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In vitro estimation of oral bioaccessibility of brominated flame retardants in indoor dust by fasted and fed physiologically extraction test

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Abstract

Aim: There is a dearth of information on *in vitro* oral bioaccessibility, challenging the evaluation of the health risks arising from indoor dust exposure to the brominated flame retardants, tetrabromobisphenol A (TBBPA), and hexabromocyclododecane (HBCDD). Here, we estimate the human oral bioaccessibility of TBBPA and HBCDD in indoor dust by applying the standardized bioaccessibility test under fasting (UBM-like test) and fed (FOREhST test) conditions.

Methods: *In vitro* bioaccessibility of HBCDD and TBBPA of sixteen indoor dust samples was conducted under fasted and fed states. In the fed test, food components, including healthy and unhealthy food. The concentrations of HBCDD and TBBPA were analyzed using LC-MS/MS. Bioaccessibility was calculated from the ratio of the amount of HBCDD and TBBPA in a simulated gut solution to that in indoor dust. The average daily dose

($EDD_{bioaccessibility}$) was calculated from the estimated daily intake and percentage of bioaccessibility.

Results: The concentration of TBBPA and HBCDD in indoor dust ranged from 137 to 14,671 ng g^{-1} and < 0.7 to 528 ng g^{-1}, respectively. A higher bioaccessible concentration was observed in the small intestine than in the stomach and mouth. The condition of the fed state with food containing fat showed greater bioaccessibility of TBBPA and HBCDD at 74.0% ± 9.5% and 62.2% ± 10.1%, respectively. In contrast, the fed state with lower fat food containing fiber presented the lowest bioaccessibility with a mean of 54.7% ± 10.7% for TBBPA and 53.7% ± 10.8% for HBCDD. Moreover, children are more exposed than adults, especially those who ingest indoor dust with fatty food.

Conclusion: The oral bioaccessibility of TBBPA and HBCDD in indoor dust was highest in the fed state with fatty food, followed by fasted and fed states with lower fat, higher fiber food. Similarly, the estimated daily dose ($EDD_{bioaccessibility}$) for children exceeded that for adults. Therefore, this study indicated that food consumption is a factor influencing the bioaccessibility of TBBPA and HBCDD present in indoor dust.

Keywords: Flame retardants, hexabromocyclododecane, tetrabromobisphenol A, indoor dust, oral bioaccessibility, risk assessment

INTRODUCTION

People spend more than 70% of their time indoors, in microenvironments such as homes, workplaces, and schools[1]. As a result, the potential health risks from pollutants in indoor environments, including the risks associated with brominated flame retardants (BFRs), have become a significant topic of investigation[2,3]. Hexabromocyclododecane (HBCDD) and tetrabromobisphenol A (TBBPA) are two BFRs that are widely used to meet fire safety regulations in various jurisdictions around the world[4,5], with extensive applications in electronic equipment enclosures, back coatings on fabrics, and building materials[6-9]. These compounds can migrate from products such as indoor furniture or materials to the indoor environment and enter indoor dust[8,10-12]. Unintentional ingestion by hand-to-mouth behavior is one of the potentially important pathways of human exposure to chemical pollutants, including HBCDD and TBBPA[1,13-15]. However, evidence suggests that the total amount of contaminant ingested does not amount to 100% of what is available to the body[16-18]. Several factors are involved in determining the amount of contaminants taken up by the body, such as the release of pollutants from the solid matrix to the gastrointestinal system, the absorption rate, and the metabolism of substances in the intestine and liver[19,20].

Additionally, assessments of human exposure to contaminants present in soil and dust are likely overestimated if they do not account for the fraction that is available for uptake across the gastrointestinal tract[2]. Therefore, to assess the risk of human exposure to toxic chemicals present in matrices such as soil and dust, several recent studies have used *in vitro* bioaccessibility tools to measure the fraction of contaminants released from an ingested matrix, which become dissolved in gastrointestinal tract (GIT) fluids, and are thereby potentially available for absorption into the systemic circulation[2,16,18,21,22]. Furthermore, the Bioaccessibility Research Group of Europe (BARGE) has recently proposed the unified bioaccessibility method (UBM)[23], in which physiological conditions during human digestion are simulated using three compartments (mouth, stomach, and small intestine) with simulated saliva, gastric acid, bile, and pancreatic fluids under fasted conditions. For example, BARGE launched the fasted unified BARGE method to estimate inorganic contaminants through an oral bioaccessibility test[24,25]. Subsequently, the FOREhST (Fed ORganic Estimation human Simulation) approach was developed to assess the oral bioaccessibility of organic substances such as Polycyclic Aromatic Hydrocarbons (PAH) in soil. Based on the UBM (fasted state) approach, it adds food supplements to the human digestive system under simulated

feeding conditions[26]. Results of previous studies have shown that dietary fat-containing food components might increase the dissolution of organic compounds into the human GIT fluid[21,26,27].

Moreover, enzymes and bile salts acting as surfactants might also increase the solubility of organic compounds in the human gastrointestinal system[28]. However, the BARGE (fasted state) and FORESHT (fed state) methods have not yet been applied to TBBPA, HBCDD, and indoor dust. Moreover, simulations of the fed state using a combination of the five nutrients of food components related to human eating behavior have yet to be studied. In this study, we assess the *in vitro* oral bioaccessibility of TBBPA and HBCDD in indoor dust samples using fasted and fed state methods. In addition, human health risks to these substances from fasted and fed states were evaluated using the hazard quotient (HQ) approach.

EXPERIMENTAL

Chemicals and reagents

The standards and the internal standard used for extraction and analysis, namely TBBPA, α-, β-, and γ-HBCDD, $^{13}C_{12}$-α-HBCDD, $^{13}C_{12}$-β-HBCDD, $^{13}C_{12}$-γ-HBCDD, and $^{13}C_{12}$-TBBPA (each with a purity of ≥ 98%), were procured from Cambridge Isotope Laboratories (Andover, MA, USA), with d_{18}-γ-HBCDD obtained from Wellington Laboratories (Guelph, ON, Canada). All solvents used (hexane, dichloromethane, and methanol) were of HPLC quality grade and purchased from Merck (Darmstadt, Germany). Concentrated sulfuric acid (98% purity) and silica gel 60 (0.063-0.200 mm) were supplied by Merck (Darmstadt, Germany), while indoor dust reference material (SRM 2585) was obtained from the U.S. National Institute of Standards and Technology (NIST, Gaithersburg, MD, USA).

KCl, KSCN, NaH_2PO_4, Na_2SO_4, NaCl, $NaHCO_3$, NH_4Cl, KH_2PO_4, $MgCl_2.6H_2O$, $CaCl_2.2H_2O$, NaOH, HCl, NH_2CONH_2, uric Acid, D-glucuronic Acid, D-glucosamine Hydrochloride, and bile salts purchased from Merck (Darmstadt, Germany) were used for the gastrointestinal extraction method. Bovine serum albumin (BSA), pepsin (pig), pancreatin (pig), mucin (pig), lipase (pig), α-Amylase (bacillus species), lipase (pig) were procured from Sigma Aldrich Ltd. (Dorset, U.K.). Thai jasmine rice porridge, soybean oil, and lard were obtained from a local supermarket in Thailand. Nutrilite chewable fiber blend (Amway Thailand Ltd) and Proflex whey isolate protein powder (Power Corporation Thailand Co., Ltd) were obtained from a food supplement center in Thailand.

Sample collection

Sixteen dust samples were collected from houses (n = 5) and workplaces, specifically offices (n = 3), child day care centers (n = 1), and e-waste dismantling workshops (n = 7). House, office, and child day care center dust samples were collected as per previously published studies[4,29,30]. Briefly, dust samples were collected from each site using a vacuum cleaner with a nylon sock with a 25 μm pore size into the nozzle of the vacuum cleaner tube. In houses, offices, and child daycare centers, a 1 m^2 area of carpeted flooring was sampled for 2 min, while in rooms without carpets, a 4 m^2 area of bare flooring was vacuumed for 4 min. After the collection of each sample, the sock was closed, wrapped with aluminum foil, and sealed in a plastic bag. For samples collected from e-waste dismantling workshops, dust samples were collected according to a previously described procedure[31]. New brushes were used to collect dust samples deposited on the surface of e-waste at different sampling points. The dust samples were individually wrapped in aluminum foil, sealed in a plastic bag and transported to the laboratory in a cooler with ice. In the laboratory, each dust sample was sieved through a pre-cleaned 250 μm mesh to remove coarse particles, wrapped in clean aluminum foil, sealed in plastic bags, and stored at -20 °C until analysis.

Food components preparation for fed state bioaccessibility test

In the fed organic estimation human simulation (fed) test, food components, including healthy and unhealthy food, were prepared according to the Recommended Daily Intake for the Thai population (Thai RDI)[32]. Recommended nutrients for daily intake were based on an energy demand of 2,000 kcal/day. Total energy (T.E.) intake is represented by the proportion of macronutrients, including carbohydrates, protein, and fat. According to Thai RDI, T.E. should be 45%-65% carbohydrates, 10%-15% protein, 20%-35% fat, and 20 g fiber. Details of the proportions of macronutrients in Thai RDI[32], and of the various types of simulated diet are presented in Supplementary Table 1.

Preparation of the gastrointestinal fluids

Four simulated fluids, specifically simulated salivary fluid (SSF), simulated gastric fluid (SGF), simulated duodenal fluid (SDF), and simulated bile fluid (SBF), were prepared according to the procedures described in previous studies[21,27,33-35]. Each simulated fluid was prepared into three sections: enzyme, organic, and inorganic solution, similar to the relevant human body fluids. The individual simulated fluid comprised 250 mL organic and 250 mL inorganic solutions (see composition in Supplementary Table 2). Two solutions were homogenously combined in a 500 mL container containing several enzymes. All simulated fluids were prepared the day before the test to ensure that the solution and all the enzyme components were active. Prior to the *in vitro* bioaccessibility test, the pH of each simulated fluid was checked and adjusted with dropwise addition of 1.0 mol/L NaOH or concentrated HCl (37%) to ensure it fell within the range of gastrointestinal tract conditions: 6.5 ± 0.5 for salivary fluid, 1.0 ± 0.1 for gastric fluid, 7.4 ± 0.2 for duodenal fluid and 8.0 ± 0.2 for bile fluid. In addition, all simulated fluids were pre-warmed at 37 °C for 1 h before use.

Fasted and fed bioaccessibility test

In vitro bioaccessibility tests under fasted and fed states were conducted under conditions that simulated three compartments of the human gastrointestinal tract: mouth, stomach, and small intestine, as described in previous studies with modifications[21,25,26,34]. The same conditions and reagents are used in both the fasted and fed procedures.

In the fed test, food components combined with dust samples, including healthy and unhealthy food, were added. The solid to fluid ratio was maintained at 1: 100 in experiments[36]. The volume ratio of simulated fluids for saliva and gastric fluid was conducted at 1:2 (v/v), and the ratio of the simulated fluids for duodenal and bile fluid was also fixed at 1:2 (v/v). The fed state bioaccessibility test was carried out by duplicate by weighing samples (0.1 g) of sieved dust sample into a 50 mL screw cap glass test tube with approximately 1 g of food components (healthy or unhealthy). Unhealthy food was defined here as high in saturated fat, while healthy food was lower in fat and contained more vegetables (fiber)[37]. The healthy food component included 0.58 g of Thai jasmine rice porridge, 0.15 g of whey isolate protein powder, 0.18 mL of soybean oil, 0.09 mL of lard, 0.2 g of Nutrilite chewable fiber, and 0.6 mL of milli-Q water. For unhealthy food, a mixture of 0.23 g of Thai jasmine rice porridge, 0.25 g of whey isolate protein powder, 0.25 mL of soybean oil, 0.20 mL of lard, and 0.6 mL of milli-Q water was added to the glass test tube. Then, 4.5 mL of simulated saliva fluid was added to the glass test tube and the solution was shaken for 3 min at 100 rpm and 37 ± 2 °C in a shaking incubator. After that, the solution was centrifuged at 3,000 rpm for 5 min to separate the bioaccessible saliva solution and residual bioaccessible sample. Next, an aliquot of 1.5 mL of bioaccessible saliva solution was filtered using a syringe filter and kept at 4 °C until extraction and clean-up. A residual bioaccessible sample was then simulated in the stomach phase by adding 9.0 mL of simulated gastric fluid. The pH was controlled by adding 1 mol/L NaOH or 37% HCl at 1.6 ± 0.2, and the gastric solution was incubated and shaken at 100 rpm for 2 h at the same temperature. After 2 h, the stomach phase was stopped, and the solution was centrifuged at 3,000 rpm for 5 min. The 4.0 mL of bioaccessible gastric

solution was collected, filtered, and kept at 4 °C until further analysis.

Finally, 9.0 mL of simulated duodenal fluid plus 4.5 mL of simulated bile fluid were added to the residual sample. The small intestine solution was adjusted to pH 6.0 ± 0.2 and shaken at 100 rpm for 2 h at 37 ± 2 °C throughout this period. After the small intestine phase, the solution was centrifuged at 3,000 rpm for 5 min. Finally, the bioaccessible small intestine solution was collected, filtered, and kept at 4 °C for further determination of HBCDD and TBBPA analysis. The same protocol was followed for the fasted state bioaccessibility test, except that food components were not added to the experiment.

Sample extraction and clean-up

The extraction and clean-up of dust and bioaccessibility samples were done as per a previously described procedure[29,30,38]. Before extraction, approximately 0.1 g of the sieved dust sample or 1.5, 4.0, and 16.0 mL of the bioaccessible samples from the mouth, stomach, and small intestine, respectively, were spiked with 25 ng of each internal (or surrogate) standard ($^{13}C_{12}$-TBBPA,$^{13}C_{12}$-α-HBCDD, $^{13}C_{12}$-β-HBCDD and $^{13}C_{12}$-γ-HBCDD). The sample was extracted by adding 7 mL of a hexane:dichloromethane mixture (1:1, v/v) to each sample tube. Then, the suspension was vortexed for 5 min and sonicated in an ultrasonic bath at 20 °C for 30 min. The resultant extracts were centrifuged for 5 min at 3,500 rpm to separate the supernatants. The supernatant was collected and then transferred to clean glass tubes. The residual samples were extracted by another two cycles, making three extraction cycles in total. The combined supernatants from the three cycles were reduced to approximately 0.5 mL under a gentle nitrogen gas flow and reconstituted with 1 mL of hexane. The sample extract was then treated with 1 mL of concentrated sulfuric acid to remove lipids and interferences from organic compounds. An SPE cartridge packed with 4 g of pre-cleaned acidified silica (44% concentrated sulfuric acid, w/w) was used to purify the extract during the clean-up process. Before the clean-up procedure, the cartridge was pre-conditioned with 3 mL of hexane: dichloromethane (1: 1, v/v). After that, the extract (1 mL) was loaded onto the SPE cartridges with 3 1 mL hexane rinses. Then, 25 mL of the hexane: dichloromethane mixture (1:1, v/v) was used to elute the target analytes. After the clean-up process, eluents were evaporated by a stream of nitrogen and reconstituted in 200 μL of methanol containing 25 pg/μL d_{18}-γ-HBCDD as a recovery determination (or syringe) standard used to determine recoveries of internal standards for quality assurance/quality control purposes. The reconstituted samples were then transferred to sample vials for further analysis by LC-MS/MS.

Instrumental analysis

Determination of TBBPA and HBCDD isomers (α-, β-, and γ-HBCDD) was performed using an Agilent 1200SL HPLC system coupled with an Agilent 6400 tandem mass spectrometer. Chromatographic separation was conducted by an Agilent Pursuit XRS3 C18 reversed-phase analytical column (2 × 150 mm, 3 μm particle size) maintained at 40 °C. Injection volumes (10 μL) and a mobile phase flow rate of 0.15 mL/min were used throughout. The mobile phase comprised (A) 1:1 methanol/water and (B) methanol. Negative electrospray ionization in multiple reaction monitoring (MRM) was used for detection. MRM mode was used based on m/z 540.8-78.8 and m/z 552.8-78.8 for native and ^{13}C-TBBPA, respectively. The quantitative determination of MRM for native and ^{13}C-HBCDD labeled diastereomers was m/z 640.4-78.8 and m/z 652.4-79, respectively. Other instrumental parameters were as follows: nebulizer pressure: 50 psi, capillary voltage: 3500 V, drying gas (N_2) flow rate: 10 L/min, and drying gas temperature: 300 °C.

Quality assurance/quality control and statistical analyses

Procedural blanks, the certified reference material SRM 2585 (organics in indoor dust; n = 3), and a sample duplicate were analyzed with each batch of 5 dust samples. None of the target compounds were detected in procedural blanks. The recovery rate of TBBPA ranged from 80%-113%, and HBCDD ranged from 82%-115%. A signal-to-noise ratio (S/N) of 10:1 was used to calculate the limit of quantification (LOQs) of

each chemical in indoor dust samples. LOQs thus determined were 0.1 and 0.7 ng g^{-1} for TBBPA and HBCDD, respectively. The procedure used SRM 2585 (n = 3) as a reference material to evaluate the accuracy of HBCDD and TBBPA determination in the bioaccessibility experiment. After extraction, HBCDD and TBBPA in bioaccessible solution were detected at recoveries of 78%-102% and 80%-105%, respectively. Statistical analyses and descriptive statistics were conducted, including analysis of minimum, maximum, mean, median, and standard deviation of TBBPA and HBCDD concentration in dust and human exposures. In cases where target compound concentrations were below the LOQ, concentrations were set to zero for the purposes of data analysis.

Calculation of bioaccessibility and daily intake of TBBPA and HBCDD

The bioaccessibility (% B.A.) of TBBPA and HBCDD in the mouth, stomach, and small intestine was calculated as the ratio of the amount of TBBPA and HBCDD in a liquid digestive fluid (saliva, gastric and duodenal solutions) to that present in indoor dust following equation (1)[2].

$$\%BA = [(C_{\text{compound in digestive fluid}})/C_{\text{compound in indoor dust}}]*100 \quad (1)$$

where $C_{\text{compound in digestive fluid}}$ is the concentration of HBCDD and TBBPA in digestive fluids (ng g^{-1}). $C_{\text{compound in indoor dust}}$ is the concentration of HBCDD and TBBPA in house dust (ng g^{-1}). Bioaccessibility can range from 0% to 100%, where 0% means not bioaccessible, and 100% means that the HBCDD and TBBPA in indoor dust are totally bioaccessible.

The following equations from previous studies[10,13,39] were used to estimate daily intake (EDI, ng kg^{-1} bw day^{-1}) of HBCDD and TBBPA through dust ingestion using equation (2).

$$EDI_{\text{Ingestion}} = [\ ((C_H \times F_H) + (C_W \times F_W)) \times IR] / BW \quad (2)$$

The estimated average daily dose ($EDD_{\text{bioaccessibility}}$) via dust ingestion of TBBPA and HBCDD for the Thai population exposure to indoor dust from several indoor environments, and the hazard quotient (HQ) associated with the risk of human adverse health effects were calculated using equations (3) and (4)[2,31].

$$EDD_{\text{bioaccessibility}} = [\ ((C_H \times F_H) + (C_W \times F_W)) \times BA\ (\%) \times IR] / BW \quad (3)$$

$$HQ = EDD_{\text{bioaccessibility}} \text{ or } EDI_{\text{Ingestion}} / RfD \quad (4)$$

Where $EDD_{\text{bioaccessibility}}$ is the average daily dose (ng kg^{-1} bw day^{-1}), C_H and C_W are the concentrations of the target contaminant in house and workplace dust samples, respectively (ng g^{-1}), IR is the daily ingestion rate (g day^{-1}), F_H and F_W are the estimated fraction of time spent within the house and workplace each day, respectively, and BW is the body weight (kg) where the values assumed were: children (31.8 kg) and adults (63 kg)[4,13,40,41].

0.02 and 0.05 g day^{-1} for adults[4,13,29,42,43]. Based on previous research, the exposure fraction spent at home in a day is assumed to be 67% (16 h/24h = 0.67)[13]. An exposure fraction value of 33% (8 h/24 h = 0.33) was used for time spent in the workplace, such as office and school[31,44]. The reference dose (RfD) for daily intake of TBBPA was 600,000 ng kg^{-1} bw day^{-1}, which has been observed to cause uterine hyperplasia in rats[45,46]. The oral RfD for HBCDD was 3,000 ng kg^{-1} bw day^{-1}[47].

RESULTS AND DISCUSSION

TBBPA and HBCDD in indoor dust

We determined that TBBPA concentration ranged from 137 ng g^{-1} to 14,671 ng g^{-1}, with a median of 2,143 ng g^{-1}, and HBCDD concentration ranged from < 0.7 to 528 ng g^{-1}, with a median value of 18 ng g^{-1} [Table 1]. For comparison, dust was divided into house dust and workplace dust, which included offices, child day care centers, and e-waste dismantling workshops. The highest concentration of TBBPA was found in workplace dust from the e-waste dismantling workshop (14,671 ng g^{-1}), and the lowest was recorded in house dust (137 ng g^{-1}). This may be because the e-waste dismantling workshop contained many unused electronic devices, such as televisions, computers, and several office electronic items. TBBPA does not react chemically with polymer materials, is released during volatilization as well as abrasion from electronic items or transport, and is absorbed into indoor dust[4,12].

Similarly, our previous results[48,49] showed that a high concentration of TBBPA was related to many electronic devices in the room. This study found that TBBPA concentrations in dust collected from e-waste dismantling workshops were higher than in indoor dust from offices, schools, and houses. A previous study on TBBPA concentrations in dust collected from e-waste recycling workshops in China and Vietnam reported high TBBPA concentrations of 87,000 ng g^{-1}[50] and 9,100 ng g^{-1}[31], respectively. The e-waste recycling workshops from the two countries were located in large e-waste recycling parks. These are larger areas than the e-waste dismantling sites in our study; hence, the TBBPA concentration in the e-waste recycling workshops was 6 times higher in China and 1.5 times higher in Vietnam compared to our study. This suggested that the high TBBPA concentration in the dust collected from e-waste processing workshops is due to the presence of a large quantity of electronic devices[31,50]. Our results showed that TBBPA was detected in e-waste dismantling workshop dust at a high concentration, indicating that workers in the e-waste dismantling workshop and residents who live in this area could be more exposed to TBBPA via dust ingestion than residents in other areas.

We found HBCDD contamination in only nine dust samples. This is because HBCDD has rarely been utilized in applications, such as building insulation foams in Thailand[51], and was classified in Annex A of the Stockholm Convention on Persistent Organic Pollutants (POPs) in 2013[52]. However, one house dust sample in our study had the highest HBCDD concentration in dust (528 ng g^{-1}), probably owing to the several pieces of furniture present. Moreover, previous studies have reported that HBCDD was added to the back coating of foam-filled furniture fabric covers to reduce the product's flammability[53]. Therefore, a room with a lot of furniture upholstered with fabric leads to high contamination of HBCDD in the dust. A previous study in Europe showed a median HBCDD of 280 ng g^{-1} in house dust in the UK[30] and 129 ng g^{-1} in house dust in Spain[42], which were14 times and 6 times higher than those in our study, respectively. Additionally, the median HBCDD concentration in e-waste recycling workshops in China was 1,200 ng g^{-1} [50], which was 75 times higher than that in the e-waste dismantling workshops in our study. This may be because Europe and China are much larger consumers of HBCDD flame-retardant-containing products than Thailand[5,54].

Table 1. The concentration (median and ranges) of HBCDD and TBBPA in indoor dust from Thailand and bioaccessibility of three compartments of the gastrointestinal system

Chemicals		Mass concentrations (ng g^{-1}) Median (min-max)	Bioacessibility-bioaccessible fraction (%)			Total Bioacessibility (%)
			Mouth	Stomach	Small intestine	
TBBPA	House dust	1,302 (137-2,300)	0.8 ± 0.4	28.7 ± 10.8	33.5 ± 10.9	63.0 ± 10.2
	Workplace dust*	5,018 (676-14,671)	1.6 ± 1.0	28.7 ± 7.6	32.8 ± 10.5	63.1 ± 11.5
	Total**	2,143 (137-14,671)	1.3 ± 0.9	29.0 ± 8.7	33.0 ± 10.6	63.0 ± 10.7
HBCDD	House dust	20 (< 0.7-528)	1.4 ± 0.5	31.0 ± 11.2	36.8 ± 4.4	69.3 ± 10.1
	Workplace dust*	16 (< 0.7-67)	1.6 ± 1.3	25.6 ± 8.5	28.0 ± 8.5	55.2 ± 9.1
	Total**	18 (< 0.7-528)	1.5 ± 1.2	26.7 ± 9.3	29.8 ± 8.6	58.0 ± 10.5

*Workplace dust is the sum of contaminants in e-waste dismantling workshop, office, and school dust; **Total is the sum of contaminants in house, office, school, and e-waste dismantling workshop dust; HBCDD: hexabromocyclododecane; TBBPA: tetrabromobisphenol A.

Oral bioaccessibility in each gastrointestinal compartment

The bioaccessible fractions of TBBPA and HBCDD were calculated from leachable compounds from indoor dust during human digestion in the gastrointestinal tract. The bioaccessible fraction represents the maximum amount of bioavailable compounds reaching systemic blood circulation. The oral bioaccessibility of TBBPA and HBCDD in the gastrointestinal tract, including the mouth, stomach, and small intestine, is described in Table 1. The overall view of the two models (fasted and fed state) showed that TBBPA was bioaccessible and available for absorption from the gastrointestinal tract at 63.0% ± 10.7% (range: 21.2%-91.0%). It was slightly higher than HBCDD, which was 58.0% ± 10.5% (range: 39.5%-79.0%). Although HBCDD is highly lipophilic (log *K*ow = 5.82) and has low water solubility (0.0034 mg L^{-1})[55-57] compared to TBBPA (log *K*ow = 4.5, 0.72 mg L^{-1} water solubility)[58], the solubility of TBBPA increases with higher pH[58]. Thus, TBBPA can be leached from dust and dissolved in gastrointestinal solutions at higher concentrations than HBCDD, especially in states containing lipids in food components[36]. Regarding each compartment, higher bioaccessibility of these substances was observed in the small intestine (33.0% ± 10.6%), followed by the stomach (29.0% ± 8.7%) and mouth (1.3% ± 0.9%).

Similarly, for HBCDD, the mean percentage of bioaccessibility in the small intestine was 29.8% ± 8.6%, followed by the stomach (26.7% ± 9.3%) and mouth (1.5% ± 1.2%). This is possible because some enzymes enhance the digestion process and potentially facilitate the release of chemicals from solid matrices[20,26,34,59]. Bile extracts in the duodenal fluid accelerate the release of toxic compounds from dust by increasing apolar conditions to improve the solubility of hydrophobic compounds such as TBBPA and HBCDD in the small intestine[2,27,60]. Furthermore, an increase in the pH of the small intestine can partially increase the solubility of these substances[2]. In addition, the small intestine may also contain modest amounts of saliva and stomach secretions. Consequently, the bioaccessible portions of these compounds exhibited greater solubility in the small intestine compared to the stomach.

Oral bioaccessibility using fasted and fed state

The bioaccessibility percentages of TBBPA and HBCDD under fed and fasted conditions are presented in Figure 1. We divided the fed state experiment into two experiments, adding healthy and unhealthy food components to the processes. Food components were not added to the fasting process. The oral bioaccessibility (%) of TBBPA was significantly higher in the fed state with unhealthy food (74.0% ± 9.5%) than in the fasted state (60.6% ± 11.3%) and fed with healthy food (54.7% ± 10.7%). The percentage of oral bioaccessibility of HBCDD was greater in the fed state with unhealthy food (62.2% ± 10.1%) than in the fasted state (58.1% ± 10.1%) and fed with healthy food (53.7% ± 10.8%). Although dust is ingested into the

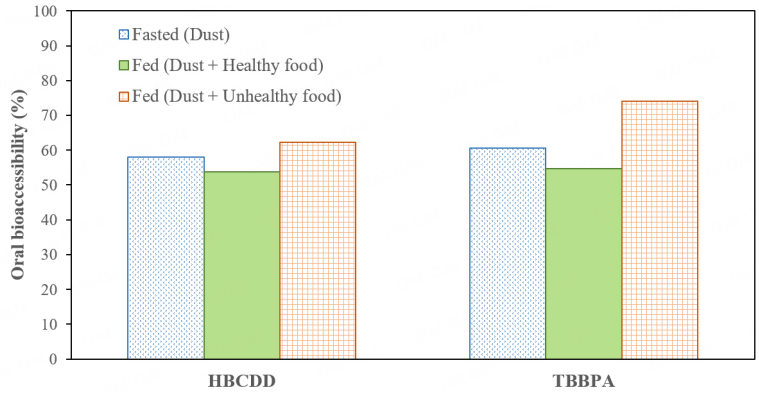

Figure 1. The mean value of oral bioaccessibility of HBCDD and TBBPA based on fasted and fed state. HBCDD: hexabromocyclododecane; TBBPA: tetrabromobisphenol A.

body via incidental dust ingestion (fasted state), chemical substances are released from the dust and dissolved in the gastrointestinal solution. The ingestion of dust and food (fed state) into the gastrointestinal tract also affected the amount of the bioaccessible fraction in the digestive system.

Briefly, in fasted conditions, the oral bioaccessibility of TBBPA (60.6% ± 11.3%) was slightly higher than that of HBCDD (58.1% ± 10.1%). Similarly, a previous study on the bioaccessibility of TBBPA and HBCDD in the CE-PBET test, which mimicked the three compartments, the stomach, small intestine, and colon, showed that the bioaccessibility of the stomach and small intestine compartments was 81% ± 5.5% for TBBPA and 59% ± 3.6% for HBCDD[36]. This is because TBBPA has better solubility in solutions as the pH increases[57,58]. Additionally, the pH increases from the stomach to the small intestine in the digestive system. Therefore, the amount of TBBPA dissolved in the solution was higher than that of HBCDD.
In the fed state with healthy food, the mean *in vitro* oral bioaccessibility was 54.67% ± 10.7% for TBBPA and 53.68% ± 10.8% for HBCDD. When the three methods, fasting, fed (with healthy food), and fed (with unhealthy food), were compared, our results showed that subjects provided with healthy food had lower bioaccessibility than the other two methods. Thus, healthy foods can reduce the bioaccessible fraction of TBBPA and HBCDD dissolved in the gastrointestinal tract. Similarly, a previous study added food components such as spinach as fiber in a bioaccessibility experiment and reported that dietary fiber could significantly decrease the amount of toxic chemicals ingested and dissolved in solution in the digestive system from 29.7% to 15.0%[61]. This suggests that the fiber absorbs toxic substances released from the solid matrices in the small intestine[61,62]. In addition, fiber increases gastrointestinal motility and reduces the absorption of toxic compounds into the blood circulation[63]. However, our study used a commercial chewable fiber blend that differed from the one used in a previous study[61], which involved the use of fresh spinach that was dried before experimentation. Commercial chewable fiber blends may not contain complete fiber content and may include other ingredients. Our results showed that the percentage of oral bioaccessibility with or without fiber in the gastrointestinal system was not significantly different. Further, the fed state procedure should assess the dry fiber from several fresh vegetables and fruits in the experiment to confirm the results.

In the fed state with unhealthy food, where the food component was added in a different ratio from the healthy food condition without including fiber, we applied the same gastrointestinal tract condition as a fed state with healthy food. Our results revealed that the percentage of oral bioaccessibility of TBBPA in fed states with unhealthy food was 1.3 and 1.2 times higher than in healthy food and fasted condition

procedures, respectively. For HBCDD, the oral bioaccessibility in fed states with unhealthy food was 1.2 and 1.0 times higher than that in healthy food and fasted condition procedures, respectively. This is because these substances are highly hydrophobic and lipophilic by their log Kow of 5.82 for HBCDD[55-57] and 5.9 for TBBPA[4,8], respectively. In addition, fat is the primary content in the fed states with unhealthy food. Thus, fat releases substances from dust and mobilizes hydrophobic organic contaminants into the aqueous phase[26], increasing the bioaccessible fraction of TBBPA and HBCDD in the gastrointestinal system of the fed state with unhealthy food.

Similarly, in a previous study[27], solid ingestion of an individual fat (oleic acid) increased the bioaccessibility of PCB in digestive fluids (77% ± 15%), followed by proteins (59% ± 14%) and glucose (58% ± 16%). However, some researchers studied the bioaccessibility of organophosphate esters (OPEs) in indoor dust under fasting and fed conditions. Lipophilic food components, such as creamy organic food and sunflower oil, were added to the fed state in the experiment. Their results showed that the bioaccessibility of fasted states (79%-116%) was not different from that of fed states (76%-109%). They suggested that lipophilic food might foster the binding of OPEs from indoor dust to free fatty acids from this food[34]. As a result, the bioaccessible fraction in the gastrointestinal solution decreases. Therefore, it can be concluded that the composition of the food affects the bioaccessibility of each substance differently, depending on the physical and chemical properties of these substances. Therefore, further studies should measure the contribution of each selected individual food type by varying the proportion of enzymes in the digestive fluid under actual conditions. This approach to each food type influenced bioaccessibility. Nevertheless, it provided useful information on substance bioaccessibility relative to food consumption that was expected to alter the bioaccessible fraction of toxic chemicals in the gastrointestinal system.

Implication for health risk assessment

The estimated daily intake (EDI) and estimated daily intake dose ($EDD_{bioaccessibility}$) of TBBPA and HBCDD via dust ingestion by children and adults are described in Table 2. The EDI of TBBPA and HBCDD was double that of $EDD_{bioaccessibility}$. This is because the EDI value was calculated based on bioaccessibility, assuming that 100% of the contaminants are bioavailable. However, the $EDD_{bioaccessibility}$ value was used to calculate the total bioaccessibility (% B.A.) of the substances that dissolve in the gastrointestinal tract and are available for uptake into the circulatory system. Thus, the $EDD_{bioaccessibility}$ value was lower than the EDI value.

Moreover, our results revealed that children were more likely to be exposed to TBBPA and HBCDD than adults. For the $EDD_{bioaccessibility}$ of TBBPA, children were exposed to TBBPA five times more compared to adults. Furthermore, children exposed to these compounds had the highest values recorded in fed states with unhealthy food ($EDD_{bioaccessibility}$ = 2.94 ng kg^{-1} bw day^{-1}) followed by fasting (2.41 ng kg^{-1} bw day^{-1}) and fed states with healthy food conditions (2.17 ng kg^{-1} bw day^{-1}) in the median-exposure scenario. Similarly, $EDD_{bioaccessibility}$ values for children exposed to HBCDD were 0.2, 0.19, and 0.17 ng kg^{-1} bw day^{-1} for the fed states with unhealthy food and fasted and fed states with unhealthy food, respectively. This implies that the food type is a factor that affects the percentage of bioaccessibility in the gastrointestinal tract and may increase the risk of human exposure to these substances and cause adverse health effects.

Our results showed that HQ values were less than 1.0, which indicates no adverse health effects and non-carcinogenicity to humans. However, considering this study, the potential health risks associated with these substances should not be ignored. They should continue to be a concern in specific population groups, particularly children who are more likely to be exposed to these compounds than adults. Furthermore, exposure to these substances is likely to occur not only through dust ingestion but also through other pathways, such as inhalation. Therefore, additional studies are needed to examine the inhalation of TBBPA

Table 2. The estimated daily dose (EDI and $EDD_{bioaccessibility}$) of TBBPA and HBCDD via dust ingestion by children and adults

Compounds	Exposure scenarios	Population group	EDI (ng kg^{-1} bw day^{-1})	HQ_{EDI}	$EDD_{bioaccessibility}$ (ng kg^{-1} bw day^{-1})		
					Fasted	Fed with healthy food	Fed with unhealthy food
TBBPA	Median exposure	Children	3.98	6.63E-06	2.41	2.17	2.94
		Adult	0.80	1.34E-06	0.49	0.44	0.59
	High-end exposure	Children	39.71	6.62E-05	6.02	5.43	7.35
		Adult	28.25	4.71E-05	3.04	2.74	3.71
HBCDD	Median exposure	Children	0.32	1.06E-04	0.19	0.17	0.20
		Adult	0.06	2.15E-05	0.04	0.03	0.04
	High-end exposure	Children	1.38	4.60E-04	0.20	0.19	0.21
		Adult	0.85	2.85E-04	0.10	0.09	0.11

HBCDD: hexabromocyclododecane; TBBPA: tetrabromobisphenol A; EDI: estimate daily intake.

and HBCDD in dust through the respiratory system, enabling more comprehensive health risk assessments.

CONCLUSIONS

In this study, we assessed the potential health risks of bioaccessible TBBPA and HBCDD in indoor dust under fasted and fed conditions. The total concentration of TBBPA and HBCDD in indoor dust ranged from 137 to 14,671 ng g^{-1} and < 0.7 to 528 ng g^{-1}, respectively. We also sampled houses, workplaces, including offices and child day care centers, and e-waste dismantling workshops. The e-waste dismantling workshop showed the highest TBBPA concentration among all the sampling points. Bioaccessibility tests under fasted and fed states were conducted in the mouth, stomach, and small intestine. The small intestine was observed to have a higher percentage of bioaccessibility of TBBPA and HBCDD than the stomach or mouth, owing to the several enzymes and bile salts increasing the solubility of these compounds in the duodenum. The oral bioaccessibility of these substances in indoor dust was the highest in the fed state with unhealthy food, followed by fasted and fed states with healthy food. For human exposure, the estimated daily dose from bioaccessibility showed that children were more exposed to these substances than adults. In particular, children who ingested indoor dust in fed states with unhealthy fat-containing food were exposed to higher concentrations of TBBPA and HBCDD and those ingesting healthy foods containing fiber can reduce bioaccessibility in the gastrointestinal system. This finding suggests that food type affects the percentage of oral bioaccessibility of these compounds in the gastrointestinal system. Thus, food types, especially fiber, and fat should be studied further with other compounds to confirm the effect of oral bioaccessibility.

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Authors' contributions

Made substantial contributions to the conceptualization and design of the study, sample collection and analysis, performed data analysis and interpretation, provided content, and wrote and edited the manuscript for submission: Waiyarat S

Conceptualized and designed the study; data analysis; edited the manuscript; and provided administrative, technical, material support, and funding acquisition: Boontanon SK
Made a significant contribution to the methodology of sample analysis and validation of these procedures: Boontanon N
Made substantial contributions to the conceptualization, methodology of sample collection and analysis, and edited the manuscript: Harrad S, Abdallah MAE, Drage DS
Sample analysis and edited the manuscript: Santhaweesuk K

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Conflicts of interest
All authors declare that they have no conflict of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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