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Characterization of placental transfer of polychlorinated dibenzo-*p*-dioxins, dibenzofurans and polychlorinated biphenyls in normal pregnancy

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Abstract

Aim: Prenatal exposure to dioxins may result in many adverse health effects. However, the mechanisms by which dioxins are transferred from mother to fetus through the placenta are not well understood. The aim of this study was to investigate the differences in dioxin concentrations between maternal blood, the placenta, and cord blood in normal pregnant women, and to identify which individual congeners of these compounds are transferred from mother to fetus through the placenta.

Material and Methods: Samples were collected from 19 pregnant Japanese women. Specific congeners of seven polychlorinated dibenzo-*p*-dioxins (PCDDs), 10 polychlorinated dibenzofurans (PCDFs), and four non-*ortho* polychlorinated biphenyls (PCBs) were analyzed.

Results: The TEQ concentrations of PCDDs, PCDFs, and non-*ortho* PCBs were 8.03, 3.39, and 3.95 pg TEQ/g lipid, respectively, in the maternal blood; 8.78, 3.61, and 0.87 pg TEQ/g lipid in the placenta; and 4.33, 1.25, 1.08 pg TEQ/g lipid in the cord blood. Among specific congeners, 1,2,3,7,8-PentaCDD and 2,3,4,7,8-PentaCDF exhibited a placenta to maternal blood ratio greater than 1.0, while OctaCDD exhibited the greatest cord blood to placenta ratio. The cord blood to maternal blood ratio of total PCDDs was significantly higher than that of total PCDFs and total non-*ortho* PCBs.

Conclusion: The dioxin concentration in cord blood was approximately half of the amount in maternal blood, despite congeners showing a high toxic equivalency factor accumulating in the placenta. PCDDs were transferred more readily than PCDFs and non-*ortho* PCBs from maternal blood to the fetus through the placenta.

Key words: dioxin, pharmacology, placental physiology, placental transfer, polychlorinated biphenyl.

Introduction

Polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and dioxin-like polychlorinated biphenyls (PCBs) are highly toxic compounds that do not readily undergo biodegradation. The widespread persistence of these highly lipophilic compounds in the environment has led to their accumulation and concentration in the organs and fatty tissues of humans. Accumulated maternal dioxins are passed on to the fetus through the placenta.[1] Several human studies have suggested that maternal exposure

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to PCDDs, PCDFs, and PCBs may result in many adverse health effects, including fetal growth restriction,[2,3] neurological developmental disorders,[4,5] reproductive toxicity,[6] impaired immune response,[5,7] and lower thyroid hormone levels.[8] Thus, it is important to elucidate the mechanisms by which dioxins are transferred from mother to fetus through the placenta as an initial step in assessing the infant health risks associated with maternal exposure to the compounds.

There are only a small number of studies on maternal–fetal transfer of dioxins in humans. Schecter *et al*.[9] measured dioxin concentrations of PCDDs, PCDFs, and coplanar PCBs in maternal blood, the placenta, and cord blood from five pregnant American women living in New York. The total toxic equivalent quantity (TEQ) in blood was 12.1 pg TEQ/g lipid in maternal blood, 10.5 pg TEQ/g lipid in the placenta, and 5.8 pg TEQ/g lipid in cord blood. The dioxin concentration in cord blood was approximately half of that in the maternal blood. Suzuki *et al*.[10] also measured dioxin concentrations in maternal blood ($n = 4$), the placenta ($n = 21$), and cord blood ($n = 16$) in pregnant Japanese women living in Nara Prefecture. Total PCDD/PCDF TEQ concentrations were 26 pg TEQ/g lipid in maternal blood, 31 pg TEQ/g lipid in the placenta, and 14 pg TEQ/g lipid in cord blood. An accumulation of congeners with high toxic equivalency factor (TEF) values, such as 2,3,7,8-TetraCDD; 1,2,3,7,8-PentaCD; and 2,3,4,7,8-PentaCDF, was found in the placental samples.

The aim of this study was to investigate the differences in the concentrations of PCDDs, PCDFs, and PCBs between maternal blood, the placenta, and cord blood in normal pregnant women, and to identify which individual congeners of these compounds are transferred from mother to fetus through the placenta.

Material and Methods

Samples

Nineteen pregnant Japanese women who lived in Fukuoka city, Japan, and delivered at Kyushu University Hospital between October 2009 and February 2011 participated in the study. The mean age at delivery was 31.8 ± 5.8 years (range: 20–42 years). Five (30%) had vaginal delivery and 14 (70%) underwent cesarean section. The mean gestational age at delivery was 38.1 ± 1.1 weeks (range: 36.9–41.0 weeks). Maternal blood (20 mL), cord blood (20 mL), and placenta (20 g) were collected immediately after delivery. All samples were frozen below –20°C in glass containers until they were analyzed. The Institutional Ethics Committee approved the study design (No. 20–58, FCH 62, FIHES 21-3). Samples were obtained only after receipt of written informed consent.

Analyses of PCDDs, PCDFs and non-*ortho* PCBs

Analyses of PCDDs, PCDFs and non-*ortho* PCBs were performed according to a previously published method.[11–13] The levels of PCDDs, PCDFs, and non-*ortho* PCBs in blood and placental samples were measured using high-resolution gas chromatography/high-resolution mass spectrometry (HRGC/HRMS) equipped with a solvent-cut large-volume injection system (SGE Ltd, Victoria, Australia) at Fukuoka Institute of Health and Environmental Sciences. The gas chromatograph was an Agilent 7890A (Agilent Technologies Inc., Palo Alto, CA, USA) equipped with an Autospec-Premier mass spectrometer (Waters Corp., Milford, MA, USA). Specific congeners of seven PCDDs, 10 PCDFs, and four non-*ortho* PCBs were analyzed. Detection limit values on a lipid weight basis were as follows: PCDDs and PCDFs, 0.3–2 pg/g lipid for placenta and umbilical cord blood and 1–4 pg/g lipid for maternal blood; non-*ortho* PCBs, 0.3–0.6 pg/g lipid for the placenta, 0.3–1 pg/g lipid for umbilical cord blood, and 10 pg/g lipid for maternal blood.

After the concentration of dioxins was determined on a lipid basis, TEQs were calculated by multiplying the levels of individual congeners by their TEF values, as listed by the World Health Organization (WHO) 2005.[14] Values below the limits of detection are reported as half values of the detection limits as previously described.[12,15]

Statistical analysis

Differences in dioxin concentration between pairs of maternal blood and placenta, placenta and cord blood, and maternal blood and cord blood were analyzed using the Wilcoxon signed–rank test. To investigate which dioxins are transferred from mother to fetus through the placenta, statistical comparisons of placenta-maternal blood ratios, cord-placenta ratios, and cord-maternal blood ratios for total PCDDs, total PCDFs and total non-*ortho* PCBs were made using the Steel–Dwass test following the Kruskal–Wallis test. Multidimensional similarities among specific congeners were identified with cluster analysis using 'nearest neighbor' linking with euclidic distances for normalization based on concentration ratios between maternal blood, the placenta and cord blood. Results of this type of analysis are generally presented in a

tree-like diagram (dendrogram). All statistical analyses were performed using the Statistics Package for Social Sciences (SPSS, Inc., Chicago, IL, USA) software for Windows version 13.0 J. All tests were two-tailed, and *P*-values <0.05 were considered statistically significant.

Results

Table 1 shows the blood TEQ concentrations of PCDDs, PCDFs and non-*ortho* PCBs in maternal blood, the placenta, and cord blood. The TEQ concentrations of PCDDs, PCDFs, and non-*ortho* PCBs were 8.03, 3.39, and 3.95 pg TEQ/g lipid, respectively, for maternal blood; 8.78, 3.61, and 0.87 pg TEQ/g lipid for the placenta; and 4.33, 1.25, 1.08 pg TEQ/g lipid for the cord blood. These results showed that TEQ concentrations of PCDDs and PCDFs were greatest in the placenta, while non-*ortho* PCBs demonstrated the lowest TEQ concentration in the placenta. Analysis of specific congeners revealed that the TEQ concentrations of 1,2,3,7,8-PentaCDD and 2,3,4,7,8-PentaCDF in the placenta were significantly higher than those in maternal blood, while the TEQ concentrations of OctaCDD and 3,3′,4,4′,5-PentaCB in the placenta were significantly lower than those in both the maternal and cord blood. Thus, the TEQ concentration of each congener differs among different samples.

Figure 1 shows the ratio of the concentration of each group of compounds between the placenta and maternal blood, cord blood and the placenta, and cord blood and maternal blood. The placenta to maternal blood median ratios showed that total non-*ortho* PCBs (0.23) was significantly lower than that of total PCDFs (1.18) and total PCDDs (1.05). The cord blood to placenta ratio of total non-*ortho* PCBs (1.21) was significantly higher than that of total PCDFs (0.36) and total PCDDs (0.55). The cord blood to maternal blood ratio of total PCDDs (0.55) was significantly higher than that of total PCDFs (0.38) and total non-*ortho* PCBs (0.25).

Figure 2 and Table 1 show concentration ratios for dioxin congeners between maternal blood and the placenta and cord blood. 1,2,3,7,8-PentaCDD and 2,3,4,7,8-PentaCDF exhibited a placenta to maternal blood ratio greater than 1.0. OctaCDD exhibited the greatest cord blood to placenta ratio (3.83). For the cord blood to maternal blood ratio, all 16 congeners, which were at or above the detection limits, had a ratio smaller than 1.0.

Figure 3 shows the dendrogram of hierarchical cluster analysis for dioxin congeners based on concentration ratios between maternal blood, the placenta and cord blood. Three main clusters can be identified: the first cluster contains 1,2,3,7,8-PentaCDD and 2,3,4,7,8-PentaCDF, the second large cluster includes some HexaCDD and HexaCDF congeners and some non-*ortho* PCB congeners, and the last cluster includes only OctaCDD. Each cluster exhibited the following distribution pattern of dioxin concentrations: placenta > maternal blood > cord blood for cluster 1, maternal blood > placenta > cord blood for cluster 2, and maternal blood > cord blood > placenta for cluster 3. The depth profile of the clusters provides an easier way to identify the best correlation among the set of different congeners. Substances that are linked most closely to their neighbors and that form a small cluster in the dendrogram, exhibit a certain level of similarity.

Discussion

Dioxins can be transferred from the mother to the fetus through the placenta.[1,9,10] Placental transfer of toxic chemicals is thought to occur primarily by simple passive diffusion.[16] Important properties of these chemicals that determine the rate and extent of placental transfer by passive diffusion include molecular weight, ionization (p*K*a), lipid solubility, and protein binding.[17] Toxic chemicals that are lipophilic and not protein-binding transfer more easily through the placenta. Other possible mechanisms of placental transport are facilitated diffusion, transporter mediated transport, pinocytosis, and filtration.[16,17]

In the present study, the TEQ concentrations of PCDDs and PCDFs were greatest in the placenta, while non-*ortho* PCBs demonstrated the lowest TEQ concentration in the placenta. For specific congeners, the TEQ concentrations of 1,2,3,7,8-PentaCDD and 2,3,4,7,8-PentaCDF in the placenta were significantly higher than in the maternal blood. These findings are consistent with a previous report.[10] In addition, an *in vitro* study using explants of human placental tissue showed that 2,3,7,8-TetraCDD, 1,2,3,7,8-PentaCDD, and 2,3,4,7,8-PentaCDF accumulated more in human placental cells than did highly substituted congeners.[18] Placental transfer of dioxins is reportedly affected by the affinity of dioxins for the arylhydrocarbon (Ah) receptors present on the placenta.[19] Affinity of the Ah receptor is an important consideration when evaluating the toxicity of a dioxin, and it now serves as the basis for determination of the toxic equivalency factor (TEF).[20] The TEF values of 2,3,7,8-TetraCDD, 1,2,3,7,8-PentaCDD, and 2,3,4,7,8-PentaCDF (0.3 to 1) are higher than those of other dioxin congeners, which range

Table 1 TEQ concentrations (pg TEQ/g lipid) of PCDDs, PCDFs and non-*ortho* PCBs in maternal blood, the placenta, and cord blood

Congeners	Maternal blood ($n = 19$)						Placenta ($n = 15$)						Cord blood ($n = 19$)					
	% > DL	TEQ concentration			Mean ratio†	*P*-value†	% > DL	TEQ concentration			Mean ratio‡	*P*-value‡	% > DL	TEQ concentration			Mean ratio§	*P*-value§
		Mean	Min	Max				Mean	Min	Max				Mean	Min	Max		
PCDDs																		
2,3,7,8-TetraCDD	42	0.96	0.50	2.71	0.74	NA	100	0.96	0.50	2.23	0.79	**0.0060**	58	0.62	0.50	1.11	0.46	NA
1,2,3,7,8-PentaCDD	100	4.82	1.43	12.31	1.56	**0.0022**	100	7.17	2.78	19.79	0.50	**0.0007**	95	3.07	0.50	8.19	0.71	**0.0003**
1,2,3,4,7,8-HexaCDD	21	0.16	0.10	0.59	0.59	NA	87	0.15	0.10	0.37	0.33	NA	5	0.10	0.10	0.12	0.20	NA
1,2,3,6,7,8-HexaCDD	100	1.46	0.16	5.21	0.25	**0.0007**	100	0.32	0.10	1.14	0.99	0.8203	68	0.32	0.10	1.35	0.32	**0.0001**
1,2,3,7,8,9-HexaCDD	58	0.24	0.10	0.97	0.25	NA	33	0.11	0.10	0.25	1.13	NA	16	0.11	0.10	0.26	0.32	NA
1,2,3,4,6,7,8-HeptaCDD	100	0.27	0.06	0.71	0.19	**0.0007**	100	0.05	0.02	0.25	1.56	0.0535	100	0.06	0.03	0.14	0.28	**0.0001**
OctaCDD	100	0.11	0.05	0.27	0.14	**0.0007**	100	0.02	0.01	0.03	3.83	**0.0007**	100	0.06	0.02	0.12	0.58	**0.0003**
PCDFs																		
2,3,7,8-TetraCDF	47	0.19	0.05	0.66	0.48	NA	100	0.08	0.05	0.18	1.25	NA	21	0.05	0.05	0.09	0.13	NA
1,2,3,7,8-PentaCDF	0	0.02	0.02	0.02	NA	NA	60	0.02	0.02	0.02	1.21	NA	37	0.02	0.02	0.02	NA	NA
2,3,4,7,8-PentaCDF	100	2.33	0.73	6.72	1.41	**0.0231**	100	2.95	1.13	8.06	0.23	**0.0007**	100	0.70	0.21	1.95	0.35	**0.0001**
1,2,3,4,7,8-HexaCDF	63	0.27	0.10	1.09	0.69	0.0691	100	0.21	0.10	0.71	0.52	**0.0012**	53	0.11	0.10	0.33	0.31	**0.0022**
1,2,3,6,7,8-HexaCDF	74	0.32	0.10	1.24	0.37	**0.0051**	80	0.13	0.10	0.37	1.03	0.8886	63	0.13	0.10	0.39	0.38	**0.0010**
2,3,4,6,7,8-HexaCDF	26	0.14	0.10	0.33	NA	NA	7	0.10	0.10	0.10	1.62	NA	26	0.11	0.10	0.16	0.52	NA
1,2,3,7,8,9-HexaCDF	0	0.10	0.10	0.10	NA	NA	0	0.10	0.10	0.10	NA	NA	0	0.10	0.10	0.10	NA	NA
1,2,3,4,6,7,8-HeptaCDF	37	0.020	0.010	0.087	NA	NA	0	0.010	0.010	0.010	NA	NA	37	0.012	0.010	0.040	0.38	NA
1,2,3,4,7,8,9-HeptaCDF	0	0.010	0.010	0.010	NA	NA	0	0.010	0.010	0.010	NA	NA	0	0.010	0.010	0.010	NA	NA
OctaCDF	0	0.0006	0.0006	0.0006	NA	NA	0	0.0006	0.0006	0.0006	NA	NA	0	0.0006	0.0006	0.0006	NA	NA
non-*ortho* PCBs																		
3,4,4′,5-TetraCB(#81)	0	0.0015	0.0015	0.0015	NA	NA	13	0.0015	0.0015	0.0015	1.72	NA	16	0.0015	0.0015	0.0015	NA	NA
3,3′,4,4′-TetraCB(#77)	16	0.0006	0.0005	0.0014	0.24	NA	20	0.0005	0.0005	0.0005	NA	NA	58	0.0007	0.0005	0.0013	0.22	NA
3,3′,4,4′,5-PentaCB(#126)	89	3.06	0.50	9.13	0.22	**0.0007**	100	0.68	0.15	1.92	1.30	**0.0018**	100	0.90	0.24	2.93	0.30	**0.0001**
3,3′,4,4′,5,5′-HexaCB(#169)	100	0.89	0.40	1.97	0.20	**0.0007**	100	0.18	0.08	0.36	0.88	0.1398	100	0.18	0.05	0.51	0.20	**0.0001**
Total dioxins																		
Total PCDD TEQ	100	8.03	3.12	22.78	1.25	0.5321	100	8.78	3.64	23.92	0.48	**0.0007**	100	4.33	1.39	11.23	0.54	**0.0002**
Total PCDF TEQ	100	3.39	1.22	9.68	1.39	0.2115	100	3.61	1.65	9.48	0.26	**0.0007**	100	1.25	0.71	3.03	0.35	**0.0001**
Total non-*ortho*-PCB TEQ	100	3.95	0.90	11.10	0.27	**0.0007**	100	0.87	0.27	2.28	1.19	**0.0146**	100	1.08	0.34	3.45	0.32	**0.0001**
Total dioxins TEQ	100	15.38	6.61	43.56	0.94	0.0535	100	13.25	5.86	35.67	0.47	**0.0007**	100	6.67	3.02	17.71	0.43	**0.0001**

Statistical comparisons were made using the Wilcoxon signed–rank test when the detection rate in the sample was ≥50%. †Placenta to maternal blood; ‡Cord blood to placenta; §Cord blood to maternal blood. Bold fonts show significant difference. CB, chlorinated biphenyl; CDD, chlorinated dibenzo-*p*-dioxin; CDF, chlorinated dibenzofuran; DL, detection limit; NA, not applicable; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDF, polychlorinated dibenzofurans; TEQ, total toxic equivalent quantity.

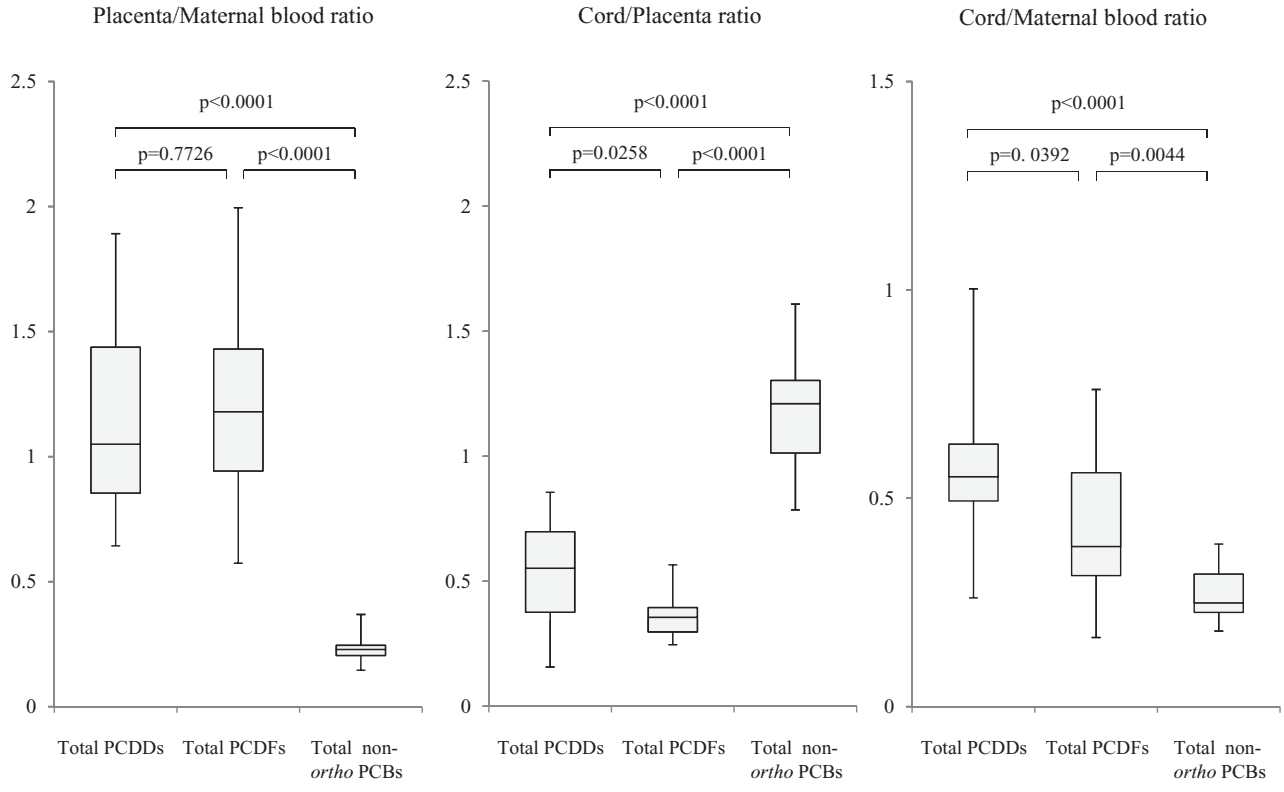

Figure 1 Box-and-whisker plot of placenta/maternal blood ratios, cord/placenta ratios, and cord/maternal blood ratios. The small box denotes the median or 50th percentile, the large box encloses data between the 25th and 75th percentiles, and the whiskers indicate the minimum and maximum values. The Steel–Dwass test of multiple groups was applied following the Kruskal–Wallis test. CB, chlorinated biphenyl; CDD, chlorinated dibenzo-*p*-dioxin; CDF, chlorinated dibenzofuran.

from 0.1 to 0.0001.[14] These findings suggest that congeners with high TEF values accumulate in the placenta, resulting in the greatest TEQ concentrations of PCDDs and PCDFs in the placenta. In addition to the affinity of the Ah receptor, some dioxins bind to cytochrome P450 1A2 (CYP1A2) protein in a process that is closely related to the accumulation of dioxins.[21] 2,3,4,7,8-PentaCDF binds with extremely high affinity to CYP1A2.[21] Therefore, expression of CYP1A2 in the placenta[16] is a plausible explanation for the observed sequestration of dioxins to the placenta.

In contrast, the dioxin concentration in cord blood was approximately half of that in the maternal blood, despite the accumulation of PCDDs and PCDFs in the placenta. The TEQ concentrations of all congeners were also significantly lower in the cord blood than in the maternal blood. Thus, the transfer of these dioxins from maternal to cord blood was restricted, independent of placental accumulation.

PCDDs transferred more readily than PCDFs and non-*ortho* PCBs from the maternal blood to cord blood through the placenta. This finding is consistent with a previous report in which the child to mother ratio of PCDD concentration in the blood was higher than that of PCDFs and non-*ortho* PCBs in Yusho patients exposed to rice oil contaminated with PCBs, PCDDs and PCDFs.[22] Among specific congeners, OctaCDD exhibited the greatest cord blood to placenta ratio with significantly higher TEQ concentration in cord blood than in the placenta. Hierarchical cluster analysis showed that the distribution pattern of OctaCDD, that is maternal blood > cord blood > placenta, is different from other congeners. These results suggest that the OctaCDD placental transport mechanism differs from that of the other congeners. Transfer of dioxins across the placenta is related to the concentration of free dioxins in the maternal blood.[10] 2,3,7,8-TetraCDD in the blood is mostly bound to lipoprotein (80%), as well as other plasma proteins (15%) and red blood cells (5%).[23] OctaCDD is bound to lipoprotein (45%) and other plasma proteins (50%) in the blood.[24] It is also thought that high lipophilic chemicals transfer readily across

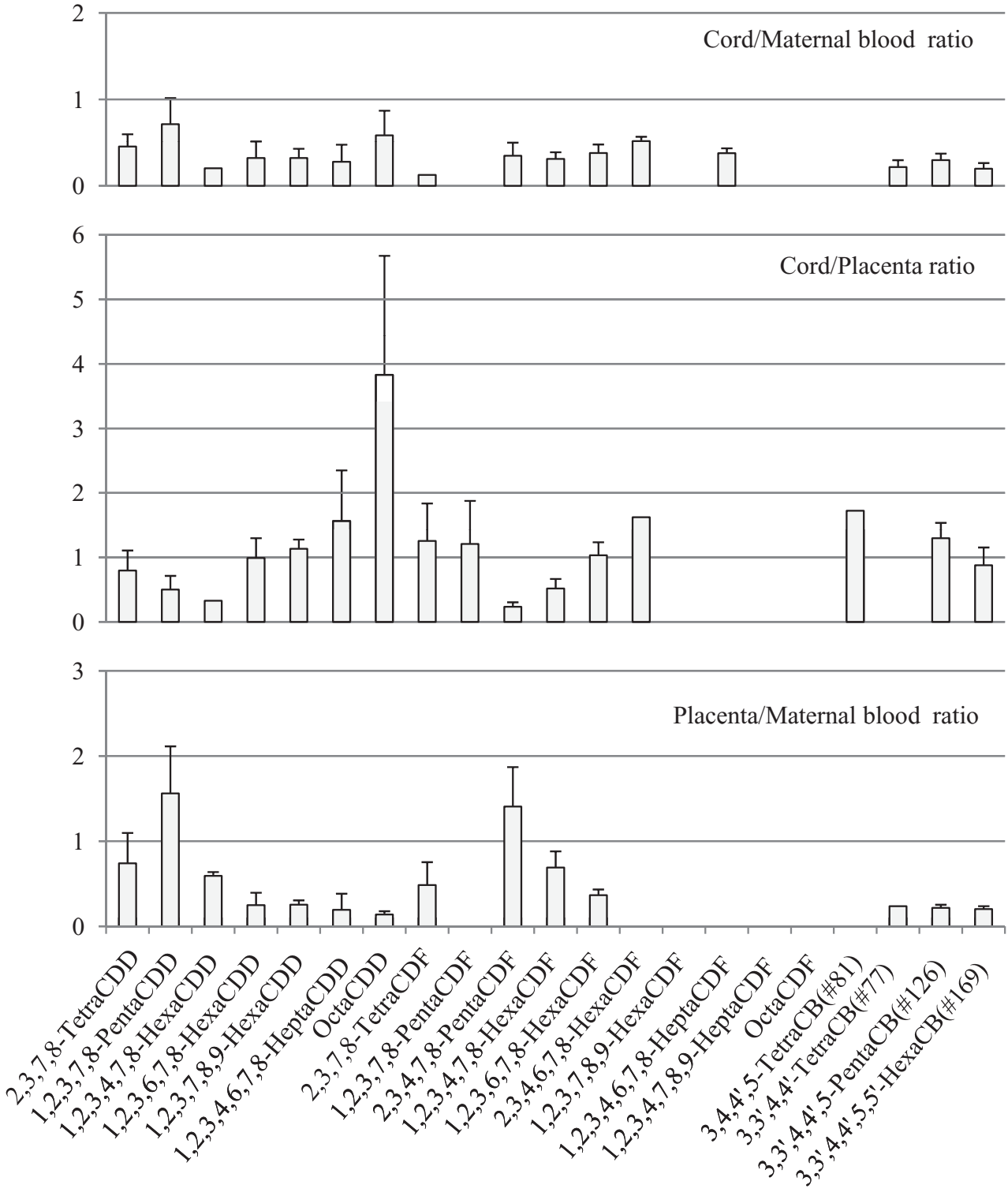

Figure 2 Mean concentration ratios for dioxin congeners between maternal blood and placenta and cord blood. Only detected results included. Error bars indicate +1SD. CB, chlorinated biphenyl; CDD, chlorinated dibenzo-*p*-dioxin; CDF, chlorinated dibenzofuran.

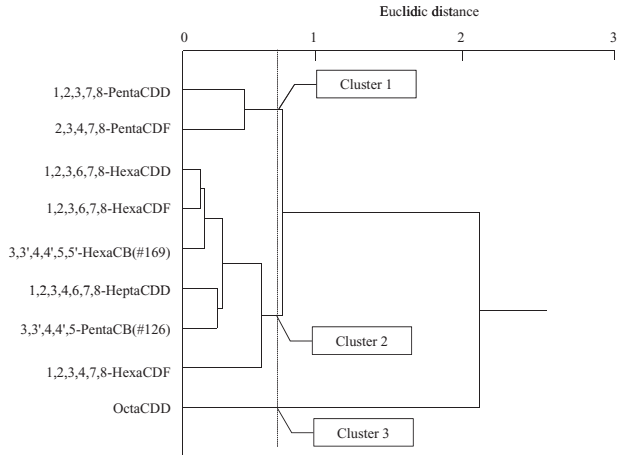

Figure 3 Dendrogram of hierarchical cluster analysis for dioxin congeners based on concentration ratios between maternal blood, the placenta, and cord blood. Only samples with a detection rate ≥50% were included. CB, chlorinated biphenyl; CDD, chlorinated dibenzo-*p*-dioxin; CDF, chlorinated dibenzofuran.

the placenta.[17] OctaCDD is the most lipophilic congener among the PCDDs,[25] PCDFs,[26] and dioxin-like PCBs.[27] These findings suggest that the binding capacity of dioxins to serum protein and the lipophilicity play important roles in the transfer of OctaCDD from maternal to cord blood through the placenta. In addition, the aqueous solubilities of PCDDs are also lower than those of PCDFs with the same chlorine substitution pattern.[26] Thus, the transfer of dioxins from maternal to cord blood may reflect the rate of placental transfer by passive diffusion. Moreover, differential distribution of transporters between the maternal and fetal sides of the placental membrane may also affect transplacental transfer.[16] Further studies are required to determine the mechanism and kinetics of maternal-fetal dioxin transfer.

In conclusion, dioxin concentration was approximately 50% lower in cord blood than in maternal blood, despite the placental accumulation of congeners with high toxic equivalency factors. PCDDs were transferred more readily than PCDFs and non-*ortho* PCBs from maternal blood to the fetus through the placenta. These findings could have important public-health implications for assessing infant health risks associated with maternal exposure to dioxins.

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Disclosure

The authors declare that they have no financial interests.

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