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# Polybrominated diphenylethers (PBDE) and hexabromocyclododecane (HBCD) in paired samples of blood serum and breast milk – a correlation study

Sanna Lignell, Marie Aune, Anders Glynn, Tatiana Cantillana, Martin Isaksson

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**Rapportförfattare**
Sanna Lignell, Livsmedelsverket
Marie Aune, Livsmedelsverket
Anders Glynn, Livsmedelsverket
Tatiana Cantillana, Livsmedelsverket
Martin Isaksson, Livsmedelsverket

**Utgivare**
Livsmedelsverket

**Postadress**
Box 622, 751 26 Uppsala

**Telefon**
018-175500

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**Sammanfattning**

I denna studie analyserades de bromerade flamskyddsmedlen PBDE och HBCD i parade prover av blodserum och modersmjölk från 30 förstföderskor i Uppsala. Proverna samlades in ca 3 veckor efter förlossningen, och syftet var att undersöka korrelationer mellan blodserum- och modersmjölkshalter för att utvärdera om halter av PBDE/HBCD i modersmjölk är en bra indikator på mammans kroppsbelastning och möjligtvis också på barnets exponering under fosterperioden.

PBDE (kongenerna BDE-28, -47, -66, -99, -100, -138, -153, -154, -183, -209) och HBCD analyserades med en metod baserad på gaskromatografisk separation och lågupplösande masspektrometisk detektion (ECNI-SIM). Halter under metodens kvantifieringsgräns (LOQ) användes i de statistiska analyserna eftersom de, trots större osäkerhet, ger värdefull information om spridningen i halter. I blodserum var medianhalten av BDE-209 högst (0,90 ng/g fett), följt av BDE-153 (0,72 ng/g fett) och BDE-47 (0,36 ng/g fett). I modersmjölk uppmättes de högsta halterna för BDE-153 (0,45 ng/g fett), följt av BDE-47 (0,46 ng/g fett), HBCD (0,22 ng/g fett) och BDE-100 (0,13 ng/g fett). Summan av de tio analyserade PBDE-kongenerna var ungefär dubbelt så hög i blodserum (median 2,8 ng/g fett) som i modersmjölk (median 1,5 ng/g fett).

För BDE-66, BDE-99, BDE-138 och HBCD kunde inga korrelationer mellan blod- och mjölkhalter utvärderas eftersom halterna låg under LOQ i de flesta proverna. För övriga kongener var samtliga korrelationer signifikanta ($p<0,05$). Korrelationskoefficienterna (Pearson) för de tri- till hexabromerade kongenerna (BDE-28, -47, -100, -153) varierade mellan 0,83 och 0,98. Korrelationerna för de hexa-, hepta- och deka-brominerade kongenerna BDE-154, -183 och -209 var svagare (0,38-0,66). De svagare korrelationerna för vissa kongener beror åtminstone delvis på större osäkerhet i analysresultaten (låga halter och många prover med halter under LOQ i blodserum och/eller modermjölk).

Generellt minskade fördelningen av PBDE till modersmjölk med ökande bromeringsgrad. Mediankvoten mellan serum och mjölk varierade från 0,83 (BDE-47) till 17 (BDE-209). BDE-209 överförs i mycket liten utsträckning till mjölk.

Sammanfattningsvis var korrelationerna mellan PBDE-halter i serum och modersmjölk signifikanta för samtliga analyserade kongener och starka för de tri- till hexabromerade kongenerna. Modersmjölks-halter av PBDE kan alltså användas som mått på mammans kroppsbelastning och sannolikt också på exponeringen av barnet under fosterperioden. Skillnaderna i absoluta nivåer i serum och modersmjölk kan vara viktiga att ta hänsyn till vid exponeringsbedömningar.

# INTRODUCTION

With funding from the Swedish Environmental Protection Agency (EPA), the Swedish National Food Agency (NFA) has made recurrent measurements of persistent halogenated organic pollutants (POP) in mother's milk from primiparae women in Uppsala since 1996. The study is called POPUP (Persistent Organic Pollutants in Uppsala Primiparas), and the aim is to estimate the body burdens of POP among pregnant and nursing women and to estimate temporal trends of the exposure of fetuses and breast-fed infants. Temporal trends of polychlorinated biphenyls (PCBs), polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), chlorinated pesticides (e.g. DDT-compounds) and brominated flame retardants (polybrominated diphenylethers (PBDE) and hexabromocyclododecane (HBCD)) in breast milk between 1996 and 2010 have been established (Lignell et al., 2009; Lignell et al., 2012).

Lipid-adjusted breast milk levels of chlorinated POPs like PCBs, PCDD/Fs and *p,p´*-DDE can be used to estimate prenatal exposure since there is a high correlation between levels in breast milk, maternal blood and cord blood (Ayotte et al., 2003; Needham et al., 2011). For some participants in the POPUP study, mono- and di-*ortho* PCBs and *p,p´*-DDE have been analysed in paired samples of breast milk and blood serum (sampled in late pregnancy). The correlation between these levels were strong (Pearson correlation coefficients 0.85-0.97, $p<0.001$) and the median quotients between breast milk and blood serum levels were close to one (0.91, 1.0 and 1.2 for di-*ortho* PCBs, mono-*ortho* PCB TEQ and *p,p´*-DDE respectively). However, there are few studies on correlations between levels of brominated compounds in different matrices. The aim of the present study was to investigate correlations between blood serum and breast milk levels of PBDEs and HBCD in paired samples from 30 mothers in the POPUP cohort and to evaluate if the concentration of PBDE/HBCD in breast milk is a good indicator of maternal body burden and possibly also of prenatal exposure of the infant.

# MATERIALS AND METHODS

### *Recruitment and sampling*

Women were randomly recruited among first-time mothers who were Swedish by birth and delivered at Uppsala University Hospital from January to December 2010 (N=30). The participating rate was 42%.

The participating mothers sampled milk at home during the third week after delivery (day 14-21 *post partum*). Milk was sampled during nursing using a manual mother's milk pump and/or a passive mother's milk sampler. The women were instructed to sample milk both at the beginning and at the end of the breast-feeding sessions. The goal was to sample 500 mL from each mother during 7 days of sampling. During the sampling week, the milk was stored in the home freezer in acetone-washed bottles. Newly sampled milk was poured on top of the frozen milk. At the end of the sampling week, a midwife visited the mother to collect the bottles. On that occasion, the participants also donated a blood sample. Blood sampling was done using 9 ml Vacutainer® or Vacuette® serum tubes and serum was stored at -20°C.

***Chemical analysis***

Extraction and clean-up

*Serum*: Thawed serum (4 g) was mixed with methanol (4 ml) by vortexing in a 16 ml test tube. A mixture of diethyl ether and n-hexane (5 ml, 1+1 V/V) and 100 µl of a solution containing the internal surrogate standards, BDE-85 (2 pg/µl) and $^{13}C_{12}$ BDE-209 (1 pg/µl) was added. The sample was extracted on a rotary mixer for 15 min and then centrifuged at 2500 rpm for 10 min. After centrifugation, the top layer, organic phase, was transferred to a test tube containing aqueous potassium chloride (4 ml, 1 % w/w). The denaturated serum was re-extracted with diethyl ether and n-hexane (5 ml, 1+1 V/V) and the organic phase was combined with the first extract. The pooled extracts and the potassium chloride solution was mixed on a rotary mixer for 15 min and then centrifuged at 2500 rpm for 5 min. The organic phase was transferred to a pre-weighed test tube. The potassium chloride solution was re-extracted and the extracts were combined. The solvent was evaporated using a gentle stream of nitrogen and the lipid weight was determined gravimetrically.

In order to remove the lipids and other polar materials the lipid extract was re-dissolved in n-hexane (2 ml) using ultra-sonication and then treated with concentrated sulfuric acid (2 ml) by inverting the test tube 15 times and then centrifuged at 2000 rpm for 15 min. The organic phase was transferred to a test tube (5 ml) and the volume was reduced to 0.5 ml by using a gentle stream of nitrogen. In order to remove any remaining lipids the sample was transferred to an sulfuric acid impregnated silica gel column (8 mm id, 1 g, 1+2 w/w) and eluted with a mixture of dichloromethane and n-hexane (12 ml, 1+1 V/V). The eluent was reduced to 0.5 ml. The lipid-free extract was transferred to a pre-washed silica gel column (8 mm id, 2 g of 3 % deactivated silica gel) and eluted with n-hexane (8 ml). A second fraction, containing the

brominated flame retardants, was eluted with a mixture of dichloromethane and n-hexane (12 ml, 1+1 V/V). The second fraction was reduced to 1 ml using a rotary evaporator and transferred to a test tube where the solvent was changed to n-hexane. The final volume of the sample was adjusted to 100 µl using a gentle stream of nitrogen and then kept in an amber GC vial until analysis.

*Milk*: Human milk (4 g) was mixed with n-hexane and acetone (10 ml, 1+1, V/V) and 100 µl of a solution containing the internal surrogate standards, BDE-85 (2 pg/µl) and $^{13}C_{12}$ BDE-209 (1 pg/µl) was added. The sample was extracted on a rotary mixer for 15 min and then centrifuged at 2500 rpm for 10 min. After centrifugation, the top layer, organic phase, was transferred to a pre-weighed test tube. The extraction was repeated once with n-hexane and acetone (4 ml, 1+1 V/V) and the organic layers were combined. Ethanol (1 ml, 99.5 %) was added to the combined extract before the solvent was evaporated using a gentle stream of nitrogen. The lipid weight was determined gravimetrically.

In order to remove the lipids and other polar materials the lipid extract was re-dissolved in n-hexane (2 ml) using ultra-sonication and then treated with concentrated sulfuric acid (8 ml) by inverting the test tube 25 times and then centrifuged at 2000 rpm for 15 min. The organic phase was transferred to a test tube (5 ml) and the volume was reduced to 0.5 ml by using a gentle stream of nitrogen.

The lipid-free extract was transferred to a pre-washed silica gel column (8 mm id, 4,5 g of 3 % deactivated silica gel) and eluted with n-hexane (17 ml). A second fraction, containing the brominated flame retardants, was eluted with a mixture of dichloromethane and n-hexane (25 ml, 1+1 V/V). The second fraction was reduced to 1 ml using a rotary evaporator and transferred to a test tube where the solvent was changed to n-hexane. The final volume of the sample was adjusted to 100 µl using a gentle stream of nitrogen and then kept in an amber GC vial until analysis

Analysis on GC-LRMS

The quantification of the analytes was performed using capillary gas chromatography and mass selective detection in electron capture negative ionization and selected ion monitoring modes (GC/LRMS/ECNI-SIM). The system used for quantification consisted of an Agilent 6890N GC equipped with an Agilent 5973N MS.

The sample, 6 µl (2 x3 µl), was injected in pulsed splitless mode using a programmable temperature vaporizing (PTV) injector with an initial temperature of 70°C followed by rapid

heating to 300°C after injection. The analytes were separated on a DB-5MS (15 m x 0.25 mm x 0.10 μm, J&W Scientific) capillary column using a ramped carrier gas (helium) flow. The oven temperature was programmed from 60°C to 325°C including several ramps. The mass fragments m/z 79 and 81 were monitored for PBDE-28, -47, -66, -85, -99, -100, -116, -138, -153, -154 and -183; m/z 79, 81 and 160 for HBCD; m/z 486.6/484.6 and 494.6/496.6 (target/qualifier) were monitored for BDE-209 and $^{13}C_{12}$ BDE-209, respectively. Methane was used as reaction gas and the ion source, quadrupole and transfer line temperatures were kept at 210°C, 110°C and 310°C, respectively.

Calibration standard solutions corresponding to a level range (fresh weight) in serum or milk of 1.25-100 ng/kg for BDE-28 through BDE-183 (2.5-200 ng/kg for BDE-47 and HBCD) and 0.625-750 ng/kg for BDE-209 were included in the run. n-Hexane was injected in between sample and calibration standard series to make sure there were no memory effects.

The different analytes were identified by their retention times relative to the internal standards. The samples were quantified using calibration curves created from the calibration standards analysed in the same run. Quadratic regression with inverse square of concentration as weighting of individual levels was used for the calibration curves. The internal surrogate standard used for the quantification of BDE-28, -47, -66, -100, -99, -154, -153, -138 and -183 as well as HBCD was BDE-85. $^{13}C_{12}$ BDE-209 was used for the quantification of BDE-209 (isotope dilution technique).

The brominated biphenyl BB-153 and the brominated diphenyl ether BDE-154 are known to co-elute in some GC/MS-methods. Since both analytes give the same mass fragments m/z 79 and 81, m/z 483, being specific for BDE-154 (or hexabromo diphenyl ethers in general), is monitored as a qualifier ion. Unfortunately the m/z 483 signal is low in relation to m/z 79 and 81, making it difficult to detect at low concentrations. Since the method lacks specificity for BDE-154, the concentration of BDE-154 is reported as a sum of BDE-154 and BB-153.

Quality Assurance / Quality Control

A chemical blank (4 g of MilliQ water) was included in each extraction series to monitor background levels. To avoid possible analyte loss, the chemical blank was never evaporated until dryness. A spiked in-house control sample was also included in each extraction series. All solvents used were tested for trace amounts of analytes. The glassware was either rinsed with acetone or heated in an oven at 450°C for at least 3 hours before use. Due to possible UV induced degradation of the analytes, particularly for BDE-209, all sample extracts and standard solutions were stored in amber glassware. For each batch of samples, the

corresponding blank sample levels were subtracted from the sample levels. The limit of quantification (LOQ) was determined as ten times the standard deviation of the blanks analysed together with the samples or the lowest calibration level. The LOQ varied between 1.25 and 9.8 ng/kg fresh weight, depending on the blank sample levels of the different analytes. Levels below LOQ were also reported in order to improve the possibilities to analyse the results statistically.

### *Calculations and statistics*

Blood serum and breast milk levels of PBDE/HBCD were lipid-adjusted before the statistical analyses. Concentrations below LOQ (adjusted for chemical blank levels) were used in the statistical analyses. Despite larger uncertainty in these measurements, it is advantageous to use them since they add information about the distribution of data below LOQ. Pearson's correlation analysis and linear regression were used to investigate correlations between blood serum and breast milk levels. Median quotients between blood serum and breast milk levels of PBDEs were calculated to study the partitioning between blood and milk.

## RESULTS AND DISCUSSION

The mean age of the participating mothers was 30 years (range 20-41). 18 mothers (60%) had more than 3 years of higher education, 9 mothers (30%) had 1-3 years of higher education and 3 mothers (10%) had no higher education than high school. There were 2 women (7%) who smoked during pregnancy.

Levels of PBDEs and HBCD in blood serum and breast milk are presented in Table 1. BDE-209 showed the highest median level in blood serum, followed by BDE-153 and BDE-47. LOQ for BDE-99 in blood serum was high and the levels were <LOQ in all samples. This resulted in a high median BDE-99 level when ½LOQ was used in the calculations in comparison to the median when values below LOQ were used. In breast milk, BDE-153 showed the highest median concentration, followed by BDE-47, HBCD and BDE-100. The median sumPBDE level was higher in blood serum compared with breast milk. However, when ½LOQ was used in the calculations, the median level of sumPBDE in blood serum (4.6 ng/g lipids) was probably overestimated. Using determined concentrations below LOQ, the median level of sumPBDE in blood serum (2.8 ng/g lipids) was about two times higher than the median level in breast milk (1.5 ng/g lipids).

***Table 1***. Concentrations (ng/g lipid) of PBDEs and HBCD in blood serum and breast milk sampled from first-time mothers in Uppsala in 2010 (N=30). When the levels were below LOQ, ½ LOQ was used to calculate medians and sumPBDE. Concentrations including estimated levels below LOQ are presented in brackets ([ ]).

| | **Blood serum** | | | | **Breast milk** | | | |
|---|---|---|---|---|---|---|---|---|
| **Congener** | **Median** | **Min** | **Max** | **N<LOQ [N=0][a]** | **Median** | **Min** | **Max** | **N<LOQ [N=0]** |
| BDE-28 | 0.14 [0.06] | <0.18 [0.005] | 0.39 | 29 [0] | 0.03 [0.04] | <0.03 [0.01] | 0.47 | 19 [0] |
| BDE-47 | 0.70 [0.36] | <0.88 [0] | 2.1 | 26 [3] | 0.27 [0.46] | <0.22 [0.10] | 2.1 | 17 [0] |
| BDE-66 | 0.14 [0] | <0.18 [0] | <0.36 [0.01] | 30 [29] | 0.02 [0.005] | <0.03 [0] | <0.09 [0.05] | 30 [9] |
| BDE-99 | 1.1 [0.05] | <1.4 [0] | <2.8 [1.1] | 30 [13] | 0.13 [0.07] | <0.16 [0] | 0.48 | 27 [1] |
| BDE-100 | 0.24 [0.18] | <0.30 [0] | 1.7 | 26 [1] | 0.13 [0.13] | <0.05 [0.03] | 1.4 | 6 [0] |
| BDE-138 | 0.14 [0] | <0.18 [0] | <0.36 [0.27] | 30 [29] | 0.02 [0] | <0.03 [0] | <0.08 [0.01] | 30 [19] |
| BDE-153 | 0.72 | 0.40 | 6.6 | 0 | 0.45 | 0.21 | 3.4 | 0 |
| BDE-154[b] | 0.14 [0.12] | <0.18 [0.01] | 0.21 | 29 [0] | 0.04 [0.05] | <0.03 [0.01] | 0.11 | 12 [0] |
| BDE-183 | 0.14 [0.04] | <0.18 [0] | <0.36 [0.17] | 30 [1] | 0.02 [0.01] | <0.03 [0] | <0.08 [0.04] | 30 [1] |
| BDE-209 | 0.90 [0.90] | <0.59 [0.35] | 2.3 | 8 [0] | 0.07 [0.06] | <0.09 [0.02] | 0.18 | 29 [0] |
| sumPBDE[c] | 4.6 [2.8] | 3.0 [1.0] | 12 [11] | - | 1.4 [1.5] | 0.65 [0.53] | 6.6 [6.6] | - |
| HBCD | 0.27 [0] | <0.35 [0] | 0.36 [0.40] | 30 [23] | 0.22 [0.22] | <0.13 [0.07] | 1.0 | 1 [0] |

[a]number of samples with levels estimated to 0 after chemical blank subtraction [b]sum of BDE-154 and the brominated biphenyl BB-153 [c]sum of all ten analysed PBDE congeners

Correlations between blood serum and breast milk levels of BDE-66, BDE-99, BDE-138 and HBCD were not evaluated since the levels were below LOQ and/or reported levels below LOQ were estimated to be zero in most samples. Correlations between the other PBDE congeners in serum and breast milk are presented in Table 2 and in Figure 1. All correlations were significant. Pearson's correlations coefficients for the tri- to hexa-brominated congeners (BDE-28, -47, -100 and -153) ranged from 0.83 to 0.98, while the correlations for the hexa-, hepta- and deca-brominated BDE-154, BDE-183 and BDE-209 were weaker. The weaker correlations may be due to larger uncertainties in the analytical results for these congeners

(low levels and many samples with levels below LOQ in blood serum and/or breast milk). Generally, partitioning of PBDEs to breast milk decreased with increasing bromination. The lowest median blood serum/breast milk-quotient was observed for BDE-47 (0.83), and the highest for BDE-209 (17). The deca-brominated BDE-209 is a large molecule which seems to be transferred to milk to a very limited extent.

***Table 2***. Correlations between blood serum and breast milk levels of PBDEs sampled from first-time mothers in Uppsala in 2010 (N=30). Reported levels below LOQ were used in the analyses.

| | **Pearson correlation** | | **Linear regression[a]** | | **Median quotient** |
|---|---|---|---|---|---|
| **Congener** | **Corr coeff** | **p** | **β** | **$R^2$ (%)** | **(blood serum/breast milk)** |
| BDE-28 | 0.97 | <0.001 | 0.81 | 93 | 1.3 |
| BDE-47 | 0.83 | <0.001 | 0.96 | 67 | 0.83 |
| BDE-100 | 0.97 | <0.001 | 1.2 | 94 | 1.3 |
| BDE-153 | 0.98 | <0.001 | 1.8 | 95 | 1.6 |
| BDE-154[b] | 0.66 | <0.001 | 1.4 | 42 | 2.2 |
| BDE-183 | 0.57 | 0.001 | 2.2 | 30 | 3.4 |
| BDE-209 | 0.38 | 0.040 | 3.9 | 11 | 17 |
| sumPBDE[c] | 0.83 | <0.001 | 1.2 | 67 | 1.8 |

[a]serum level = α + β*breast milk level [b]sum of BDE-154 and the brominated biphenyl BB-153 [c]sum of all ten analysed PBDE congeners

***Table 3***. Quotients between blood serum and breast milk levels of PBDEs in the present study (N=30) and in two to five other studies reviewed by Mannetje et al. (2012).

| | **Present study** | **Mannetje et al. (2012)** | | |
|---|---|---|---|---|
| **Congener** | **median quotient** | **mean quotient** | **range** | **Sample pairs (N)** |
| BDE-28 | 1.3 | 0.9 | 0.7-1.0 | 100 |
| BDE-47 | 0.83 | 0.7 | 0.5-0.9 | 151 |
| BDE-100 | 1.3 | 0.7 | 0.7-0.8 | 149 |
| BDE-153 | 1.6 | 1.0 | 0.9-1.2 | 144 |
| BDE-154 | 2.2 | 1.8 | 1.5-2.0 | 100 |
| BDE-183 | 3.4 | 2.7 | 2.3-3.0 | 100 |
| BDE-209 | 17 | 25 | 10-40 | 100 |

In a recent review of studies reporting serum/breast milk ratios of PBDEs and other POPs (Mannetje et al., 2012), the authors included five studies of PBDEs where serum and breast milk levels were reported on a lipid weight basis and where the samples were fully paired (Inoue et al., 2006; LaKind et al., 2009; Needham et al., 2011; Schecter et al., 2010; Schecter et al., 2006) (Table 3). The range in serum/milk ratios reported by Mannetje et al. (2012), and the differences compared with the ratios in our study (Table 3) probably have several explanations. Timing of sampling, analytical procedures and differences in exposure levels

and routes may have influenced the results. Despite differences in serum/milk ratios, Mannetje et al. (2012) observed a similar increase in serum/milk ratio with increasing bromination as we did in our study. In addition, Mannetje et al. (2012) concluded that the ratios increased with increasing molecular weight, molar volume and hydrophobicity. In the study by Needham et al. (2011), blood serum was collected in late pregnancy and breast milk during days 3-5 after delivery. There were strong correlations between blood serum and breast milk levels of BDE-47, -BDE-100 and BDE-153 (Needham et al., 2011), indicating that PBDEs in breast milk is a good indicator of maternal body burden during pregnancy, and possibly also of fetal exposure.

## CONCLUSION

We investigated correlations between blood serum and breast milk levels of PBDEs in paired samples from 30 first-time mothers sampled in Uppsala in 2010. The correlations between serum and breast milk levels were generally strong, with weaker correlations for PBDE congeners with low levels in one or both matrices. Consequently, we conclude that PBDE levels in breast milk can be used as an indicator of maternal body burden and probably also of prenatal exposure. The median serum/milk quotients ranged from 0.83 to 17, with quotients around 1 for tri- to penta-brominated congeners and increasing quotients with increasing bromination. The differences in absolute levels in blood serum and breast milk may be important to consider in exposure assessments.

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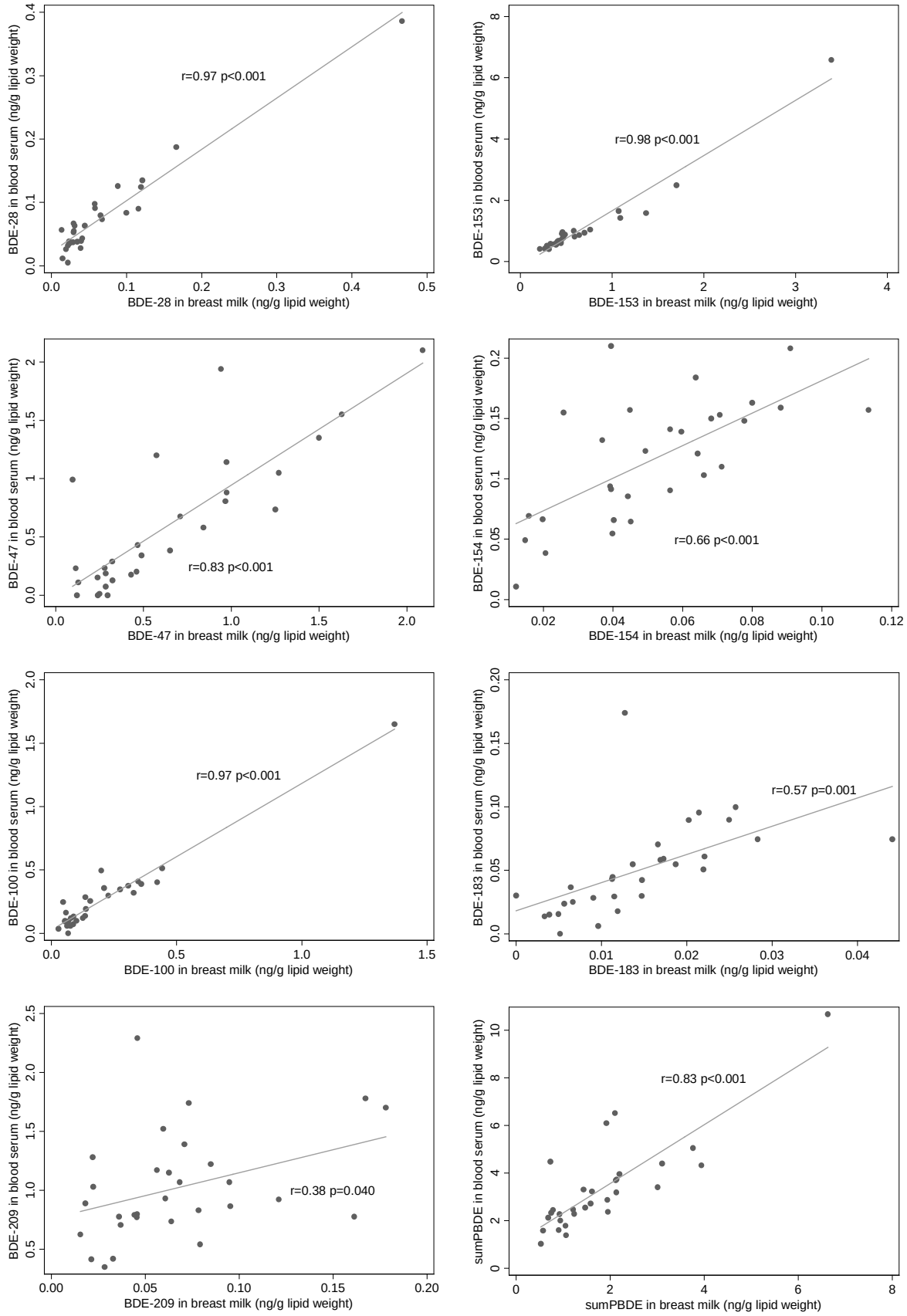


***Figure 1.*** Concentrations (ng/g lipid) of PBDEs in paired samples of blood serum and mother's milk sampled from first-time mothers in Uppsala in 2010 (N=30). Fitted lines (linear regression) and Pearson's correlation coefficients (r) are shown.

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