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Concentrations of organophosphorus, polybromobenzene, and polybrominated diphenyl ether flame retardants in human serum, and relationships between concentrations and donor ages

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HIGHLIGHTS

- Organophosphorus flame retardants, polybromobenzenes and polybrominated diphenyl ethers in human serum were detected.
- Tri (2-chloroethyl) phosphate (TCEP) was found at a higher concentration than the other chemicals.
- Many kinds of alternative flame retardants were accumulated more in young people.

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ABSTRACT

Organophosphorus flame retardants, polybromobenzenes, and polybrominated diphenyl ethers (PBDEs) were determined in pooled human serum samples collected in an area in which these chemicals are produced in North China. Tri (2-chloroethyl) phosphate (TCEP) was found at a higher concentration than the other chemicals, and the mean TCEP concentration was 480.4 ng/g lipid. This is the first time TCEP has been detected in human serum from China. The PBDE concentration in serum was found to have decreased between 2007 and 2013. BDE-209 remained the dominant PBDE congener, and its mean concentration was 91.3 ng/g lipid in this study. The polybromobenzene concentrations were relatively low, but pentabromobenzene and pentabromotoluene were found in very many of the samples. The highest TCEP, tris(2-butoxyethyl)phosphate, pentabromobenzene, and pentabromotoluene concentrations were found in samples from young people (<30 y old). This suggests that the risks posed by these alternative flame retardants also need more concerns.

1. Introduction

Brominated flame retardants (BFRs), such as polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane, have been found in environmental media in many studies (de Wit, 2002). Some BFRs are considered to be toxic and persistent (Covaci et al., 2011; Gauthier et al., 2007), and some have been found to accumulate through the food chain (Cocaci et al., 2012). PBDEs are the mostly used BFRs in China, thereby causing serious pollution in the environment media and biota (Chen et al., 2012b), even in human samples like serum (Jin et al., 2009; He et al., 2013) and hair samples (Lu et al., 2014; Zheng et al., 2014). Legislation has therefore been introduced banning the production and use of commercial "PentaBDE" and "OctaBDE" mixtures in 2009 and restricting the production and use of commercial "DecaBDE" mixtures (Chen et al., 2012b). However, flame retardants still need to be used in many products to meet modern fire safety standards. The production and use of alternative flame retardants has therefore increased (Covaci et al., 2012; Li et al., 2015). Two important groups of alternative flame retardants are the organophosphorus flame retardants (PFRs) and the polybromobenzenes. The PFRs include tri-n-butylphosphate (TnBP), tri(2-chloroethyl)phosphate (TCEP), triphenyl phosphate (TPhP), tris(2-butoxyethyl) phosphate (TBOEP), tri-*o*-tolylphosphate (o-TCP), tri-*m*-tolylphosphate (m-TCP), and tri-*p*-tolylphosphate (p-TCP), and the polybromobenzenes include 2,3,5,6-tetrabromo-*p*-xylene (PTBX), pentabromobenzene (PBBz), pentabromotoluene

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(PBT), hexabromobenzene (HBB), and pentabromoethylbenzene (PBEB).

The total amount of flame retardants that was consumed in 2012 was 1.8×10^6 t. The consumption of PFRs is expected to increase more quickly than the consumption of other flame retardants (BBC, 2013). It has been estimated that 100,000 t of PFRs were produced in China in 2011 (Li et al., 2015), and the demand for PFRs is expected to increase by 15% each year (Yuxiang, 2011). Organophosphorus compounds are used not only as flame retardants but also as plasticizers and anti-foaming agents in a range of products, such as electronics, floor finishing products, plastics, textiles and upholstered furniture (Li et al., 2015). Like PBDEs, PFRs are not chemically bonded to the materials they are used in, so they can easily be released from the material into the environment through volatilization, abrasion, or dissolution (Wang et al., 2014a). The large amounts of PFRs that have been produced and consumed have led to PFRs frequently being detected in air (Bergh et al., 2011), indoor dust (Araki et al., 2014), soil (Fries and Mihajlovic, 2011), sediment (Cao et al., 2012), sewage sludge (Cristale et al., 2016) and surface water(Tsao et al., 2011), thus it has been suggested that PFRs are now ubiquitous in the environment. PFRs have been found in biota in some studies. Total PFR concentrations of >1000 ng/g lipid have been found in marine and freshwater biota from Swedish lakes and in different species of fish from Manila Bay in The Philippines (Kim et al., 2011). Lower amounts of PFRs were detected in herring gull eggs from the North American Great Lakes (Chen et al., 2012a). TnBP has once been detected in human milk collected in Sweden (Sundkvist et al., 2010). Ten types of PFR have been found in human breast milk collected in Japan, Vietnam, and Philippines (Kim et al., 2014). Nevertheless, PFRs have rarely been detected in human serum samples.

Polybromobenzenes are organic bromides that each have one phenyl ring with several bromine atom substituents. Polybromobenzenes are used as alternative flame retardants in plastic products, polyurethane foam, textiles, and wood products. Polybromobenzenes have been found to accumulate in wildlife and to be hepatotoxic (Covaci et al., 2011). Limited information is available on the production and use of polybromobenzenes. HBB was used as an additive flame retardant in Japan in 2001, but relatively little (~350 t) was used (Watanabe and Sakai, 2003). In China, 600 t of HBB is produced each year in Weifang City, Shandong Province. It has been reported that PBT has been widely used in the USA under the trade name FR-105. No information is available on the current and past uses of PBBz and PTBX. Polybromobenzenes have been found in biota and human serum in some studies (Zhu et al., 2009; Papachlimitzou et al., 2012). PBEB has been found in herring gull eggs and glaucous gull tissues (Gauthier et al., 2007; Verreault et al., 2007) and in air samples from Chicago, USA (Hoh et al., 2005). Very limited information is available on the exposure of humans to polybromobenzenes in China.

2. Materials and methods

2.1. Serum sample collection

Serum was collected during routine pathology tests at Weifang Binhai People's Hospital (information about Weifang city can be found in Supporting Information). Approximately 100 serum samples (excluding hepatopath samples) were available on each of 10 consecutive days. A pooling strategy was adopted in our research because pooling biological samples had been found to offer advantages in terms of the analytical effort and resources required, statistical analysis, and ethics (Heffernan et al., 2014). We collected a 0.50 mL aliquot of each of about 60 samples each day. In total, 595 serum samples were collected, 306 from males and 289 from females. All of the serum samples were stored in glass tubes which is free of the compounds of interest. The samples were stratified according to the ages and sexes of the donors, then the samples were combined to form 10 pooled samples. The age groups for the pooled samples were 20–29, 30–39, 40–49, 50–59, and ≥60 y. The donors ranged in age from 20 to 88 y, and the mean ages of the male and female donors were 45 and 48 y, respectively. The number of volunteers, age range, and mean age for each pooled sample are shown in Table 1. All of the volunteers lived on the south coast of Laizhou Bay, Shandong Province. Every donor gave informed consent after we had clearly explained the details of the project. Ethical approval for the study was provided by the Weifang Binhai People's Hospital ethics committee.

2.2. Chemicals

Isotope-labeled PBDE standards ($^{13}C_{12}$-labeled BDE-139 and $^{13}C_{12}$-labeled BDE-209) and isotope-labeled PFR standards (TCEP-d_{12} and TPhP-d_{15}) were obtained from Cambridge Isotope Laboratories (Andover, MA, USA). Non-labeled PBDEs (BDEs 28, 47, 99, 100, 153, 154, 183 and 209), Hexabromobenzene (HBB), Pentabromoethylbenzene (PBEB), 2,3,5,6-tetrabromo-*p*-xylene (PTBX), Pentabromotoluene(PBT), Pentabromobenzene (PBBz), Triphenyl phosphate (TPhP), Tris(2-butoxyethyl) phosphate (TBOEP), Tri-*m*-tolylphosphate (m-TCP), Tri-*n*-butylphosphate (TnBP), Tri(2-chloroethyl)phosphate (TCEP) were purchase from Accustandard (NH, USA). Dichloromethane, acetone, methyl *tert*-butyl ether, and hexane were of pesticide analysis grade (J.T. Baker, Phillipsburg, NJ, USA). Water was purified using a Milli-Q system (Millipore, Billerica, MA, USA). Nitrogen (99.999%) and helium (99.999%) were obtained from Chengweixin (Beijing, China). Anhydrous sodium sulfate was of analytical grade and was baked at 450 °C for 5 h before use. Silica gel (100–200 mesh) was from Merck (Darmstadt, Germany), and neutral alumina (60 mesh) was from Alfa Aesar (Ward Hill, MA, USA). The silica gel and alumina were extracted with dichloromethane, activated (at 105 °C for the silica gel and at 130 °C for the alumina) for 12 h, then cooled and deactivated by adding 3% of the sorbent weight of deionized water.

2.3. Extraction and cleanup

The serum samples were extracted and cleaned for BFR analysis using a previously reported method (Hovander et al., 2000; He et al., 2012). Briefly, each sample (3 mL pooled serum) was spiked with known amounts of internal standards (4 ng $^{13}C_{12}$-labeled BDE-139 and 50 ng $^{13}C_{12}$-labeled BDE-209), then 1 mL hydrochloric acid (6 M) and 4 mL isopropanol were added. Each sample was then extracted twice with 3 mL hexane/methyl *tert*-butyl ether mixture (1:1 v: v), then the extract was washed with 4 mL aqueous potassium chloride (1% w/w) and then evaporated to dryness. Next, 4.0 mL hexane and 2.0 mL 0.50 mol/L KOH were added to each

Table 1
Information on the pooled serum samples that were analyzed.

Pooled sample	No. of volunteers	Age range	Mean age
Male 1	56	20–29	24
Male 2	50	30–39	35
Male 3	80	40–49	45
Male 4	40	50–59	55
Male 5	80	≥60	68
Female 1	30	20–29	25
Female 2	42	30–39	35
Female 3	77	40–49	44
Female 4	21	50–59	56
Female 5	120	≥60	69