99 (14.99)	14.66 ± 4.29 (15.49)	0.12	16.84 ± 2.86 (16.39)	15.02 ± 4.69 (14.64)	14.54 ± 4.16 (15.49)	0.02
C22:4	1.28 ± 0.33 (1.30)	1.17 ± 0.35 (1.19)	1.16 ± 0.36 (1.39)	0.25	1.35 ± 0.29 (1.25)	1.11 ± 0.36 (1.21)	1.16 ± 0.35 (1.30)	0.04
C22:5	0.57 ± 0.16 (0.60)	0.51 ± 0.20 (0.51)	0.47 ± 0.16 (0.49)	0.07	0.62 ± 0.15 (0.57)	0.48 ± 0.19 (0.53)	0.46 ± 0.15 (0.48)	0.003
Total $n-3$ PUFA	5.08 ± 1.46 (5.09)	4.98 ± 1.53 (5.34)	4.53 ± 1.61 (4.83)	0.20	5.20 ± 1.01 (5.11)	4.94 ± 1.88 (4.93)	4.46 ± 1.51 (4.83)	0.04
C18:3	0.17 ± 0.03 (0.17)	0.18 ± 0.06 (0.17)	0.21 ± 0.07 (0.20)	0.06	0.17 ± 0.04 (0.17)	0.18 ± 0.06 (0.19)	0.21 ± 0.07 (0.19)	0.08
C20:5	0.14 ± 0.05 (0.12)	0.17 ± 0.09 (0.14)	0.15 ± 0.09 (0.12)	0.64	0.15 ± 0.06 (0.12)	0.15 ± 0.09 (0.14)	0.16 ± 0.09 (0.12)	0.70
C22:5	0.66 ± 0.20 (0.77)	0.68 ± 0.21 (0.74)	0.60 ± 0.24 (0.63)	0.26	0.70 ± 0.14 (0.77)	0.63 ± 0.23 (0.72)	0.61 ± 0.25 (0.63)	0.27
C22:6	4.12 ± 1.24 (4.03)	3.96 ± 1.27 (4.33)	3.57 ± 1.32 (3.71)	0.16	4.18 ± 0.83 (4.13)	3.97 ± 1.62 (3.92)	3.48 ± 1.19 (3.71)	0.03

[d]Abbreviations: PCDD, polychlorinated dibenzo-*para*-dioxins; PCDF, polychlorinated dibenzofurans; total SFA, sum of saturated fatty acids listed; total MUFA, sum of monounsaturated fatty acids listed; total PUFA, sum of polyunsaturated fatty acids listed.
[a] Fatty acid (% of total fatty acids) across different dioxin TEQ levels are expressed as mean ± SD (median).
[b] Trends of fatty acid (% of total fatty acids) against dioxin TEQ levels are tested using pearson or spearman correlations.
[c] Low, mid and high levels of PCDD/F or PCB were classified as 33.3 and 66.6 percentiles for PCDD, PCDF, total indicator PCB and dioxin-like PCB.

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Table 3
Placental fatty acid profiles among pregnant women with different TEQ levels of PCB[a,b,c].

	Dioxin-like PCBs				Indicator PCBs			
	% of total fatty acids by weight (wt.%)							
	Low	Medium	High	P^b	Low	Medium	High	P^b
Total SFA	45.41 ± 8.09 (44.24)	45.61 ± 4.93 (45.98)	41.73 ± 4.14 (39.94)	0.26	45.28 ± 8.30 (44.18)	43.64 ± 4.18 (42.91)	44.01 ± 5.49 (42.18)	0.77
Total MUFA	12.26 ± 1.41 (12.00)	12.97 ± 2.77 (12.35)	13.35 ± 2.11 (13.56)	0.16	12.38 ± 1.29 (12.00)	11.92 ± 1.14 (12.12)	14.38 ± 2.94 (14.23)	0.11
Total $n-6$ PUFA	35.06 ± 7.53 (37.40)	34.25 ± 5.45 (33.26)	36.52 ± 5.40 (38.44)	0.89	35.17 ± 7.60 (36.37)	36.60 ± 4.01 (37.27)	33.84 ± 6.46 (35.84)	0.57
C18:2	13.16 ± 2.44 (13.78)	13.81 ± 1.42 (13.55)	14.43 ± 2.13 (13.85)	0.17	13.21 ± 2.38 (13.78)	13.71 ± 1.45 (13.62)	14.49 ± 2.16 (13.75)	0.18
C20:3	4.60 ± 1.15 (5.12)	3.93 ± 0.96 (4.18)	4.33 ± 1.10 (4.30)	0.18	4.51 ± 1.12 (5.12)	4.54 ± 0.89 (4.59)	3.76 ± 1.12 (4.16)	0.04
C20:4	15.44 ± 4.26 (15.29)	14.88 ± 4.01 (15.00)	16.09 ± 4.02 (17.24)	0.90	15.58 ± 4.30 (15.29)	16.50 ± 2.59 (16.48)	14.18 ± 4.89 (14.21)	0.64
C22:4	1.28 ± 0.39 (1.21)	1.15 ± 0.31 (1.18)	1.18 ± 0.34 (1.30)	0.62	1.29 ± 0.36 (1.25)	1.30 ± 0.21 (1.26)	1.01 ± 0.38 (0.90)	0.26
C22:5	0.59 ± 0.20 (0.61)	0.47 ± 0.16 (0.46)	0.50 ± 0.16 (0.55)	0.08	0.58 ± 0.20 (0.61)	0.55 ± 0.10 (0.53)	0.41 ± 0.17 (0.31)	0.04
Total $n-3$ PUFA	4.84 ± 1.56 (5.09)	4.46 ± 1.55 (4.27)	5.34 ± 1.40 (5.17)	0.70	4.80 ± 1.58 (5.05)	5.29 ± 1.15 (5.19)	4.47 ± 1.77 (4.97)	0.70
C18:3	0.16 ± 0.06 (0.15)	0.19 ± 0.04 (0.19)	0.21 ± 0.06 (0.19)	0.01	0.16 ± 0.06 (0.15)	0.19 ± 0.06 (0.19)	0.20 ± 0.05 (0.19)	0.03
C20:5	0.14 ± 0.09 (0.12)	0.12 ± 0.07 (0.11)	0.20 ± 0.06 (0.20)	0.01	0.13 ± 0.08 (0.11)	0.16 ± 0.07 (0.13)	0.17 ± 0.08 (0.15)	0.05
C22:5	0.66 ± 0.24 (0.74)	0.58 ± 0.20 (0.63)	0.71 ± 0.18 (0.74)	0.63	0.64 ± 0.23 (0.64	0.69 ± 0.14 (0.74)	0.61 ± 0.26 (0.67)	0.84
C22:6	3.89 ± 1.24 (4.10)	3.57 ± 1.33 (3.29)	4.22 ± 1.24 (4.13)	0.87	3.88 ± 1.31 (4.13)	4.24 ± 0.99 (4.20)	3.49 ± 1.47 (3.73)	0.48

[d]Abbreviations: PCB, polychlorinated biphenyls; indicator PCB, IUPAC 28,52,101,138, 153,180; dioxin-like PCBs, IUPAC77,81,126,169,105,114,118,123,156,157,167,189; total SFA, sum of saturated fatty acids listed; total MUFA, sum of monounsaturated fatty acids listed; total PUFA, sum of polyunsaturated fatty acids listed.
[a] Fatty acid (% of total fatty acids) across different dioxin TEQ levels are expressed as mean ± SD (median).
[b] Trends of fatty acid (% of total fatty acids) against dioxin TEQ levels are tested using pearson or spearman correlations.
[c] Low, mid and high levels of PCDD/F or PCB were classified as 33.3 and 66.6 percentiles for PCDD, PCDF, total indicator PCB and dioxin-like PCB.

Table 4
Association between TEQ levels of PCDD/Fs or PCBs and placental fatty acids using multiple linear regression analysis[a,b].

	PCDD			PCDF			Dioxin-like PCB			Indicator PCB[c]		
	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P
Total SFA	0.425	0.673	0.68	0.706	0.708	0.40	−0.656	0.890	0.68	−0.051	0.064	0.69
Total MUFA	0.241	0.236	0.12	0.455	0.241	0.05	0.585	0.300	0.08	0.066	0.019	0.04
Total $n-6$ PUFA	−0.564	0.669	0.56	−1.024	0.693	0.24	−0.215	0.897	0.67	−0.023	0.065	0.44
C18:2 $n-6$	0.328	0.224	0.15	0.382	0.236	0.12	0.613	0.285	0.04	0.048	0.020	0.03
C20:3 $n-6$	−0.167	0.114	0.15	−0.253	0.116	0.04	−0.217	0.151	0.16	−0.022	0.011	0.05
C20:4 $n-6$	−0.655	0.427	0.14	−1.021	0.431	0.03	−0.465	0.582	0.43	−0.038	0.042	0.37
C22:4 $n-6$	−0.036	0.037	0.33	−0.076	0.037	0.05	−0.088	0.047	0.07	−0.007	0.003	0.04
C22:5 $n-6$	−0.035	0.018	0.06	−0.057	0.017	<0.01	−0.057	0.023	0.02	−0.004	0.002	0.02
Total $n-3$ PUFA	−0.197	0.161	0.23	−0.350	0.162	0.04	0.026	0.218	0.91	−0.011	0.016	0.48
C18:3 $n-3$	0.010	0.006	0.27	0.007	0.007	0.49	0.016	0.008	0.11	0.001	0.001	0.38
C20:5 $n-3$	0.002	0.009	0.92	−0.003	0.010	0.80	0.024	0.011	<0.01	0.001	0.001	0.17
C22:5 $n-3$	−0.024	0.023	0.26	−0.043	0.023	0.13	0.007	0.031	0.74	−0.001	0.002	0.88
C22:6 $n-3$	−0.184	0.133	0.18	−0.312	0.133	0.03	−0.021	0.182	0.91	−0.011	0.013	0.39

[a] Data is expressed as beta (SE) based on original values. *P* values were determined based on age- and BMI adjusted multiple linear regression or rank-transformed multiple linear regression.
[b] Abbreviations used: PCDDs, polychlorinated dibenzo-*para*-dioxins; PCDFs, polychlorinated dibenzofurans; indicator PCB, IUPAC 28, 52, 101, 138, 153, 180; dioxin-like PCBs, IUPAC77, 81, 126, 169, 105, 114, 118, 123, 156, 157, 167, 189; total SFA, sum of saturated fatty acids listed; total MUFA, sum of monounsaturated fatty acids listed; total PUFA, sum of polyunsaturated fatty acids listed.
[c] Indicator PCBs (TEQ)/1000.

may be driven by the highest level of C20:5$n-3$ in the upper tertile of dioxin-like PCB. Additionally, C18:3$n-3$ also correlated positively with total indicator PCB ($p = 0.03$). No other specific trends were noted between concentrations of PCB and $n-6$ or $n-3$ PUFA.

3.3. Relationships between PCDD/F and placental DHA and ARA using multiple linear regressions

The independent associations between PCDD/F or PCB and the various classes of fatty acids are presented in Table 4. After adjusting for potential confounding factors (age and BMI), we found a significant and weak negative association between concentrations of PCDF and placental ARA and DHA. A one-TEQ level increase in PCDF was accompanied with 1.021 wt.% incremental decreases in placental ARA ($\beta = -1.021$, $p = 0.03$) and 0.312021 wt.% incremental decreases in DHA ($\beta = -0.312$, $p = 0.03$). After adjustment, there remained independent and weak negative associations between PCDF and other $n-6$ LC-PUFA (C20:3$n-6$, $\beta = -0.253$ $p = 0.04$; C22:5$n-6$, $\beta = -0.057$ $p < 0.01$ ($p = 0.003$). We also found a marginal association between PCDF and C22:4$n-6$ ($\beta = -0.076$, $p = 0.05$).

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For PCB, dioxin-like PCB and total indicator PCB positively correlated with C18:2$n-6$ and negatively with C22:5$n-6$ (p = 0.02–0.04). A weak association was also found between indicator PCB and C22:4$n-6$ (p = 0.04).

4. Discussion

This study investigated the relationships between placental PCDD/F and PCB and placental $n-6$ and $n-3$ LC-PUFA, including ARA and DHA, in 34 pregnant women in Taiwan. We found that placental ARA or DHA did not vary with placental PCDDs or PCB (total indicator PCB and dioxin-like PCB) concentrations. On the other hand, a significant and negative association existed between placental TEQ levels of PCDF and ARA or DHA concentrations, indicating that the increased placental accumulation of PCDF may be possibly contribute to altered placental ARA and DHA accretion or transport.

To date, no studies have investigated relationship between placental dioxin/PCB concentrations and the accumulation of placental ARA/DHA. There has been only one study investigating the impacts of total PCB exposure on LC-PUFA accumulation in paired maternal and cord serum in a birth cohort from a fishing community (Grandjean and Weihe, 2003). That study found 0.17% (wt.%) and 0.31% (wt.%) decreases in ARA phospholipid concentrations in maternal serum and cord serum with each doubling of total PCB exposures after adjusting for possible confounding factors. The decreases in ARA in that human study might be a result of inhibition of delta-6 and delta-5 desaturase activities, as has been observed in two animal studies (Matsusue et al., 1997, 1999). Rats given a single dose 3,3′,4,4′,5-pentachlorobiphenyl PCB (IUPAC PCB126) at 25 mg/kg wt (2.5×10^6 pg-TEQ/g weight), which is considered extreme high exposure dose for mammals, were found to have a 50% and 30% less liver ARA and DHA than paired-fed control animals (Matsusue et al., 1997). Further, one in vitro experiment (Matsusue et al., 1999) has also reported that treatment with 3,3′,4,4′,5-pentachlorobiphenyl PCB led to a decrease in delta-6 and delta-5 desaturase activities in rat liver microsome homogenates. The results of these studies suggest that PCB exposure may lead to impaired conversion of C18 $n-6$ or $n-3$ precursors to their respective longer chain longer chain PUFA by inhibiting of desaturase activities. DHA and ARA can be either derived from their 18 carbon precursors through endogenous synthesis via a series of desaturations or obtained as preformed one from diet. Since studies have demonstrated that delta-6 and delta-5 desaturase activities are not detectable in human placenta (Chambaz et al., 1985; Kuhn and Crawford, 1986), it might be reasonable to postulate that the decreases of placental ARA and DHA that are found when placental PCDF body burden increased may be due to either an alteration of $n-3$ and $n-6$ desaturation in maternal circulation similar to those reported by a birth cohort study (Grandjean and Weihe, 2003) or a direct alteration of placental PUFA transport by environmental contaminants such as PCDF.

It has been established that DHA and ARA concentrations in the circulation of fetuses is greater than their mothers (Crawford et al., 2003), and in vivo and in vitro experiments have also showed placenta to be capable of preferentially extracting or transporting LC-PUFA from maternal to the fetus site. A selective preferential transport of ARA and DHA has been documented from in vitro (Haggarty et al., 1999) and in vivo (Larque et al., 2003) experiments showing an order of preference DHA > ARA > ALA > LA. Some data suggests that non-esterified PUFA derived from maternal triglyceride-rich lipoprotein by lipoprotein lipase is transported across the placenta and then taken up by a protein-mediated transport system composed of plasma membrane fatty acid binding protein, fatty acid translocase and a family of fatty acid transport protein (Dutta-Roy, 2000). One possible explanation for the diminished placental ARA/DHA concentrations in the current study may be that the expressions or functions of placental transport proteins for $n-3$ or $n-6$ LC-PUFA were impaired by increased placental of PCDF. Alternatively, the DHA enrichment of umbilical erythrocytes suggests that they may be involved in placental transport of placental transport of LC-PUFA via an uncharacterized mechanism (Ruyle et al., 1990). The other possible mechanism to explain the inverse association between PCDF and some $n-6$ and $n-3$ LC-PUFA is that some of the dioxins are retained in the placenta (Pedersen et al., 2010), while DHA and ARA are constantly being channeled to the fetus, though this would require further studies to confirm. The interaction between lipophilic organo-chlorines and the placental PUFA transporting systems remains largely unexplored.

Organ accretion of nutrients is accompanied by accumulation of environmental toxins. The mammalian placenta grows throughout gestation and is the only organ that is discarded after several months of use. In humans, it therefore represents a rare opportunity to perform detailed study of tissue composition non-invasively. From week 9 gestation to term, the fetus completely depends on the placenta for nourishment (Haggarty, 2004). The placenta preferentially transfers DHA and ARA to the fetus. As a vascular organ, placental retains substantial ARA in membrane lipids and lower but significant amounts of DHA and serves as a transport pool for these LC-PUFA. The fatty acid composition of placental tissue is, therefore, dependent on nutrient supply from the maternal storage and diet during pregnancy and may serves as a marker for ARA and DHA accretion for fetus (Haggarty, 2004). Moreover, the placenta is a major vascular organ highly exposed to diet-derived environmental toxins (Schecter et al., 1998). As such, it represents an alternative to blood or breast milk sampling, both of which are faithful indicators of maternal LC-PUFA intake after birth (Brenna and Lapillonne, 2009).

Although the mean placental TEQ levels of PCDD/F and PCB in the current study are far lower than those reported for six women in YuCheng, where there was a dioxin/PCB outbreak (Schecter et al., 1996), they are similar to those found in a general population of the United States (PCDD/F: 9.4 pg-WHO-TEQ/g lipid; PCB: 1.05 pg-WHO-TEQ/g lipid) (Schecter et al., 1998) and are notably lower than PCDD/Fs and PCB levels reported in a Japanese study analyzing 21 placentas (Nakano et al., 2005). Hence, fetal exposure to dioxins and PCB may be minor in our study. Fish are an important source of LC-PUFA and other nutrients vital for optimal development. Numerous agencies, e.g., the UK Scientific Advisory Committee on Nutrition (SACN), caution women of reproductive age to consume up to 2 portions (1 portion = 140 g) of oily fish weekly which would help limit the intake of dioxins and PCB below 2 pg WHO-TEQ/kg of body weight per day. When pregnant and lactating, a woman who had not previously consistently exceeded the guideline range could increase her consumption of oily fish consumption above the guideline levels (SACN). In the years 1993–96, adult women in Taiwan consumed an average of 19 g fresh water fish, 21 g marine fish and 28 g fish products per day (Department of Health, 1998). Our previous study of the results based on food frequency questionnaires in 109 pregnant women reported that placental PCDD/F TEQ correlated with freshwater fish and dairy product intake, but not with marine fish (Huang et al., 2007). In the 34 subjects analyzed in this study, marine fish consumption was also not found to correlate with dioxin/PCB (data not shown), a finding probably due to the limited sample size. Because perinatal exposure to dioxins and PCB in our cohort was relatively low (Schecter et al., 1998; Nakano et al., 2005; Wang et al., 2004) and amount of marine fish or fish product consumption was moderate in this population, and it is therefore inappropriate to discourage Taiwanese women from consuming marine fish during

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pregnancy. Besides dioxin and PCB, methylmercury is another concern related to risk assessment of marine fish consumption. Recommendations have been made to avoid a small number of species, specifically shark, swordfish and king mackerel to minimize methylmercury exposure. However, emphasis must be placed on adequate consumption (12 oz per week) (Mozaffarian and Rimm, 2006) of other fish and shell fish to provide reasonable amounts of DHA and to prevent further decreases in seafood intake in childbearing age women (Schober et al., 2003).

There are some limitations in this study. The sample size is relatively small and may not be representative for childbearing women from a general population in Taiwan. Based on our results, future studies investigating this association powered at the usual level of 0.8 would require at least 50 samples. The placenta is but one tissue and the concentration of contaminants cannot accurately reflect all organs. PCDD/F and PCB are not the only contaminants of concern in fish; for instance, methyl mercury is a concern for a limited number of marine fish as well as of putative concern for fish harvested from isolated bodies of water. Thus, while our data supports the contention that the risk of harm from contaminants is much less than the risk of seafood deficiency, it cannot address all possible situations. Future study was directed to increase the sample size with food consumption and cord blood levels being both considered.

This study found no variation of placental ARA and DHA with PCDD or dioxin-like PCB or total indicator PCB TEQ levels, and only weak negative correlation with placental PCDF. However, little research has been undertaken to clarify the relationships between contaminant exposure and accretion of critical LC-PUFA in humans, and thus further study is needed to determine the clinical significance of the associations between the two and to explore the mechanism through which one would affect the other.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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