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1 **Estimation of dietary intake and sources of organohalogenated contaminants among**  
2 **infants: 24-h duplicate diet survey in Fukuoka, Japan**

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15

16 **Abstract**

17 The widespread occurrence of persistent organic pollutants (POPs) in the environment is a  
18 matter of concern. In this study, selected organohalogenated contaminants, including  
19 dichlorodiphenyltrichloroethane and its metabolites (DDTs) polychlorinated biphenyls (PCBs),  
20 chlordanes (CHLs), hexachlorobenzene (HCB), polybrominated diphenyl ethers (PBDEs),  
21 hexabromocyclododecanes (HBCDs), tetrabromobisphenol A (TBBPA), 2,4,6-tribromophenol  
22 (TBP), were measured in complete meal sets (24-h duplicate-diet) of Japanese infants to  
23 investigate the levels, profiles, and possible sources of contamination. In total, 46 whole-day  
24 meals of infants (7 to 24-months old) were collected during 2017 from Fukuoka, Japan. To the  
25 best of our knowledge, this is the first study based on the duplicate-diet method for infants. The  
26 median intakes among the POP groups were highest for  $\Sigma$ DDTs (18 ng/day, maximum 251  
27 ng/day), followed by  $\Sigma$ PCBs (17 ng/day, maximum 198 ng/day),  $\Sigma$ CHLs (14 ng/day, maximum  
28 105 ng/day), HCB (11 ng/day, maximum 64 ng/day), TBP (3.5 ng/day, maximum 109 ng/day),  
29  $\Sigma$ HBCDs (1.9 ng/day, maximum 70 ng/day), TBBPA (0.72 ng/day, maximum 34 ng/day), and  
30  $\Sigma$ PBDEs (0.11 ng/day, maximum 4.5 ng/day). Among the PCBs, PCB-138 and PCB-153 were the  
31 most abundant congeners (27% and 23%, respectively). *p,p'*-DDE, the major DDT metabolite,  
32 accounted for 96% of total DDTs. Among PBDEs, BDE47 was the only detected congener  
33 (present in 4% of the samples). The dietary intake of the targeted compounds was lower than the  
34 intake via breast milk, suggesting that the exposure from baby food was limited. In the principal  
35 component analysis, chlorinated and brominated compounds were separated on principal  
36 component 1, while TBP and  $\alpha$ -HBCD were separated on principal component 2, likely  
37 suggesting a differing emission time trend or source. PCB-153, PCB-138, trans-chlordane,  
38 cis-chlordane, and trans-nonachlor were correlated with seafood consumption (Spearman's  
39  $\rho=0.45$  to  $0.57$ ,  $p<0.05$ ), while TBP was correlated with seaweed consumption (Spearman's  
40  $\rho=0.46$ ,  $p<0.05$ ). Four species of commercial edible seaweed in Japan were analyzed to confirm  
41 the findings of the duplicate-diet study. The relatively high concentration of TBP ( $5.5 \pm 6.6$

42 ng/g w.w.) was observed in the seaweed samples, indicating that seaweed is a potential exposure  
43 source of TBP.

44

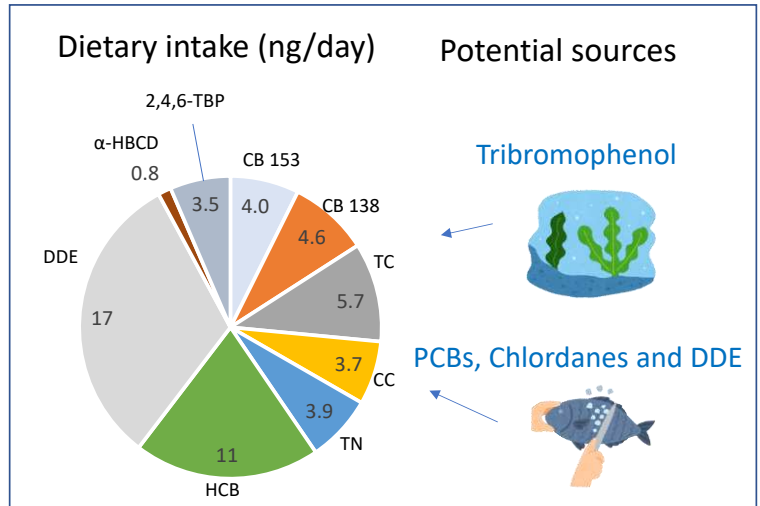
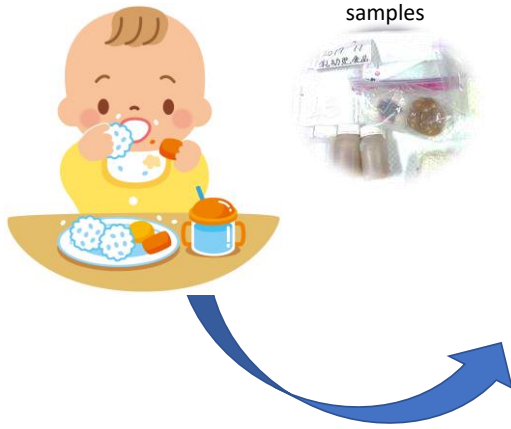
45 **Keywords:** organohalogenated compounds; duplicate-diet; baby food; Japanese infants;  
46 edible seaweed; dietary intake

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48

49 **Graphical abstract**

24-h duplicate-diet of infants



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52

## 53 1. Introduction

54 The widespread occurrence of persistent organic pollutants (POPs) in the environment is a matter  
55 of great concern. Due to their stability and long-range transport properties, POPs are now widely  
56 distributed around the world and are even found in places where they have never been used, such  
57 as the arctic regions (European-Commission, 2017). Given their long half-lives and fat solubility,  
58 POPs tend to bioaccumulate in the food chain and detected in the human diet (Bramwell et al.,  
59 2016; Xu et al., 2017). Over the last decade, the priority list of POPs has been updated to include  
60 brominated flame retardants (BFRs), such as polybrominated diphenyl ethers (PBDEs) and  
61 hexabromocyclododecanes (HBCDs) (European-Commission, 2017). Despite such strict  
62 regulations, even long-banned POPs still linger in the environment; some are still in use and are  
63 directly being emitted, and new POPs may be identified for which we have limited information  
64 (European-Commission, 2017).

65 Brominated phenols are technically produced by bromination of phenol to contain 2, 3 or 5  
66 bromine substituents. 2,4,6-TBP is also naturally produced in the marine environment (Gribble,  
67 2010), and has been detected in seaweed samples in Asia (Haraguchi et al., 2010). Brominated  
68 phenols of natural origin can thus accumulate in the marine food webs. Multiple sources may  
69 explain its presence in various environmental compartments, while its presence in marine water  
70 (Vetter et al., 2009), sediments (Sim et al., 2009), invertebrates (Löfstrand et al., 2010), and fish  
71 (Chung et al., 2003; Wan et al., 2009) seems to be mainly the result of natural production.

72 Infants are considered a vulnerable population for chemical exposure. The younger and more  
73 immature the individual, the more different its response is from that of an adult (Bruckner, 2000).  
74 Food ingestion is a major pathway of exposure to POPs in the general population (Fraser et al.,  
75 2009). So far, however, most human monitoring studies have focused on human breast milk as an  
76 exposure pathway of halogenated compounds to Japanese infants (Fujii et al., 2011; Fujii et al.,  
77 2012b; Fujii et al., 2012c; Fujii et al., 2018; Haraguchi et al., 2009; Konishi et al., 2001; Kunisue  
78 et al., 2006; Soleman et al., 2020). Although baby food has been considered to be a potential

79 exposure source, reported data is still limited.

80 In the present study, we investigated the dietary exposure to selected classes of  
81 organohalogenated compounds among 46 Japanese infants (< 2 years old) using the duplicate-diet  
82 approach. The pollutant levels of individual food items (ng per g of food) do not necessarily  
83 reflect the daily intakes of infants, owing to the variety of available food items and cooking  
84 processes. Therefore, the dietary intake of pollutants needs to be evaluated based on the levels in  
85 complete meals consumed in 24 hours (per day per person). Also, the composition of the selected  
86 contents in the duplicate-diet samples (seafood, meat, and seaweed) was also analyzed to  
87 elucidate the possible exposure sources to organohalogenated compounds. Moreover, four species  
88 of edible seaweed from Japan (*Sargassum fusiforme*, *Undaria pinnatifida*, *Gloiopeltis*, and  
89 *Eisenia bicyclis*) were analyzed to confirm the findings of the duplicate-diet study.

90

## 91 **2. Material and methods**

### 92 **2.1. Sample collection**

#### 93 **2.1.1 Duplicate-diet**

94 Baby duplicate-diet from volunteer Japanese families with children under 2 years old were used  
95 for the evaluation. Basic characteristics of the participants (sex, age in month, body weight, food  
96 consumption per day) are summarized in Table1. The overall average age of the children was  
97  $12\pm 4$  months and the body weight was  $9.0\pm 1.2$  kg. This value was close to the average weight of  
98 1-year olds in the National Health and Nutrition Survey of Japan, which is 10.2 kg (MHLW, 2017).  
99 The Ethics Committee of the Daiichi University of Pharmacy approved this study (No. 17001)  
100 and appropriate written informed consent was obtained from all participants. Participants were  
101 asked to donate duplicate portions of all food and drinks consumed by their children during a 24-h  
102 period. The food self-record sheet, which was previously used for the environmental specimen  
103 bank at Kyoto University (Koizumi et al., 2009), was used with slight modifications. In this study,  
104 all the cooking was done at home by parents and the cooked food was collected by the national

105 registered dietitians and briefly confirmed to be reasonable amount and contents for each infant's  
106 age, then sent to the laboratory. This method has been established as a food duplicate method and  
107 can assess the exact amount of xenobiotics which the infants took (Koizumi et al., 2009;  
108 Watanabe et al., 1985). A total of 46 duplicate-diet from 46 families (one duplicate-diet per  
109 family) were collected as indicated in Table 1. The mean ( $\pm$  standard deviation (SD)) age of the  
110 participant children was  $12 \pm 4$  months.

111 Each duplicated-diet portion from every participant was separated and weighed, considering the  
112 food self-record sheet, and then coded per food composition tables (Table S1) (Harada et al., 2013).  
113 The food items consumed by the subjects were divided into 18 different groups. After that, the  
114 duplicate-diet portions were homogenized per every participate. The final volumes were recorded,  
115 and the samples were freeze-dried. The water content was determined based on the sample weight  
116 after freeze-drying.

### 117 **2.1.2 Edible seaweed samples**

118 Since the result of the duplicate-diet study showed the correlation between intake of  
119 organohalogenated compounds and seaweed consumption (see section 3.3 Correlations between  
120 intake of organohalogenated compounds and food consumption), dry edible seaweed samples  
121 (including *Sargassum fusiforme*, *Undaria pinnatifida*, *Gloiopeltis*, and *Eisenia bicyclis*) were  
122 purchased at Japanese markets in 2018. All seaweed samples originated from Japanese coastal  
123 areas. The edible portions of seaweed were homogenized for chemical analyses. A theoretical dry  
124 fraction of 0.2 was used to express the concentrations on a wet weight (ww) basis.

125

## 126 **2.2. Chemicals**

127 A total of 41 organic compounds were analyzed in this study; polychlorinated biphenyls  
128 (PCBs) (20 congeners from penta-PCBs to hepta-PCBs: CB 99, 101, 105, 118, 128, 138, 146,  
129 153, 156, 170, 171, 174, 177, 180, 183, 187, 196/203, 199, 206, and 209), 9 organochlorine  
130 pesticides (OCs) and their metabolites (oxychlordan (OxC), trans-nonachlor (TC), cis-chlordane



131 (CC), trans-nonachlor (TN), cis-nonachlor (CN), hexachlorobenzene (HCB),  
132 *p,p'*-dichlorodiphenyldichloroethylene (DDE), *p,p'*-dichlorodiphenyldichloroethane (DDD) and  
133 *p,p'*-dichlorodiphenyltrichloroethane (DDT)) and 4 groups of brominated flame retardants  
134 (BFRs): PBDEs (7 congeners from tri-BDE to penta-BDE; BDE 28, 47, 99, 100, 154, 153 and  
135 183), HBCDs (3 isomers:  $\alpha$ -HBCD,  $\beta$ -HBCD,  $\gamma$ -HBCD), TBBPA and 2,4,6-TBP. Full names and  
136 detailed information about the targeted chemicals are listed in Table S2.

137

### 138 **2.3. Determination of organohalogenated compounds in duplicate-diet**

139 Analyses of the targeted compounds in duplicate-diet were performed according to previously  
140 established methods (Malarvannan et al., 2014; Poma et al., 2019), with slight modifications.  
141 Briefly, 1 g of dry sample was spiked with 50  $\mu$ L of an internal standard (IS) mixture A (mixture  
142 A; CB-143: 500 pg/ $\mu$ L, BDE-103: 100 pg/ $\mu$ L,  $^{13}$ C-HCB: 50 pg/ $\mu$ L), and spiked with 50  $\mu$ L of an  
143 IS mixture B (mixture B; *alpha*- and *gamma*- $^{13}$ C-HBCD: 250 pg/ $\mu$ L, *beta*- $^{13}$ C-HBCD: 125 pg/ $\mu$ L,  
144  $^{13}$ C-TBBPA: 250 pg/ $\mu$ L,  $^{13}$ C-TBP: 250 pg/ $\mu$ L) and added 5 mL of hexane:acetone (3:1, v/v). The  
145 tube was sonicated 5 min, then vortexed 2 min, centrifuged at 3,000 rpm for 5 min, and the  
146 supernatant was transferred to a glass tube. This procedure was repeated with 5 mL of the same  
147 clean solvent. The extract was concentrated under a gentle nitrogen stream to a volume of 0.5 mL  
148 and cleaned-up by passage onto 6 g of acidified silica (AS 44% H<sub>2</sub>SO<sub>4</sub>) in a 25 mL empty  
149 cartridge eluted with 20 mL of hexane and 15 mL of dichloromethane (DCM). The eluate was  
150 concentrated to 0.5 mL, and was further cleaned-up by passage onto a Silica bond elute SPE  
151 cartridge (particle size: 40  $\mu$ m, compounds types; polar compounds). Agilent Technologies, Santa  
152 Clara, CA, USA) topped with 100 mg acid silica (44%), and eluted with 6 mL hex (Fraction A for  
153 PCBs, pesticides and PBDEs, followed by 12 mL of DCM (Fraction B for HBCDs, TBBPA, and  
154 TBP). Fraction A and B were concentrated to near dryness.  
155 Fraction A was reconstituted in 50  $\mu$ L of isooctane and 50  $\mu$ L recovery standard (RS) (CB-207, 50  
156 pg/ $\mu$ L) and further analyzed with an Agilent 6890 GC coupled to an Agilent 5973 MS operated in

157 electron capture negative ionization (ECNI) mode with methane gas (Agilent Technologies, Santa  
158 Clara, CA, USA). The GC system was equipped with a DB-5 capillary column (30 m x 0.25 mm  
159 x 0.25  $\mu$ m). The MS was operated in selected ion monitoring (SIM) for the quantification of  
160 targeted compounds. Fraction B was reconstituted in 50  $\mu$ L of MeOH and 50  $\mu$ L of RS  
161 (d18- $\gamma$ -HBCD, 250 pg/ $\mu$ L) and further analyzed with an Agilent 1290 Infinity LC system coupled  
162 to an Agilent 6460 triple Quadrupole mass spectrometer MS/MS (Agilent Technologies, Santa  
163 Clara, CA, USA). The LC system was equipped with a Luna® 3 $\mu$ m C18(2) 100 Å column (150  
164 mm x 2 mm; 3  $\mu$ m). The MS was operated in Multiple Reaction Monitoring (MRM) for the  
165 quantification of targeted compounds. All targeted ions are described in Malysheva et al. (2018)  
166 and Poma et al. (2019).

## 167 **2.4. Quality assurance**

168 To control for potential background contamination, six procedural blanks were run in parallel  
169 with the samples. When a compound was present in the blanks, the mean blank signal was  
170 subtracted from the sample concentration and the limits of quantification (LOQs) were defined by  
171 3 x SD of the blank values. For compounds absent in the blanks, LOQs were based on a  
172 signal/noise ratio of 10 (S/N = 10). LOQs of the targeted compounds (ng/g wet weight) are listed  
173 in Table S2. IS recovery (average  $\pm$  SD) was 82 $\pm$ 6% for CB143 and 93 $\pm$ 7 for BDE103. The  
174 calibration was linear and characterized by good correlation coefficients (> 0.9) for all studied  
175 compounds.

## 176 **2.5. Statistical analyses**

### 177 **2.5.1 Duplicate-diet**

178 Correlations among the targeted compounds and food items were tested using Spearman's  
179 rank correlation coefficient. Principal component analysis (PCA) was used to identify differences  
180 between the targeted compounds. These statistical analyses were conducted using JMP® 10 (SAS  
181 Institute Inc., Cary, NC, USA). Values below LOQ were calculated as detection frequency  $\times$  LOQ  
182 (James et al., 2002). The dietary intake from the baby duplicate-diet was calculated using the

183 following formula: Concentration of the target compounds (ng/g w.w.) × total amount of baby  
184 food per day (g in w.w./day) (Desalegn et al., 2011; Fujii et al., 2012a; Harada et al., 2013).

### 185 **2.5.2 Edible Seaweed samples**

186 We used Monte Carlo simulations in Microsoft Excel 2016 (Redmond, WA, USA) to estimate  
187 dietary intake of TBP by multiplying food consumption of seaweed and concentrations of TBP of  
188 seaweed therein from random sampling from given distributions (Fujii et al., 2020). One thousand  
189 trials of 365 days were repeated in the following two scenarios: 1) individual consumption of  
190 seaweed was constant throughout the 365 days and TBP concentration of seaweed varied from  
191 day to day, and 2) individual consumption of seaweed and TBP concentrations were constant  
192 throughout the 365 days (conservative estimate). For scenario 1, average TBP intakes were  
193 examined for 365 days. Distributions of consumption and concentration were fitted under a  
194 normal distribution and when sampled values were negative, zero was substituted. Calculated  
195 intake was summarized to the median, 90th percentile, and 95th percentile values.

196

## 197 **3. Results and Discussion**

### 198 **3.1. Organohalogenated compounds in 24-h baby duplicate diet**

199 We examined dietary exposure to organohalogenated compounds among Japanese infants. To  
200 the best of our knowledge, this is the first study based on the duplicate-diet method for infants. A  
201 total of 46 sets of duplicate-diet samples were analyzed in this study. Among the 41 targeted  
202 compounds, 19 compounds were detected in at least one of the 46 samples (LOQ; 0.005 to 0.02  
203 ng/g-w.w.) (Table 2, Table S2). HCB was most frequently detected (78%), followed by *p,p'*-DDE  
204 (65%), and TC (57%) (Table 2). The median intakes among the groups of compounds were  
205 highest for  $\Sigma$ DDTs (18 ng/day, maximum 251 ng/day), followed by  $\Sigma$ PCBs (17 ng/day, maximum  
206 198 ng/day),  $\Sigma$ CHLs (14 ng/day, maximum 105 ng/day), HCB (11 ng/day, maximum 64 ng/day),  
207 TBP (3.5 ng/day, maximum 109 ng/day),  $\Sigma$ HBCDs (1.9 ng/day, maximum 70 ng/day), TBBPA  
208 (0.72 ng/day, maximum 34 ng/day), and  $\Sigma$ PBDEs (only BDE-47 was detected; 0.11 ng/day,

209 maximum 4.5 ng/day). Among PCBs, PCB-138 and PCB-153 were the most abundant congeners  
210 (27% and 23%, respectively). Among the indicator PCBs, PCB-101, 138, 153 and 180 were  
211 analysed in this study since penta to hepta PCBs were targeted. The sum of PCB-101, 138, 153  
212 and 180 were reached 82% of  $\Sigma$ PCBs. *p,p'*-DDE accounted for 96% of all DDTs, suggesting that  
213 it is a reminder of the past emission. The median intakes of each individual compound were  
214 highest for *p,p'*-DDE (17 ng/day), followed by TC (5.7 ng/day), HCB (4.4 ng/day), PCB-101 (4.9  
215 ng/day), and PCB-138 (4.6 ng/day). The brominated compounds, 2,4,6-TBP,  $\alpha$ -HBCD,  $\gamma$ -HBCD,  
216 TBBPA and BDE47 were trace levels (3.5, 0.76, 0.34, 0.72 and 0.11 ng/day, respectively).

217 Some reports have discussed the dietary intakes of organohalogenated compounds in baby food  
218 from the US and China (Liu et al., 2014), Australia (Toms et al., 2016), Korea (Jeong et al.,  
219 2014a; Jeong et al., 2014b) and Spain (Lorán et al., 2010). These studies were not based on 24-h  
220 duplicate-diet, but rather on an individual ingredient or commercial-, homemade- baby food. The  
221 estimated dietary levels of BDE-47 in the US and China (12.9 and 5.91 ng/day; 1 to 12 months  
222 old) (Liu et al., 2014) were higher than those in Korea (0.9 ng/day; 12 months old, the body  
223 weight was assumed to be 10 kg) (Jeong et al., 2014b) and Japan (0.11 ng/day) (this study). DDT  
224 levels in Japan (18 ng/day) (this study) were comparable to previous studies from Korea (17  
225 ng/day), while PCBs and CHLs in Japan (17 ng/day and 13 ng/day) (this study) were slightly  
226 higher than those in Korea (8 ng/day and 3 ng/day) (Jeong et al., 2014a). The highest value of  
227 PCB intake was reported from commercial baby food in Spain (38 ng/day, 12 months old) (Lorán  
228 et al., 2010). These differences may reflect the contamination pattern in those countries. Moreover,  
229 the difference of sampling method may affect the value of daily dietary intakes: These  
230 ingredient-based methods might not be completely representative of the levels of dietary intakes  
231 because they only partially reflect habitual diet and dilution effects.

232 According to the latest national infant nutrition survey of Japan (MHLW, 2015), weaning with  
233 baby food has started by 6 months of age in most cases (88% of total). On the other hand,  
234 weaning with baby food most often finished between 13 to 15 months of age (33.3%), and 68% of

235 the total had finished by 15 months of age. Thus, the food samples in this study were divided into  
236 two groups, the early stage (from 7 to 12 months old, n=26, 10 months old on average) and the  
237 late stage (from 13 to 24 months old, n=18, 16 months old on average), according to the infant  
238 habits. In the early stage, the median intakes were highest for *p,p'*-DDE (6.3 ng/day), followed by  
239 TC (4.9 ng/day), HCB (4.4 ng/day), PCB-101 (4.0 ng/day), PCB-138 (3.8 ng/day),  
240 trans-nonachlor (TN) (2.7 ng/day) and PCB-153 (2.6 ng/day). For the late stage, the intakes were  
241 highest for *p,p'*-DDE (48 ng/day), followed by HCB (21 ng/day), TC (9.8 ng/day), TN (5.5  
242 ng/day), PCB-101 (5.4 ng/day), PCB-138 (4.8 ng/day), PCB-153 (4.6 ng/day) and CC (4.2  
243 ng/day). The median intakes of CC, TN, HCB and  $\alpha$ -HBCD were significantly lower in the early  
244 stage than in the late stage ( $p < 0.05$ , t-test;  $p < 0.05$ , Mann-Whitney U-test). Our previous research  
245 demonstrated that organohalogenated compounds in breast milk in Japan were 112 ng/g lipid for  
246 PCBs (sum of 11 isomers: PCB-74, 99, 105, 118, 138, 153, 156, 170, 180, 183, and 187), 16 ng/g  
247 lipid for HCB, 30 ng/g lipid for TN and 2.2 ng/g lipid for  $\alpha$ -HBCD (Fujii et al., 2012b; Fujii et al.,  
248 2018). The representative value of average breast milk consumption of Japanese 10-month-old  
249 infants was reported to be 432 g/day (AIST, 2017). If we assume that the breast milk contained  
250 3.5% of lipids, the dietary intake of organohalogenated compounds from breast milk was 2900  
251 ng/day for PCB, 420 ng/day for HCB, 790 ng/day for TC, 58 ng/day for  $\alpha$ -HBCD. These intake  
252 values of breastmilk were 10 to 200 times higher than those of duplicate diet in the early stage (10  
253 months old), indicating that the intake of POPs through food consumption for Japanese infants is  
254 limited. In other words, these results indicate that breast milk is the main exposure source of  
255 POPs in infancy. However, it is important to stress that; 1) future extend study is required to  
256 confirm these results because a relatively small number of participants in this study may prevent  
257 the generalization of the findings and 2) the risk-benefit balancing approach is needed since  
258 breastmilk has the medical and neurodevelopmental advantages (Eldelman, 2012).

### 259 **3.2. Correlation and principal component analysis among the targeted compounds**

260 The nonparametric correlation coefficients among the selected targeted compounds (with DF >

261 30%: TC, CC, TN, HCB, *p,p'*-DDE, PCB-153, PCB-138,  $\alpha$ -HBCD and TBP) are listed in Table  
262 S3. We found moderate to strong associations between the compounds ( $\rho = 0.36\text{--}0.95$ ,  $p < 0.05$ )  
263 except between PCB153, PCB138 and TBP. Thus, principal component analysis (PCA) was  
264 conducted to identify clusters of the studied compounds (Fig. 1). The first and second PCA  
265 accounted for 48% and 17% of the total variance, respectively; Eigenvalues were 4.3 and 1.6,  
266 respectively. Principal component (PC) 1 had high loading matrixes on chlorinated compounds  
267 (TC, CC, TN, HCB, *p,p'*-DDE, PCB-153 and PCB-138; loading matrixes are 0.69 to 0.85), but  
268 not on brominated compounds ( $\alpha$ -HBCD and TBP, loading matrixes are 0.30 and 0.25,  
269 respectively) (Fig. 1). On the other hand, PC2 showed a difference between TBP and  $\alpha$ -HBCD  
270 (0.71 and -0.31, respectively). These differences may reflect the emission trend of the compounds.  
271 PC1) Time trend: the chlorinated compounds, PCBs and OCs, were already banned between 1974  
272 to 1986 in Japan (Ministry of Justice, 1974 (last version 2018)). Therefore, the current exposure to  
273 PCBs and OCs was likely caused by past and secondary emission sources before the 1980s. On  
274 the other hand, exposure to brominated compounds (HBCDs and TBP) can be attributed to more  
275 recent emissions, as HBCDs were banned more recently (until 2010) in Japan (Ministry of Justice,  
276 1974 (last version 2018)) and TBP is still used. PC2) Emission differences: It is known that some  
277 of the TBP is not only from artificial origins (used as a BFR or as a preservative in the timber  
278 industry) (Howe et al., 2005) but also from natural origins (occurring in marine biotas, such as  
279 marine polychaetes and fish/prawns) (Whitfield et al., 1997). Such emission differences may thus  
280 be reflected in the length and direction of the loading matrixes.

### 281 **3.3. Correlations between intake of organohalogenated compounds and food** 282 **consumption**

283  
284 The correlations between selected targeted compounds (with DF > 30%: TC, CC, TN, HCB,  
285 *p,p'*-DDE, PCB-153, PCB-138,  $\alpha$ -HBCD, and TBP) and selected food groups (seafood (fish and  
286 shellfish), meat and seaweed) were examined for the 46 duplicate-diet samples (Table 3). Seafood  
287 and meat were used for this analysis because contamination with halogenated compounds was

288 previously reported in such food items (Endo et al., 2016; Nishioka et al., 2004; Teruya et al., 2002).  
289 Seaweed was also included in this analysis because naturally-occurring halogenated compounds  
290 have been detected in wild seaweed (Haraguchi et al., 2010) and these may also be present in edible  
291 seaweed.

292 The intake of seafood was positively correlated with the intake of PCB-153, PCB-138, CC, TC,  
293 TN (Spearman's  $r=0.45$  to  $0.57$ ;  $p<0.05$ ), while the intake of meat was positively correlated with the  
294 intake of TC, TN, HCB,  $p,p'$ -DDE and  $\alpha$ -HBCD (Spearman's  $r =0.42$  to  $0.70$ ;  $p<0.05$ ). On the other  
295 hand, the intake of seaweed was only moderately correlated with the intake of 2,4,6-TBP  
296 (Spearman's  $r =0.46$ ;  $p<0.05$ ). These findings indicate that seafood and meat are potential exposure  
297 sources of PCBs, OCs and HBCDs, while seaweed is a potential source of TBP. No negative  
298 correlations were observed among the food items and the compounds.

### 299 **3.4. Seaweed as a source of TBP exposure**

300 In this study, as mentioned above, PCBs and CHLs were correlated with seafood consumption,  
301 while TBP was correlated with seaweed consumption (Table 3). It is important to note that there  
302 might be confounding factors among the food intakes and pollutant concentrations. As an example,  
303 infants who eat more meat typically also eat more grains and, as a result, the pollutants present in  
304 grains may correlate with meat intake. Seafood is reported to be the main exposure source of PCBs  
305 and chlordanes in the Japanese adult population, and meat is also an exposure source of chlordanes  
306 in some areas of Japan (Nishioka et al., 2004; Teruya et al., 2002). However, there are no previous  
307 reports about TBP and seaweed consumption. To confirm these findings, four species of edible  
308 seaweed in Japan, which were frequently consumed by the Japanese population, were analyzed. The  
309 mean concentration ( $\pm$ SD) of 2,4,6-TBP was  $5.5\pm 6.6$  ng/g-w.w. (Table 4). We estimated TBP intake  
310 to assess the contribution of seaweed to TBP exposure in Japanese infants. The average intake of  
311 seaweed was  $1.2 \pm 1.9$  g/day (Table S1). We conducted Monte Carlo simulations of daily intake for  
312 365 days for 1,000 subjects, as shown in Table 4. In the first scenario, the 95th and 50th percentile  
313 values of TBP intake from seaweed were estimated to be 30.2 and 7.9 ng/day, respectively. In the

314 second scenario (conservative estimate), the 95th percentile value of TBP intake was higher and  
315 estimated to be 44.8 ng/day. This suggests that seaweed consumption is a potential source of TBP in  
316 the infant period.

### 317 **3.5. Limitations of the study**

318 In the current study, there are potential confounding factors among the food and pollutant  
319 intakes. In future studies, exposure estimates via seafood and meat should be confirmed by  
320 individual food analysis. Our study assumes that all consumed seaweed contains similar TBP levels  
321 to the four analyzed species. This may limit the generalization of the results. As the Japanese  
322 population consumes a wide range of seaweed and seaweed extracts, distributions by the species  
323 should also be investigated. Also, it should be noted that these findings were based on a small  
324 number of selected volunteer samples which collected only in the Fukuoka region. These features  
325 prevented to analyze the data in detailed categories such as sex, weight, district of residence.  
326 Considering these limitations, a future, more extensive study is required to further confirm these  
327 findings.

328

### 329 **4. Conclusions**

330 In this study, we first evaluated the dietary intakes of organohalogenated compounds, based on  
331 the levels in the complete meals of infants (per day per person). The median intakes were highest  
332 for  $\Sigma$ DDTs, followed by  $\Sigma$ PCBs, and  $\Sigma$ CHLs. On the other hand, the levels of BFRs were  
333 relatively lower. The dietary intake of the targeted compounds was lower than the intake via  
334 breast milk, suggesting that the exposure from baby food was limited. PCA revealed a difference  
335 between chlorinated- and brominated- compounds, suggesting a differing emission time trend or  
336 source. Several compounds were statistically correlated with the amount of seafood, meat, and  
337 seaweed consumption, indicating that the food group is a potential exposure source of  
338 organohalogenated compounds in infants. According to the individual ingredient analysis,  
339 contribution of seaweed to the total intake of TBP is discernible. More future monitoring surveys



340 of environmental pollutants by the complete meal sets are needed to reveal the accurate values of  
341 dietary intakes for infants.

342

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353

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458

Table 1. Demographic characteristics and average food intakes of the study participants

	<i>n</i>	Sex	Age	Bodyweight	Food consumption	
		Male/female	(months)	(kg)	(g-ww <sup>2</sup> /day)	(g-lipid/day)
Total	46 <sup>1)</sup>	20/26	12 ± 4.0	9.0 ± 1.2	519 ± 290	11 ± 10
Early stage (7 to 12 months)	28	14/14	9.6 ± 1.7	8.6 ± 0.86	370 ± 231	5.6 ± 6.0
Late stage (13 to 24 months)	18	6/12	16 ± 3.2	9.6 ± 1.3	752 ± 207	19 ± 11

Data are presented as mean ± SD.

1) 46 duplicate-diet from 46 families (one duplicate-diet per family)

2) wet weight

Table 2. Dietary intake of the targeted compounds from 24h duplicate-diet (ng/day)

Compounds	n > LOQ (%)	Total (n=46)			Early-stage (n=28) (7 to 12 months)		Late stage (n=18) (13 to 24 months)		t-test (two-tailed test)	Ma h
		Median	Range (Min-Max)	P95	Median	Range (Min-Max)	Median	Range (Min-Max)		
PCBs <sup>a</sup>										
CB 101	20	4.9	0.85 - 34	18	4.0	0.85 - 19	5.4	3.0 - 34	n.s.	
CB 99	2	0.46	0.074 - 27	1.0	0.27	0.074 - 27	0.60	0.34 - 1.0	n.s.	
CB 118	13	1.6	0.28 - 8.0	5.6	1.2	0.28 - 8.0	1.8	1.0 - 3.0	n.s.	
CB 146	2	0.23	0.037 - 14	0.48	0.14	0.037 - 14	0.30	0.17 - 0.49	n.s.	
CB 153	48	4.0	1.3 - 55	42	2.6	1.3 - 55	4.6	2.6 - 52	n.s.	
CB 138	50	4.6	1.3 - 43	29	3.8	1.3 - 33	4.8	1.9 - 43	n.s.	
CB 187	7	0.36	0.055 - 22	10	0.21	0.055 - 22	0.45	0.25 - 14	n.s.	
CB 177	2	0.11	0.018 - 4.2	0.24	0.07	0.018 - 4.2	0.15	0.084 - 0.25	n.s.	
CB 180	9	0.48	0.074 - 15	10	0.29	0.074 - 12	0.68	0.34 - 15	n.s.	
CB 170	2	0.11	0.018 - 4.2	0.24	0.07	0.018 - 4.2	0.15	0.084 - 0.25	n.s.	
ΣPCBs	-	17	6.2 - 198	126	14	6.2 - 198	22	11 - 161	n.s.	
Organochlorine pesticides <sup>b</sup>										
TC	57	5.7	0.48 - 27	21	4.9	0.48 - 27	9.8	2.2 - 23	n.s.	
CC	41	3.7	0.35 - 31	24	2.5	0.35 - 20	4.2	1.6 - 31	*	
TN	43	3.9	0.37 - 50	36	2.7	0.37 - 20	5.5	1.7 - 50	*	
ΣCHLs	-	14	1.2 - 105	66	11	1.2 - 60	19	5.5 - 105	*	
HCB	78	11	0.76 - 64	42	4.4	0.76 - 32	21	9.0 - 64	*	
<i>p,p'</i> -DDE	65	17	1.1 - 239	178	6.3	1.1 - 73	48	5.0 - 239	*	
<i>p,p'</i> -DDT	7	0.65	0.11 - 106	30	0.41	0.11 - 1.3	1.2	0.50 - 106	n.s.	
ΣDDTs	-	18	1.2 - 251	213	6.8	1.2 - 75	49	5.6 - 251	*	

BFRs <sup>c</sup>	BDE 47	4	0.11	0.018 - 4.5	2.1	0.068	0.018 - 3.2	0.15	0.084 - 4.5	n.s.
	$\alpha$ -HBCD	35	0.76	0.13 - 67	23	0.48	0.13 - 1.5	1.5	0.59 - 67	*
	$\gamma$ -HBCD	17	0.34	0.055 - 12	6.7	0.21	0.055 - 6.1	0.55	0.25 - 12	n.s.
	$\Sigma$ HBCDs	-	1.9	0.22 - 70	26	0.97	0.22 - 15	9.3	1.0 - 70	*
	TBBPA	28	0.72	0.11 - 34	9.2	0.46	0.11 - 9.0	1.0	0.50 - 34	n.s.
	2,4,6-TBP	39	3.5	0.33 - 109	100	2.1	0.33 - 94	4.1	1.9 - 109	n.s.

\* $p < 0.05$ , significant differences between the early stage and late stage. n.s. not significant

a. CB 105, 183, 128, 174, 171, 156, 199, 196/203, 206, 209 were not detected in the all samples (Table S2)

b. OxC, CN, and  $p,p'$ -DDD were not detected in any sample (Table S2)

c. BDE28, 100, 99, 154, 153, 183 and  $\beta$ -HBCD were not detected in any sample (Table S2)

Table 3 Spearman's rank correlation coefficients between targets compounds and food intakes

Compounds <sup>a</sup>	Seafood		Meat		Seaweed	
	$\rho$	p value	$\rho$	p value	$\rho$	p value
CB 153	<b>0.57</b>	<.0001	0.18	0.221	0.27	0.067
CB 138	<b>0.56</b>	<.0001	0.12	0.430	0.19	0.22
CC	<b>0.55</b>	<.0001	0.38	0.0089	0.30	0.044
TC	<b>0.45</b>	0.0019	<b>0.42</b>	0.0033	0.22	0.14
TN	<b>0.52</b>	0.00020	<b>0.45</b>	0.0017	0.26	0.085
HCB	0.17	0.25	<b>0.70</b>	<.0001	0.28	0.061
<i>p,p'</i> -DDE	0.30	0.040	<b>0.56</b>	<.0001	0.29	0.051
alpha-HBCD	0.15	0.32	<b>0.60</b>	<.0001	0.27	0.072
2,4,6-TBP	0.060	0.69	0.36	0.014	<b>0.46</b>	0.0012

a. Detection frequency of > 30% was selected (See Table 2). Bold text is used to highlight components with values more than 0.4.



Table 4. 2,4,6-TBP concentrations in edible seaweed and the dietary intake among Japanese infants estimated by Monte Carlo simulation.

A. 2,4,6-TBP concentration in edible seaweed

Seaweed species	ng/g-w.w.
<i>Sargassum fusiforme</i>	10
<i>Undaria pinnatifida</i>	15
<i>Gloiopeltis</i>	0.80
<i>Eisenia bicyclis</i>	0.90
Average ( $\pm$ SD)	5.5 ( $\pm$ 6.6)

B. Dietary intake of TBP via seaweed consumption estimated by Monte Carlo simulation<sup>a</sup>

**Scenario 1**- individual seaweed consumption was constant throughout the year and TBP concentration varied day-by-day

	ng day <sup>-1</sup>
(1) 95 percentile value	30
(2) 90 percentile value	26
(3) 50 percentile value	7.9

**Scenario 2**-individual seaweed consumption and TBP concentration thereof were constant throughout the year (conservative)

	ng day <sup>-1</sup>
(4) 95 percentile value	45
(5) 90 percentile value	34
(6) 50 percentile value	2.8

a. Average TBP concentration in seaweed was used ( $5.5 \pm 6.6$ ). Average consumption of seaweed was used as reported value in Table S2 ( $1.2 \pm 1.9$ ). Distributions of consumption and concentration were fitted under a normal distribution and when sampled values were negative they were substituted with zero.

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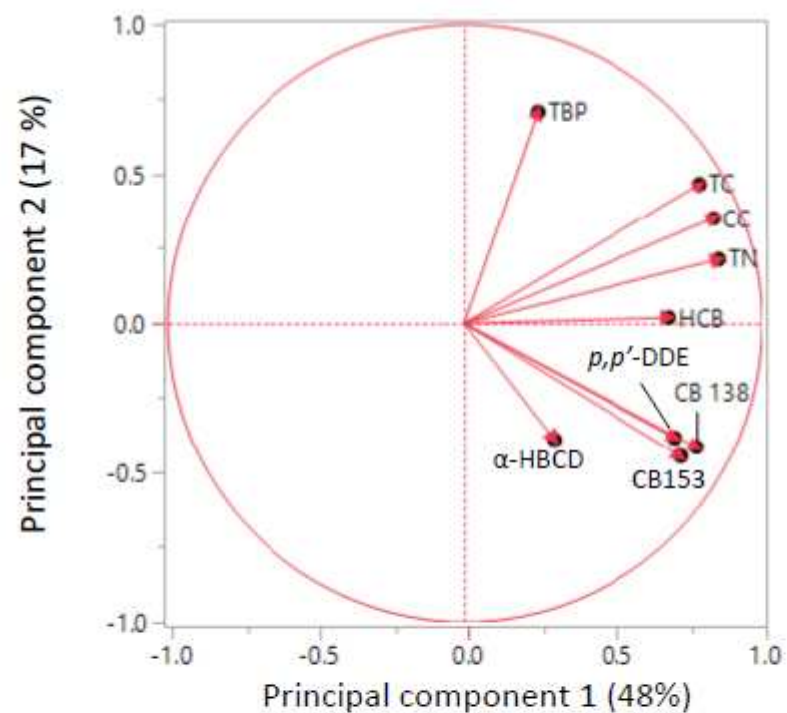


Fig.1. Principal component analysis among the target compounds  
 2,4,6-Tribromophenol (TBP), Trans-chlordane (TC), Cis-chlordane (CC), Trans-nonachlor (TN),  
 Hexachlorobenzene (HCB), Dichlorodiphenyldichloroethylene (*p,p'*-DDE), 2,2',3,4,4',5'-  
 Hexachlorobiphenyl (CB 138), 2,2',4,4',5,5'-Hexachlorobiphenyl (CB 153), alpha-  
 Hexabromocyclododecane ( $\alpha$ -HBCD)

467 **Supporting Information**

468

469 **Estimation of dietary intake and sources of organohalogenated contaminants among**  
470 **infants: 24-h duplicate diet survey in Fukuoka, Japan**

471

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**Table S1. Composition of the 24-h duplicate-diet samples**

Food group	Duplicate-diet (g wet weight./day)			
	Total	Early-stage (7 to 12 months)	Late-stage (13 to 24 months)	
	<i>n</i> =46	<i>n</i> =28	<i>n</i> =18	
1. Rice	95 ± 57	67 ± 43	139 ± 47	*
2. Other cereals	28 ± 31	21 ± 29	39 ± 33	
3. Potatoes	11 ± 19	7.2 ± 8.8	17 ± 28	
4. Beans	15 ± 15	11 ± 12	22 ± 17	*
5. Nuts and seeds	0.022 ± 0.15	0.0±0.0	0.056 ± 0.24	
6. Vegetables	55 ± 40	48 ± 28	67 ± 53	
7. Vegetable juice	6.7 ± 25	0.50 ± 2.5	16 ± 39	*
8. Fruits	32 ± 44	13 ± 19	61 ± 54	*
9. Fruit juice	4.5 ± 20	6.0 ± 25	2.3 ± 10	
10. Mushrooms	2.9 ± 5.6	1.3 ± 2.4	5.3 ± 8.0	*
11. Seaweed	1.2 ± 1.9	0.93 ± 1.7	1.6 ± 2.3	
12. Seafood <sup>a</sup>	7.0 ± 8.3	6.3 ± 7.8	8.2 ± 9.2	
13. Meat	12.1 ± 11	8.3 ± 7.0	18 ± 13	*
14. Eggs	7.9 ± 17	2.1 ± 6.7	17 ± 24	*
15. Milk	80 ± 111	54 ± 98	122 ± 120	*
16. Confectioneries	8.6 ± 20	3.5 ± 8.5	16 ± 30	*
17. Beverages	97 ± 103	58 ± 72	158 ± 116	*
18. Liquids <sup>b</sup>	114 ± 89	107 ± 94	123 ± 83	
Water content (%)	64 ± 12	68 ± 13	59 ± 6.7	*

Data are presented as means ± SD.

\**p*<0.05, significant differences between the early stage and late-stage (Student's *t*-test)

a. fish and shellfish

b. Liquids include tap water, soup, seasonings and oils

Table S2 Targeted compounds information

	Abbreviation	Full name	Instrument	LOQ (ng/g w.w.)	% of detected samples	
<i>PCBs</i>	CB 101	2,2',4,5,5'-Pentachlorobiphenyl	GC-ECNI/MS	0.04	20	
	CB 99	2,2',4,4',5-Pentachlorobiphenyl	GC-ECNI/MS	0.04	2	
	CB 105	2,2',4,5,5'-Pentachlorobiphenyl	GC-ECNI/MS	0.04	0	
	CB 118	2,2',4,4',5-Pentachlorobiphenyl	GC-ECNI/MS	0.02	13	
	CB 146	2,2',3,4',5,5'-Hexachlorobiphenyl	GC-ECNI/MS	0.02	2	
	CB 153	2,2',4,4',5,5'-Hexachlorobiphenyl	GC-ECNI/MS	0.01	48	
	CB 138	2,2',3,4,4',5'-Hexachlorobiphenyl	GC-ECNI/MS	0.01	50	
	CB 128	2,2',3,3',4,4'-Hexachlorobiphenyl	GC-ECNI/MS	0.01	7	
	CB 156	2,3,3',4,4',5-Hexachlorobiphenyl	GC-ECNI/MS	0.01	0	
	CB 170	2,2',3,3',4,4',5-Heptachlorobiphenyl	GC-ECNI/MS	0.01	0	
	CB 171	2,2',3,3',4,4',6-Heptachlorobiphenyl	GC-ECNI/MS	0.01	0	
	CB 174	2,2',3,3',4,5,6'-Heptachlorobiphenyl	GC-ECNI/MS	0.01	2	
	CB 177	2,2',3,3',4,5',6'-Heptachlorobiphenyl	GC-ECNI/MS	0.01	0	
	CB 180	2,2',3,4,4',5,5'-Heptachlorobiphenyl	GC-ECNI/MS	0.01	0	
	CB 183	2,2',3,4,4',5',6-Heptachlorobiphenyl	GC-ECNI/MS	0.01	9	
	CB 187	2,2',3,4',5,5',6-Heptachlorobiphenyl	GC-ECNI/MS	0.01	2	
	CB 199	2,2',3,3',4,5,5',6'-Octachlorobiphenyl	GC-ECNI/MS	0.01	0	
			2,2',3,3',4,4',5,6'-Octachlorobiphenyl			
		CB 196/203	2,2',3,4',4,4',5,6'-Octachlorobiphenyl	GC-ECNI/MS	0.01	0
		CB 206	2,2',3,3',4,4',5,5',6-Nonachlorobiphenyl	GC-ECNI/MS	0.01	0
	CB 209	Decachlorobiphenyl	GC-ECNI/MS	0.01	0	
<i>Pesticides</i>	OxC	Oxychlorane	GC-ECNI/MS	0.01	0	
	TN	<i>Trans</i> -nonachlor	GC-ECNI/MS	0.01	57	
	CN	<i>Cis</i> -nonachlor	GC-ECNI/MS	0.01	41	
	TC	<i>Trans</i> -chlordane	GC-ECNI/MS	0.01	43	
	CC	<i>Cis</i> -chlordane	GC-ECNI/MS	0.01	0	
	pp-DDE	Dichlorodiphenyldichloroethylene	GC-ECNI/MS	0.02	78	
	pp-DDD	Dichlorodiphenyldichloroethane	GC-ECNI/MS	0.02	65	
	pp-DDT	Dichlorodiphenyltrichloroethane	GC-ECNI/MS	0.02	0	
	HCB	Hexachlorobenzene	GC-ECNI/MS	0.01	7	
<i>BFRs</i>	BDE 28	2,4,4'-Tribromodiphenyl ether	GC-ECNI/MS	0.005	0	
	BDE 47	2,2',4,4'-Tetrabromodiphenyl ether	GC-ECNI/MS	0.005	0	

	BDE 100	2,2',4,4',6-Pentabromodiphenyl ether	GC-ECNI/MS	0.005	0
	BDE 99	2,2',4,4'5-Pentabromodiphenyl ether	GC-ECNI/MS	0.005	0
	BDE 154	2,2',4,4',5,6'-Hexabromodiphenyl ether	GC-ECNI/MS	0.005	0
	BDE 153	2,2',4,4',5,5'-Hexabromodiphenyl ether	GC-ECNI/MS	0.005	0
	BDE 183	2,2',3,4,4',5',6-Heptabromodiphenyl ether	GC-ECNI/MS	0.005	0
	$\alpha$ -HBCD	alpha-Hexabromocyclododecane	LC-MS/MS	0.005	35
	$\beta$ -HBCD	beta-Hexabromocyclododecane	LC-MS/MS	0.005	0
	$\gamma$ -HBCD	gamma-Hexabromocyclododecane	LC-MS/MS	0.005	17
	TBBPA	Tetrabromobisphenol A	LC-MS/MS	0.005	28
	TBP	2,4,6-Tribromophenol	LC-MS/MS	0.01	39
<i>IS</i>	CB-143	2,2',3,4,5,6'- Hexachlorobiphenyl	GC-ECNI/MS	-	-
	BDE-103	2,2',4,5',6-Pentabromodiphenyl ether	GC-ECNI/MS	-	-
	<sup>13</sup> C-HCB	<sup>13</sup> C-Hexachlorobenzene	GC-ECNI/MS	-	-
	$\alpha$ - <sup>13</sup> C-HBCD	alpha- <sup>13</sup> C-Hexabromocyclododecane	LC-MS/MS	-	-
	$\beta$ - <sup>13</sup> C-HBCD	beta- <sup>13</sup> C-Hexabromocyclododecane	LC-MS/MS	-	-
	$\gamma$ - <sup>13</sup> C-HBCD	gamma- <sup>13</sup> C-Hexabromocyclododecane	LC-MS/MS	-	-
	<sup>13</sup> C-TBBPA	<sup>13</sup> C- Tetrabromobisphenol A	LC-MS/MS	-	-
	<sup>13</sup> C-TBP	<sup>13</sup> C-2,4,6-Tribromophenol	LC-MS/MS	-	-
<i>RS</i>	CB-207	2,2',3,3',4,4',5,6,6'-Nonachlorobiphenyl	GC-ECNI/MS	-	-
	d18- $\gamma$ -HBCD	d18-gamma- Hexabromocyclododecane	LC-MS/MS	-	-

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**Table S3. Spearman's rank correlation coefficients between the targeted compounds**

Compounds <sup>a</sup>	CB 153	CB 138	CC	TC	TN	HCB	p,p'-DDE	$\alpha$ -HBCD	2,4,6-TBP
CB 153	-								
CB 138	<b>0.92</b>	-							
CC	<b>0.60</b>	<b>0.48</b>	-						
TC	<b>0.53</b>	<b>0.41</b>	<b>0.92</b>	-					
TN	<b>0.62</b>	<b>0.49</b>	<b>0.95</b>	<b>0.89</b>	-				
HCB	<b>0.50</b>	<b>0.36</b>	<b>0.65</b>	<b>0.64</b>	<b>0.69</b>	-			
p,p'-DDE	<b>0.71</b>	<b>0.57</b>	<b>0.63</b>	<b>0.64</b>	<b>0.69</b>	<b>0.84</b>	-		
$\alpha$ -HBCD	<b>0.56</b>	<b>0.42</b>	<b>0.61</b>	<b>0.56</b>	<b>0.63</b>	<b>0.78</b>	<b>0.82</b>	-	
2,4,6-TBP	0.27	0.21	<b>0.46</b>	<b>0.50</b>	<b>0.40</b>	<b>0.57</b>	<b>0.44</b>	<b>0.46</b>	-

Bold;  $p < 0.05$ , significant correlation.

a. A detection frequency of 30% or more was selected.