Partition of Environmental Chemicals between Maternal and Fetal Blood and Tissues

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Passage of environmental chemicals across the placenta has important toxicological consequences, as well as for choosing samples for analysis and for interpreting the results. To obtain systematic data, we collected in 2000 maternal and cord blood, cord tissue, placenta, and milk in connection with births in the Faroe Islands, where exposures to marine contaminants is increased. In 15 sample sets, we measured a total of 87 environmental chemicals, almost all of which were detected both in maternal and fetal tissues. The maternal serum lipid-based concentrations of organohalogen compounds averaged 1.7 times those of cord serum, 2.8 times those of cord tissue and placenta, and 0.7 those of milk. For organohalogen compounds detectable in all matrices, a high degree of correlation between concentrations in maternal serum and the other tissues investigated was generally observed ($r^2 > 0.5$). Greater degree of chlorination resulted in lower transfer from maternal serum into milk. Concentrations of pentachlorbenzene, γ-hexachlorocyclohexane, and several polychlorinated biphenyl congeners with low chlorination were higher in fetal samples and showed poor correlation with maternal levels. Perfluorinated compounds occurred in lower concentrations in cord serum than in maternal serum. Cadmium, lead, mercury, and selenium were all detected in fetal samples, but only mercury showed close correlations among concentrations in different matrices. Although the environmental chemicals examined pass through the placenta and are excreted into milk, partitions between maternal and fetal samples are not uniform.

Introduction

Developmental exposures to environmental chemicals have become an important public health concern because of their possible toxic impact on sensitive development and programming of organ functions ([1]). Unfortunately, the degree to which different persistent pollutants pass from the mother to the child is only partially known ([2]). Thus, the partition between maternal and fetal tissues is of importance to the risk assessment of environmental chemicals and to selection of samples for biological monitoring.

Cord blood has the advantage of being a noninvasive sample and has been used for assessing exposure to a variety of metals and organohalogen compounds ([3–8]). While collecting the umbilical cord is easy, this tissue has been utilized only occasionally for exposure assessment, e.g., for methylmercury ([9]). Despite a low lipid content, analyses of the cord for lipophilic contaminants have also been reported ([10–12]). The placenta is a more complex tissue, because of its mixed maternal/fetal origin, thus ideally requiring removal of the maternal part before chemical analysis ([7, 13]). Placental concentrations of environmental chemicals reflect the accumulation at the barrier—e.g., in the case of cadmium ([14–16]). Finally, human milk concentrations reflect the maternal body burden as well as the nursing infant's lactational exposure ([7, 17, 18]).

The relation between concentrations of environmental chemicals in maternal and fetal tissues and tissue fluids, and the conversion factors for concentrations in commonly used samples have not been systematically documented. Previous studies of paired samples suggest that organohalogen pollutant concentrations, when expressed on a lipid basis, tend to be somewhat higher in milk than in maternal serum, which again contains higher levels than umbilical cord serum ([6, 19–25]). While the distribution may depend on the molecular weight of the compound, molecular size, differences in lipophilicity, and affinities to biological molecules ([26]), the overall effect of the physicochemical properties is difficult to predict. The present study therefore aimed at determining the extent to which important environmental chemicals follow similar partitions between media frequently used for biological monitoring purposes. We collected paired mother–child samples to measure the concentrations of 87 environmental chemicals, including 20 polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and coplanar polychlorinated biphenyls (PCBs); 58 other PCBs, organochlorine pesticides, and polybrominated diphenyl ethers (PBDEs); five perfluorinated compounds; and four trace elements. These substances are also part of the Centers for Disease Control and Prevention's National Human Health and Nutrition Examination Survey (NHANES), which is a biannual survey of the noninstitutionalized population of the United States ([27]).

Matched mother–child samples were obtained in connection with consecutive normal parturitions in the Faroe Islands. We chose to carry out the study in this fishing community because of an anticipated wide range of exposures. The traditional Faroese diet includes pilot whale, which

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TABLE 1. Characteristics of Births from Which Sample Sets Were Collected for Analysis for Environmental Chemicals[a]

maternal variables	Group 1	Group 2	Group 3
age (years)	21, 22, 22, 31, 32	23, 29, 29, 30, 38	25, 31, 32, 37, 39
parity	0, 0, 0, 1, 2	0, 1, 1, 2, 3	0, 1, 2, 3, 4
weight (kg)	49, 54, 60, 70, 86	54, 59, 60, 61, 95	56, 65, 65, 72, 85
weight gain during pregnancy (kg)	9, 17, 20, 21, 28	0, 12, 15, 15, 15	10, 11, 12, 12, 12

[a] Group 1: No recent intake of traditional food. Group 2: High hair-mercury concentration at parturition. Group 3: High PCB concentration in transition milk.

accumulates high concentrations of PCBs, certain pesticides, and other persistent lipophilic compounds in the blubber, while methylmercury is accumulated in the meat (28, 29).

Materials and Methods

Subjects, Sample Collection, and Chemical Analyses. In connection with the recruitment of a cohort from consecutive births at the National Hospital in Torshavn, Faroe Islands (30), maternal blood, maternal hair (for mercury analysis), placenta (fetal part), umbilical cord tissue, cord blood, and milk were obtained. Detailed information on sampling, chemical analyses, and abbreviations is given in the Supporting Information (S1).

Virtually complete sample sets were obtained from 106 normal births. Two weeks after childbirth, each mother was interviewed by use of a questionnaire on the frequency of meals and portion sizes that included traditional foods, such as pilot whale meat, pilot whale blubber, fish, fulmars, and other seabirds. The Faroese diet is otherwise similar to the Scandinavian diet.

Hair from all sample sets was first analyzed for mercury, and all milk samples were analyzed for major PCB congeners. On the basis of these initial results, 15 complete sample sets—maternal hair, whole blood, serum and milk, placenta, and infant cord tissue, whole blood, and serum—were selected for pollutant analyses. Five sets represented mothers who had not eaten whale meat or blubber at all during pregnancy (Group 1). Five represented the highest hair-mercury concentrations among the samples analyzed, as a likely reflection of a high intake of whale meat in the recent past (Group 2). The last five sets of samples had the highest milk-PCB concentrations as an indication of a high lifetime blubber intake (Group 3). Background information on relevant parameters was extracted from the obstetrical charts.

The project was approved by the Faroese ethical review committee and subsequently by the IRB at Harvard School of Public Health; written informed consent was obtained from each mother.

Statistical Analysis. Concentration ratios were calculated for the various matrices in regard to the concentration in maternal blood. Each set of pairwise data was processed when at least five pairs of samples had results for the specific analyte above the detection limit, and an average concentration ratio was calculated if Pearson's correlation coefficient was at least 0.7 ($r^2 \geq 0.5$). For each matrix, the ratios obtained for the analytes were ranked, and extreme results were eliminated sequentially until the overall average showed a coefficient of variation of no more than 20%. This strategy ensured that almost all individual ratios for the different analytes were within one standard deviation from the overall average. If based on results with correlation coefficients above 0.7, outlier ratios are reported separately as the arithmetic means. Ratios based on correlation coefficients below 0.7 are reported separately as medians. Concentration dependence of the ratios was assessed by calculating regression coefficients, where the regression line was forced through the origin. Apart from increased uncertainty of results close to the detection limit, regression coefficients were in accordance with the average ratios, and regression analyses are therefore not reported.

Results

Maternal age, parity, body weight, and weight gain during the 15 pregnancies are shown in Table 1. The three exposure-based groups differed only slightly from one another in regard to background information. Whereas maternal serum and milk were analyzed for the complete set of 87 environmental chemicals, the 20 PCDDs, PCDFs, and coplanar PCBs were not determined in cord blood, cord tissue, and placenta due to insufficient sample sizes combined with low lipid contents. The perfluorinated compounds (PFCs) were analyzed in 12 sets of maternal serum, cord serum, and milk. Of the 58 organohalogen compounds determined in fetal samples, only 2,2,5,5,8,9,9,10,10-nonachlorobornane (Parlar-62), BDE-85, and PCB-18 were below the detection limit for all samples. Parlar-62 was detected in maternal serum, although in only three samples. In general, environmental chemical concentrations for Group 1, who did not eat traditional food during pregnancy, tended to be lower than the results for the two other groups, and the results for Group 3 with the high milk-PCB concentrations were among the highest also for most of the chemicals analyzed. Thus, the sampling strategy ensured a wide range of results.

Concentrations in umbilical cord serum and milk, and to a lesser extent those from cord tissue and placenta, correlated well with the maternal serum concentrations. In cord serum, only pentachlorobenzene (PCBz) and γ-HCH seemed to diverge from this pattern. In placenta and cord tissue, the highly chlorinated PCBs correlated the best with the maternal serum concentration, whereas PCB congeners 28, 44, 49, 52, 66, 101, 105, 128, and 149 showed much scattering. Greater variability in the apparent partition occurred at concentrations close to the detection limit. The *a priori* requirement of at least five sample pairs with detectable concentrations reduced the numbers of sample pairs to 43, 45, 50, and 59 for cord serum, cord tissue, placenta, and milk, respectively. A correlation coefficient of at least 0.7 resulted in further reduction to 39, 34, 29, and 56 sample pairs. Based on the required agreement with an overall ratio in regard to maternal serum, the partition ratios for the four specimens were based on 33, 22, 21, and 38 sample pairs.

Based on the overall mean ratios, cord serum, cord tissue, and placenta had lower lipid-based concentrations of organohalogen substances than maternal serum, while the relative lipid-based concentrations in milk were higher (Table 2). Support for these overall results was also obtained from several median ratios calculated for sample pairs with correlation coefficients below 0.7 (Tables S1—S3). Among the brominated substances, BDE-47 and, less clearly, BDE-100 tended to show increased concentrations in tissue and milk compared to maternal serum (Table S1). The chlorinated pesticides PCBz and γ-HCH showed a relative excess in fetal samples (Table S2). When compared to the β-HCH concentrations, the results for the gamma isomer were generally almost 2 orders of magnitude lower in maternal serum and milk, but of similar magnitude in the fetal samples. p,p-DDE

TABLE 2. Overall Average Ratio of Organohalogen Concentrations in Fetal Samples and Human Milk in Comparison with the Concentration in Maternal Serum, with and without Lipid Adjustment

matrix	number of analytes	lipid concentration relative to maternal serum[a]	average lipid-based ratio (s.d.)	average ratio (s.d.) based on fresh weight
cord serum	33	0.34	0.58 (0.11)	0.20 (0.04)
cord tissue	22	0.29	0.37 (0.07)	0.11 (0.02)
placenta	21	1.5	0.35 (0.07)	0.53 (0.11)
milk	38	2.6	1.48 (0.28)	3.85 (0.73)

[a] Mean maternal lipid concentration, 8.9 g/L.
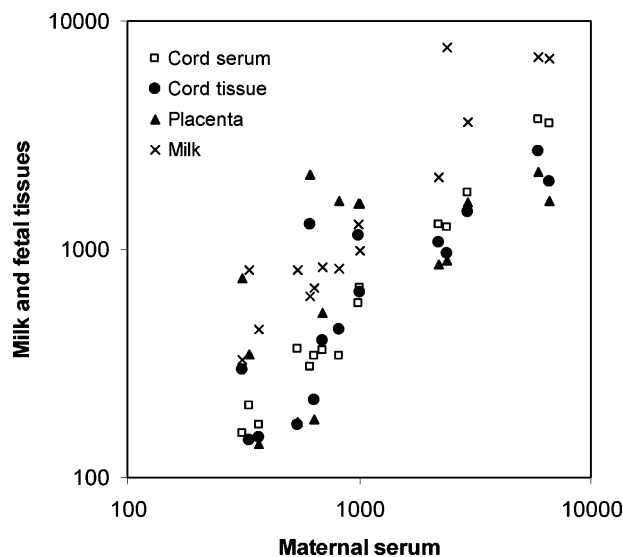
FIGURE 1. Lipid-based concentration (ng/g) of the sum of all quantified polychlorinated biphenyl congeners in milk and fetal tissues (identified by different symbols), as compared to the concentration in maternal serum in fifteen sets of samples.

FIGURE 2. Average partition ratio between lipid-based concentrations of polychlorinated biphenyl congeners in milk and maternal serum from 15 sample pairs in regard to the number of chlorine substitutions of each congener measured.

concentrations showed averages about 50-fold higher than those of the DDT isomers, which had less stable ratios. Several pesticides showed concentrations in milk that were higher than anticipated from the overall average ratio.

For the sum of polychlorinated biphenyls (Figure 1), the lipid-based cord serum concentration correlated very well with that of the maternal serum ($r = 0.99$) and showed a concentration ratio of 0.56. For milk, the correlation was not as close ($r = 0.87$), and the average ratio was 1.35. Cord tissue PCB concentrations correlated as well as milk ($r = 0.88$), although with an average ratio of 0.64, while placenta concentrations showed a poorer correlation of 0.53.

Some PCB congeners showed higher lipid-based concentrations in fetal samples than in maternal serum and milk (Table S3), but some of these ratios may be imprecise due to concentrations close to the detection limit and poor correlations between paired samples. When the PCBs were grouped according to chlorination, the partition between maternal serum and milk decreased at higher number of chlorine substitutions (Figure 2). For the other paired samples, correlations between partitions and the degree of chlorination were less clear and more variable.

Concentrations of the dioxin-like compounds varied somewhat less than other halogenated substances. Still, several PCDDs and PCDFs, and PCB congeners 126 and 169, showed high correlations between paired maternal serum and milk samples, and they were in agreement with regard to the relative distribution in the two matrices. Overall, the partitioning between the lipid phases agreed with the ratio of approximately 1.5 for milk versus maternal serum for 1,2,3,7,8-pentachlorodibenzo-p-dioxin (12378D), 123478D, 123678D, 2,3,4,7,8-pentachlorodibenzofuran (23478F), 123478F,
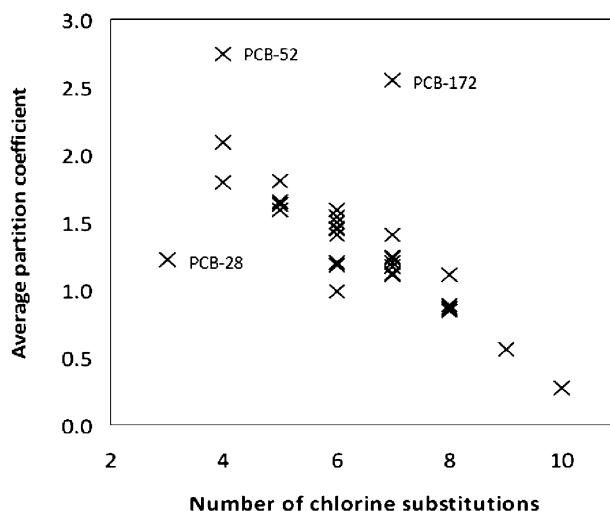
123678F, and PCB congeners 126 and 169. Although sufficient numbers of detectable concentrations were not available for several dioxin-like substances, increased chlorination tended to show a lower ratio between milk and maternal serum concentrations.

All five PFCs were detected in the samples analyzed. Perfluorooctanic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA) revealed excellent correlation between maternal and cord serum concentrations, with ratios of 0.72, 0.34, 0.50, and 0.29, respectively (Table 3). Perfluorohexane sulfonic acid (PFHxS) showed a poor correlation, but the median ratio of 0.74 confirmed that transplacental passage occurred. In the milk samples, only PFOA was detected, and then only in 7 of 11 samples analyzed. Assuming a PFOA concentration of 0 in the milk samples below the detection limit, the correlation with the maternal serum PFOA concentration was 0.80 and with cord blood was 0.72.

In regard to the trace elements (Table 4), lead was below the detection limit in all cord tissue samples. Although poorly correlated, the average lead concentrations were quite similar in cord blood and milk, but higher in the placenta. Cadmium showed a 100-fold excess in placenta in comparison to that in cord blood, but blood concentrations close to the detection limit made partition calculations unstable. Mercury and selenium showed similar partition ratios, although the average ratio for cord tissue versus cord blood was much higher for mercury than for selenium. Mercury showed excellent correlations among concentrations in different matrices (Figure 3), while selenium showed much scattering. In the matrices analyzed, the two elements correlated only poorly (e.g., $r = 0.27$ for cord blood), and the average molar concentration of selenium in cord blood, placenta, and milk exceeded that of mercury by approximately 20-fold.

TABLE 3. Average (Median) Concentrations (in ng/mL) of Perfluorinated Compounds in 12 Sets of Maternal Serum, Cord Serum, and Milk Samples, with the Ratio and Correlation Coefficient for Maternal v. Cord Serum

matrix	perfluorohexane sulfonic acid (PFHxS)	perfluorooctanic acid (PFOA)	perfluorooctane sulfonic acid (PFOS)	perfluoro-nonanoic acid (PFNA)	perfluoro-decanoic acid (PFDA)
maternal	12.3	4.2	19.7	0.76	0.34
cord	9.1	3.1	6.6	0.37	0.10
milk[a]		(0.1)			
	concentration in cord/maternal serum				
ratio	0.74	0.72	0.34	0.50	0.29
correlation	0.05	0.91	0.82	0.84	0.91

[a] Four of eleven samples available had a PFOA concentration below the detection limit, and none of the other analytes were detected.

TABLE 4. Average (Median) Concentrations of Trace Elements in 15 Sets of Cord Blood, Cord Tissue, and Placenta, with the Ratio and Correlation Coefficient for Each of the Other Matrices with the Cord Blood Concentration

	mercury	selenium	lead	cadmium
cord blood (μg/L)	12.1	105	6.0	0.33
cord tissue (μg/g)	0.085	0.20	n.d.[a]	0.003
placenta (μg/g)	0.087	0.81	0.053	0.035
milk (μg/L)	2.31	16.4	8.5	0.23
ratio to cord blood (correlation coefficient)				
cord tissue	7.0 (0.97)	1.9 (0.60)	n.d.[a]	8.7 (−0.30)
placenta	7.2 (0.97)	7.7 (0.35)	8.9 (0.34)	107 (0.12)
milk	0.19 (0.69)	0.16 (0.48)	1.41 (−0.24)	0.70 (0.14)

[a] n.d., not detected.
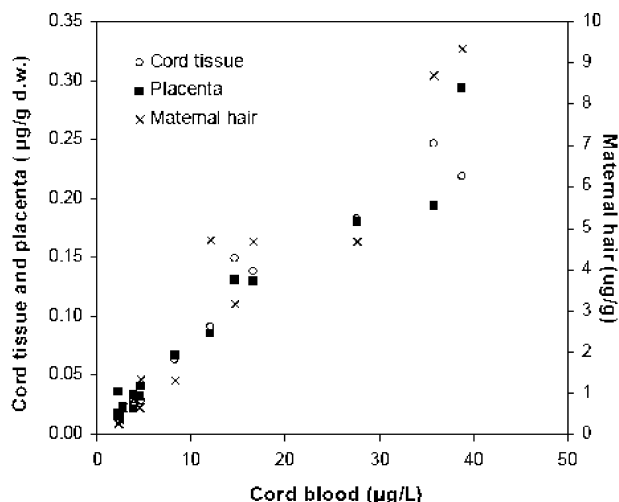
FIGURE 3. Total mercury concentrations in cord tissue and placenta (left vertical scale), and maternal hair (right vertical scale) in relation to those in cord blood (horizontal scale) from 15 sets of samples.

Discussion

This study addressed the partition between maternal and fetal tissues for a large number of environmental chemicals of toxicological interest. The samples were selected from normal births in a fishing community, where elevated exposures to marine contaminants occur. A range of exposures was intended for determination of relative partitions at different concentration levels. The results cover a large number of important environmental chemicals, particularly substances commonly present in human samples.

Virtually all substances detected in the samples were present in fetal tissues and cord blood as an indication that transplacental passage had occurred. Concentrations of cadmium were relatively increased in the placenta, thus suggesting a partial barrier for this trace element, as also reported in previous publications (14−16). For the lipophilic substances, possible placental accumulation was observed only for some low-chlorination PCBs, although increases also occurred for concentrations in cord tissue and cord serum.

Cord serum concentrations of lipophilic substances averaged slightly more than half of the levels in maternal serum after adjustment for lipid concentrations. The average lipid concentration in maternal serum (8.9 g/L) was 3-fold higher than in cord serum (3.0 g/L), and on a volume basis, concentrations in cord serum therefore averaged only 20% of those occurring in maternal serum. Lipids are likely to pass more rapidly than the contaminants into the fetal circulation, but may then be metabolized, thereby lowering the concentration on the fetal side.

Lipid-adjusted concentrations in placenta and cord tissue were slightly more than one-third of the results observed for maternal serum. The lipid concentration of the placenta was about 5-fold higher than in cord tissue, but only small differences occurred in the number of samples of these tissues with detectable concentrations of the lipophilic substances. Overall, the correlations between paired samples and the partition of lipophilic substances in maternal and fetal samples extend similar observations reported in previous studies (3−8).

The dioxins and related substances were measured only in paired serum and milk samples. The lipid-based concentration of dioxins tended to be about 50% higher in human milk, but the ratio was not constant for all analytes. However, in general, deviations were rather small. Two highly chlorinated substances—OCDD and 1234678D—were excreted to a lesser extent into milk compared to maternal serum concentrations. This finding suggests that the passage into milk may be more difficult for larger molecular sizes (5, 24), as also seen for PCB congeners (Figure 2). Although the dioxin-related substances were not measured in fetal samples, other studies suggest that some degree of barrier may exist in the placenta (31).

Considerable differences have been reported in lipid-adjusted concentrations of some environmental chemicals in maternal serum and milk from the same individual (32). In particular, a uniform distribution in the lipid phase between the samples had been called into question for PCBz, γ-HCH, HCB, and the more lightly chlorinated PCBs (8, 25). The present study confirmed that several substances deviate from a uniform pattern of distribution, in particular PCBs with low chlorination, such as congeners 28, 44, 49, 52, 66, 101, 110, and 149. Compared to their concentrations in maternal serum, the gamma, but not the beta, HCH stereoisomer showed much higher concentrations in cord serum and fetal tissues. The reasons for such discrepancies are unclear, but they could reflect a difference between maternal and immature fetal metabolism or an enantiospecific uptake.

However, the observation that some lipophilic contaminants differ in their relative distribution across the placenta must also be considered in regard to short-term toxicokinetic differences. Because the maternal serum was collected in the 32nd week of pregnancy, analytical results are compared for samples collected up to two months apart. The relatively short elimination half-life of lightly chlorinated PCBs could therefore lead to unstable tissue concentrations, and variable exposures could then easily affect the calculated partition coefficients. However, such variability would not be likely to explain the large differences in average concentrations.

Brominated substances have been previously reported to be less efficiently transferred into cord blood, while much higher concentrations are present in human milk than in serum (33). Thus, BDE47 concentrations were reported to be similar in maternal and cord blood plasma, but poor correlations were obtained for the more highly brominated congeners, BDE99, BDE100, and BDE153, which tended to show lower concentrations in cord blood plasma, thereby suggesting a less efficient passage through the placenta (34). These substances have been reported to accumulate in the fetal liver, while very little is retained in the placenta (35). In the present study, a low ratio for BDE153 in cord serum was corroborated and our findings also support the notion of increased milk concentrations of BDE congeners 47 and 100, while congeners 99 and 153 were closer to the overall average ratio, and PBB153 was lower. These results suggest that relative bromination may affect the partition to a greater extent than chlorination, perhaps as a result of differences in molecular size.

The PFC concentrations were higher in maternal serum than in cord serum, and the ratio suggested that the length of PFC chain as well as the active group affected the ability to pass the placenta. PFCs with a short chain length showed higher relative cord serum concentrations than PFCs with a longer chain length. PFCs with sulfonic acid as the active group seemed to pass more easily into the fetal circulation than PFCs with carboxylic acid as the active group. These results appear to fit in well with the findings of a previous study that examined maternal and cord serum concentrations of four PFCs (36). While a significant association with serum levels was found for PFOS, the milk concentrations were very low, as has previously been reported (37, 38).

Among the trace elements, mercury showed excellent correlations among concentrations in different matrices; the correlations thus support the use of all the specimens included in the present study, including easily collected umbilical cord tissue (39). However, much greater variability was seen with cadmium, lead, and selenium (15, 40).

The close correlation between lipid-based concentrations in maternal serum and milk for a large number of lipophilic substances supports the notion that either matrix is appropriate for assessment of exposure levels. A general proportionality factor can be considered as a feasible approximation for comparing the results, as only few of the contaminants commonly measured will require a substance-specific conversion factor. Positive correlation coefficients also indicate that these chemicals are readily transported from mother to fetus. However, measured concentrations in cord tissue and placenta are more variable, the former perhaps affected by the low lipid content. These matrices are therefore not as useful for monitoring purposes, except perhaps for cadmium, which accumulates in the placenta. Although DeKoning et al. (20) recommended that several types of specimens be collected to assess perinatal exposure levels, the present study suggests that an efficient strategy would emphasize specimens with a high rate of detectable concentrations.

The main finding of this study is that the contaminants tend to be present in all matrices examined. In general, lipid-based concentrations of lipophilic chemicals in maternal serum are correlated with concentrations in the other media. However, the transfer to the fetal circulation results in lower concentrations, while milk levels tend to be about 50% higher than the maternal serum. These patterns are complex, and the complexity must be taken into account when selecting samples for analysis and when interpreting the results.

Supporting Information Available
Details of the specimen sampling and chemical analyses, and detailed results for analytes that did not contribute to the overall average partition ratios. This material is available free of charge via the Internet at http://pubs.acs.org. The complete set of raw data is available at www.chef-project.dk.

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