Dietary Exposure Assessment of Chinese Adults and Nursing Infants to Tetrabromobisphenol-A and Hexabromocyclododecanes: Occurrence Measurements in Foods and Human Milk

ARTICLE *in* ENVIRONMENTAL SCIENCE AND TECHNOLOGY · JUNE 2009

Impact Factor: 5.33 · DOI: 10.1021/es8035626 · Source: PubMed

Dietary Exposure Assessment of Chinese Adults and Nursing Infants to Tetrabromobisphenol-A and Hexabromocyclododecanes: Occurrence Measurements in Foods and Human Milk

ZHI-XIONG SHI,[†,‡] YONG-NING WU,[*,†,‡] JING-GUANG LI,[†] YUN-FENG ZHAO,[†] AND JIN-FANG FENG[*,‡]

National Institute of Nutrition and Food Safety, Chinese Center for Disease Control and Prevention, Beijing 100050, China, and School of Public Health and Family Medicine, Capital Medical University, Beijing 100069, China 1

Received December 16, 2008. Revised manuscript received April 6, 2009. Accepted April 10, 2009.

Tetrabromobisphenol A (TBBPA) and hexabromocyclododecane diastereoisomers (α, β, and γ-HBCD) were determined in 24 pooled human milk samples and 48 Chinese total diet study (TDS) samples collected in 2007. On the basis of ultra performance liquid chromatography−mass spectrometry (UPLC-MS/MS) analysis, levels of TBBPA ranged from <LOD to 5124 pg/g lipid weight (lw) in human milk and from <LOD to 2044 pg/g lw in TDS samples. The α-HBCD diastereoisomer, which ranged from <LOD to 2776 pg/g lw in human milk and from <LOD to 2224 pg/g lw in TDS samples, was generally the most abundant isomer comparing with β- and γ-HBCD. The average estimated daily intake (EDI) of TBBPA via human milk for nursing infants with a range 320−37240 pg/kg bodyweight (bw)/day was 5094 pg/kg bw/day, while that of ΣHBCD was 5837 pg/kg bw/day with a range 670−17320 pg/kg bw/day. The medium bound (<LOD = $^1/_2$LOD) EDI_{TBBPA} for a "reference" man via animal origin foods was 256 pg/kg bw/day and $EDI_{\Sigma HBCD}$ was 432 pg/kg bw/day. Meat and meat products were the main source in the total dietary intake of TBBPA and ΣHBCD. Our research on the estimated daily intake of TBBPA and ΣHBCD by the Chinese population indicated large variations in TBBPA and ΣHBCD levels between provinces. Overall, our data indicate the Chinese EDI was lower than the EDI from similar studies in Europe.

Introduction

Hexabromocyclododecane (HBCD) and tetrabromobisphenol A (TBBPA) are two brominated flame retardants (BFRs) currently in use all over the world. The total market demand for TBBPA and HBCD in 2001 is 119 600 and 16 700 t (*1*). In commercial HBCD, γ-HBCD is the main component, consisting of 75−89% of the total weight (α-HBCD, 10−15%; β-HBCD, 0.5−12%). The production capacity of TBBPA and HBCD in China are about 18 000 and 7500 t in 2007, respectively (*2*). Since the first report on detecting polybrominated biphenyl ethers (PBBEs) in fish from the River Viskan in 1981 (*3*), BFRs are now ubiquitous contaminants in the environment and the human population. This is a result of their widespread use and toxicological properties. Studies indicated that BFRs are bioaccumulative and persistent compounds, thus they should be regarded as persistent organic pollutants (POPs) (*4*).

It is generally accepted that human exposure to BFRs is mainly through diet. Up to now, there were relatively few studies reporting the presence of HBCD and TBBPA in the foodstuffs or human milk from China. TBBPA and HBCD have been detected in samples of a U.K. 2004 total diet study (TDS) and shellfish (oysters, mussels, and scallops) collected from Scotland. In this research, HBCD was detected in most samples while TBBPA was not detected in any samples (*5*). TBBPA and HBCD have also been found in breast milk samples (*6*−*14*). Although the evidence for the presence of HBCD and TBBPA in food and human milk is minute, their presence in a wide range of matrices promotes a potential health concern.

The purpose of this research is to examine the levels of HBCD diastereomers (α, β, and γ-HBCD) and TBBPA in two categories of samples: pooled human milk samples collected in 2007 from 12 provinces of China and TDS samples from the fourth Chinese total diet study in 2007, including four animal-origin food groups. On the basis of the data we obtained, we can estimate the human daily intake of TBBPA and HBCD via human milk and food consumption in China.

Materials and Methods

TDS Sample Collection. The fourth Chinese total diet study was carried out in 2007. Overall study design and experimental methods were similar to those carried out in 1990 (*15*). The food composite approach was used to study the total diet in 12 provinces representing the average dietary patterns of different geographical areas on the mainland China and covering about 50% of the Chinese population (*16*).

The 12 provinces are Heilongjian, Liaoning, Hebei, Henan, Shanxi, Ningxia, Jiangxi, Fujian, Hubei, Sichuan, and Guangxi provinces and Shanghai City. Their locations are shown in Supporting Information (SI) Figure S1. In each province, three survey sites (one urban and two rural) were selected as representatives of the local dietary pattern. Average food consumption of a "reference" man was used as the standard food consumption pattern. The food consumption data for the "reference" man was the result of the third Chinese total diet study performed by Chinese CDC in 2000. The survey covers 1080 households and nearly 4000 individuals (*17*). The information on age, sex, diet consumption data, and food habits of the participants was collected by questionnaire and weighted household survey. Dietary intakes of the two BFRs were standardized per "reference man" for easy comparison. "Reference man" was defined as an adult male, 18−45 years of age and 63 kg of body weight, undertaking light physical work. Body weight of 63 kg was the average body weight of all the male participants with an age of 18 and undertaking light physical work.

A total of 662 food items consumed by "reference" man were aggregated into 13 food groups. Four animal-origin food groups of these 13 groups were subjected to HBCDs and TBBPA analysis: (1) eggs and egg products, including chicken and duck eggs, and salted and limed duck eggs; (2) aquatic

* Address correspondence to either author. Phone: 86-10-83132933 (Y.-N.W.); 86-10-83911651 (J.-F.F.); fax: 86-10-83132933 (Y.-N.W.); e-mail: wuyncdc@yahoo.com.cn (Y.-N.W.); fengjin5802@sina.com (J.-F.F.).

† Chinese Center for Disease Control and Prevention.

‡ Capital Medical University.

10.1021/es8035626 CCC: $40.75
Published on Web 05/06/2009

foods, including fish, shrimp, and oysters; (3) milk and milk products, including cow milk, cow milk powder, yogurt, and sheep milk; (4) meat and meat products, including pork, mutton, beef, chicken, duck, rabbit, pork liver, and swine blood.

The samples were collected from local markets, grocery stores, and rural households. In order to achieve more realistic dietary exposure estimates, the foods were prepared and cooked to a "table ready" state according to local cuisine and then blended to form the respective group composites with weights proportional to the average daily consumption of each province. These provincial composites were shipped to the National Institute of Nutrition and Food Safety, and frozen at −20 °C until analysis.

Human Milk Collection. In 2007, 1237 breast milk samples were collected from 1237 healthy donors living in the same 12 provinces of China as in the TDS (SI Figure S1). In each province, there are 50 urban donors and 50−60 rural donors according to the living area. The samples were collected within 3−8 weeks after child birth. Each milk donor had resided in her place for more than five years. Occupation, age, diet, and smoking habits, as well as the birth weight and sex of each infant, were recorded in a questionnaire when the samples were collected. The questionnaires revealed no occupational exposure among these mothers. All of the mothers were primiparous and none of them were smokers; all donors were told the objective of this study and signed the participant information and consent form.

About 50 mL of breast milk was collected from each milk donor. All samples were stored in refrigerators at −20 °C. After thawing to ambient temperature, individual samples (10 mL from each sample) were shaken for homogeneity and pooled either into one rural sample or one urban sample from each province.

Reagents and Chemicals. All HPLC-grade quality solvents used in the extraction and analysis procedures were purchased from Fisher Scientific (U.S.); reagent grade sulfuric acid and anhydrous sodium sulfate were purchased from Beijing Chemical Factory (China). Standard solution of α-, β-, and γ-HBCD (50 μg/mL in toluene), TBBPA (50 μg/mL in methanol), isotopic internal standard (IS), $^{13}C_{12}$-labeled α-, β-, and γ-HBCD (50 μg/mL in toluene), and $^{13}C_{12}$-labeled TBBPA (50 μg/mL in methanol) were obtained from Cambridge Isotope Laboratories (U.S.).

Sample Preparation and Analysis. The methodology used for the analysis of TBBPA and HBCD isomers was based on Soxhlet extraction, GPC cleanup, and UPLC-MS/MS detection. Briefly, about 20−30 mL of pooled breast milk or 5−30 g of composite food sample were freeze-dried (the value of sampling depend on water content). After spiking with IS (10 ng of $^{13}C_{12}$-labeled α-, β-, γ-HBCD and $^{13}C_{12}$-labeled TBBPA) and equilibrating for 5 h, the samples were ground with anhydrous sodium sulfate and extracted in a Soxhlet apparatus with a mixture of n-hexane and acetone (1:1, v/v) for 20−24 h. This extract cleanup was performed by gel permeation chromatography (GPC) followed by a sulfuric acid treatment. GPC cleanup was performed on an AccuPrep MPS GPC cleanup system (J2 Scientific Inc., U.S.) using a low-pressure column (GPC, Bio-Beads S-X3, Bio-Rad, CA, 2 cm i.d. × 50 cm). After Soxhlet extraction, the extract was evaporated to dryness and lipid content was determined by gravimetry. Then, the extract was redissolved in ethyl acetate/cyclohexane (1:1 v/v) and injected onto the GPC system. The GPC column was eluted with an ethyl acetate/cyclohexane mixture (1:1, v/v), and the flow rate was 5 mL/min. Fractions were collected from 18 to 30 min, evaporated to dryness, reconstituted in 5 mL n-hexane, and then shaken with 1 mL concentrated sulfuric acid to degrade the remaining lipid. The final hexane extract was concentrated to dryness and reconstituted to 200 μL using methanol.

TABLE 1. Concentrations (pg/g lw) of α-HBCD and TBBPA in Human Milk from China[a]

	α-HBCD		TBBPA	
location	rural	urban	rural	urban
Hebei	2287	1129	4458	1641
Shanxi	433	325	239	482
Liaoning	671	1397	3920	195
Heilongjiang	2776	1543	331	232
Hubei	2427	1220	110	158
Fujian	989	997	ND	ND
Ningxia	ND	361	ND	957
Henan	702	ND	631	ND
Jiangxi	1031	1185	ND	5124
Shanghai	1600	675	1271	394
Guangxi	753	528	172	1134
Sichuan	813	899	313	816
mean	1209	857	961	933

[a] The concentrations below LOD were treated as $^1/_2$LOD for arithmetic mean. ND, not detected.

The four analytes were quantified using the isotope dilution method to the corresponding $^{13}C_{12}$-labeled IS. UPLC-MS/MS detection was performed on a Waters Acquity ultraperformance liquid chromatographic system coupled with a Micromass-Quattro Premier triple quadrupole mass detector (Waters Company, MA, USA). The mass detector was equipped with electrospray ionization (ESI) interface and operated in the negative ionization mode. The UPLC column was a 50 mm × 2.1 mm i.d. (1.7 μm particle size) Acquity UPLC BEH C_{18} column, and the injection volume was 10 μL. MS parameters and LC conditions are given in Supporting InformationTables S1 and S2.

Quality Assurance/Quality Control. Method blank samples were performed every 10 samples to check for interferences or contamination from solvents and glassware. Levels of all the analytes in the procedural blanks were lower than LOD. Therefore, we did not subtract the blank values from the sample measurements.

For recovery tests, a matrix spiking test was conducted. Those matrices included grass carp muscle, pork, egg, and cow milk. Two spiked levels, 2.0 and 10.0 ng/g, were performed. Recoveries of the 4 analytes lie in the range 85−120% with RSDs less than 15% ($n = 5$) for all matrices. We did not correct reported concentrations based on the recovery data. Limits of detection (LODs) were defined as three times the noise level. The LODs of α-, β-, γ-HBCD and TBBPA in meat were 40, 20, 10, 70 pg/g wet weight (ww); in fish were 60, 30, 40, 100 pg/g ww; in milk were 50, 30, 20, 60 pg/g ww; and in egg were 20, 30, 20, 50 pg/g ww, respectively.

The laboratory performance was validated by participating in an interlaboratory comparison study of HBCDs organized by the Norwegian Institute of Public Health in 2007 and 2008. Several food items such as salmon fish muscle, chicken meat, and eel muscle were analyzed for α-, β-, and γ- HBCD and ΣHBCD. Data from our laboratory were within acceptable range of the consensus values.

Results and Discussion

Levels of TBBPA and HBCDs in Breast Milk. This study is the first to report the levels of TBBPA and HBCDs in human milk in China. As shown in Table 1, TBBPA was found in 80% of the pooled human milk samples with concentrations ranging from <LOD to 5124 pg/g lw. Concentrations of TBBPA in 75% of the samples were lower than 1000 pg/g lw. Relatively high concentrations were found in several samples including the rural samples from Liaoning and Hebei and the urban sample from Jiangxi. Since the number of samples analyzed is small, further studies are needed to examine the sources and distribution of TBBPA.

Unlike the constitution in environmental samples and manufactured products, α-HBCD was the predominant diastereoisomer in human milk samples, probably due to selective metabolism or biotransformation process (*18, 19*). α-HBCD was detected in most of the samples with concentrations ranged from <LOD to 2776 pg/g lw. γ-HBCD was only detected in rural sample of Hebei (462 pg/g lw) and β-HBCD was not detected in any samples. No significant difference in α-HBCD levels was observed between rural and urban pooled samples (*t* test by SPSS 11, $p > 0.05$).

As indicated above, TBBPA is manufactured and used in greater quantity than HBCD in China; however, in 63% of the pooled human milk samples, the concentrations of TBBPA were lower than that of HBCD. Our data support the suggestion made by Johnson-Restrepo et al. (*20*). The finding of higher HBCD concentrations than TBBPA concentrations can be explained by the differences in the usage and bioaccumulation potential of the two BFRs. HBCD is an additive BFR, while TBBPA is a reactive BFR. TBBPA is bound chemically to the polymer structure; thus, the leaching/release of TBBPA into the environment is limited (*21*). In addition, pharmacokinetics of the two BFRs in the human body is different; TBBPA is rapidly metabolized by the mammalian liver and eliminated into bile (*22*).

In comparison to PBDEs, another important BFR, much less information is available on the occurrence of TBBPA and HBCD in human tissues. In a study by Cariou et al., TBBPA was detected and quantified in 34 of the 77 analyzed breast milk samples collected in Toulouse, France, at levels varying from 62 to 37 344 pg/g lw with a mean value of 4110 pg/g lw (73 pg/g fresh weight) (*6*). The mean concentration and highest concentration were much higher than the values in the present study. In another study, a value of 67 pg/g lw was reported by Thomsen et al. for a mixture of 9 milk samples from Norwegian women (*7*). Until now, no data for TBBPA in breast milk in North American and Asia have been reported.

Compared to TBBPA, more data for HBCDs in human milk have been reported. Kakimoto et al. investigated the time trend of the stereoisomer-specific concentrations of HBCD in human milk samples collected from Japanese women from 1973 to 2006. Their result revealed that the concentration was below the detection limit in the samples collected between 1973 and 1983 and increased in those collected since 1988. Between 1988 and 2006, α-HBCD was detected in all 11 pooled human milk samples with the levels ranging from 430 pg/g lw to 1900 pg/g lw, similar to our study (*8*). Schecter et al. measured levels of HBCDs in 40 human milk samples collected from the U.S. in 2002 and 2004, where only α-HBCD was found (160−1200 pg/g lw) (*9*). HBCDs were detected in human milk collected in 2001 from primiparous Swedish women with the mean and maximum concentrations being 450 and 2400 pg/g lw (*10*). HBCDs were also found in Norwegian human milk at concentrations between 250 and 20 000 pg/g lw (*11, 12*). In contrast, in 10 individual human milk samples from northern Norway collected in 2000−2001, HBCD was only detected in one sample (130 pg/g lw) (*13*). The level of ΣHBCD in the Belgian pooled sample from a WHO-coordinated survey was 1500 pg/g lw (*14*). Generally, the TBBPA and HBCDs concentrations observed so far in human milk were lower than total PBDE concentrations.

Estimated Daily Intake (EDI) via Human Milk. EDI_{TBBPA} and $EDI_{\Sigma HBCD}$ via human milk were calculated on the basis of levels of TBBPA and HBCDs in breast milk and infant ingest data (742 mL/day) and body weight data from the U.S. Environmental Protection Agency (*23*), assuming that human milk is the only food source for nursing infants (1−6 months old). As the levels of TBBPA or HBCDs in certain samples were below the LOD, <LOD was replaced by $^1/_2$LOD when calculating EDI. The average EDI_{TBBPA} via human milk was 39 730 pg/day for nursing infants (1−6 months old) with a range 2480−290 500pg/day; and the average $EDI_{\Sigma HBCD}$ via human milk was 45 520 pg/day with a range of 5200 135100 pg/day. When assuming a 7.8 kg body weight for a 6-month-old boy, the mean EDI of TBBPA and ΣHBCD was 5094 and 5837 pg/kg bw/day, respectively.

TABLE 2. Levels of TBBPA and α-HBCD in TDS Samples (pg/g lw)

	TBBPA				α-HBCD			
location	meat	eggs	aquatic food	milk	meat	eggs	aquatic food	milk
Hebei	217	ND	ND	ND	872	1156	ND	437
Shanxi	102	ND	877	323	ND	ND	464	ND
Liaoning	546	349	1046	ND	ND	ND	1213	ND
Heilongjiang	145	267	1283	466	ND	144	315	ND
Hubei	227	692	606	ND	859	315	410	ND
Fujian	209	ND	1682	ND	ND	357	992	ND
Ningxia	184	ND	ND	ND	ND	258	201	ND
Henan	ND[a]	476	ND	848	420	ND	809	853
Jiangxi	ND	ND	ND	ND	ND	570	1037	ND
Shanghai	1386	ND	2044	ND	183	ND	2224	407
Guangxi	ND	368	574	148	137	429	114	ND
Sichuan	ND	ND	541	541	173	ND	914	ND
mean	263	194	738	211	230	273	727	160

[a] The concentrations below LOD were treated as $^1/_2$LOD for arithmetic mean.

Levels of TBBPA and HBCDs in Foods. These results are listed in Table 2. TBBPA was detected above the LOD in about 70% of the whole samples. The highest contamination level was found in the aquatic food group followed by the meat/meat products group. The lowest concentrations occurred in the egg/egg products group.

Overall, the HBCD concentrations detected ranged from <LOD to 9208 pg/g lw. Similar to the pattern of HBCD in human milk, in the four animal origin food groups, α-HBCD was the predominant diastereoisomer except in the aquatic food composite of Shanghai City. β-HBCD and γ-HBCD were not detected in most of the samples. α-HBCD was detected in all the aquatic food samples except the sample from Hebei province. Similar to TBBPA, the highest contamination level was also found in this group. Unlike TBBPA, the mean and median levels of α-HBCD in the meat group were both lower than those in the egg group. The lowest concentrations occurred in the milk/milk products group.

β-HBCD and γ-HBCD were found in only a few samples. β-HBCD was detected in the aquatic food of Jiangxi (193 pg/g lw). γ-HBCD was detected in the aquatic food of Liaoning and Jiangxi, meat samples from Hubei, and milk from Henan, with levels of 1149, 274, 386, and 628 pg/g lw, respectively. In particular, the highest levels of HBCDs were found in the aquatic food composite of Shanghai City, where the concentrations of α-, β-, and γ- HBCD were 2224, 358, and 6626 pg/g lw, respectively. The pattern of HBCDs in this sample was significantly different from the other animal origin foods. However, the pattern is similar to that of HBCD in environmental samples and manufactured products, in which the γ-HBCD is higher than α-HBCD, and the level of β-HBCD was the lowest. The special HBCD pattern in aquatic food of Shanghai may result from the high level of γ-HBCD in some kinds of fishes. In another study, Xian et al. had reported that high levels of HBCDs (12−330 ng/g lw) were detected in fishes from the Yangtze River Delta, where Shanghai City is located (*24*). In that study, 17 freshwater fishes belonging to nine species were examined. α-HBCD was found to be the predominant isomer in most of the fish species and tissues, followed by γ- and β-HBCD. However, γ-HBCD was found to be predominant in the muscle and egg of Mandarin fish (Siniperca chuatsi). The reason for this particular pattern of

TABLE 3. Estimated Dietary TBBPA and ΣHBCD Intake (pg/kg bodyweight/day) in China

	TBBPA				ΣHBCD			
	lower bound intake	medium bound intake	upper bound intake	% of total intake[a]	lower bound intake	medium bound intake	upper bound intake	% of total intake[a,b]
meat	123	133	143	52	81	144	207	44
eggs	17	20	24	8	20	56	91	17
milk	17	25	32	10	6	51	96	15
aquatic food	75	78	81	30	151	181	211	24
daily total	232	256	280	100	258	432	605	100

[a] On the basis of the medium bound intake estimate. [b] Value of aquatic food of Shanghai City was excluded in arithmetic calculation.

HBCDs in Mandarin fish is still unknown, and may be the result of differences in metabolism and/or other sources of exposure. In addition, the concentration of TBBPA in the aquatic food composite of Shanghai City is also the highest. High levels of BFRs in aquatic animals may result from high market demand of BFRs in Shanghai. Shanghai, being an industrialized and urbanized area, has a large amount of polymer raw materials, textiles, electronic appliances, and fine petrochemicals, which could be sources of BFRs in the surrounding areas and eventually lead to high level of BFRs in animals and the environment.

Extensive studies on TBBPA and HBCDs in food are rather rare. Furthermore, comparison of results in other studies is complicated by the fact that there is no standardized method of detecting these two BFRs. Driffield et al. performed a similar TDS in the U.K. (*5*). In that study, TBBPA was not detected above the LOD in all of the 20 food groups, and the HBCD concentrations were low. Levels of HBCD in animal origin foods ranged from <LOD to 240 pg/g wet weight, which is in the same range as in the present study (<LOD to 222 pg/g wet weight). In a 2003 study on the dietary intake of BFRs by the Dutch population, concentrations of TBBPA and HBCD were measured in 91 samples from various food categories. TBBPA was only found in fish and hard cheese with levels ranging from 60 to 3400pg/g, while HBCD was presented in 15 out of 18 categories of food with levels ranging from 500 to 8900 pg/g (*25*). In Sweden, Remberger et al. detected HBCDs in several commercially purchased Swedish food samples collected in 1999. In this study, HBCD levels varied from <1000 to 51 000 pg/g lw. The highest levels were detected in samples of mixed fish and wild Baltic salmon (48 000 and 51 000 pg/g lw), with the lowest in fat from lamb, pork, and veal (<1000 to 1400 pg/g lw) (*26*).

More recent reports on TBBPA and HBCDs are mainly focused on wild animals, especially fish and other aquatic organisms and marine mammals (*24, 27*). The levels of these two BFRs in wild animals were higher in general when compared to the levels in foodstuffs. This may be due to the difference in sample processing. When the animal samples were analyzed, most analyses were done on fresh unprocessed samples. But the food samples in TDS were cooked. Cooking processes have been shown to lead to the reduction of PCBs and other organochlorines in trout, via the loss of fat (*28*). Other processes that occur during food preparation can also reduce the pollutant load of foods, such as decomposition, volatilization, and extraction into the cooking oil. It can be assumed that similar losses of TBBPA and HBCDs will also occur following cooking.

Estimated Daily Intake (EDI) via Foods. Daily dietary intakes (pg/day or pg/kg bw/day) of TBBPA and ΣHBCD for the "reference" man (63 kg body weight) were estimated by multiplying the measured concentrations (pg/g wet weight) of TBBPA and ΣHBCD with the daily consumption data (g/day) from the survey mentioned above.

The consumption data of the "reference" man for the four animal-origin food groups is shown in SI Table S3. Maximum consumption of animal-origin foods was found in Shanghai (529.93 g/day). A large difference in food consumption pattern among provinces was found. This is believed to be due to differences in geographical conditions, food habits, culture, and economic level between regions in China. For example, few fish or shellfish are produced in interior provinces such as Shanxi, Ningxia, Henan and Sichuang, so consumption of aquatic foods is very low in these provinces. Thus, the estimated dietary intake for each province was evaluated individually.

Because levels of TBBPA and HBCDs in certain samples were below the LOD, EDI of TBBPA and HBCDs via foods are therefore classified in lower, medium, and upper bounds, according to whether levels below LOD for individual analytes were replaced by 0, $^1/_2$LOD, or LOD, respectively (Table 3). The percentage contribution from the four food groups varied between provinces. For the medium bound EDI_{TBBPA}, although the contamination level of aquatic food was the highest, the contribution from aquatic food (30%) was less than that from meat/meat products (52%) as its consumption was higher than that of aquatic food in China. For the medium bound $EDI_{\Sigma HBCD}$, with the highest contamination level and relative high consumption, the contribution from the aquatic food group (42%) was greatest, a result from the high levels of HBCDs in aquatic food sample from Shanghai City. If the value of aquatic food of Shanghai City was excluded from the discussion, the contribution from meat and meat products is greatest (44%), followed by aquatic foods (24%), eggs (17%), and milk (15%). In summary, meat and meat products account for a major fraction of daily intake because of high consumption in China. This was in contrast to similar studies performed in Europe. A study performed on Swedish food samples suggested that fish is a major source of dietary HBCD intake due to the high proportion of fish in the Swedish diet and high HBCD levels in fish (*26, 29*). In a similar TDS in U.K., green vegetable and animal origin foods were found to be the major source of dietary HBCD intake (*5*). In a study into the dietary intake of BFRs by the Dutch population carried out in 2003, TBBPA was only found in fish and hard cheese, while HBCD was presented in 15 out of 18 category of foods, beef (40%) and poultry (27%) being the major source of dietary ΣHBCD intake (*25*).

Table 4 shows the medium bound EDI (replace <LOD by $^1/_2$LOD) of TBBPA and ΣHBCD from the four food groups individually and in total for each province. The large difference in intake levels among provinces was thought to result from variation in food consumption values and contamination levels in the areas. The data show that the sequence for intake levels for the 12 provinces is the same as that for food consumption and contamination levels. For example, in some provinces such as Shanxi, Ningxia, Jiangxi, and Guangxi, both contamination levels and consumption of animal-origin foods were low, so the intake values of the two BFRs were lowest accordingly. Maximum daily intake was in Shanghai City, which resulted from high animal origin food consumption and high BFRs levels in those foods.

TABLE 4. Medium Bound EDI (pg/kg bw/day) of TBBPA and ΣHBCD

	TBBPA					ΣHBCD				
location	meat	eggs	milk	aquatic food	total	meat	eggs	milk	aquatic food	total
Hebei	40	5	11	10	66	199	127	24	31	380
Shanxi	16	3	10	7	34	20	17	42	9	88
Liaoning	211	32	44	14	302	89	70	78	109	346
Heilongjiang	43	35	87	18	183	49	59	48	53	210
Hubei	56	90	1	86	233	310	85	3	110	507
Fujian	127	7	13	471	617	115	62	27	464	668
Ningxia	36	2	6	5	50	60	17	13	16	106
Henan	24	39	14	2	80	204	37	29	9	280
Jiangxi	20	6	0	6	32	53	66	0	43	163
Shanghai	947	12	59	285	1304	239	79	120	1285	1723
Guangxi	27	11	1	23	62	137	22	4	20	182
Sichuan	50	4	50	9	113	250	29	220	27	526
mean	133	21	25	78	256	144	56	51	181	432

EDI values of TBBPA and ΣHBCD by Chinese population were lower than those observed in U.K. study. In the U.K., the estimated upper bound adult dietary intakes of TBBPA was 5980 pg/kg bw/day, and ΣHBCD was 39 280 pg/kg bw/day (*5*). In the study into the dietary intake of BFRs by the Dutch population, total average dietary intake of TBBPA and HBCD was 40 and 2900 pg/kg bw/day, respectively (*25*). However, the percentage of nondetects is high in these studies. In about 40−100% of the whole samples, no TBBPA/HBCDs could be detected. The high percentages of nondetects strongly influences the outcome of the intake estimate. Thus, the uncertainty is large and can only be minimized by the development of more sensitive analytical techniques.

Until now, a tolerable daily intake (TDI) for HBCD has not been agreed on internationally because of limited toxicological data. The U.K. Independent Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) did recommend a TDI of 1 mg/kg bw/day for TBBPA (*30*). Obviously, the EDI_{TBBPA} in the present study was well below the threshold.

Assessment of Human Exposure to TBBPA and HBCDs. Human exposure to TBBPA/HBCDs occurs from multiple routes. For nonoccupationally exposed persons, the major intake of TBBPA/HBCDs is probably from food and indoor air or dust. In our study, the average TBBPA and ΣHBCD intake values via human milk for a 6-month-old boy were 5094 and 5837 pg/kg bw/day, which were much higher than that for a "reference" man (256 and 432 pg/kg bw/day). In addition, Meng et al. reported that the median total PBDEs intakes via human milk for nursing infants (0−1 years old) was 6870 pg/kg bw/day for a male and 7370 pg/kg bw/day for a female in China (*31*). It is indicated that the body BFRs burden of a nursing infant in China is much higher than that of adult. The possible toxicological impact of such a high daily intake should certainly be investigated.

Air or indoor dust inhalation was thought to be another source of TBBPA/HBCDs intake. Unfortunately, few studies report the presence of HBCD and TBBPA in air or dust in China. Yu et al. reported that three HBCD diastereoisomers were detected in air samples collected in Guangzhou City in Southern China with a mean ΣHBCD level of 1.4 pg/m^3 (*32*). That is the first to report the concentration of HBCDs in air and soil samples of China. In combination of this value with the inhalation rate data from the U.S. Environmental Protection Agency, the median $EDI_{\Sigma HBCD}$ values via air were 6.5 and 21.28 pg/day for the nursing infants and adults (male), respectively. It indicates that exposure via air inhalation may not be a main route of total HBCDs intake by the Chinese population.

Acknowledgments

This research was financially supported by the National High-Tech Research and Development research project (2006AA06Z043), the National Key Technologies Research and Development Programme (2006BAK02A10), National Nature Science Foundation (20837003 and 30771812), and the Science and Technology Development Programme of Beijing Municipal Commission of Education (KM200810025022).

Note Added after ASAP Publication

Due to a production error, this paper published ASAP May 6, 2008 with incorrect information in the second paragraph of the Materials and Methods section; the correct version published ASAP May 8, 2009.

Supporting Information Available

Map of the total diet study area and breast milk collecting area, MS parameters, and LC conditions used during the analysis of HBCD and TBBPA. Consumption data (g/day) of the "reference" man. This material is available free of charge via the Internet at http://pubs.acs.org.

Literature Cited

(1) *Brominated Flame Retardants in Consumer and Commercial Products*; Bromine Science and Environmental Forum (BSEF), **2001**; www.bsef.com.

(2) Jiang, Y. Q. The status quo and development of brominated flame retardants. *Chin. J. Flame Retardant Mater. Technol.* **2007**, *2*, 1–7.

(3) Andersson, Ö.; Blomkvist, G. Polybrominated aromatic pollutants found in fish in Sweden. *Chemosphere* **1981**, *10*, 1051–1060.

(4) Sellström, U.; Bignert, A.; Kierkegaard, A.; Häggberg, L.; de Wit, C.; Olsson, M.; Jansson, B. Temporal trend studies on tetra- and pentabrominated diphenyl ethers and hexabromocyclododecane in guillemot egg from the Baltic Sea. *Environ. Sci. Technol.* **2003**, *37*, 5496–5501.

(5) Driffield, M.; Harmer, N.; Bradley, E.; Fernandes, A. R.; Rose, M.; Mortimer, D.; Dicks, P. Determination of brominated flame retardants in food by LC-MS/MS: Diastereoisomer-specific hexabromocyclododecane and tetrabromobisphenol A. *Food Addit. Contam.: Part A* **2008**, *25*, 895–903.

(6) Cariou, R.; Antignac, J. P.; Zalko, D.; Berrebi, A.; Cravedi, J. P.; Maume, D.; Marchand, P.; Monteau, F.; Riu, d. A.; Andre, F.; Le bizec, B. Exposure assessment of French women and their newborns to tetrabromobisphenol-A: Occurrence measurements in maternal adipose tissue, serum, breast milk and cord serum. *Chemosphere* **2008**, *73*, 1036–1041.

(7) Thomsen, C.; Leknes, H.; Lundanes, E.; Becher, G. A new method for determination of halogenated flame retardants in human milk using solid-phase extraction. *J. Anal. Toxicol.* **2002**, *26*, 129–137.

(8) Kakimoto, K.; Akutsu, K.; Konishi, Y.; Tanaka, Y. Time trend of hexabromocyclododecane in the breast milk of Japanese women. *Chemosphere* **2008**, *71*, 1110–1114.

(9) Schecter, A.; Harris, T. R.; Shah, N.; Musumba, A.; Päpke, O. Brominated flame retardants in US food. *Mol. Nutr. Food Res.* **2008**, *52*, 266–272.
(10) Aune, M.; Barregård, L.; Claesson, A.; Darnerud, P. O. *Organic environmental pollutants in breast milk from Gothenburg, Sweden, 2001 report 219 0108 to the Swedish EPA*; The Swedish National Food Administration: Uppsala, Sweden, 2002; http://www.imm.ki.se/National/Datavard/PDF/sakrapport%20brostmjolk%202001%20Gbg.pdf (accessed November 2008).
(11) Thomsen, C.; Frøshaug, M.; Leknes, H.; Becher, G. Brominated flame retardants in breast milk from Norway. *Organohalogen Compd.* **2003**, *64*, 33–36.
(12) Thomsen, C.; Frøshaug, M.; Broadwell, S. L.; Becher, G.; Eggesb, M. Levels of brominated flame retardants in milk from the Norwegian human milk study; HUMIS. *Organohalogen Compd.* **2005**, *67*, 509–512.
(13) Polder, A.; Thomsen, C.; Lindström, G.; Løken, K. B.; Skaare, J. U. Levels and temporal trends of chlorinated pesticides, polychlorinated biphenyls and brominated flame retardants in individual human breast milk samples from Northern and Southern Norway. *Chemosphere* **2008**, *73*, 14–23.
(14) Colles, A.; Koppen, G.; Hanot, V.; Nelen, V.; Dewolf, M. C.; Noël, E. Fourth WHO-coordinated survey of human milk for persistent organic pollutants (POPs): Belgian results. *Chemosphere* **2008**, *73*, 907–914.
(15) Chen, J. S.; Gao, J. Q. The Chinese total diet study in 1990. *J. AOAC Int.* **1993**, *76*, 1193–1205.
(16) Zhao, Y. F.; Wu, Y. N.; Wang, X. Q.; Gao, J. Q.; Chen, J. S. Study on of dietary pesticide residues in Chinese residents. *Chin. J. Epidemiol.* **2003**, *24*, 661–664.
(17) Zhang, L.; Gao, J. Q.; Li, X. W. Chinese total diet study in 2000: Cadium intakes by different age-sex population groups. *Chin. J. Hygiene* Res. **2008**, *37*, 338−342.
(18) Zegers, B. N.; Mets, A.; van Bommel, R.; Minkenberg, C.; Hamers, T.; Kamstra, J. K.; Pierce, G. J.; Boon, J. P. Levels of hexabromocyclododecane in harbor porpoises and common dolphins from western European seas, with evidence for stereoisomer-specific biotransformation by cytochrome P450. *Environ. Sci. Technol.* **2005**, *39*, 2095–2100.
(19) Law, K.; Palace, V. P.; Halldorson, T.; Danell, R.; Wautier, K.; Evans, B.; Alaee, M.; Marvin, C.; Tomy, G. T. Dietary accumulation of hexabromocyclododecane diastereoisomers in juvenile rainbow trout (Oncorhynchus mykiss). I. Bioaccumulation parameters and evidence of bioisomerization. *Environ. Toxicol. Chem.* **2006**, *25*, 1757–1761.
(20) Johnson-Restrepo, B.; Adams, D. H.; Kannan, K. Tetrabromobisphenol A (TBBPA) and hexabromocyclododecanes (HBCDs) in tissues of humans, dolphins, and sharks from the United States. *Chemosphere* **2008**, *70*, 1935–1944.
(21) de Wit, C. A. An overview of brominated flame retardants in the environment. *Chemosphere* **2002**, *46*, 583–624.
(22) Schauer, U. M.; Volkel, W.; Dekant, W. Toxicokinetics of tetrabromobisphenol A in humans and rats after oral administration. *Toxicol. Sci.* **2006**, *91*, 49–58.
(23) *Exposure Factors Handbook*; U.S. Environmental Protection Agency, http://www.epa.gov/ncea/pdfs/efh/front.pdf (accessed November 2008).
(24) Xian, Q. M.; Ramu, K.; Isobe, T.; Sudaryanto, A.; Liu, X. H.; Gao, Z. S.; Takahashi, S.; Yu, H. X.; Tanabe, H. Levels and body distribution of polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecanes (HBCDs) in freshwater fishes from the Yangtze River, China. *Chemosphere* **2008**, *71*, 268–276.
(25) de Winter-Sorkina, R.; Bakker, M. I.; van Donkersgoed, G.; van Klaveren, J. D. *Dietary Intake of Brominated Flame Retardants by the Dutch Population*; RIVM rapport 310305001; http://www.rivm.nl/bibliotheek/rapporten/310305001.pdf (accessed November 2008).
(26) Remberger, M.; Sternbeck, J.; Palm, A.; Kaj, L.; Stromberg, K.; Brorstro-Lundén, E. The environmental occurrence of hexabromocyclododecane in Sweden. *Chemosphere* **2004**, *54*, 9–21.
(27) Law, R. J.; Bersuder, P.; Allchin, C. R.; Barry, J. Levels of the flame retardants hexabromocyclododecane and tetrabromobisphenol A in the blubber of harbor porpoises (Phocoena phocoena) stranded or bycaught in the U.K., with evidence for an increase in HBCD concentrations in recent years. *Environ. Sci. Technol.* **2006**, *40*, 2177–2183.
(28) Zabik, M. E.; Booren, A. M.; Zabik, M. J.; Welch, R.; Humphrey, H. Pesticide residues, PCBs and PAHs in baked, charbroiled, salt boiled and smoked Great lake trout. *Food Chem.* **1996**, *55*, 231–239.
(29) Lind, Y.; Aune, M.; Atuma, S.; Becker, W.; Bjerselius, R.; Glynn, A.; Darnerud, P. O. Food intake of the polybrominated flame retardants PBDEs and HBCD in Sweden. *Organohalogen Compd.* **2002**, *58*, 181–184.
(30) *COT Statement on TBBPA. Review of Toxicological Data*; COT, Committee on Toxicity of Chemicals in Food, Consumer Products and Environment; http://www.food.gov.uk/multimedia/pdfs/cotstatements04tbbpa.pdf; 2004 (accessed November 2008)
(31) Meng, X. Z.; Zeng, E. Y.; Yu, L. P.; Guo, Y.; Mai, B. X. Assessment of Human Exposure to Polybrominated Diphenyl Ethers in China via Fish Consumption and Inhalation. *Environ. Sci. Technol.* **2007**, *41*, 4882–4887.
(32) Yu, Z. Q.; Peng, P. A.; Sheng, G. Y.; Fu, J. M. Determination of hexabromocyclododecane diastereoisomers in air and soil by liquid chromatography-electrospray tandem mass spectrometry. *J. Chromatogr. A* **2008**, *1190*, 74–79.

ES8035626