

# Partitioning Behavior of Heavy Metals and Persistent Organic Pollutants among Feto–Maternal Bloods and Tissues

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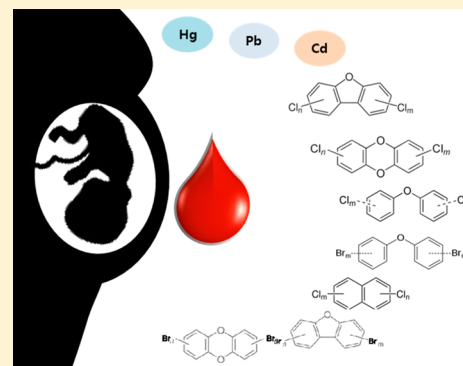
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## S Supporting Information

**ABSTRACT:** Heavy metals and persistent organic pollutants (POPs), including Pb, Cd, T-Hg, MeHg, PCDD/Fs, PCBs, PBDEs, PCNs, and PBDD/Fs, were analyzed in 20 paired samples of cord blood, maternal blood, maternal urine, and placenta. The samples were collected from pregnant mothers and neonates from South Korea in 2010. The distribution of heavy metals among the samples varied with their physicochemical characteristics. The concentrations of Pb and Hg in the maternal and the cord blood samples were significantly correlated each other, implying efficient transplacental transport (TPT). Cd and Hg were accumulated in the placenta, forming protein conjugates, and T-Hg was higher in the cord blood samples than the maternal blood samples due to the binding affinity of Hg with fetal proteins. POPs generally showed the highest concentrations in the maternal serum samples, and the POPs levels in the cord serum and the placenta samples were dependent on the degree of halogenation. The TPT of POPs was seemingly related to lipoprotein transportation. Some PBDE congeners, however, showed their highest concentrations in the cord serum samples, suggesting an additional TPT mechanism. This is the first study to detect PCNs and PBDD/Fs in the cord serum samples, showing that the PCN levels were comparable to other POPs. According to the principal component analysis (PCA) results of the contaminant levels, POPs and heavy metals showed significantly different characteristics, whereas PBDEs had an intermediate attribute. Despite the limited number of participants, the comprehensive analysis of trace contaminants in the paired sample sets enabled us to infer the distribution and TPT mechanism of various contaminants.



## INTRODUCTION

The human fetus has nine months of intrauterine life for its development and growth. A fetus in the maternal uterus is protected from outer environments, surrounded by an amnion and amniotic fluid. The circulating system of a fetus is connected with the maternal circulating system through the umbilical cord, and material exchanges occur in a special organ called the placenta. This organ plays a protective role as a barrier that transfers selective antibodies, filters out certain infectious agents and drugs, and metabolizes xenobiotics with enzyme expression. As the material-exchanging site, a placenta also has breathing, nutritive, and excretory roles. A fetus exchanges nutrients, gases, and waste products with its mother through simple diffusion, active transport, osmosis, and vesicular transport. Transplacental transport (TPT) of these materials is facilitated by many dense, tiny villi and a thin membrane in the placenta consisting of trophoblast and epithelial cells.

Persistent organic pollutants (POPs) and heavy metals, which are toxic and bioaccumulating environmental contaminants, have been reported to also penetrate into the fetal system,<sup>1,2</sup> despite the protective role of placenta. POPs and heavy metals are recalcitrant to metabolism and excretion and thereby accumulate in the fetal system, causing a variety of adverse health effects on several systems: neurobehavioral function,<sup>3,4</sup> development,<sup>5,6</sup> cognitive ability,<sup>7</sup> cardiovascular function,<sup>8</sup> thyroid function,<sup>9–11</sup> and TPT of nutrients.<sup>12</sup> These toxic potentials of the contaminants demonstrate the need to assess the doses, mechanisms, and health effects of prenatal exposure.

To evaluate prenatal exposure, several types of approaches could be conducted, such as biomonitoring, modeling, and

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probabilistic method. For example, Verner et al. estimated the POP concentrations in compartments of the fetomaternal body system with a physiologically based pharmacokinetic (PBPK) model<sup>13</sup> and found a relationship between the polychlorinated biphenyl levels with the infant attention and activity in a later study.<sup>14</sup> A. Stern estimated the maternal methyl mercury dose based on the measured cord blood methyl mercury levels with a revised probabilistic method.<sup>15</sup> Among the various methods for prenatal exposure assessment, the most common method is the biomonitoring of the contaminants in the maternal and fetal samples, as it is the most direct method and provides basic data for indirect methods.

The samples in previous biomonitoring studies included maternal blood, cord blood, placenta and cord tissue, amniotic fluid, and meconium.<sup>1,16–23</sup> However, a biomonitoring study on the fetomaternal unit has difficulties with sampling. Recruiting enough sample donors and the actual sample collection require much exertion due to concern about the health of the mother and the fetus. Consequently, a single study has analyzed only a few contaminants, with especially with high concentrations. This limitation has made it impossible to comprehensively understand the distribution, interrelation, and health effects of various contaminants.

In this study, we analyzed a series of heavy metals and POPs, including Cd, Pb, total mercury (T-Hg), methyl mercury (MeHg), polychlorinated dibenzo-*p*-dioxins and furans (PCDD/Fs), polybrominated dibenzo-*p*-dioxins and furans (PBDD/Fs), polychlorinated naphthalenes (PCNs), polychlorinated biphenyls (PCBs), and polybrominated diphenyl ether (PBDEs) in cord blood, maternal blood, maternal urine, and placenta. For POPs analysis, the maternal urine samples were excluded, because POPs are known not to be excreted via urine, and PCNs and PBDD/Fs could be analyzed only in the cord serum samples due to the limited sample size. Twenty pairs of samples were collected from the pregnant mothers and neonates and were analyzed by appropriate methods. By comparing and correlating contaminant levels, we investigated the distributions in the fetomaternal system, the accumulations in the placenta, and the relationships with physicochemical properties of the contaminants.

## EXPERIMENTAL SECTION

**Subjects and Sampling.** The subjects were pregnant women with prenatal care and without a premature rupture of membrane (over 24 h) or high-risk pregnancy, who were recruited from the hospital. All subjects had no infectious, congenital, or genetic diseases. Table 1 presents demographic characteristics of the study population. The age of participants ranged from 21 to 42 with 75% of the mothers aged 31 to 40. The BMI values before pregnancy were 15.6–33.3, and 85% of the mothers gained weight during pregnancy, whereas 15% lost weight. The parity of the mothers was zero, one, and two in six, eight, and six participants, respectively. Five neonates were delivered by normal spontaneous vaginal delivery (NSVD), and 15 were delivered by cesarean section (C-section). Most neonates had normal gestational age and fetal weight, but two of them had gestational ages less than 252 days (36 weeks) and four of the neonates weighed less than 2500 g at birth.

Samples were collected just after delivery with advance explanation by a doctor and the consent of patients at Kyungpook National University Hospital in Daegu, South Korea in 2010. The cord blood and placental tissue samples were collected directly after the delivery, while the maternal

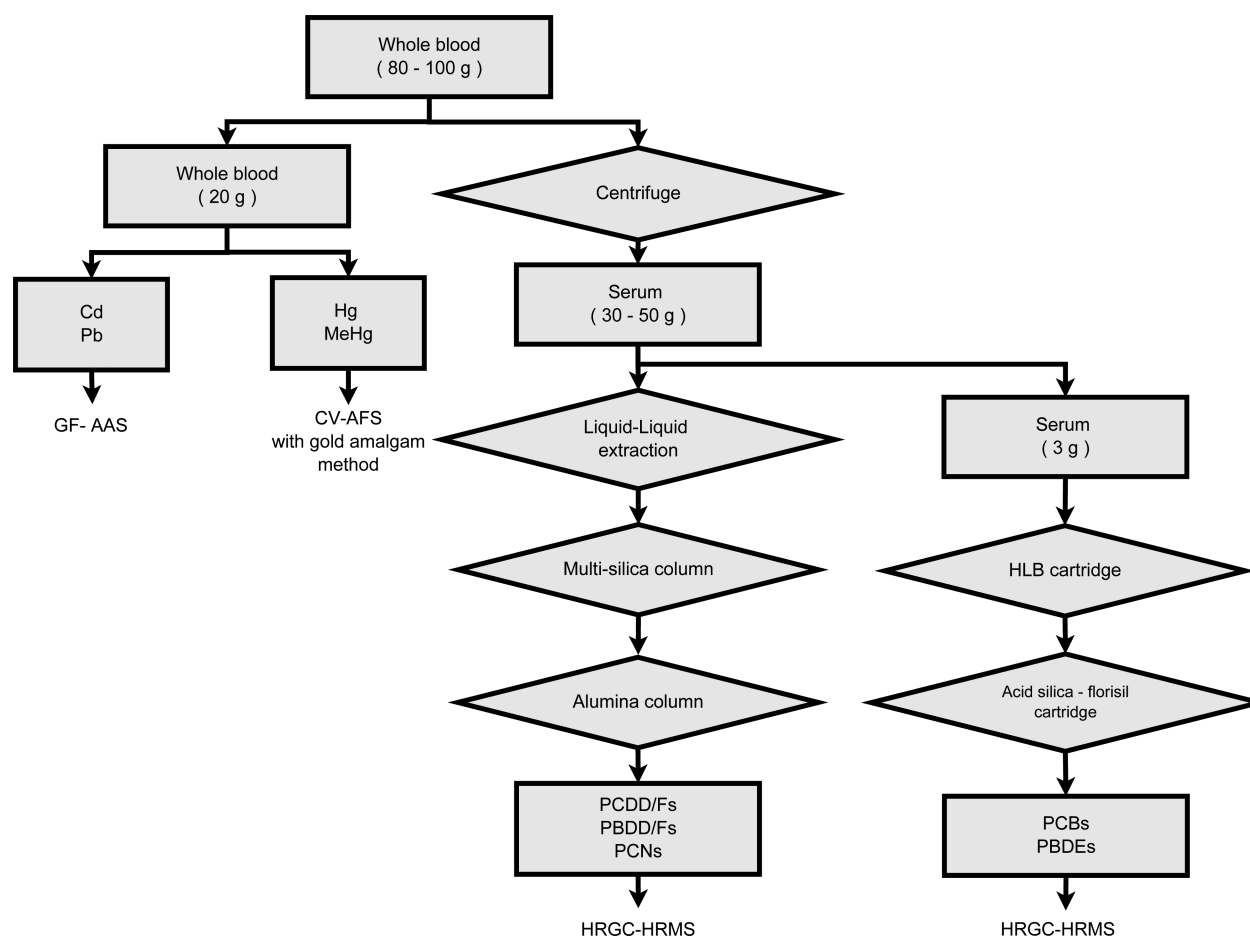
**Table 1. Main Characteristics of Participating Mothers and Neonates**

	maternal age ( <i>n</i> )	
21–30		4
31–40		15
41–50		1
	BMI (kg/m <sup>2</sup> )	
before pregnancy		15.6–33.3
after birth		18.4–33.6
change (%)		–29.1–32.3
	delivery method ( <i>n</i> )	
NSVD		5
C-sec		15
	reproductive history ( <i>n</i> )	
0		7
1		8
2		5
	gestational age (days)	
<250		2
251–260		3
261–270		10
271–280		4
>281		1
	birth weight (g)	
<2000		1
2000–2500		3
2500–3000		7
3000–3500		6
>3500		3

blood and urine samples were collected within 24 h before the delivery. The cord blood sample quantities were in the range of 60–120 mL, and the maternal blood and urine samples averaged 50 mL. For the maternal and cord blood samples, 10 mL of each whole blood sample were stored for the analysis of heavy metals and lipids. The remaining portion of the blood sample was centrifuged to separate the serum. Placental samples weighed 30 g on average and were freeze-dried followed by grinding with a mortar and pestle. All samples were stored at –20 °C until analysis. This study was approved by the Institutional Review Board of Kyungpook National University Hospital.

**Analysis of Heavy Metals and POPs.** Figure 1 presents a schematic diagram for the comprehensive analysis of Pb, Cd, T-Hg, MeHg, PCDD/Fs, PCBs, PBDEs, PCNs, and PBDD/Fs in the maternal and cord blood samples. All heavy metals were measured in all samples, and PCBs, PCDD/Fs, and PBDEs were measured in the maternal and cord blood samples and the placenta. PCNs and PBDD/Fs were measured in the cord blood samples.

Before the pretreatment of the blood samples, 20 g of the whole blood samples was taken for heavy metal analysis, and then, the remaining portions were centrifuged to separate the serum. For PCB and PBDE analysis, 3 mL of the serum was loaded onto preconditioned Oasis HLB cartridges (540 mg) followed by purification by Sep-Pak silica (500 mg) and silica-acid silica cartridges (0.1–1.0 g). This solid-phase extraction method was presented by Sjödin et al.<sup>24</sup> and applied with a small modification. The resulting serum aliquots (20–40 mL) for PCDD/F, PBDD/F, and PCN analysis were separated into lipid extracts and waste with liquid–liquid extraction, and the extracts were dried to measure the lipid content. After weighing



**Figure 1.** Schematic diagram of comprehensive analysis of POPs and heavy metals.

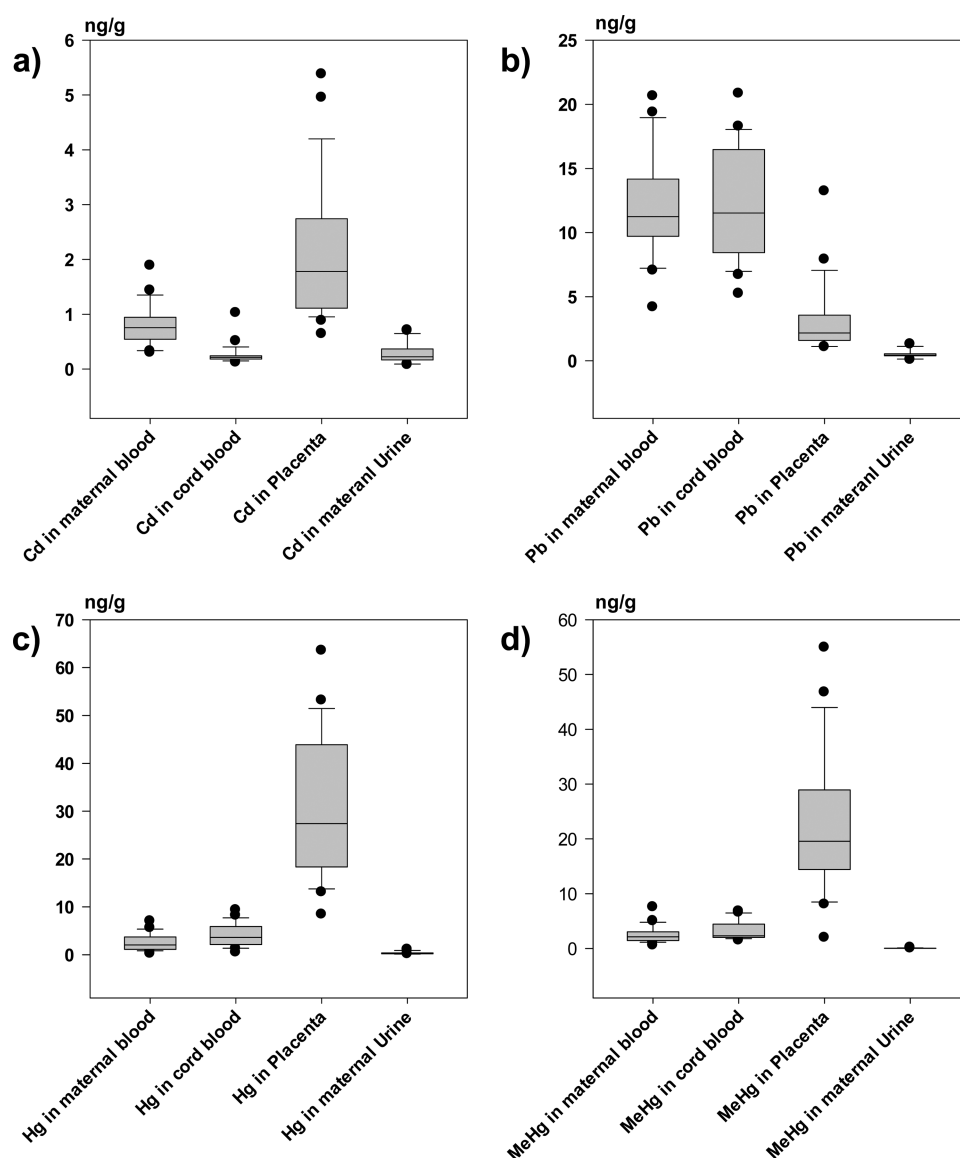
the lipid content, the samples were cleaned up with a multisilica column and an alumina column, as presented by Park et al.<sup>25</sup> The same procedure was applied to the urine samples with a modification, which was the omission of the centrifugation step. For placental tissue pretreatment, we replaced an extraction procedure with Soxhlet extraction and added an acid digestion step to remove the abundant lipids. A high-resolution gas chromatograph (Hewlett-Packard 6890, USA) coupled with a high-resolution mass spectrometer (Jeol JMS-800D, Japan) (HRGC–HRMS) was employed for the POPs analysis.

Pb and Cd were analyzed with a graphite furnace atomic absorption spectrometer (GF-AAS) after an acid digestion at the Neodin Medical Institute. T-Hg and MeHg were analyzed at the Gwangju Institute of Science and Technology (GIST). For T-Hg analysis, a cold vapor atomic fluorescence spectrometer (CV-AFS) with the gold amalgam method was employed. MeHg was analyzed with a GC–CV-AFS equipped with a purge and trap after acid leaching ( $\text{H}_2\text{SO}_4$ –KBr– $\text{CuSO}_4$ ), solvent extraction (dichloromethane), Milli-Q water back extraction, and derivatization with tetra-propyl borate ( $\text{NaBPr}_4$ ), according to the method developed by Gibicar et al.<sup>26</sup>

**QA/QC.** For the analysis of POPs, an isotope dilution method was employed. Before pretreatment, the internal standards for each chemical were spiked (EPA-1613LCS and 68B-LCS were purchased from Wellington Laboratories Inc. and ECN-5102 and EDF-5071 from Cambridge Isotope Laboratories, Inc.), and the final eluents were spiked with recovery standards (EPA-1613ISS 68B-IS ECN-5260 EDF-

5073). The recoveries of all  $^{13}\text{C}$ -labeled standards were within 50–120%. The analytical accuracy was evaluated using commercial standard reference materials (SRM1958 and SRM1947 from NIST, and WMF-01 from Wellington Laboratories Inc.) and in-house reference materials. The results were within 15% of the reference values and the recoveries ranged from 70 to 110%. The limit of detection (LOD) of a chemical was three times the signal-to-noise ratio (S/N ratio). The mean LOD values of Cd, Pb, Hg, and MeHg concentrations were 0.1, 0.1, 0.001, and 0.01 ng/g, respectively. The LOD ranges of POP concentrations were 0.005–0.01, 0.01–0.1, 0.1–0.5, 0.01–0.1, and 0.01–0.1 ng/g-lipid for PCDD/Fs, PCBs, PBDEs, PCNs, and PBDD/Fs, respectively. For HRGC–HRMS, the resolution was greater than 10 000 at 10% height, and the  $r^2$  of calibration curve was more than 0.99. The relative standard deviations (RSD) of the relative response factor (RRF) and the isotopic ratio between two observed selective ions were less than 15%.

**Statistical Analysis.** To compare the concentrations in the paired samples from the mothers and related neonates, we employed paired  $t$  test and Wilcoxon signed-ranks test. Spearman rank correlations were conducted with the correlations among contaminants concentrations. The concentrations below LOD were assigned 0 in the descriptive and bivariate analysis. Principal component analysis (PCA) was employed to assess the relationships among the levels of each chemical in the cord serum samples. Chemicals detected in more than 90% of the samples were used for PCA input data, and the concentrations of each chemical were standardized to



**Figure 2.** Levels of Cd, Pb, Hg, MeHg in maternal blood, cord blood, placenta, and maternal urine. (ng/g wet weight).

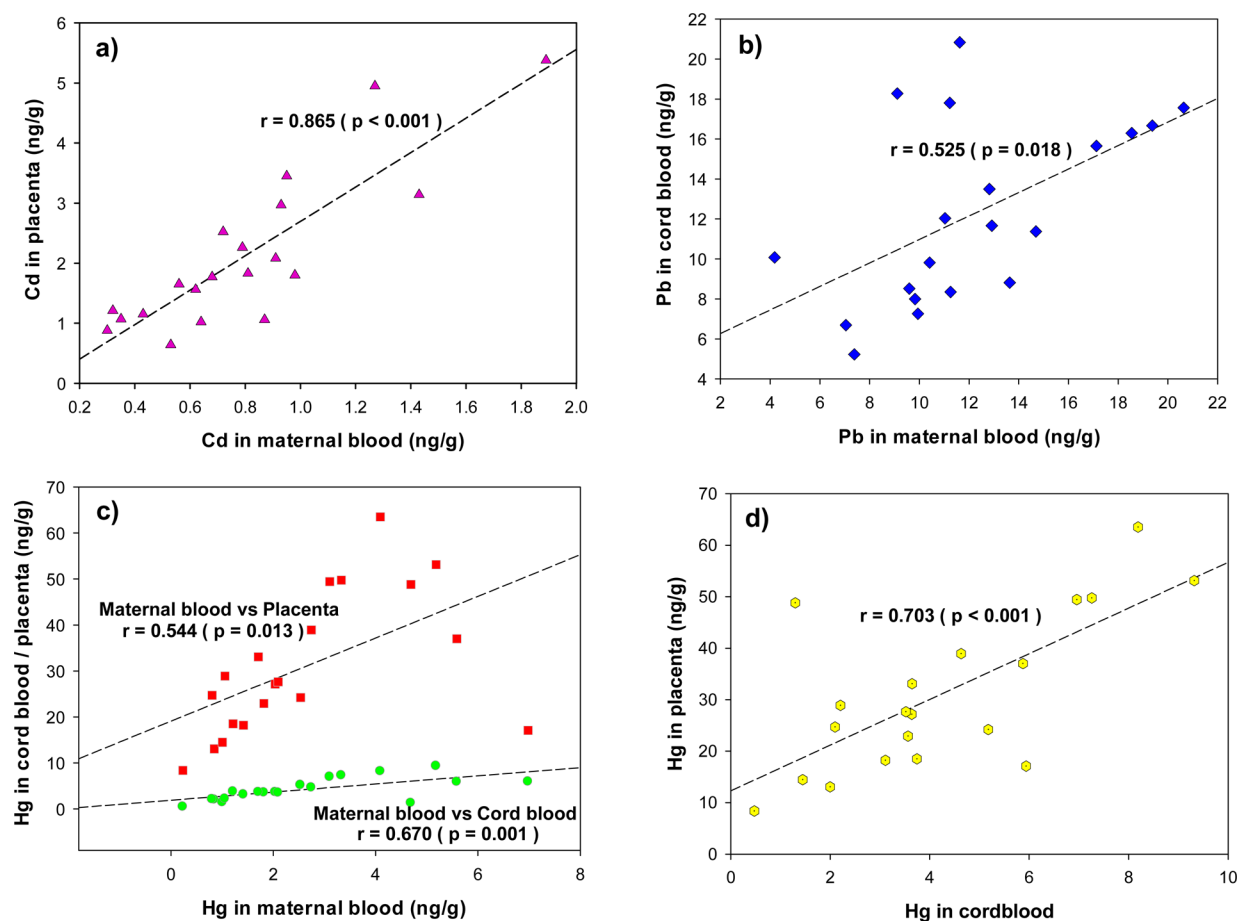
reduce bias by scale and distribution. The concentrations below LOD were assigned for LOD/2 in PCA. SPSS 18.0 was employed for all statistical analysis.

## RESULTS AND DISCUSSION

**Heavy Metals: Cd, Pb, and Hg.** Figure 2 shows box and whisker plots of Cd, Pb, T-Hg, and MeHg levels in maternal blood, cord blood, placenta, and maternal urine. Scatter plots among significantly correlated samples are presented in Figure 3. Generally, the highest concentrations of heavy metals were found in the placenta, followed by the maternal and cord blood, and urine samples. As exceptions, the Cd levels in the maternal urine samples were comparable to those in the cord blood samples, and the Pb levels in the placenta were lower than those in the blood samples. The levels of T-Hg and MeHg were relatively lower compared with previous studies on the maternal and fetal blood,<sup>27,28</sup> and the Cd, Pb, and T-Hg levels in this study were also lower than those of the general population, as determined by the Korea National Health and Nutrition Examination Survey from 2008 to 2010.<sup>29,30</sup> Meanwhile, their distributions among the fetomaternal

samples were comparable to those of previous studies.<sup>31–34</sup> All heavy metals seemed to easily pass through the placental barrier as the high concentrations in the cord blood were shown. Detailed concentrations of heavy metals, including the range and the median and mean values, are presented in Supporting Information (SI) Table S1.

The median concentrations of Cd were 0.76, 0.21, 1.78, and 0.20 ng/g in the maternal blood, cord blood, placental tissue, and maternal urine samples, respectively. The correlation of Cd was not significant in the maternal blood–cord blood pairs, but it was significant in the maternal blood–placenta pairs, as observed in previous studies.<sup>12,34</sup> Caserta et al. reported that the limited correlation between the fetomaternal serum and placental accumulation of Cd suggested the effectiveness of the placental barrier to Cd transfer.<sup>35</sup> The mechanism of Cd accumulation in the placenta is known as the formation of metallothionein which alters the TPT of nutrients and toxicants, such as Cu, Zn and Cd.<sup>12</sup> Pb levels were significantly higher than Cd in all samples. The median concentrations of Pb were 16.46, 15.61, 12.15, and 1.21 ng/g in the maternal blood, cord blood, placental tissue, and maternal urine samples,



**Figure 3.** Scatter plots and correlation coefficients of (a) Cd, (b) Pb, and (c), (d) Hg.

respectively. The Pb levels in the maternal and cord blood sample pairs were not significantly different and had significant correlation, supporting the previous findings by Baghurst et al.<sup>36</sup> and Goyer.<sup>37</sup> Goyer reported that the TPT mechanism of Pb is passive diffusion and that a placental membrane does not inhibit the transport of Pb.<sup>37</sup> Therefore, the Pb concentrations in the cord and maternal blood samples were identical, as a result of statistical test, in this study. Although Pb has been reported to coprecipitate with Ca in placental microvilli,<sup>32</sup> the concentration of Pb in the placenta was less predominant than that in the maternal and cord blood samples.

The placenta samples had the highest median concentration of T-Hg, followed by the cord blood, maternal blood, and maternal urine samples, and their concentrations were 27.42, 3.65, 2.55, and 0.28 ng/g, respectively. We found high T-Hg accumulation in the placenta that was likely due to the binding of  $\text{Hg}^{2+}$  and MeHg to thiol-groups in the placenta,<sup>38</sup> but it did not indicate the inhibition of Hg transport. The T-Hg levels in the cord serum samples were significantly higher than those in

the maternal blood samples, and the preferential accumulation of Hg in cord blood was suggested to be derived from special proteins, such as alpha-fetoprotein and fetal hemoglobin, in cord blood with binding affinity to Hg.<sup>16,38</sup> Significant correlations were found between the cord blood–maternal blood, the placental tissue–maternal blood, and the placental tissue–cord blood pairs, suggesting the effective TPT of Hg. Kajiwarra et al. reported that MeHg is actively transported to the fetal system with binding to thiol-groups in cysteine,<sup>16</sup> and Ask et al. suggested that inorganic Hg penetrates into the placenta in the form of  $\text{Hg}^{0,38}$  although it is slower than MeHg. This cooperative transporting mechanism, which is the passive transport and carriage with an amino acid, seems to aid the efficiency of TPT. Indeed, the levels of both T-Hg and MeHg were significantly higher in the cord blood than maternal blood ( $p < 0.001$ ), implying that fetuses are more vulnerable to Hg exposure during pregnancy.

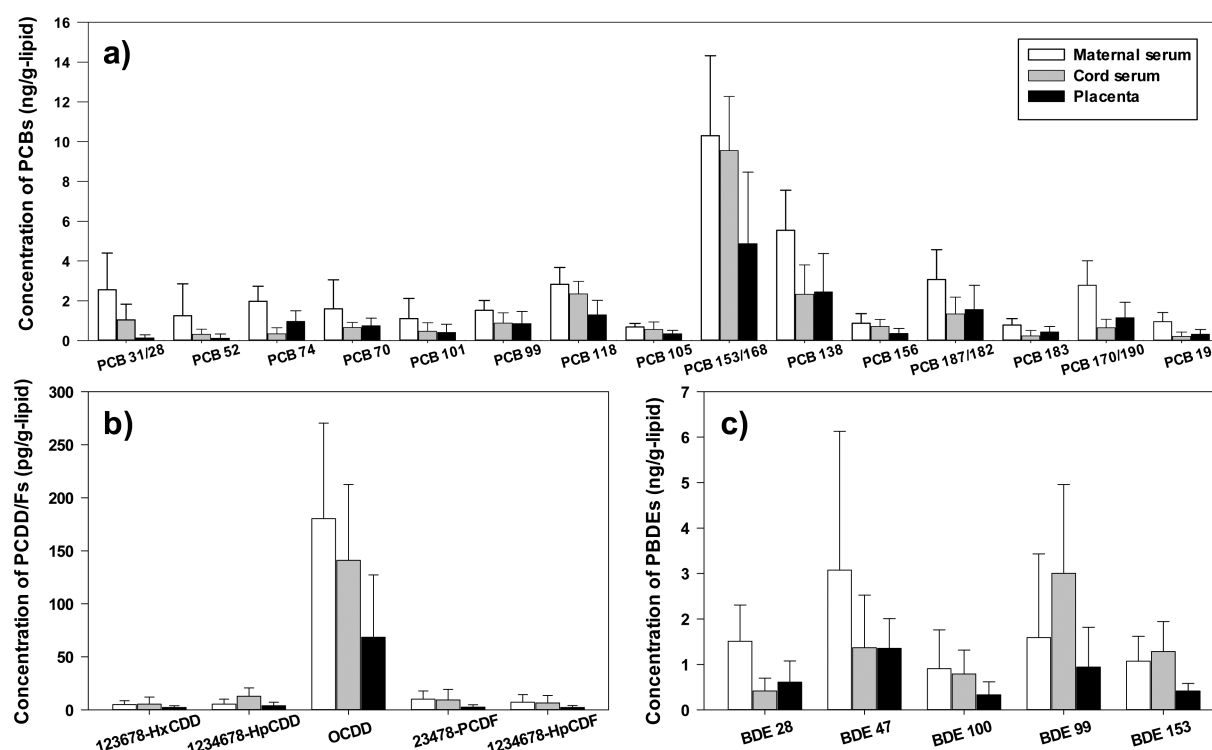
To assess the methylation rate of Hg in the fetomaternal unit, we used the following equation:

$$\text{Methylation rate of Hg} = \frac{\text{Concentration of MeHg} \times (\text{Molecular weight of Hg/Molecular weight of MeHg})}{\text{Concentration of T-Hg}}$$

The methylation rate of Hg was highest (86.1%) in the maternal blood with insignificant differences (paired *t* test) from cord blood (66.0%). The methylation rate in the placental tissue (70.3%) indicated that the majority of Hg in the tissue and blood existed as MeHg rather than inorganic Hg. However,

for the maternal urine, the methylation rate was 19.8% and much lower than the other samples, which was beneficial for excretion. Our results agreed with those of Ask et al.<sup>38</sup> and showed that MeHg is also a predominant Hg species in the





**Figure 4.** Average levels and standard deviations of (a) polychlorinated biphenyls, (b) polychlorinated dibenzo-*p*-dioxins and furans, and (c) polybrominated biphenyls.

placenta, ascribing it to the abundance of thiol-containing molecules in the placenta.

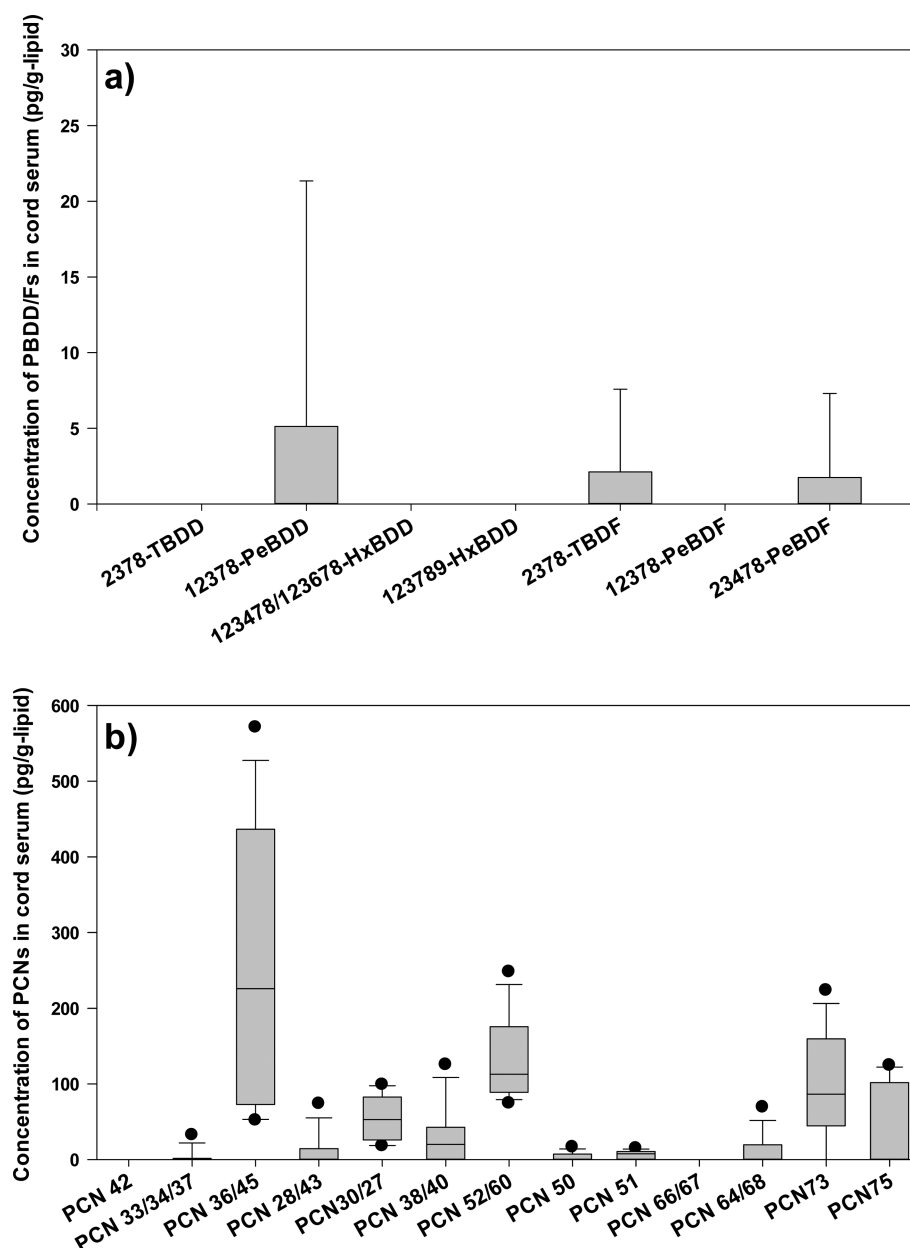
**Persistent Organic Pollutants: PCBs, PBDEs, and PCDD/Fs.** Figure 4 shows the average lipid-adjusted concentrations of PCBs, PBDEs, and PCDD/Fs in the cord serum, maternal serum, and placenta samples, and the detailed concentrations are presented in SI Table S2. The maternal serum levels and congener patterns of PCBs and PCDD/Fs were similar to those of previous biomonitoring studies by Kim et al.<sup>39</sup> and Park et al.<sup>40</sup> The highest levels of congeners in the maternal serum samples were for PCB 153/168, followed by PCB 138, PCB 187/182, PCB 118, and PCB 170/190. Among the PCDD/Fs congeners, OCDD showed the highest concentrations in all samples, and 123678-HxCDD, 1234678-HpCDD, 23478-PCDF, and 1234678-HpCDF were detected in more than 70% of the samples. All of the PCBs and PCDD/Fs congeners showed their highest concentrations in the maternal serum samples, possibly due to an effective placental barrier and dilution during fetal growth. The detailed mechanism of POPs placental transfer, however, has not been investigated.

It is well-known that circulating POPs are transported by lipoproteins and albumin in blood vesicles due to their lipophilicity. In addition, many studies identified receptors for lipoproteins in the placental membrane, and reported that lipoproteins in the membrane microvilli were decomposed into fatty acid and cholesterol.<sup>41–43</sup> Decomposed fatty acid and cholesterol can transfer into the fetal system by diffusion and specific transporter. Therefore, the deduced TPT mechanism of POPs is related to the transport mechanism of lipoproteins, such as passive diffusion and uptake by lipoprotein receptors. Although we could not identify the detailed TPT mechanism of POPs, it is noteworthy that the PCB distribution between the cord blood and placenta samples showed a pronounced tendency that low chlorinated congeners were higher in the

cord blood and high chlorinated congeners were the opposite, ascribing molecular size and lipophilicity.

The congener pattern of PBDEs in the maternal serum samples agreed with those of previous studies in Korea<sup>44,45</sup> and other Asian and European countries,<sup>46</sup> which showed the highest levels in BDE 47, followed by BDE 99 and BDE 153. In comparison with the fetomaternal samples, PBDEs did not show the highest concentrations in the maternal serum samples, but BDE 99 and 153 were highest in the cord blood. There were inconsistent reports about the PBDE ratios between the cord and maternal serum. Mazdai et al.<sup>19</sup> and Needham et al.<sup>47</sup> reported that all PBDE congeners were higher in the maternal serum samples, whereas Gómara et al.<sup>48</sup> and Foster et al.<sup>46</sup> showed opposite trends. Frederiksen et al. reported that the fetomaternal ratios of low-brominated congeners were higher than one,<sup>49</sup> decreasing with the degree of bromination. They ascribed the trend to higher affinity of higher brominated congeners on a tissue and proved it with an experimental study on the kinetics of the PBDE placental transfer.<sup>50</sup> Foster et al., however, proposed that the TPT of PBDEs was not effectively inhibited by the placental barrier and that the degree of bromination did not affect the TPT of PBDE congeners,<sup>46</sup> which agreed with our results.

Previous studies have suggested various hypotheses, including an ineffectiveness of the placental barrier,<sup>47</sup> an immature metabolism of the fetus,<sup>22</sup> and a catabolic redistribution of lipids in the maternal body during the last trimester.<sup>46</sup> However, these hypotheses could not explain the remarkable accumulation of PBDEs in cord serum, dissimilar to PCBs and PCDD/Fs. Additionally, according to the molecular size-dependent mechanism as remarked above, the general molecular size of PBDE molecules, which is larger than that of chlorinated POPs, should restrict TPT, thereby reducing the fetomaternal ratios. Therefore, we suggest that PBDEs could



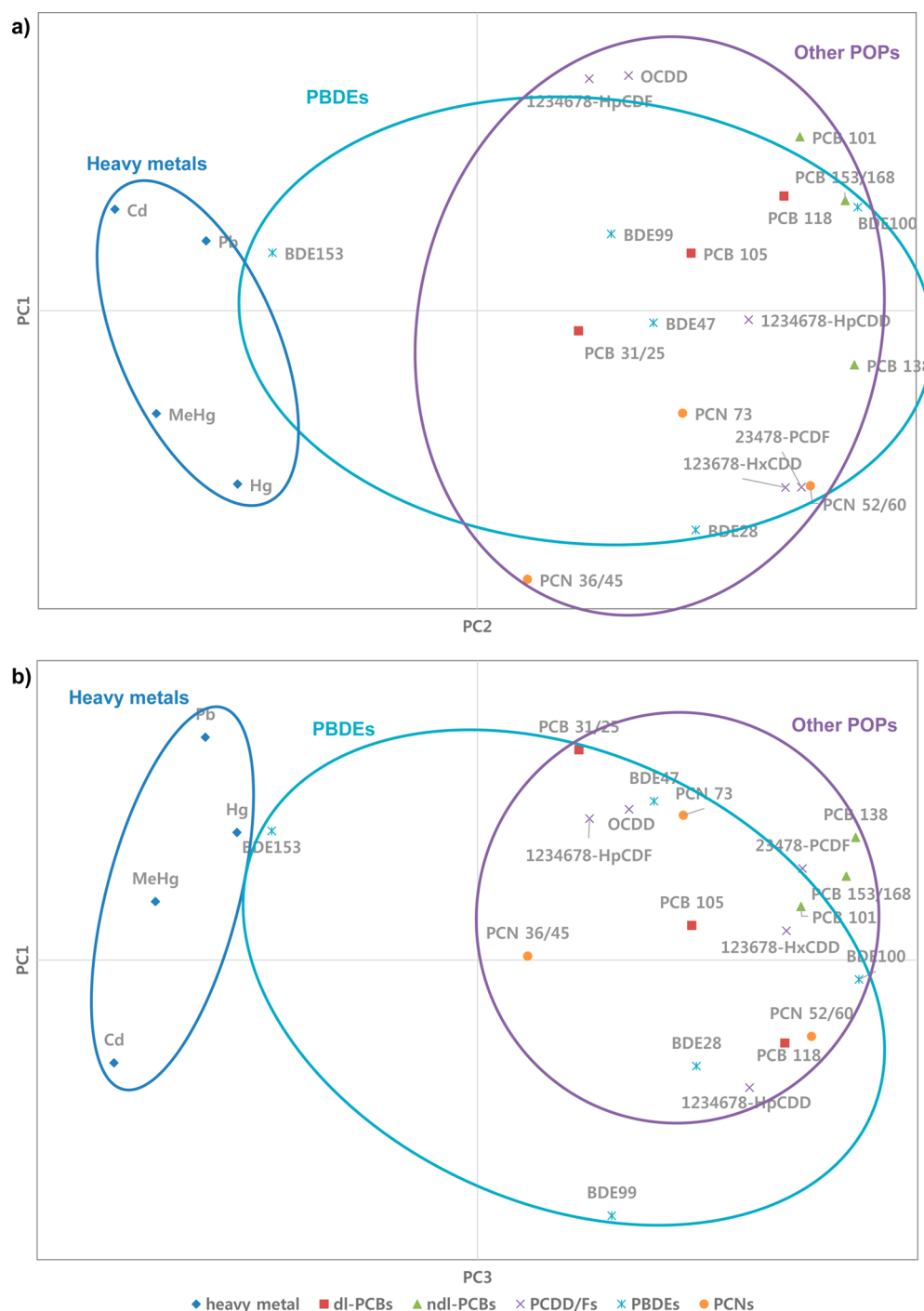
**Figure 5.** Average levels and standard deviations of (a) polybrominated dibenzo-*p*-dioxins and furans and (b) polychlorinated naphthalenes (pg/g-lipid) in cord serum.

have an additional TPT mechanism, which is related with certain active receptors or transporters.

In contrast to other POPs, PBDEs have thyroid-hormone-like structures and thus can be associated with the TPT of the thyroid hormone; indeed, relationships between the thyroid hormone and the POPs levels in cord blood were found in many previous studies.<sup>10,22</sup> The thyroid hormone has long been known to be unable to migrate from maternal circulation into fetal circulation and to produce in placental tissues. However, recent studies found contrary evidence that the maternal thyroid hormone was able to penetrate into fetal circulation by membrane transporters and carrier-mediation.<sup>51–53</sup> The membrane transporters, which have affinity to the thyroid hormone, include MCT8, MCT10, OATP1A2, OATP4A1, LAT1, and LAT2. And the specific binding of OATP with PBDEs was presented by Pacyniak et al.<sup>52</sup> Carrier-mediated TPT of the thyroid hormone has not been clearly identified,

but Landers et al.<sup>53</sup> found that the thyroid hormone could be transported by binding with transthyretin (TTR), which is one of the thyroid-binding proteins produced in the liver and the placenta. Three thyroid-binding proteins (TBPs), which are thyroxine-binding globulin, transthyretin (TTR) and albumin, carry the thyroid hormone in the circulation system. Patel et al. suggested that TBPs might have a role, as TTR and albumin are produced in the placenta cells.<sup>51</sup> In summary, the thyroid hormone has two TPT mechanisms: the membrane transporter and the carrier-mediated transport. Because PBDEs have structures similar to the thyroid hormone and also strong affinity to thyroid hormone receptors, it can be deduced that the TPT mechanisms of PBDEs and the thyroid hormone may be strongly associated with each other.

Although prenatal exposure has been concerned with neonatal thyroid functions, the mechanistic explanation on PBDE placental transport was hardly investigated. Future



**Figure 6.** Loading plots of principal component analysis of heavy metals and POPs in the cord serum: (a) PC1–PC2, (b) PC2–PC3.

studies on the feto–maternal POP ratios encompassing the TPT mechanism and the fetal physiology are required to identify the health effects of prenatal PBDE exposure.

**POP Candidates: PCNs and PBDD/Fs.** In this study, we analyzed PCNs and PBDD/Fs in the cord blood samples, and their detection rates and concentrations are presented in Figure 5 and SI Table S3. PCNs and PBDD/Fs are dioxin-like compounds which have halogen atoms and aromatic carbon backbones. In particular, PCNs are proposed for listing by the Stockholm Convention on POPs, and PBDD/Fs have become a growing concern due to their increase in usage and discharge into the environment. Despite the importance of their dioxin-

like structure and Ah-R binding affinity,<sup>54</sup> no previous studies focused on the prenatal exposure to those compounds. To our knowledge, this study is the first to detect PCNs and PBDD/Fs in the cord blood.

Regarding the PCNs, 11 congeners were detected among the 13 congeners analyzed, and only PCN 36/45 and PCN 52/60 were detected in all samples. The highest median concentrations were found for PCN 36/45, followed by PCN 52/60, PCN 73, and PCN 30/27. The congener pattern was different from a previous study of the general South Korean population,<sup>25</sup> which reported the highest concentrations in PCN 73, followed by PCN 38/40 and PCN 33/34/37. The



disagreement seems to originate from the low detection rates of this study and possibly from the different placental transporting efficiencies of the PCN congeners. The detection of PBDD/Fs was scarce, and only 2378-TBDF, 23478-PeBDF, and 12378-PeBDD were detected. The concentrations of the detected PBDD/F congeners, however, were just slightly lower than those of PCDD/Fs, which was up to 51.3 pg/g-lipid in 12378-PeBDD. Although there has been no study on PBDD/Fs for human serum in Korea, the serum levels in this study were relatively higher than Swedish plasma<sup>55</sup> and Japanese adipose tissues,<sup>56</sup> with dissimilar congener patterns.

PCDD/Fs and dioxin-like compounds, including dioxin-like PCBs (DL-PCBs), PCNs, and PBDD/Fs, have a special effect on fetal health, which is aryl hydrocarbon receptor (AhR) mediated toxicity. WHO suggested toxic equivalency factors (TEFs) of each PCDD/F and PCB, as well as PCNs and PBDD/Fs, considering the relative response factors of AhR activity.<sup>54</sup> Therefore, many studies have evaluated the precise relative toxicities of PCNs and PBDD/Fs. For example, the TEFs for PCNs were evaluated by *in vitro* and *in vivo* methods by Villeneuve et al.<sup>57</sup> and Blankenship et al.,<sup>58</sup> as well as by a QSAR approach by Puzyn and Falandysz.<sup>59</sup> In addition, Behnisch,<sup>60</sup> Olsman et al.,<sup>61</sup> and Samara et al.<sup>62</sup> proposed TEFs of PBDD/Fs based on *in vitro* assay.

On the basis of the TEFs by WHO<sup>54</sup> and Puzyn and Falandysz,<sup>59</sup> we calculated the TEQs of DL-PCBs, PCDD/Fs, and PCNs for the maternal serum and cord serum samples. PBDD/Fs were excluded due to the low detection rates. For the maternal serum, the median TEQs of DL-PCBs and PCDD/Fs were 0.14 and 4.69 pg/g-lipid, respectively. For the cord serum, the median TEQs of DL-PCBs, PCDD/Fs, and PCNs were 0.11, 2.34, and 0.87 pg/g-lipid, respectively. The total TEQs for DL-PCBs and PCDD/Fs in the maternal serum samples were much lower than those of the general Korean population, which were 4.51 pg/g-lipid for DL-PCBs and 8.15 pg/g-lipid for PCDD/Fs.<sup>63</sup> The TEQs for DL-PCBs and PCDD/Fs were lower in the cord serum samples compared with those in the maternal serum samples, reflecting a reduction with passing through a placental barrier. It is noteworthy that the TEQs of PCNs in the cord serum samples occupy  $\frac{1}{4}$  of the total TEQs, matching a previous study by Park et al.<sup>25</sup> Our results suggest the importance of conducting further risk assessment for prenatal exposure to PCNs and PBDD/Fs.

**Principal Component Analysis.** We conducted principal component analysis (PCA) for every contaminant detected in the cord serum samples to assess the relationships among the contaminants, and its loading plots and loading scores are presented in Figure 6 and Table 2, respectively. The first three principal components (PC) described 78.3 of the accumulated scores, and, thereby, 78.3% of the data were explained by PC 1 to PC 3. Despite the ambiguity in the definition of the loading scores, the loading plots (Figure 6) showed significant relationships among the contaminants. According to the loading plots, heavy metals and POPs, except PBDEs, were clearly separated; meanwhile, PBDEs showed intermediate characteristics. The distributions can be explained by the different exposure routes and the TPT mechanisms of each contaminant.

In previous studies, PCDD/Fs, PCBs, and PCNs have been reported to be exposed through dietary intake with strong correlations among each congener in human serum, implying similar exposure routes and distributions in the human body.<sup>64</sup> In addition, the feto–maternal ratios of the compounds were

**Table 2. Unrotated Principal Components Analysis of Heavy Metals and POPs in Cord Blood Samples**

variable	factor loading		
	PC 1	PC 2	PC 3
heavy metal	Cd	−0.825	0.340
	Pb	−0.618	0.235
	Hg	−0.546	−0.581
	MeHg	−0.731	−0.345
dl-PCBs	PCB 31/25	0.231	−0.067
	PCB 105	0.487	0.193
	PCB 118	0.699	0.385
ndl-PCBs	PCB 101	0.735	0.584
	PCB 153/168	0.838	0.370
	PCB 138	0.859	−0.182
PCDD/Fs	123678-HxCDD	0.702	−0.593
	1234678-HpCDD	0.618	−0.030
	OCDD	0.345	0.790
	23478-PCDF	0.738	−0.592
PBDEs	1234678-HpCDF	0.255	0.779
	BDE28	0.497	−0.735
	BDE47	0.401	−0.040
	BDE100	0.867	0.347
	BDE99	0.305	0.258
PCNs	BDE153	−0.467	0.195
	PCN 36/45	0.114	−0.901
	PCN 52/60	0.759	−0.587
	PCN 73	0.468	−0.343
eigenvalue	8.564	5.903	4.328
cumulative %	35.683	60.280	78.315

similar to one another in this study. PBDEs, on the other hand, are known to be exposed more through inhalation and dietary intake,<sup>22</sup> and the feto–maternal ratios were different from those of other POPs. Cd, Pb, and Hg have exposure routes and distributions completely different from organic pollutants.<sup>65</sup> The PCA results in this study confirm that PCDD/Fs, PCBs, and PCNs showed a similar prenatal exposure pattern, in which PBDEs and heavy metals have different characteristics from those contaminants.

## CONCLUSION

To assess the behavior and possible health effects of trace contaminants in feto–maternal units, we analyzed PCBs, PCDD/Fs, PCN, PBDD/Fs, PBDEs, Cd, Pb, T-Hg, and MeHg in 20 paired samples of maternal blood and urine, placental tissue, and cord blood. The distribution of heavy metals was influenced by the abundance of metal-binding proteins and carriers in each compartment. PCDD/Fs and PCBs showed the highest levels in the maternal serum, reflecting the placental barrier and dilution by fetal growth, and the concentration ratios among serum samples and placenta varied with molecular weight. The levels of some PBDE congeners, however, were the highest in the cord serum, which implied an additional TPT mechanism. This study described the first detection of PCNs and PBDD/Fs in fetal samples, and their levels were worthy of concern despite the low detection rates. The results of this study should be embraced cautiously, because it was possible that the contaminant levels were not in equilibrium within the body, even though the samples were collected within 24 h before delivery. Also, the sample numbers were relatively small to draw a conclusion. Nevertheless, the analyses of various trace contaminants in the paired samples

enabled us to draw a comprehensive picture for the distribution and relationship of contaminants in the fetomaternal units. In particular, the distribution of contaminants in samples was dependent on the physiochemical property of each contaminant, which gave a clue for understanding the TPT mechanisms of the contaminants.

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

Concentrations of Cd, Pb, Hg and MeHg in the fetomaternal units (Table S1); concentrations of PCDD/Fs, PCBs, and PBDEs congeners in the fetomaternal units (Table S2); concentrations of PCNs and PBDD/Fs in the cord serum samples (Table S3). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/es5051309.

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### Notes

The authors declare no competing financial interest.

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