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Research Article

Exposure assessment of fetus and newborn to brominated flame retardants in France: preliminary data

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Brominated flame retardants (BFR) are chemicals extensively used in many manufactured products to reduce the risk of fire, but also environmental pollutants. In order to assess the potential risk linked to these compounds in human, a French monitoring study was initiated to evaluate the exposure of fetus and newborn. A previously described multi-residue analytical method was used, for measuring the main classes of BFR (hexabromocyclododecane, tetrabromobisphenol-A, and tri- to deca-polybromodiphenylethers) in various biological matrices. These analyzed samples (maternal and umbilical serum, adipose tissue and breast milk) were collected on volunteer women during caesarean deliveries. Preliminary results obtained on 26 individuals (mother/newborn pairs) mainly demonstrated the presence of polybromodiphenylethers (PBDE) and tetrabromobisphenol A both in maternal and fetal matrices, and a possible risk of overexposure of newborns through breastfeeding. Contaminations levels were found globally in the ng/g lipid weight range, consistent with other published European data. Exposure results regarding highly brominated PBDE congeners (octa- to deca-BDE) appeared particularly informative and non-commonly reported, these compounds accounting for around 50% of the total PBDE load. Additional data collection and metabolism investigations are now on-going. A more complete statistical analysis related to this BFR exposition study will be provided in a next future.

Keywords: Brominated flame retardants / Endocrine disruptors / Exposure assessment / Fetus / Newborn

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1 Introduction

Brominated flame retardant (BFR) are chemicals that are extensively used in many industries including plastic, electronic, textile and other furniture [1]. The main justification for this utilization is their ability to prevent the development of fire by delaying ignition and reducing the combustion rate [2]. However, some of these substances present physico-chemical properties very similar to other classes of well known environmental contaminants, such as polychlorobiphenyls (PCB). Therefore, they are considered as persistent organic pollutants (POP) with bioaccumulation/biomagnification potential [3, 4]. Some toxicological studies have already demonstrated the hepatotoxicity of some BFR in rodents [5 – 7]. In addition, some of these substances have been considered as endocrine disruptors chemicals (EDC) [8], in particular by inducing thyroid function disorders [9, 10] and neurobehavioral troubles [11, 12]. Consequently, the impact of BFR on the environment and their potential risk for animal and human health is a present time concern for the scientific community for several years. In this general context, the effect of BFR on specific vulnerable population groups especially appears as a critical issue. Indeed, it seams now commonly admitted that the potential adverse effects of these biologically active chemicals are certainly more problematic in case of exposure occurring at critical

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Abbreviations: **BFR**, brominated flame retardant; **HBCD**, hexabromocyclododecane; **l.w.,** lipid weight; **PBDE,** polybromodiphenylethers; **TBBPA**, tetrabromobisphenol A

stages of development (fetus, newborn), *i. e*. during the neonatal period [13 – 15]. In order to investigate this question in term of risk assessment, the collection of statistically relevant and precise exposure assessment data clearly appears as a necessary prerequisite.

The presence of BFR widespread in the environment is now attested for several years [16]. Their occurrence in living organisms was also demonstrated in wildlife, with exposure assessment studies conducted in different animal species, mainly fish [17 – 19] and marine mammals [20, 21]. However, data related to the BFR concentration levels in humans, especially for general populations (not reflecting a specific occupational exposure), are clearly more limited, mainly for ethical limitations and/or analytical difficulties. Available data on this topic mainly concern Northern Europe countries [22 – 28], Asia [29 – 33], or the United States [34 – 39]. Some scarce data were also published from Southern Europe especially Spain [40 – 42], but data related to BFR contamination level were never provided in France. In this context, an ambitious analytical strategy was developed for the simultaneous multi-residue measurement of a wide range of brominated flame retardants, including hexabromocyclododecane (HBCD), tetrabromobisphenol A (TBBPA) and polybromodiphenylethers (lowly and highly brominated PBDE from tri- to decaBDE) from various human biological matrices (serum, adipose tissue, breast milk). This procedure, which was fully validated according to current European standard, was described and detailed elsewhere [43]. This methodology was then applied in the frame of a French monitoring survey, promoted by the Centre Hospitalier Universitaire (CHU) de Toulouse and financially supported by the Agence Française de Sécurité Sanitaire de l'Environnement et du Travail (AFSSET).

The totality of this study concerns about 100 volunteer women (mother/newborn pairs). The purpose of the present work is to give preliminary data illustrating some main results and tendencies related to the BFR concentration levels found in the first analyzed serum, adipose tissue, and breast milk samples.

2 Materials and methods

2.1 Samples

All the samples analyzed in this study were collected by the gynecology-obstetric unit of the Paule de Viguier Hospital, belonging to the Centre Hospitalier Universitaire (CHU) de Toulouse, France. These samples (including maternal and umbilical serum, maternal adipose tissue and breast milk) were obtained from volunteer women during caesarean deliveries. This preliminary dataset concerned 26 mother/newborn pairs included in the study in 2005. The protocol was approved by a local ethical committee in accordance with French regulation, and the informed consent of all participating subjects was obtained.

2.2 Reagents and chemicals

Most solvents were Picograde® quality and provided by LGC Promochem (Wesel, Germany) or analytical grade and purchased from Sigma (Steinheim, Germany), Aldrich (Steinheim, Germany) or Solvents Documentation Synthesis (Peypin, France). β-Glucuronidase from *Helix pomatia* (H5 type) was provided by Sigma. Enzymatic kit from Randox Laboratories (Crumlin, UK) was used for total lipids determination in serum samples. Oasis® HLB SPE cartridges (500 mg, 6 mL) were provided by Waters (Milford, MA, USA) and SiOH SPE cartridges (1 g, 6 mL) were purchased from United Chemical Technologies (Bristol, UK) or Interchim (Montluçon, France). Silica gel (G60) was provided by Fluka (Buchs, Switzerland). The ^{12}C-native and ^{13}C-labeled reference compounds were purchased from Cambridge Isotope Laboratories (Andover, MA, USA) or Wellington Laboratories (Guelph, Canada). The 27 monitored target analytes were α,β,γ-HBCD, TBBPA, triBDE-28/37, tetraBDE-47/49/75, pentaBDE-85/99/100/118, hexaBDE-153/154/155, heptaBDE-183/190, octaBDE-#1/#2/#3/#4/#5, nonaBDE-206/207/208 and decaBDE. The ^{13}C-labeled compounds used as internal standards for quantification according to the isotopic dilution method included γ-HBCD, TBBPA, and BDE-28/47/99/154/153/183/209. The ^{13}C-BDE-139 was used as external standard. While tri- to hepta- and deca-BDE congeners were quantified using the previously developed and validated method by isotope dilution [43], the given values for octa- and nona-BDE congeners were estimations based on the following methodology. The ^{13}C-heptaBDE 183 was used as internal standard, and the relative response factors observed for nona-BDE 206 and octa-BDE 196 (these two compounds being available as pure reference substances) were used for the quantification of all nona-BDE and octa-BDE congeners, respectively. The estimated contribution of higher brominated congeners due to partial thermal degradation in the GC injector was systematically taken into account. Thus, quantification was only performed if this contribution was found lower than 20% of the total monitored signal.

2.3 Sample preparation

The developed sample preparation procedure was described elsewhere [43]. Briefly, a preliminary liquid/liquid extraction was performed both for serum and breast milk samples, using ethyl acetate for serum while a dichloromethane/acetone mixture was preferred for breast milk. Then, a liquid/liquid partitioning using an ACN/*n*-hexane mixture was applied for all the analyzed sample types, permitting the separation of PBDE from the other BFR. The PBDE fraction was purified using two successive SPE steps (Oasis® HLB cartridge followed by multilayer H_2SO_4-activated silica). After an enzymatic hydrolysis for deconjugation of glucuronide and sulfate phase II metabolites, the TBBPA +

HBCD fraction was purified onto two successive SPE cartridges (Oasis® HLB and SiOH stationary phases), the first column permitting to separate TBBPA from HBCD. Finally, the HBCD fraction was analyzed in LC-MS/MS, while the TBBPA and PBDE fractions were separately analyzed by GC-high-resolution MS (HRMS).

2.4 LC-MS/MS and GC-HRMS measurements

Separation of the α-, β- and γ-HBCD stereoisomers was achieved using an Alliance® 2690 HPLC pump and a Symmetry® C_{18} stationary phase (150 × 2.1 mm, 3.5 μm + guard column 10 × 2.1 mm) from Waters. Elution solvents were methanol (A), ACN (B) and water containing 0.5% v/v acetic acid (C). Mobile phase composition (A:B:C, v/v/v) was 30:10:60 from 0 to 1 min, and linearly reached 50:50:0 at 4.5 until 24 min, before returning to initial conditions. Flow rate and injected volume were 0.25 mL/min and 20 μL, respectively. MS/MS was performed on a QuattroLC® triple quadrupole instrument (Micromass, Manchester, UK) operating in negative ESI and multiple reactions monitoring acquisition mode. Monitored product ions were the bromine atoms (m/z = 79, 81) produced after fragmentation of the $[M\text{-}H]^-$ precursor ion.

Separation of TBBPA and PBDE was achieved using a Hewlett Packard 5890 (Palo Alto, CA, USA) gas chromatograph with capillary column (15 m × 0.25 mm × 0.10 μm) coated with low bleeding diphenyl (5%)-dimethylpolysiloxane (95%) copolymer (UB5-P, Interchim, Montluçon, France). The temperature gradient started from 120°C (2 min), rose to 280°C (10°C/min) and then to 320°C (20°C/min, 8 min). Injected volume was 2 or 3 μL (splitless mode). Helium was used as carrier gas at 1 mL/min. Detection of TBBPA and PBDE was performed on high resolution (R = 10 000) double focusing electromagnetic sector mass analyzers. Two instruments were used at this stage, *i.e.* a Jeol SX-102A (for TBBPA measurement) and a Jeol MS-700D (for PBDE measurement) (Jeol, Tokyo, Japan). Electron ionization energy was set at 70 eV for TBBPA, which correspond to the more classical and reference value used in electron impact ionization, while a lower value set at 42 eV was preferred for PBDE. Indeed, such relatively low ionization energy is commonly used in the field of halogenated contaminants such as dioxins or PCB, in order to take benefit of the lower ionization potential characteristic of these compounds and subsequent reduced background noise appearing on the diagnostic ion chromatograms. Monitored ions were the two most intense ones among the $[M\text{-}CH_3]^+$, $[M]^{+\bullet}$ or $[M\text{-}Br_2]^{+\bullet}$ ion clusters, respectively for TBBPA, tri- to pentaBDE and hexa- to decaBDE. As commonly observed with these compounds, a non-negligible external contamination was observed for some PBDE congeners (BDE-47, 99 and 209), although the final protocol was specifically designed to limit and control this phenomenon. In this context, the two decision rules applied for the quantification of these congeners were (i) to quantify only samples presenting an abundance higher than three times the abundance observed in procedural blank samples systematically included in each batch of analysis, and (ii) to subtract systematically the amount estimated in these blank samples from the amount measured in the quantified samples.

3 Results and discussion

3.1 General comments

Volunteer women included in this study were between 24 and 46 years old (mean = 34). The presented exposure results concerned 26 maternal serum, 26 umbilical serum, 26 maternal adipose tissue and 23 breast milk samples, which were collected from March to September 2005. For serum samples, some practical and ethical limitations led to very restricted collected amount (no higher than 4 g/sample). Considering in addition the extremely low fat content in serum, the determination of BFR in this matrix represented an important analytical challenge. For adipose tissue and breast milk, samples weights were around 0.5 g and 1 g dry matter, respectively.

3.2 Hexabromocyclododecane

In adipose tissue, α-HBCD was identified in approximately 50% of the analyzed samples, with concentration levels globally ranging from 1000 pg/g lipid weight (l.w.)(LOD) to 3000 pg/g l.w. Atypically higher values (6000 to 12 000 pg/g l.w.) were measured for three samples. No trace of the other diastereoisomers characteristic of this compound, *i.e.* β-HBCD and γ-HBCD, were detected in these samples. No correlation was found between these contamination levels found for α-HBCD and concentrations levels measured for the other BFR. This observation seams to attest the hypothesis of a very probable variability among the different sources of exposure affecting the individuals included in the study. Indeed, the relative proportions of TBBPA, HBCD and PBDE found in biological tissues may vary depending on several factors, including local environment, domestic pollution, or nature of the main current devices containing BFR. In breast milk, only seven samples presented α-HBCD concentration above the LOD, varying from 2500 to 5000 pg/g l.w. For serum samples, the very restricted sample amount did not allowed any measurement of HBCD with respect to the current performances of the used LC-MS/MS equipment. Taken into account this relative analytical limitation in term of sensitivity, these preliminary results demonstrated the reality of exposure to HBCD both for mother and for newborn. Indeed, the concentration levels measured in the quantifiable adipose tissue and breast milk samples where in the ng/g l.w. (or ppb) range, which is around 10 to 100 times higher than the lev-

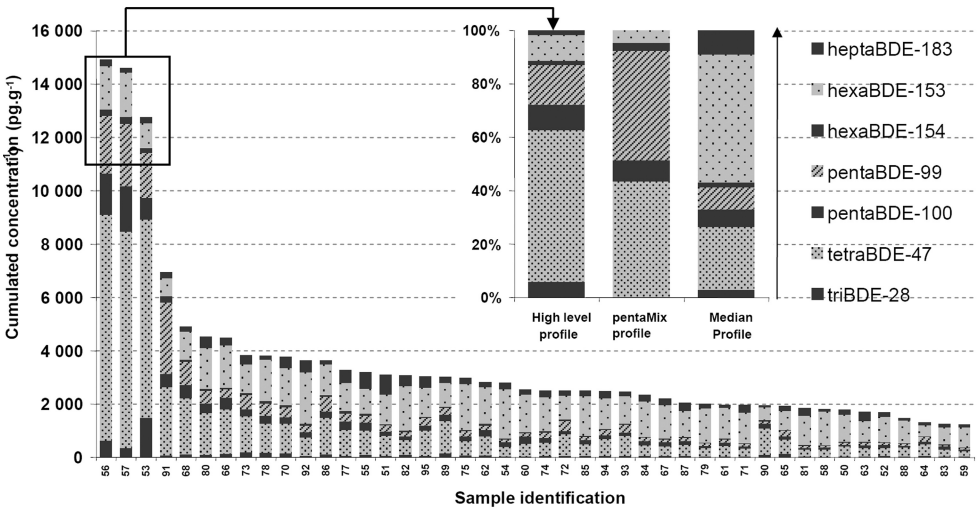

Figure 1. Contamination profiles observed for tri- to heptaBDE in adipose tissue samples.

els usually observed for other persistent organic pollutants (POP) such as dioxins.

3.3 Tetrabromobisphenol A

TBBPA was not detected in any of the analyzed adipose tissue samples. This observation was considered not surprising regarding the relatively low lipophilic properties of TBBPA. Indeed, due to the presence of two hydroxyl groups on the molecule, TBBPA was expected to be less prone to bioaccumulation in fat tissues than many other POP. In breast milk samples, TBBPA was quantified at levels varying from 34 to 9400 pg/g l.w. (median value = 172 pg/g l.w.). In serum samples, TBBPA was measured at concentration ranging from 2 to 783 pg/g f.w. in maternal serum and from 2 to 1012 pg/g f.w. in cord serum. The estimated median and average values were 7 and 54 pg/g f.w. in maternal serum and 10 and 152 pg/g f.w. in umbilical serum, respectively. No correlation was noticed between these contamination levels observed for TBBPA and the concentrations observed for α-HBCD or PBDE, probably for the same reason mentioned above (natural variability in term of exposure sources). As already observed for other hydroxylated organohalogens [44], a poor correlation observed between the TBBPA concentration levels measured in maternal and umbilical serum samples. Before evocating some metabolic and/or placental transfer issues to explain this observation, the collection of additional data were estimated to be necessary, which is currently on-going.

3.4 Tri- to heptabromobiphenylethers

In maternal adipose tissue samples (Fig. 1), the more commonly monitored seven major PBDE congeners (BDE-28, 47, 99, 100, 153, 154 and 183) were unambiguously identified. The sum of the concentrations calculated for these seven PBDE indicators compounds was in the 1 228 – 14 908 pg/g l.w. range (median value = 2515 pg/g l.w.), which appears relatively close to other published European data [28, 40, 42]. The relative contributions of these different congeners were 153 (47%), 47 (25%), 183 (8.8%), 99 (8.2%), 100 (6.2%), 28 (2.8%) and 154 (1.8%). The high proportion of BDE-153 detected in these samples appeared consistent with other studies conducted in human. This increased contribution in biological tissues compared to the proportion of this congener found in the PentaMix formulation (5%) could point out a selective bioaccumulation of PBDE in fat. However, the eventual participation of the highly brominated compounds to this monitored signal (through debromination reactions) should be also considered. Other PBDE minor congeners (BDE-37, 49, 75, 85, 118, 155 and 190) were also identified in these samples. However, the sum of their concentrations did not exceed 4% of the concentration observed for the seven major congeners. This observation tends to indicate that the monitoring of these seven indicator congeners may be sufficient in the scope of evaluating the PBDE contamination in fat. Nevertheless, measuring some minor congeners instead of major compounds should be beneficial in case of existing significant inter-correlation. In particular, this indirect determination should permit to overcome the problem of external contamination commonly retrieved with the more abundant PBDE congeners. This possibility depending on the precise relationship in-between all the monitored PBDE congeners will be further investigated on the entire dataset collected at the end of the present study.

In breast milk samples (Fig. 2), the same seven major PBDE congeners were also identified, with total cumulated concentrations ranging from 1388 to 11 626 pg/g l.w. (median value = 2655 pg/g l.w.). These values appeared in

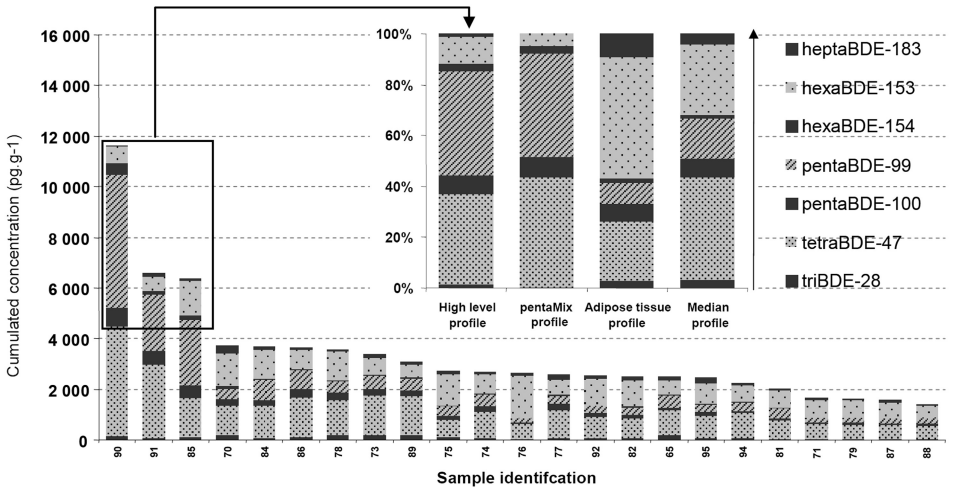

Figure 2. Contamination profiles observed for tri- to heptaBDE in breast milk samples.

the same range as the ones calculated for adipose tissue samples, and once again comparable with other European published data [22, 41]. However, the contamination profiles (*i.e.* relative abundances of the different congeners) observed in the two matrices were found notably different. Other minor congeners (BDE-37, 49, 75, 85, 118, 155 and 190) were also identified, the sum of their concentrations reaching around 4.2% of the concentration measured for the seven previous major congeners. Globally, these preliminary results seam to indicate a clear and significant presence of PBDE in breast milk at the ng/g l.w. (ppb) range, with subsequent non-negligible risk of exposure for the newborn through breastfeeding.

For serum samples, the limited sample amount as well as the very low fat content typical of this biological matrix led to recorded signals below the detection limit for most samples. On the contrary, congeners 154 and 183 were sufficiently abundant to be measured in nearly all the analyzed sera samples. PBDE-153 was present at concentration ranging from 211 to 1906 pg/g l.w. (median value = 689 pg/g l.w.) in maternal serum, and from 137 to 1083 pg/g l.w. (median value = 408 pg/g l.w.) in umbilical serum. The average concentrations measured for this specific hexaBDE congener were the higher for adipose tissue (1161 pg/g l.w.), followed in decreasing order by breast milk (828 pg/g l.w.), maternal serum (728 pg/g l.w.) and umbilical serum (436 pg/g l.w.).

A significant correlation between the concentrations levels measured in all the different analyzed biological matrices was observed for BDE-153, with coefficient of determination (R^2) values ranging from 0.57 to 0.88. Secondly, the correlation between the concentrations found in adipose tissue and in breast milk samples globally appeared the more significant, especially for several congeners such as BDE-28 and 100 (Fig. 3). Finally, correlations between the other analyzed matrices as well as for the other target compounds did not appeared statistically significant. Considering the relatively limited number of data in the frame of this preliminary study, all these correlation investigations will merit to be revaluated on the final complete dataset for attempting a definitive interpretation of these results.

3.5 Octa- to decabromodiphenylethers

In adipose tissue samples (Fig. 4), decaBDE was quantified in all samples, with concentrations globally varying from 256 to 2310 pg/g l.w. (median value = 840 pg/g l.w.) Only one sample presented an atypically high contamination level (16 856 pg/g l.w.). Three nonaBDE and five octaBDE congeners were also estimated in these samples, with cumulated minimum/maximum/median values equal to 183/1826/1255 and 520/2349/820 pg/g l.w. for this two homologue groups, respectively. One nonaBDE congener (BDE-207) and one octaBDE congener (#3) accounted for 80 and 70% of these total estimated concentrations, respectively. The eventuality of a partial decomposition of decaBDE to nonaBDE and octaBDE congeners can not be excluded as one cause contributing to these observed signals. However, some experiments and calculations performed on the ^{13}C-labeled decaBDE shown that this degradation process remains relatively limited. Indeed, the diagnostic signals expected for ^{13}C-labeled octaBDE and ^{13}C-labeled nonaBDE were monitored although these compounds were not introduced in any analyzed samples. Thus, each peaks potentially observed for these diagnostic signals were attributed to the thermal degradation of ^{13}C-decaBDE. Finally, this degradation phenomenon never reached more than 5% of the signal observed for ^{13}C-decaBDE whatever the analyzed biological samples.

In milk samples, decaBDE was quantified at concentrations ranging between 390 and 6796 pg/g l.w. (median value = 1504 pg/g l.w.). Nona- and octaBDE were also measured,

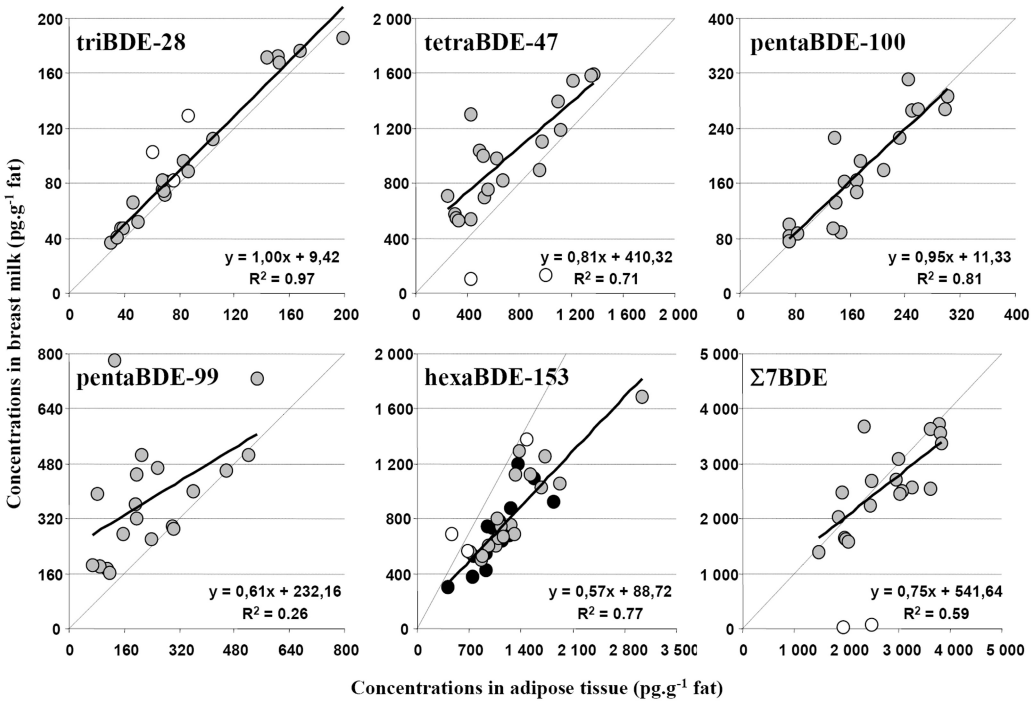

Figure 3. Correlations between the concentrations measured for several tri- to hexaBDE in adipose tissue and milk samples.

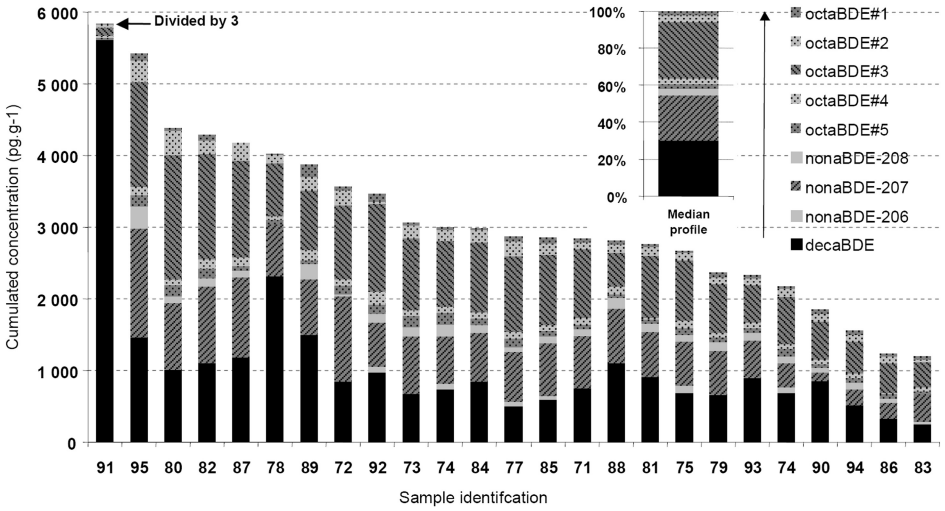

Figure 4. Contamination profiles observed for octa- to decaBDE in maternal adipose tissue samples.

with cumulated minimum/maximum/median values equal to 113/5921/742 and 210/1743/736 pg/g l.w. for this two homologue groups, respectively. For serum samples, the median values estimated for decaBDE/nonaBDE/octaBDE were 7404/2898/1560 pg/g l.w. in maternal serum, and 28 769/6263/808 pg/g l.w. in umbilical serum, respectively. The consequent analytical challenge linked to measurements of PBDE and total lipid determination from a reduced sample size, as well as the poor correlations observed between maternal and umbilical serum regarding the presence of these highly brominated congeners indicated that the present data set should be completed by additional samples before attempting to interpret these results.

Nevertheless, these exposure data related to highly brominated PBDE should be clearly underlined, considering that these congeners are very commonly excluded and/or ignored in this kind of exposure assessment study. It is a reality that analytical difficulties linked to their measurement largely participate to this lack of data [45, 46]. However, our preliminary results tend to show that octa- to deca-

BDE may represent until 50% of the total PBDE load and therefore undoubtedly merit enforced attention in term of risk assessment.

4 Concluding remarks

A multi-residue analytical method was developed and validated for measuring a wide range of brominated flame retardants (including PBDE from tri- to decaBDE, TBBPA and HBCD) in various human biological matrices (serum, adipose tissue, breast milk). The application of the proposed methodology to biological samples (maternal and newborn tissues) collected during caesarean deliveries provides the first exposure assessment data for a French population. Preliminary results on more than 20 measurement results for each sample types mainly demonstrated the presence of PBDE and TBBPA both in maternal and fetal matrices, and a possible risk of overexposure of newborns through breastfeeding. Data regarding highly brominated PBDE congeners appeared particularly informative and non-commonly reported. Additional data collection, as well as metabolism investigations, is now on-going. A more complete statistical analysis related to this BFR exposition study will be performed on the entire dataset (including more than 80 mother/newborn pairs) and will be provided in a very next future.

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The authors have declared no conflict of interest.

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