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# Congener-specific Mother-Fetus Distribution, Placental Retention, and Transport of $C_{10-13}$ and $C_{14-17}$ Chlorinated Paraffins in Pregnant Women

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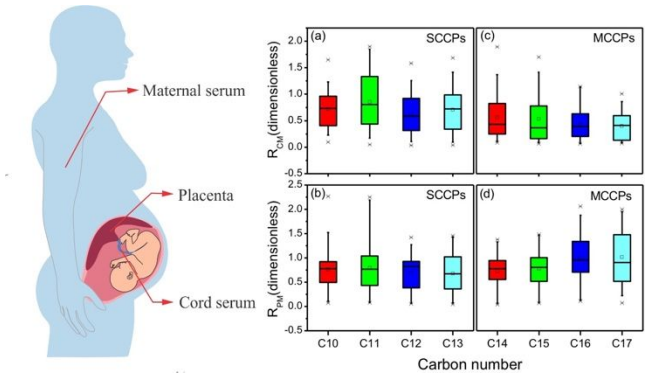
## Table of Contents Art



**ABSTRACT:** Short-chain chlorinated paraffins (SCCPs) and medium-chain chlorinated paraffins (MCCPs) are high production volume persistent and toxic industrial chemicals, found ubiquitously in various environmental matrices. However, information is scarce regarding human internal exposure. The congener-specific SCCP and MCCP levels in matched maternal serum (n= 31), umbilical cord serum (n= 31), and placenta (n= 31) were studied to investigate the maternal-placenta-fetus distribution and the placental transport mechanisms of SCCPs and MCCPs. The results indicated that lower chlorinated and shorter carbon-chain CPs were efficiently transported across placenta compared to highly chlorinated and longer carbon chain CPs. Meanwhile, ∑MCCP concentration followed the order of maternal sera > placentas > cord sera. The cord/maternal concentration fraction ratios ($R_{CM}$) of CPs exhibited similar values from $C_{10}$ to $C_{14,}$ and then from $C_{15,}$ a decreasing trend was observed with increasing carbon chain length. The log-normalized maternal SCCP concentrations were positively correlated ($P < 0.01$) with that in the cord, suggesting fetus exposure to SCCPs during pregnancy. Furthermore, the placenta/maternal concentration fraction ratio ($R_{PM}$) values for MCCPs were relatively higher than those for SCCPs, demonstrating that MCCPs were not efficiently transported and effectively retained in placenta tissues. These findings provide a better understanding of the maternal-fetal transmission and neonatal exposure to CPs.

## INTRODUCTION

Chlorinated paraffins (CPs) are a group of complex polychlorinated n-alkanes with more than ten thousand of homologues and isomers.[1-3] Based on the carbon chain length, CPs can be categorized into short-chain ($C_{10-13,}$ SCCPs), medium-chain ($C_{14-17,}$ MCCPs), and long-chain-CPs ($C_{\geq 18}$, LCCPs), with the degree of chlorination ranging between 30% and 70%. Commercially, CPs are used for a wide range of applications including metal cutting fluid, lubricant, plasticizers and flame retardants in PVC, paints, sealants, rubber, and coatings.[4] SCCPs have raised worldwide concern due to bioaccumulation, biomagnification, long-range transportability, persistence in the environment, and possible ecological and health risks to humans.[5-9] Since SCCPs have been listed as persistent organic pollutants (POPs) in the Stockholm Convention (2017),[10] their production and use are restricted worldwide.[11] The United States has also listed SCCPs as a prioritized toxic substance.[5] As a result, MCCPs are being used as alternatives because of similar physical-chemical properties.[12]

China is the largest producer and consumer of CPs in the world, and this large amount of CPs are produced without distinction by carbon chain length and without any monitoring measures.[13-15] CPs have been detected ubiquitously in different environmental matrices including water, soil, sediment, and air,[16-18] but information regarding human exposure to CPs is scarce, which is mainly due to the complexity of CP analysis and quantification, and the diversity of CPs.[19, 20] Traditionally, blood, breast milk, urine, maternal serum, cord serum, and placenta are biological matrices that are often used to investigate human exposure and placental transport mechanism.[21-24] The placenta is a transition organ between the mother and the fetus, which absorbs nutrients and oxygen from the mother's

bloodstream and transfers them to the fetus through the umbilical cord. The placenta also acts as a barrier to protect the fetus from harmful xenobiotics in the maternal blood, which are filtered and stored in the placenta tissue.[22] The passive and active transport mechanisms are responsible for the placental transport of xenobiotics, reported in exiting studies.[25, 26] As a result, it is possible for toxicants to cross the placenta and reach fetus cord blood, which poses a potential health risk to the fetus.

Fetus exposure to organic pollutants is of great concern because fetuses are more sensitive to toxicants than adults.[27, 28] The exposure of a fetus to organic pollutants may lead to irreversible negative effects on fetal development and growth.[29-31] Therefore, it is necessary to investigate the CP levels in maternal blood, placenta, and umbilical cord blood to understand the CP transplacental transfer mechanism, and to assess the potential health risks to the fetus associated with prenatal exposure to CPs. However, to the best of our knowledge, only one group studied fetus exposure to CPs via the mother, and placenta transfer was not investigated. [21]

In the present work, $C_{10\text{-}13}Cl_{5\text{-}10}$ and $C_{14\text{-}17}Cl_{5\text{-}10}$ congener groups of CPs were investigated in paired maternal serum, umbilical cord serum, and placenta. We aimed to assess the maternal-placenta and placenta-cord transport behavior of the CP congener groups by investigating the congener-specific mother-fetus distribution of SCCPs and MCCPs. Our results provided information regarding the carbon and chlorine congener-specific mother-placenta-fetus concentration distribution profiles of SCCPs and MCCPs and further insight into the placental transfer mechanisms of these chemicals.

## MATERIALS AND METHODS

## CP Standards and Reagents

SCCP standards with chlorination degrees of 51.5, 55.5 and 63.0%, MCCP standards with chlorination degrees of 42, 52 and 57% were purchased from Dr. Ehrenstorfer GmbH (Augsburg, Germany). SCCPs and MCCPs with other chlorination degrees were obtained by mixing the CP standards based on the ratios summarized in Table S1. The internal standard ($^{13}C_{10}$-*trans*-chlordane, 100 μg/ml, 99%) was purchased from Cambridge Isotope Laboratories, Inc. (Tewksbury, MA, USA). The HPLC grade dichloromethane and *n*-hexane were obtained from *J&K* Chemicals (Beijing, China).

**Sample Collection.** The participants include healthy pregnant mothers without fertility-related or other illnesses and healthy babies without congenital abnormalities. Included in this study, a total of 31 matched samples of maternal serum, placenta, and umbilical cord serum were collected from pregnant mothers at the Wuhan No. 1 Hospital in Wuhan, Hubei province, China, between November 2015 and March 2016. The demographic information of the mothers and neonates are listed in Table S2. The maternal blood samples (n= 31) were collected from each participant 2-3 days before delivery, the umbilical cord blood (n= 31) and placenta (n= 31) samples were collected immediately after delivery. Each blood sample was centrifuged for 10 min at 5000 rpm to separate the serum. A Beckman Coulter AU5800 biochemical analytic station (Beckman Coulter, Inc., USA) was used to determine the albumin (ALB) and total protein (TP) content in the serum. The samples were transferred to pre-cleaned polypropylene tubes and stored at -20 °C prior analysis. The ethical protocol was approved by the Wuhan No. 1 Hospital clinical ethics committee and Zhejiang University research ethics committee, with the consent of all participants.

**Extraction and Cleanup.** Extraction and cleanup of the maternal and cord serum were performed according to a previously described method.[32, 33] Briefly, 2 mL of serum spiked with internal standard ($^{13}C_{10}$-*trans*-chlordane) was mixed with 0.5 mL formic acid and 2.5 mL ethanol. Each sample was further diluted and extracted with 20 mL of *n*-hexane/dichloromethane (DCM) mixture (1:1, v/v). The sample was sonicated for 10 min before centrifugation (at 2000 rpm for 10 min). The organic phase was collected after centrifugation, and the extraction was repeated three times. The combined extract was evaporated to 1 mL using a BÜCHI rotavapor (R-215) (BÜCHI Labortechnik AG, Switzerland).

The placenta was washed with Milli-Q water to remove blood prior storage and homogenization. Two grams of homogenized placenta (wet weight, ww) sample was freeze-dried for 48 h in a freeze-dryer (Christ Beta 1-8 LD plus, Martin Christ Gefriertrocknungsanlagen GmbH, Osterode am Harz, Germany). The dried placenta sample was mixed with anhydrous sodium sulfate ($Na_2SO_4$, 5 g), and fortified with internal standard ($^{13}C_{10}$-*trans*-chlordane). Then, the sample was sonicated for 10 min using a 30 mL mixture of *n*-hexane/DCM (1:1, v/v), and the extraction procedure was repeated three times. The combined extract was evaporated to approximately 1 mL.

Both serum and placenta concentrated extracts were subjected to a two-step cleanup procedure reported earlier,[33] with little modification. The extract was initially passed through a multilayer silica gel column packed with 2 g anhydrous sodium sulfate ($Na_2SO_4$), 5 g acid silica gel (30% $H_2SO_4$, w/w) and 2 g activated silica gel from top to bottom. The solvent sequence was: 50 mL of n-hexane, 100 mL of n-hexane/DCM (1:1) mixture and 50 mL of n-hexane/DCM (1:2) mixture. The second and third fractions

contained CPs. Further fractionation was carried out on a basic alumina (5 g) column with 50 mL of n-hexane (discarded) and 70 mL DCM. The DCM fraction contained all SCCPs and MCCPs. Final column extract was concentrated to near dryness using a stream of nitrogen and was reconstituted in 50 μL of *n*-nonane for GC analysis.

**Instrumental Analysis and Quantification.** A total of 24 SCCP and 24 MCCP congener groups were analyzed in the serum and placenta samples by gas chromatography (GC, 7890A) coupled with electron capture negative-ion low resolution mass spectrometry (5975C) (GC-ECNI-LRMS, Agilent Technologies Inc., Santa Clara, CA, USA), using an existing method, described in supporting information (SI).[33] SCCP and MCCP congeners were identified by comparing the obtained chromatographic signal shapes, retention times, and isotope ratios. The two most abundant $[M\text{-}Cl]^-$ isotope ions of CPs were monitored in the selected ion monitoring (SIM) mode for quantification and confirmation (Table S3). The simultaneous analysis of SCCPs can interfere with MCCPs when LRMS in ECNI mode was employed. To minimize such interference and improve the sensitivity, a method reported by Zeng et al.,[34] was used (SI). All monitored ions of SCCP and MCCP congeners were divided into four groups by mutual combination: $C_{10}$-$C_{15}$; $C_{11}$-$C_{16}$; $C_{12}$-$C_{17}$; $C_{13}$-$C_{14}$, to eliminate the five carbon atoms more and two chlorine atoms less interferences. Furthermore, each sample was subjected to four individual injections. The mathematical quantification method, based on a linear correlation between the total response factors of CPs and chlorine contents, was described by Reth et al.,[35] (SI). The calibration curves were established using the three SCCP (51.5, 55.5 and 63%) and three MCCP (42, 52 and 57%) standards and their mixtures to determine the relationships between the total response factors of SCCPs and MCCPs and their calculated chlorine

contents (Figure S1). Thus, total SCCP and MCCP can be quantified. This method compensates for the differences in the response factors between the reference CP standards and the CPs pattern present in samples. The actual relative integrated signals for each congener were obtained by correcting the SIM signals of $[M\text{-}Cl]^-$ ions from isotopic abundance. The mass fraction of each CP congener group was calculated by the proportion of the relative peak area of each congener group accounting for the total SCCP or total MCCP.

**Quality Assurance/Quality Control.** Strict quality control and assurance measures were adopted to ensure the accurate identification and quantification of the target SCCP and MCCP congener groups. All glassware was heated at 400 °C overnight and rinsed three times with *n*-hexane prior use. The silica gel and anhydrous sodium sulfate were baked at 250 °C and 450 °C for 10 h, respectively. A newborn bovine serum (NBS) was used as a blank matrix for maternal and cord serum samples, while a mixture of five randomly selected placenta samples was used in the recovery and matrix effect evaluation. The recoveries of the internal standard ($^{13}C_{10}$-trans-chlordane), and SCCP and MCCP standards for the spiked matrices (NBS and placenta mixture) were determined by three replicates, and the values were in the range of 84.0-115, 87.1-97.6 and 87.7-102%, respectively. The chlorine contents of SCCPs and MCCPs in the samples were 58-65% and 50-58%, respectively. The average chlorine contents were higher than the stated chlorine contents, but that is expected with ECNI according to the literature.[33] Accuracy was controlled with spiked samples and deviated less than 10% from the expected values. The repeatability of the analysis was evaluated by analyzing five different serum and placenta samples. Each sample was processed three times, and the relative standard

deviations of SCCPs and MCCPs for each set of triplicate samples were ≤10%. The method quantification limit (MQL) was calculated to be the concentration responding to a signal-to-noise ratio of 10 in the sample matrix. The SCCP and MCCP standards with degrees of chlorination 51.5% and 42%, respectively, were used to obtain the detection limits. The MQL values for the total SCCP were estimated to be 2.1 ng/mL for serum and 3.2 ng/g (ww) for the placenta, and the corresponding values for the total MCCP were estimated to be 3.0 ng/mL for serum and 4.8 ng/g (ww) for the placenta. A procedural blank was processed with each batch of 8 samples to check for possible interference or contamination. The results were corrected with a surrogate standard. The detection levels of SCCPs and MCCPs in blanks were below or close to the MQL, and the reported concentration of CPs was not blank-corrected.

**Data Analysis.** To assess the maternal to cord transfer efficiency of the SCCP and MCCP congener groups, the matched cord/maternal concentration fraction ratio ($R_{CM}$) was used. The matched placenta/maternal concentration fraction ratio ($R_{PM}$) was used to estimate the placental retention of the investigated contaminants. If $R_{CM}$ <1, then the cord CPs concentration is smaller than for maternal and vice versa. Similarly, if $R_{PM}$ <1, then the placenta CPs concentration is smaller than for maternal and vice versa. The following equations were used for $R_{CM}$ and $R_{PM}$:[36]

$$R_{CM}\,(\text{dimensionless}) = C_{\text{Cord Serum}}/C_{\text{Maternal Serum}} \quad (1)$$

$$R_{PM}\,(\text{dimensionless}) = C_{\text{Placenta}}/(C_{\text{Maternal Serum}}/1.025\ \text{g/mL}) \quad (2)$$

$C_{\text{Cord Serum}}$, $C_{\text{Maternal Serum}}$, and $C_{\text{Placenta}}$ are the CP concentrations in cord serum, maternal serum (ng/mL, wet weight) and placenta (ng/g, wet weight), respectively. The

concentration units of serum and placenta are different, but 1 mL of blood is equivalent to approximately 1 g. Therefore, this does not have a significant influence on the ratios. In equation 2, the value 1.025 g/mL, which is the density of human plasma, was used in the formula to make $R_{PM}$ dimensionless for comparison with $R_{CM}$.[37-39]

Statistical analyses were conducted using SPSS (IBM, Version 22). Analysis of variance (ANOVA) and Independent Samples T-tests were performed to compare the differences among the congener groups in maternal sera, placentas, and cord sera. Linear regression analysis was performed for the correlation between the log-normalized distribution data sets. The normal distribution was tested by conducting the Kolmogorov-Smirnov normality test. The value of $P < 0.05$ was considered to be statistically significant.

## RESULTS AND DISCUSSION

**∑SCCP and ∑MCCP levels in Maternal serum, Cord Serum and Placenta.** A total of 24 SCCP ($C_{10-13}Cl_{5-10}$) and 24 MCCP ($C_{14-17}Cl_{5-10}$) congener groups were detected in matched maternal serum (n = 31), umbilical cord serum (n = 31), and placenta samples (n = 31), and the detection frequency of each congener group is shown in Table S4 (SI). The concentrations and chlorine contents of the SCCP and MCCP congener groups are summarized in Table S5. The ∑SCCP concentration with chlorine content ranges were 15.9 -584 ng/ml, 58.3-64.6% Cl in maternal sera, 8.46-223 ng/ml, 58.4-62.6% Cl in cord sera and 10.2-132 ng/g, 58.3-61.2% Cl in placentas, with median values of 66.2 ng/ml, 36.7 ng/ml and 33.1 ng/g, respectively. ∑MCCP concentration and chlorine content ranges were 29.3-1006 ng/ml, 50.2-57.9% Cl in maternal sera, 13.6-90.1 ng/ml, 50.7-54.9%

Cl in cord sera and 24.8-642 ng/g, 50.1-54.1% Cl in placentas, with median values of 126 ng/ml, 34.2 ng/ml and 68.3 ng/g, respectively. The occurrences of ∑SCCP and ∑MCCP in maternal sera, cord sera and placentas indicated the mother-fetus transmission of CPs.

As shown in Figure 1, the concentrations of MCCPs in maternal sera and placentas were significantly ($P < 0.05$) higher than that of SCCPs. This significantly higher concentration of MCCPs indicates that MCCPs nowadays are of growing concern, which is in line with the observation of a previous study reported on MCCPs.[40] However, SCCPs and MCCPs were present in similar concentrations in cord sera (Table S6). Besides, no significant ($P > 0.05$) difference was found between the three matrices for ∑SCCP concentrations (Table S6). This finding suggests that SCCPs may efficiently cross the placental barrier to reach the fetuses.

In contrast, the ∑MCCP concentrations followed the order of maternal sera > placentas > cord sera (Figure 1), with significant differences between maternal and cord sera ($P < 0.05$) (Table S6). The reduction in ∑MCCP concentration suggests that MCCPs may not efficiently cross the placenta barrier and are effectively filtered by the placenta in comparison to SCCPs. This may be attributed to the fact that MCCPs have relatively low mobility, and have higher molecular weight and octanol-water partitioning coefficients ($K_{OW}$) (Table S7) compared to SCCPs.[41]

**Carbon and Chlorine Congener Group Profiles of $C_{10-13}$ and $C_{14-17}$-CPs.** Figure 2 shows the carbon and chlorine congener group patterns of SCCPs and MCCPs in paired maternal serum, cord serum and placenta collected from pregnant women. Generally, the SCCP and MCCP congener group patterns in maternal sera, cord sera and placentas were

similar, even though the amounts of congener groups varied between the samples (maternal, cord sera and placentas). The SCCP congener distribution profiles were dominated by $C_{10}$ and $C_{11}$-CPs which accounted for 59% of the total SCCP concentration in maternal sera, 68% in cord sera and 62% in placentas, followed by the longer chain carbon $C_{12}$ and $C_{13}$-CPs (Figure 2a). Among the SCCPs chlorine congener groups, the lower chlorinated congener groups $Cl_5$, $Cl_6$ and $Cl_7$ were the most predominant, contributing 67, 77 and 77% to the total abundance of SCCPs in maternal sera, cord sera, and placentas, respectively, followed by the higher chlorinated congener groups $Cl_8$, $Cl_9$ and $Cl_{10}$ (Figure 2c). The SCCP congener group composition patterns were similar to that of breast milk and placenta samples previously reported.[22, 42] Moreover, no significant differences were found in the concentration of the short carbon chain congener groups $C_{10}$ ($P > 0.05$) and $C_{11}$-CPs ($P > 0.05$) between the maternal sera and the corresponding cord sera. On the other hand, the long carbon chain congener groups $C_{12}$ ($P < 0.05$) and $C_{13}$-CPs ($P < 0.05$) were found to be significantly lower in cord sera compared to maternal sera (Table S8). These findings indicated that relatively similar concentration abundances of the short carbon chain and lower chlorinated congener groups of SCCPs were found between maternal and cord serum, compared to the long and highly chlorinated congener groups.

As shown in Figure 2b, $C_{14}$ and $C_{15}$-CPs were the predominant carbon congener groups of MCCPs and contributed 69% to the total concentration abundance of MCCP congener groups in maternal sera, 80% cord sera, and 64% placentas, followed by the longer chain carbon congener groups $C_{16}$ and $C_{17}$-CPs. The congener group patterns of MCCPs were consistent with the reported patterns of MCCPs in previous studies on breast milk and

placenta samples.[22,42] The chlorine congener group profiles of MCCPs were dominated by $Cl_5$, $Cl_6$, and $Cl_7$, with percent abundances of 72, 70 and 76% in maternal sera, cord sera, and placentas, respectively (Figure 2d). Meanwhile, the higher chlorinated congener groups $Cl_{8\text{-}10}$ were less abundant. Also, the concentration abundances of longer carbon chain ($C_{16}$ and $C_{17}$-CPs) congener groups of MCCPs in cord sera were significantly ($P < 0.05$) (Table S8) lower than that in maternal sera, with percent abundances of 21% and 31%, respectively. Whereas, the concentration abundances of the short carbon congener groups of MCCPs were relatively higher in the cord sera compared to maternal sera (Figure 2b). These findings demonstrated that $C_{16}$ and $C_{17}$-CP congener groups may be partially blocked by placentas, and thus have low transportability for crossing the placental barrier compared to the shorter chain MCCPs such as $C_{14}$ and $C_{15}$-CP congener groups.

Generally, humans are exposed to POPs via various primary pathways including diet, inhalation, and dermal contact. The CP congener groups abundance patterns in the maternal sera, cord sera, and placentas obtained in the present study were consistent with those previously reported in foodstuffs,[43] indoor dust,[44] and air samples[45] from China. In China, three CP products, namely, CP-42, CP-52, and CP-70 are manufactured commercially, and the SCCP congener composition profiles in the present study were also consistent with the SCCP congener composition profiles of CP-42 and CP-52, reported in a previous study.[18] The similarity in CP congener groups patterns in environmental matrices, industrial CP products, and human bodies demonstrate that diet, dust, and air may be the important pathways responsible for the potential human exposure to the investigated contaminants.

**Placental Retention, and Transport.** The occurrence of SCCP and MCCP congener groups in the placenta and cord serum demonstrates that these contaminants can be transported to umbilical cord by crossing the placental barrier, with retention in the placenta. In the present study, $R_{CM}$ and $R_{PM}$ ratios were calculated to investigate the placental transport and retention, respectively. As shown in Figure 3(a, c), similar $R_{CM}$ values were found up to $C_{14,}$ and then from $C_{15,}$ a decreasing trend was observed. This may be attributed to the fact that the shorter carbon chain CPs are more mobile and have relatively low log $K_{ow}$ values compared to the longer carbon chain.[41] This is supported by the negative relationship between the log $K_{ow}$ and $R_{CM}$ values of CPs (Figure S3). It has been reported that the log $K_{ow}$ values of CPs increase as the carbon chain and degree of chlorination increase. [46,47,48] In general, the present study suggests that the lower molecular weight CPs were more efficiently transported through placenta than CPs with counterparts with higher molecular weight. The decreasing placental transport of PBDEs with increasing degree of bromination has also observed in human ex vivo placental perfusion model,[49] as well as in marine mammals.[50, 51] This finding is in line with similar research on polychlorinated biphenyls (PCBs), PBDEs and CPs. [21, 49, 52-56] Such a phenomenon cannot be simply rationalized by the difference in log $K_{ow}$, as the steric hindrance factor may play a vital role.[52, 55] It has to be noted that, however, an existing study shows that the $R_{CM}$ values increase with the increase of carbon chain length of CPs,[21] which is contradicting with the findings of the present study, which maybe because of the different identification and quantification methods. Nevertheless, only $R_{CM}$ values have been investigated in the previous study, where the transfer and retention efficiencies of CPs from maternal to placenta have not been investigated up to date,

318 although it is vital information for understanding placental transport mechanism.
319 Furthermore, for SCCP and MCCP chlorine congener groups, significantly higher ($P <$
320 0.05) $R_{CM}$ values were observed for lower chlorinated $Cl_{5\text{-}6}$ congener groups of both
321 SCCPs and MCCPs compared to the higher chlorinated congener groups ($Cl_{9\text{-}10}$), except
322 for $Cl_{7\text{-}8}$ (Figure S2a, c) (Table S10). We have also observed that the $R_{CM}$ value of $Cl_{10}$
323 congener group of MCCPs group was higher than the $Cl_{5\text{-}6}$ for the $C_{14}$, $C_{15}$, and $C_{16}$
324 congener groups of MCCPs. This less pronounced variation of $Cl_{10}$ is associated with the
325 low abundance of $Cl_{10}$ congeners in maternal serum (Figure 2d). These findings indicate
326 that shorter carbon chain and lower chlorinated congener groups of CPs were more
327 efficiently transported from mother to umbilical cord blood of fetus than the longer
328 carbon chain and the highly chlorinated congener groups of CPs.

329 Furthermore, as shown in Figure 3(b, d), the $R_{PM}$ ratios of CP congener groups followed a
330 slightly increasing trend with increasing carbon chain length from $C_{10}$ to $C_{17}$-CPs,
331 excluding $C_{11}$-CPs, which revealed the opposite trend to that of the $R_{CM}$ ratios of CP
332 congener groups. These findings demonstrated that the longer carbon chain-CPs were
333 more susceptible to placental filtration and accumulated more in the placenta than the
334 short carbon chain-CP congener groups. This placental retention of larger carbon chain-
335 CPs may also be attributed to the higher molecular weight and higher $K_{ow}$ values in
336 contrast to short carbon chain-CPs, which is in agreement with the transport barrier
337 properties of membranes for higher molecular compounds.[54, 55] Supporting this
338 observation, it is known that water is the main component of the maternal blood and cord
339 blood, while on the other hand, the placenta contains more lipid and proteins,[38, 57] which
340 can explain and support the above-described observation of opposite trends for the $R_{PM}$

and $R_{CM}$ ratios. The shorter carbon chain CP congener groups with less protein binding capacity and greater water solubility were partitioned efficiently in maternal blood or cord blood. Thus, we assume the increase of $R_{PM}$ values with the increase of carbon chain length of CPs may be attributed to the greater binding affinities of the longer chain congener groups of CPs to the placental proteins. Meanwhile, it is reported that active transport may also influence the placental transport.[26] Hence, these findings suggest the importance and the role of protein binding affinities of CPs that are responsible for the distribution patterns of CPs between the mother and the fetus. However, no study on the binding affinities of CPs has been reported to date, and therefore, further studies are suggested. Meanwhile, the chlorine atom-specific $R_{PM}$ values of both SCCPs and MCCPs for the lower chlorinated congener groups ($Cl_{5\text{-}7}$) were significantly higher ($P < 0.05$) than the highly chlorinated congener groups ($Cl_{8\text{-}10}$) (Figure S2b, d) (Table S10). This indicates efficient transport of lower chlorinated congener groups of CPs from maternal to placenta compared to highly chlorinated congener groups.

We have determined the placenta to umbilical cord serum transfer efficiencies of CP congener groups by calculating the $R_{CM}/R_{PM}$ ratios (Figure S4). The ratios showed that $C_{11}$-CPs (median= 1.10) cross the placenta most efficiently, followed by $C_{13}$ (median= 1.04), $C_{10}$ (median= 0.87), and $C_{12}$-CPs (median= 0.86) (Figure S4a). However, no significant differences ($P > 0.05$) (Table S9) were found among the SCCP congener groups. The $R_{CM}/R_{PM}$ ratio values of $C_{13}$-CPs were slightly, but not significantly ($P > 0.05$) higher than that of $C_{10}$ and $C_{12}$-CPs. This variation may be attributed to the differences in the pathology and physiology of the individual placentas, which might play an important role in placental differences.[58] For instance, the differences in placenta size, fat content,[59]

and inflammation were reported to be important factors related to the transplacental transfer.[60] For MCCP congener groups, the $R_{CM}/R_{PM}$ values decreased with increasing carbon chain length with significant differences (Table S9). Indeed, ratio values decreased from 0.50 to 0.43, 0.28 and 0.26 from $C_{14}$ to $C_{15}$, $C_{16}$, and $C_{17}$, respectively. This indicates that $C_{14\text{-}15}$-CPs of MCCPs group can more efficiently transfer from placenta to umbilical cord than $C_{16\text{-}17}$-CPs (Figure 4b). This also indicates that the placenta transfer efficiencies ($R_{CM}$) are presumably not the same, but rather similar to the $R_{CM}/R_{PM}$ ratios.

**Mother-Fetus Distribution and Prenatal Exposure of CPs.** To assess the congener-specific prenatal exposure of CPs, empirical relationships between maternal serum, placenta and cord serum samples were studied by measuring the concentrations in cord serum based on the concentrations in the corresponding maternal serum (Figure 4). Significant linear relationships were observed in the log-normalized concentrations of $C_{10}$ ($R = 0.51$, $P = 0.003$), $C_{11}$ ($R = 0.46$, $P = 0.009$), $C_{12}$ ($R = 0.54$, $P = 0.002$), and $C_{13}$ -CP ($R = 0.52$, $P = 0.003$) congener groups between the maternal and cord serum. Meanwhile, linear relationship was observed in each congener group of SCCPs between the maternal serum and placenta: $C_{10}$ ($R = 0.77$, $P < 0.01$), $C_{11}$ ($R = 0.57$, $P = 0.001$), $C_{12}$ ($R = 0.53$, $P = 0.002$), and $C_{13}$ -CPs ($R = 0.53$, $P = 0.002$) (Figure 4a, b). These findings suggest the potential exposure of the fetus to the SCCP congener groups. For MCCPs, a significant positive correlation was observed in the log-normalized concentrations of each congener group, $C_{14}$ ($R = 0.61$, $P < 0.01$), $C_{15}$ ($R = 0.65$, $P < 0.01$), $C_{16}$ ($R = 0.76$, $P < 0.01$), and $C_{17}$ -CP ($R = 0.73$, $P < 0.01$) between the maternal serum and placenta (Figure 4d). However, no significant relationship was found between the maternal and cord serum for each congener group of MCCPs: $C_{15}$ ($R = 0.05$, $P = 0.79$), $C_{16}$ ($R = 0.22$, $P = 0.24$), and $C_{17}$ -

CPs (R = 0.20, $P = 0.28$), except for $C_{14}$-CPs (R = 0.45, $P = 0.01$) (Figure 4c). These results suggest that MCCP congener groups may be effectively filtered by the placenta leading to reduced exposure to the fetus compared to the exposure level of the mother.

In general, the concentration levels of SCCPs and MCCPs in cord serum were relatively similar, which may be resulting in a similar exposure to the fetus. Previous studies have reported that even a low dose exposure to chemicals may lead to irreversible damage and disease in the fetus because during the embryonic and development stages fetuses are more sensitive to chemicals.[61,62] The United Nations Environment Program, persistent organic pollutants review committee suggested MCCPs as alternatives for SCCPs, considering MCCPs are relatively less toxic.[10] As stated above, nowadays, MCCP production and their environmental occurrence are of increasing relevance. Although the toxicological properties of MCCPs are less studied and still a matter of debate, special consideration should be paid to the neonatal exposure of such compounds. Our findings explicitly demonstrated that SCCP congener groups and the $C_{14}$-short carbon chain congener of MCCPs group were efficiently transported via the placental barrier, and were accumulated in the umbilical cord blood of the fetus, which might pose potential health risks to fetuses.

Furthermore, no relationships were observed between the CPs concentrations and mother/fetus demographic characteristics including mother's age, weight gain during pregnancy, parity, and gestational age and fetus gender, except for neonatal body weight (Table S2). As shown in Figure S5A, significant negative relationships were found between the baby's body weight and the SCCP concentrations in maternal sera. However, no relationships were found between the MCCP concentrations and baby's body weight

410 (Figure S5B). This finding indicated that the SCCP congener group concentrations in
411 maternal sera decreased with the increase of the fetus body weight, providing indirect
412 support for the transportation of SCCPs from the mother to the fetus. This may be
413 attributed to the fact that a fetus with larger bodyweight requires greater nutrient
414 transportation from the mother. Although no relationships were observed for cord sera
415 and placentas, this may be due to the small sample size of the present study. Further study
416 with a larger sample size should be carried out to investigate the relationship between the
417 maternal/fetus demographic characteristics and the CP congener group's concentrations
418 in matched maternal-placenta-cord serum samples.

419 **Implications and Limitations**

420 We have investigated the congener-specific mother-placenta-fetus distribution of CP
421 congener groups, as well as the maternal-placenta and placenta-cord serum transfer
422 efficiencies. The findings improved our understanding of the congener-specific
423 abundance patterns of the CPs in maternal serum, cord serum, and placenta, and further
424 enhanced our knowledge of the transplacental transport mechanisms of these emerging
425 contaminants.

426 The limitations of the present study include the appropriate analysis and quantification
427 methods of CPs, which are the challenges related to the accurate determination of CPs
428 and are still debatable. The relatively small sample size (due to sampling limitations),
429 which comprised of 31 matched maternal serum, cord serum, and placenta samples, is
430 also one of the limitations of this study. The current study provides information about the
431 congener-specific placental transport efficiencies of CPs and the prenatal exposure, based

on the passive transport mechanism. Whereas, the active transport mechanism of CPs is not investigated in this study. In this respect, overarching investigations of the active transport mechanism, prenatal exposure and human health risk assessment of CPs with larger sample size are warranted. Recently, SCCPs have been listed as POPs, and it was also reported that the shorter carbon chain CPs were relatively more toxic than the longer chain CPs.[6] In this study, the findings that the shorter carbon chain CPs can efficiently transfer from the mother to the fetus has implications for assessing the potential mother and fetus health risks associated with CPs exposure. The occurrence of MCCP congener groups in maternal serum, cord serum and placenta were relatively higher than the SCCP congener groups, which is supporting that nowadays MCCPs production and environmental occurrence are increasing. This alarming increase of CP levels in the environment warranting further monitoring studies of medium-chain and long-chain CPs. The placental transfer rates and distribution of POPs may be influenced by the phospholipids and proteins [63,64] in the maternal, cord serum and placenta. Thus, further comprehensive research studies of phospholipid partitioning and protein binding affinity of CPs in human serum and tissues are required for further enhancing the knowledge of placental transfer and prenatal exposure, and the associated potential health risks of these emerging contaminants to mother and fetus.

## ASSOCIATED CONTENT

### Supporting Information

Additional information on the analytical method; Chlorine atom-specific maternal to cord ($R_{CM}$) and maternal to placenta ($R_{PM}$) transfer efficiencies of SCCPs and MCCPs; Relationship of CPs with demographic characteristics; Mother/neonate demographic

455 characteristics; SCCP and MCCP standards and their mixtures along the degree of
456 chlorination for calibration curves; CP congener groups quantitative and qualitative ions
457 m/z values; Concentrations of SCCP and MCCP congener groups in maternal serum,
458 placenta, and cord serum; Correlations between CP congener groups in maternal-cord
459 sera; Log$K_{OW}$ values of SCCPs and MCCPs; Linear regression equations of log-
460 normalized concentrations of SCCPs and MCCPs.

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468 **Notes**

469 The authors declare no competing financial interest.

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475

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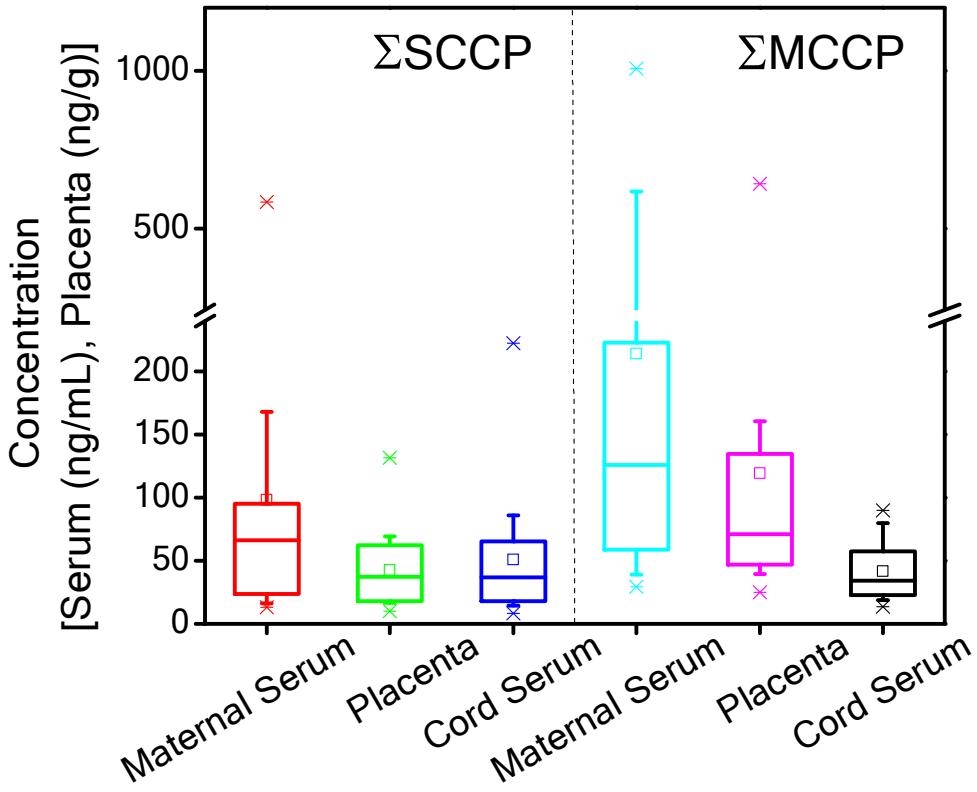



**Figure 1**. Box chart of total SCCP and MCCP concentrations in paired maternal serum (ng/mL), placenta (ng/g), and cord serum (ng/mL). The boxes represent 25$^{th}$ and 75$^{th}$ percentiles. Squares within the boxes indicate mean values. The bands inside the boxes indicate the median values. The whiskers mark 5$^{th}$ and 95$^{th}$ percentiles, and the crosses indicate outlier values.

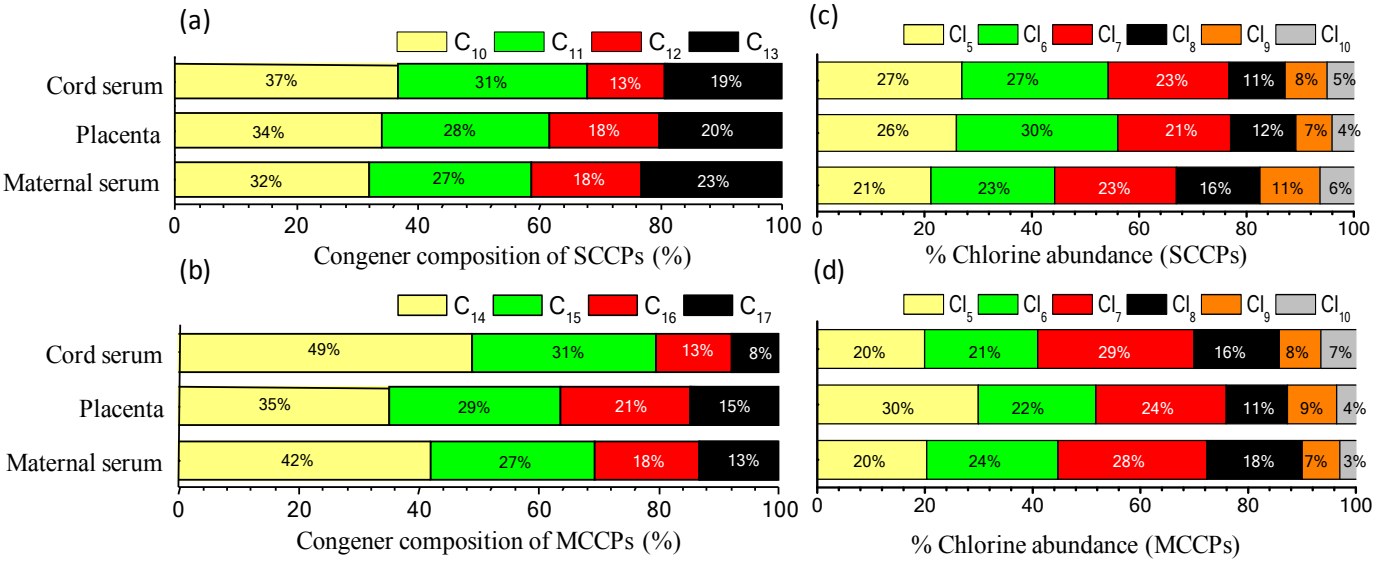
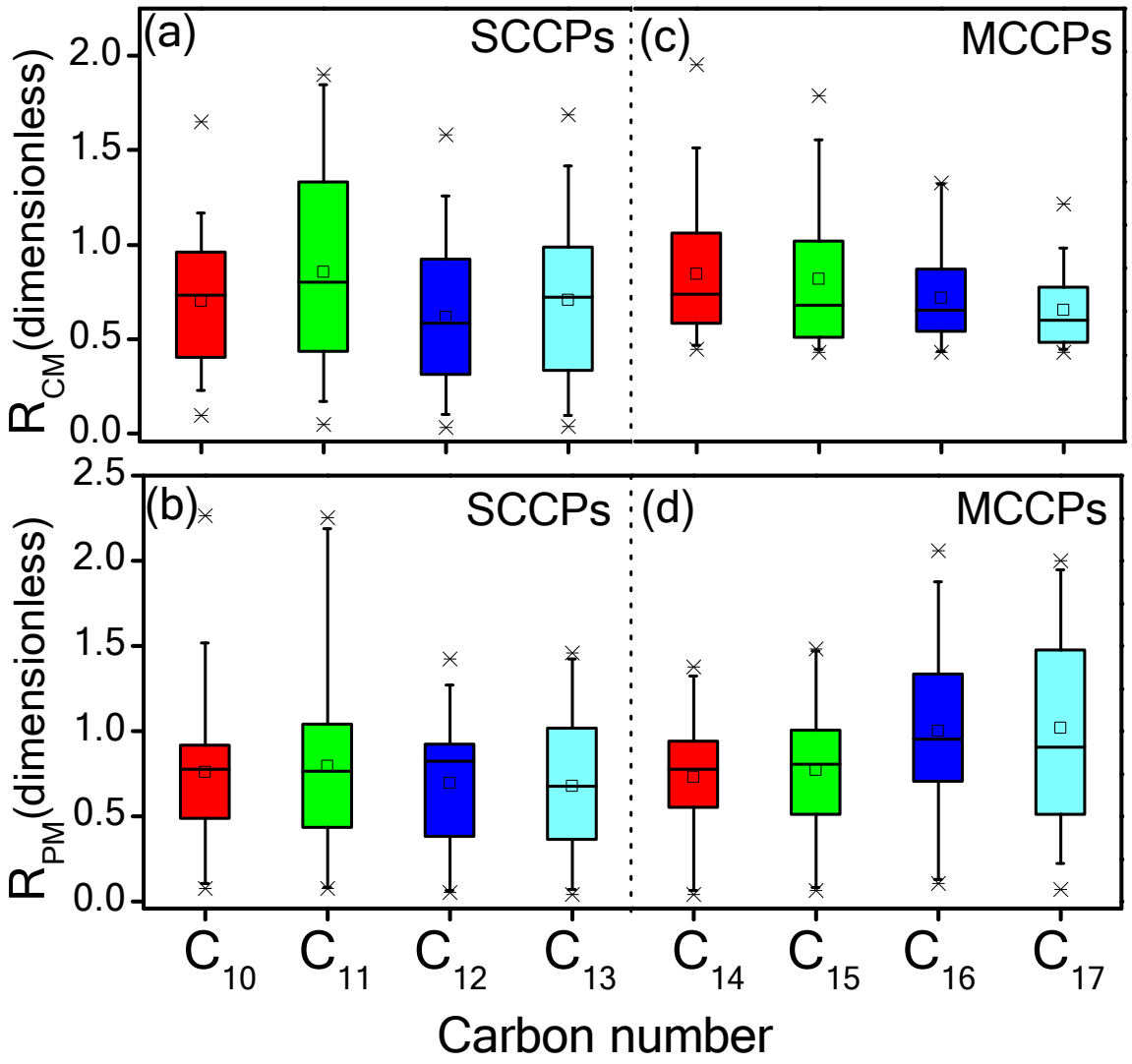



**Figure 2.** Carbon and chlorine congener groups composition (%, average) of [(a) and (c)] SCCPs and [(b) and (d)] MCCPs in maternal serum, cord serum, and placenta, respectively.

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712 **Figure 3.** Congener-specific cord-maternal ($R_{CM}$) and placenta-maternal ($R_{PM}$) ratios of
713 [(a) and (b)] SCCPs and [(c) and (d)] MCCPs. The boxes represent the 25$^{th}$ and 75$^{th}$
714 percentiles. The squares within the boxes indicate mean values. The bands inside the
715 boxes indicate the median values. The whiskers mark 5$^{th}$ and 95$^{th}$ percentiles and the
716 crosses indicate outlier values.

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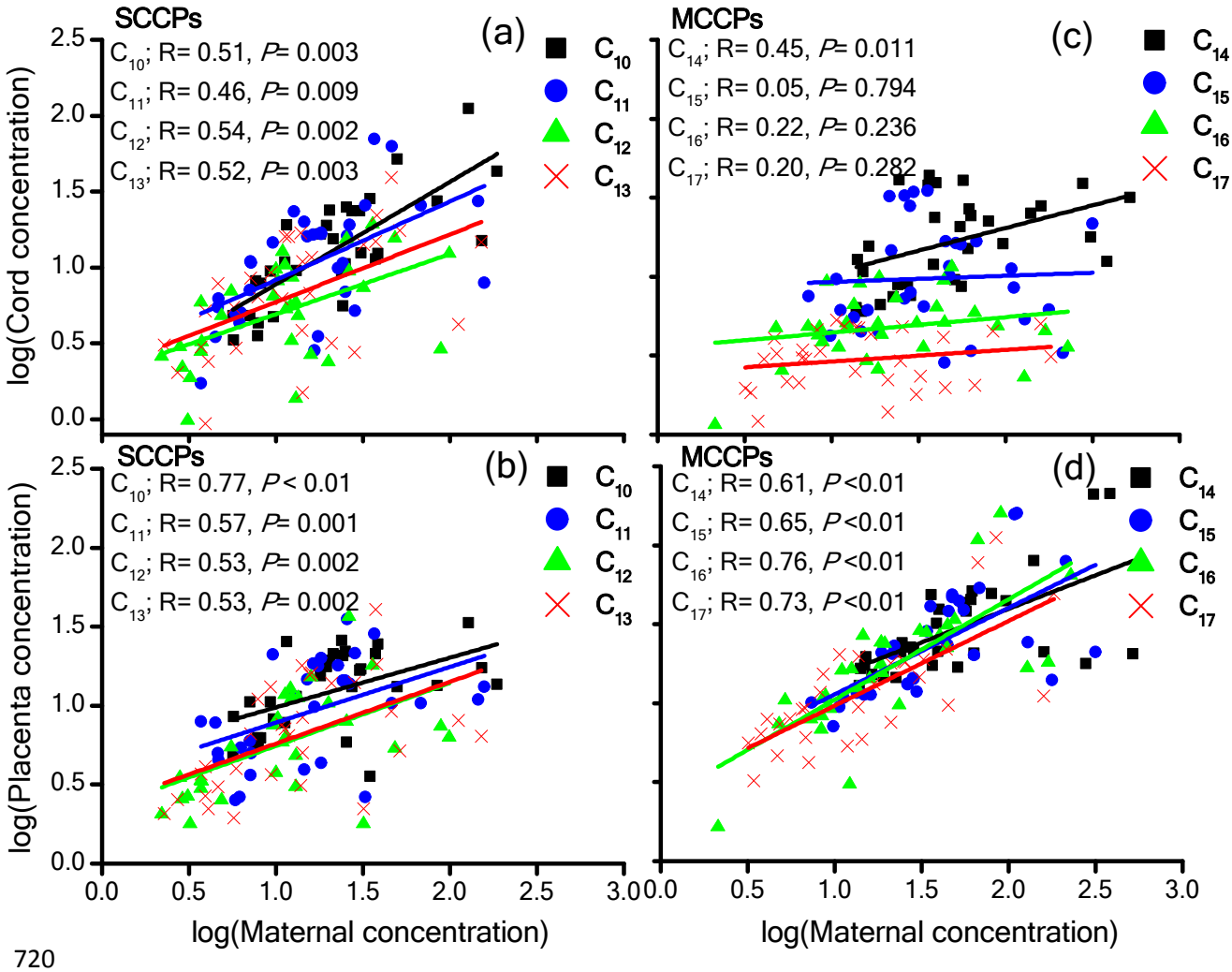


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725 **Figure 4.** Relationships between log cord-log maternal and log placenta-log maternal
726 concentrations of [(a) and (b)] SCCP and [(c) and (d)] MCCP congener groups,
727 respectively. Linear regression equations, R, and *P* values are mentioned in Table S11 (SI)
728 (Serum, ng/ml; Placenta, ng/g).