Human health risk assessment from exposure to multiple sources of Hexabromocyclododecanes (HBCDs) in Taiwan

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Abstract

Hexabromocyclododecanes (HBCDs) are endocrine-disrupting and persistent organic compounds commonly used in consumer products such as styrofoam, fire-resistant curtains, construction, aquaculture products, and food containers. Humans can expose to HBCD via dermal, ingestion, and inhalation routes; however, the inhalation exposure to HBCDs is not well characterized, especially for the size-segregated particles, which could quickly deposit into the respiratory system. In this study, we systematically characterized the dermal and inhalation exposures and performed an aggregate risk assessment of HBCDs in Taiwan. Sampling sites were selected considering the traffic or industrial contribution for air ($n = 2$, Sanchung, and Taichung) and soil sampling ($n = 19$, near the industrial zones). The quantitative analysis of HBCDs in extracted samples was achieved using LC–MS/MS. Our results showed that the concentrations of total HBCDs ranged from 0.1 to 6.6 pg m^{-3} in the particulate matter samples and 0.63 to 187 µg kg^{-1} in soil samples, where γ-HBCD was the dominant species, followed by α-HBCD and β-HBCD. The total HBCDs in the finest particles (i.e., particle size below 0.49 µm) ranged from N.D. to 1.5 pg m^{-3}. However, no consistent trend was observed for the isomer distribution of HBCDs among air samples. Furthermore, the margin of exposure was the lowest through the ingestion pathway (5152 to 22555) and the highest through the inhalation pathway (6.71×10^5 to 2.09×10^7), showing that HBCD-induced health risk can predominantly attribute to ingestion exposure. Nevertheless, the traffic and industrial contribution of inhalable HBCD deserves further studies.

Keywords Hexabromocyclododecanes (HBCDs), Size-segregated particles, Soil contaminants, Risk assessment

1 Introduction

Hexabromocyclododecanes (HBCDs), commonly used as brominated flame retardants (BFRs), are intentionally added into consumer products (e.g., polystyrene products) to form lower energetic brominated radicals and facilitate the extinction of flame [1]. HBCDs exist in 3 forms of diastereomers (α, β, and γ), where the γ form is the most abundant isomer in commercial products (~72 to 90%). Considering their environmental persistence, bioaccumulation (logK$_{ow}$ ~ 5), and long-range transport, the Stockholm Convention on Persistent Organic Pollutants (POPs) has included HBCDs since 2013 [2]. EU

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and other countries followed the conclusions of Stockholm Convention to promulgate amending regulation for prohibiting from adding HBCD in products intentionally or higher than 100 mg kg^{-1} unintentionally [3]. However, HBCDs are still popularly used in market if alternative flame retardant cannot provide the same quality and relative lower cost. For example, the annual import of HBCDs still reaches around 45,000 kg in the United States [2].

HBCDs can be found in soil, water body [4–9] and air [10–16]. For soil, the largest HBCD manufacturer in China was reported to contaminate soil nearby and air deposition was the major factor to result in soil pollution [5]. In Korea, although the highest HBCD concentration in soil was found near general industrial complex, its concentration was lower than those found near the factories using HBCD as additives or products. For HBCDs in atmosphere, HBCDs were confirmed in arctic environment, it indicated that HBCDs underwent long range transport via air [17] and also implied that the inhalation pathway of exposure assessment was needed. Moreover, particles lower than 10 μm should be noticed because HBCDs are more abundant in particulate phase [18], and the inhalable HBCDs can quickly enter the human body via the respiratory system, eliciting adverse health effects [19]. Size segregated analysis can be used to explain and simulate the health effect of fine particles in inhalation system. However, limited information was available for the concentrations of HBCDs in size segregated samples [19, 20]. Based on the results from these literatures, air and soil are two important vectors for HBCDs transport.

HBCDs can trigger many adverse effects in organisms, such as endocrine disruption, reproductive effects, and hepatotoxicity. Remarkable effects on the thyroid hormone have been reported, indicating that HBCDs are endocrine disruptors [21]. Furthermore, HBCDs had been shown to interfere with the physical development of F2 offspring in a transgenerational rat study, showing a potential reproductive and developmental effect [22]. In addition, HBCDs are known as hepatotoxicants [23] and being found in organ or tissue [19, 24]. The ubiquitous existence of HBCDs in the environment could result in human exposure to HBCDs through dermal contact, ingestion, or inhalation. Dermal contact from furniture fabric is a vital exposure pathway to HBCDs for adults and toddlers [25]. Foods have also been shown to be important sources of HBCD exposure, including milk [26], seafood [27, 28], and meat [29].

HBCDs leaked from factories still need to be monitored although many governments have imposed restriction in relative products, especially for extruded polystyrene and expanded polystyrene, which are allowed to use under EU regulation [3]. In addition, HBCDs could transport in air via particle movement or physical process such as breaking large piece of plastics products into micro or nanoplastics [30].

Besides, the exposure and risk assessments of HBCDs have received increasing concerns worldwide. A systematic review on brominated flame retardants concluded that diet was the primary source of HBCD exposure [19]. Inhalation was considered a minor exposure route; however, the particle size could be an important factor in determining the HBCDs-induced health effects. Additionally, researchers usually perform risk assessments of HBCDs based on biomonitoring data [31] or individual exposure routes [32], where the contribution of individual routes to the total exposure is not fully characterized. Therefore, this study focuses on the determinations of residual HBCD concentrations in soil and air in Taiwan to: (1) monitor the concentrations of HBCDs in soil near selected plastics factories and comparisons were made for sites after uses of HBCDs were restricted for almost 10 years; (2) analyze size-segregated particulate matter samples in two different sites to compare the health effects through inhalation pathway; and (3) comprehensively assess the HBCDs-induced health risk to the general publics..

2 Materials and methods

2.1 Chemicals
The standard solutions of α-HBCD, β-HBCD, and γ-HBCD were purchased from AccuStandard (Connecticut, U.S.A). ^{13}C-labelled counterparts for α-HBCD and γ- HBCD were obtained from LGC Standards (San Marino, Italy). ^{13}C-labelled counterparts for β-HBCD were obtained from Cambridge Isotope Laboratories (Massachusetts, U.S.A.). LC–MS grade organic solvents, including dichloromethane, n-hexane, methanol, and acetonitrile, were purchased from Honeywell (Charlotte, U.S.A). The commercial florisil SPE tubes (Product Number: 57057, 2 g, 12 mL) were purchased from Merck (Charlotte, U.S.A).

2.2 Sample collection and pre-treatments
Table 1 shows the isomer distributions of HBCDs in soil samples collected from the selected factories. In total 5 grassland samples and 1 park sample near plastics factories were collected from southern Taiwan. Another 13 samples collected from farmland, park, school, grassland and vacant space in northern Taiwan were selected for comparison because of different types of industries. All samples were collected in 2021. Surface soil samples (200 g, top 5 cm) were collected at each site, dried during lyophilization, sieved with 10 mesh sieve (≤ 2 mm),

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Table 1 Isomer distribution of HBCDs in soil samples

Region	Type of site	Near type of factory	α (%)	β (%)	γ (%)	ΣHBCD (µg kg^{-1})
South	Grassland	Polystyrene	5.3	3.5	91.2	187.2
South	Park	Complex	16.5	7.4	76.1	2.50
South	Grassland	Polystyrene	18.6	9.4	72.0	80.0
South	Grassland	Polystyrene	13.5	6.3	80.1	20.8
South	Grassland	Polystyrene	26.1	8.8	65.1	70.8
South	Grassland	Polystyrene	13.9	4.9	81.2	27.4
Central	Farmland	Car tyre	40.8	0.0	59.2	0.63
North	Park	Car tyre	42.2	13.1	44.7	1.23
Central	School	PVC	40.6	0.0	59.4	0.63
Central	Grassland	Cement	45.6	12.4	42.0	1.13
Central	Vacant space	Nylon	52.9	12.3	34.7	1.24
North	School	Car	33.5	14.3	52.2	0.78
North	School	Cement	41.2	14.8	44.0	0.88
Central	School	-	35.6	14.1	50.2	0.75
Central	School	-	36.8	14.1	49.1	0.77
North	School	-	48.9	13.6	37.5	1.20
Central	School	-	53.9	13.4	32.7	1.37
North	Vacant space	Carrier tape	40.7	0.0	59.3	0.63
East	School	Pulp	41.4	0.0	58.6	0.63

and then stored at 4 ℃ until further analyses. In addition, the air sampling was performed at two sites, including a traffic site nearby an interchange in northern Taiwan (i.e., Sanchung) (Fig. S1a, in Supplementary materials) and an on-campus site at Tunghai University in central Taiwan (i.e., Taichung) (Fig. S1b). In total, 36 particulate matter samples were collected using a high-volume air sampler equipped with a six-stage (< 0.49 µm, $0.49 - 0.95$ µm, $0.95 - 1.5$ µm, $1.5 - 3.0$ µm, $3.0 - 7.2$ µm, > 7.2 µm) cascade impactor (Model HV-RW, Shibata) from March 22 to 28, 2021. The material of filter was quartz fiber (Tissuquartz 2500QAT-UP, PALLFLEX). The impactor was operated at a constant flow rate of 1.13 m^3 min^{-1}, and each sample was continuously collected for 2 d resulting in an averaging sampling volume of 3254 m^3 for more HBCD mass for analysis. All filters were weighed before and wrapped in aluminum foil after sampling. Samples were kept at 4 ℃ until further analyses. Method blanks and field blanks were also performed with the same method.

Soil sample (5 g) spiked with a suite of ^{13}C-labelled internal standard (40 ng) was extracted using a sonicator (Qsonica Q700) with 10 mL of dichloromethane, then the extract was concentrated to dryness using a nitrogen evaporator. Next, the sample was reconstituted with hexane (3 mL) and then subject to the cleanup procedure using a florisil SPE cartridge. Briefly, 12 mL of dichloromethane and hexane were used for condition before

the reconstitute was loaded into the cartridge. After washing the cartridge with 6 mL of hexane, HBCDs were eluted with 8 mL of dichloromethane. Finally, the eluent was dried, reconstituted with 4 mL of acetonitrile and water (1:1, v/v), and stored at -10 ℃ until LC–MS/MS analysis. Particulate matter samples were processed using a similar protocol but were extracted with hexane and dichloromethane (1:1) for the broader analyte of interest.

2.3 LC–MS/MS analysis

The quantitative analysis of HBCD was performed using a Sciex 5500 Triple Quad 5500 LC–MS/MS system equipped with an electrospray in the negative ionization mode. The chromatographic separation was achieved using an Agilent Pursuit 3 PFP reversed-phase column (150 mm × 2.1 mm, 3.0 µm), with the mobile phases A (i.e., methanol and water (25:75, v:v)) and B (i.e., methanol and acetonitrile (50:50, v:v)) at a flow rate of 0.3 mL min^{-1}. The chromatographic gradient is detailed in Table S1. The injection volume was 20 µL. For ionization parameters, the source temperature was 300℃, ion spray voltage was -4.5 kV, curtain gas was 172 kPa, nebulizing gas was 400 kPa, and heating gas was 379 kPa. The quantifier and qualifier were m/z $640.6 \rightarrow 79.0$ and $642.6 \rightarrow 81.0$ for HBCDs, and the quantifier *m/z* $652.6 \rightarrow 79.0$ for ^{13}C-labelled HBCDs (Table S2). The calibration curve ranged from 0.05 to 75 ng mL^{-1} showed excellent linearity for α ($r = 0.9984$), β ($r = 0.9976$) and

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γ-HBCD ($r = 0.9978$). The lower limits of quantification were 0.03 ng g^{-1} for soil and 0.023 pg m^{-3} for air samples based on a s/n ratio of chromatographic peak close to 10. The recovery and reproducibility of the analysis were evaluated by spiking blank samples with a known amount (40 ng) of the target analyte in triplicate. For particulate matter samples, the recovery was 100 to 113% for α-HBCD, 80 to 95% for β-HBCD, and 74 to 82% for γ-HBCD. For soil samples, the recovery was 84 to 97% for α-HBCD, 95 to 101% for β-HBCD, and 78 to 93% for γ-HBCD, where the matrix effect was 90 to 97% for α-HBCD, 91 to 104% for β-HBCD, and 72 to 77% for γ-HBCD.

2.4 Aggregate exposure assessment of HBCDs

This study comprehensively evaluated the inhalation, ingestion, and dermal exposures of HBCDs. First, for the inhalation pathway, we estimated the chronic daily intake (CDI, pg kg^{-1} d^{-1}) following the Eq. (1), where the exposure parameters were adopted from a previous survey in Taiwan [33, 34]:

$$CDI_{air}\left(pg\ kg^{-1}d^{-1}\right) = \frac{C \times IR \times ET \times EF \times ED}{BW \times AT}$$
(1)

C represents particulate matter samples (pg m^{-3}); IR is inhalation rate, which is 14.0 m^3 d^{-1} for individuals under 12 years old and 17.1 m^3 d^{-1} for those above (including) 12 years old. ET is exposure time (hours/month), which is 9.26 ± 19.74 h month^{-1} ($n = 981$) for males and 7.34 ± 14.46 h month^{-1} ($n = 937$) for females. EF is the exposure days in a year with an estimated 350 daysyear^{-1} [35]. Age-stratified values of the exposure duration (ED) and averaging time (AT) were used. BW is the body weight derived from the Nutrition and Health Survey in Taiwan [36].

We adopted the exposure estimates from Lee et al. for the ingestion route to represent the dietary exposure to HBCDs in Taiwan [29].

The dermal exposure of HBCDs via soil samples and the dermal absorbed dose (DAD, pg kg^{-1} d^{-1}) were calculated according to the guideline of health risk evaluation for soil by Taiwan EPA [35], following Eqs. (2) and (3) [34]:

$$DA_{event}\left(mg\ cm2 - event\right) = C_{soil} \times AF \times ABS_d \times CF$$
(2)

DA was absorbed dose per event, and sub-parameters for DA estimation were incorporated into Eq. (2). C$_{soil}$

(mg kg^{-1}) was the concentration of HBCDs in the soil sample, and the worst-case scenario was used for the estimation; AF was the adherence factor of soil to skin, which was 0.07 mg cm^{-2} for individuals below 12 years old had and 0.2 mg cm^{-2} for those above 12 years old; Dermal absorption fraction was 0.065 [37]; CF was 10^{-6} for unit conversion (kg mg^{-1}); Frequency of event happened (EV) was 1 per day; Frequency of exposure (EF) was estimated 250 days per year. Skin surface area available for contact was 17,300 cm^2 for adults (SA$_{adult}$) and 11,400 cm^2 for children; The ratio of surface area (f$_{sa}$) between arm and body was 0.2; Exposure duration for age under 12 years old (ED$_{child}$) was 6 years, for age above 12 (ED$_{adult}$) was 25 years and included the period of childhood exposure. The average exposure time (AT) was the same as ED. BW (BW$_{adult}$, BW$_{child}$) was body weight, which was also derived from the Nutrition and Health Survey in Taiwan [36]. We applied Monte Carlo simulation to illustrate the uncertainties and variability of exposure estimates ($n = 10{,}000$) using a Python program (Version 3.10, performed on the Visual Studio Code platform).

2.5 Calculation of margin of exposure (MOE) in the general population in Taiwan

We used the point of departure (POD) value of HBCD adopted by the U.S. EPA for calculating MOE (Eq. 4). In brief, the human equivalent dose (HED) of the lowest POD value among the available animal studies (0.69 mg kg^{-1}) was selected. Criteria for MOE were set upon the consideration of uncertainty factors. Specifically, the interspecies uncertainty (UF$_A$) of 3 and the intraspecies uncertainty (UF$_H$) of 10 were assigned to the selected study, resulting in an action threshold of MOE < 30 [37].

$$MOE = \frac{POD_{HED}}{Intake\ dose} = \frac{0.689}{Intake\ dose}$$
(4)

3 Results

3.1 LC–MS/MS analysis of α, β, and γ-HBCD

Chromatograms of standard solutions and the soil sample with the greatest concentrations are shown in Fig. 1. The blank sample showed a clean chromatogram, and no interfering signal was observed (Fig. S2). α, β, and γ-HBCD were eluted at 12.37, 12.71, and 13.0 min, where

$$DAD_{dermal-soil}(pg\ kg\text{-}1\ d\text{-}1) = DA_{event} \times EV \times \left(\frac{ED_{adult} \times SA_{adult}}{BW_{adult}} + \frac{ED_{child} \times SA_{child}}{BW_{child}}\right) \times \frac{EF \times f_{sa}}{AT}$$
(3)

the retention time shifts of all real samples were less than 2.5%. The deviation of continuing calibration check
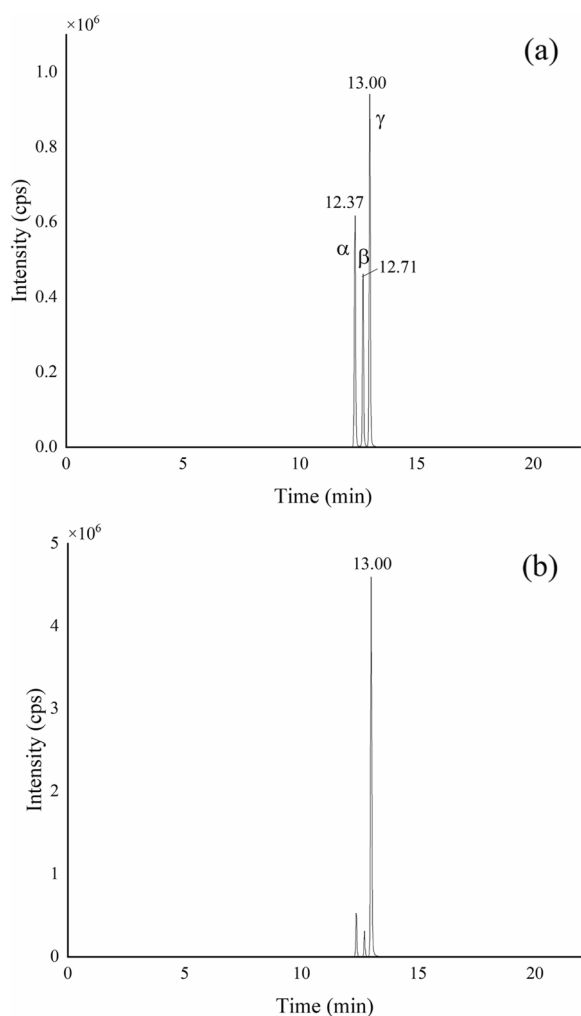
Fig. 1 **a** 25 ng mL^{-1} standard mixtures **b** the soil sample with the greatest HBCD concentrations

samples (25 ng mL^{-1}, n = 4) were from -6.8 to 5% for α-HBCD, from -8.9 to 6% for β-HBCD, and from -7.5 to 8% for α-HBCD in every 12-h analysis.

3.2 HBCDs concentrations and proportion of isomers in soil

Figure 2 summarizes the concentrations of HBCDs in soil (pie chart) and particulate matters (bar chart). The concentrations in soil samples ranged from 0.63 to 187 μg kg^{-1} (Table 1). Higher concentrations of HBCDs were observed in the five samples located in Southern Taiwan, ranging from 20.8 to 187 μg kg^{-1}, and the others were mostly below 3 μg kg^{-1}. Isomer distributions of HBCD were also determined as shown in Table 1 and Fig. 2, where the percentage range was 5 to 54% for α-HBCD, 0 to 15% for β-HBCD, and 33 to 91% for γ-HBCD. The results also showed that γ-HBCD was the dominant species in the five samples located in Southern Taiwan with higher concentrations of HBCDs, which account for at least 65% of the total HBCD in samples.

3.3 HBCDs concentrations and species distribution of isomers in particulate matters samples

The concentrations of HBCDs in particulate matter samples ranged from 2.0 to 6.6 pg m^{-3} (3.7 ± 2.5 pg m^{-3}, n = 3) in Sanchung and from 0.1 to 0.6 pg m^{-3} (0.3 ± 0.3 pg m^{-3}, n = 3) in Taichung (Fig. 2 and Table 2). The highest concentration of HBCDs was detected in the first period of sampling (March 22, 12:00 p.m. to March 24, 12:00 p.m.). The lowest concentration of HBCDs was observed in the second period of sampling (March 24, 12:00 p.m. to March 26, 12:00 p.m.), and the concentrations of HBCDs increased in the third period of sampling (March 26, 12:00 p.m. to March 28, 12:00 p.m.). Overall, the particulate matter samples collected from Sanchung reported higher HBCD concentrations compared to those collected from Taichung. The percentage of isomer distribution in Sanchung was 29 to 50% for α-HBCD, 5 to 12% for β-HBCD, and 46 to 63% for γ-HBCD. On the other hand, the percentage of isomer distribution in Taichung was 0 to 100% for α-HBCD, 0 to 16% for β-HBCD, and 0 to 100% for γ-HBCD.

3.4 Daily intake of HBCDs from inhalation and dermal exposure pathway

The CDI of all demographic groups in Sanchung (0.059 to 0.343 pg kg^{-1} d^{-1}) was higher than that in Taichung (0.010 to 0.058 pg kg^{-1} d^{-1}, Fig. 3). In general, males reported greater CDI values than females. Infants and toddlers (3 years old) also reported a greater CDI value than other age group. The whole group was separated by age 12 into two groups, child and adult, to represent the outcomes of DAD$_{soil-dermal}$ based on the definition from the guideline of health risk evaluation for soil pollution by Taiwan EPA (Table 3). The results of dermal exposure dose in the child group (588 pg kg^{-1} d^{-1}) were higher than in the adult group (151 pg kg^{-1} d^{-1}).

3.5 Human health risks from exposure to HBCDs in Taiwan

The MOEs from the three exposure pathways were all greater than the proposed action threshold 30 by U.S. EPA (Table 4) [37]. The inhalation pathway with the highest MOE contributed the least to the total HBCD exposure. For dermal exposure, the worst case of MOE was 1.2×10^6 for children under 12, which was similar to the risk of diet pathway (MOE from 1.5×10^5 to 6.8×10^5).

4 Discussions
4.1 Comparison of concentrations and characteristics of HBCDs in soil samples

The fingerprint of HBCDs deposited in soil may reveal the local emission sources. In a Sweden study, the
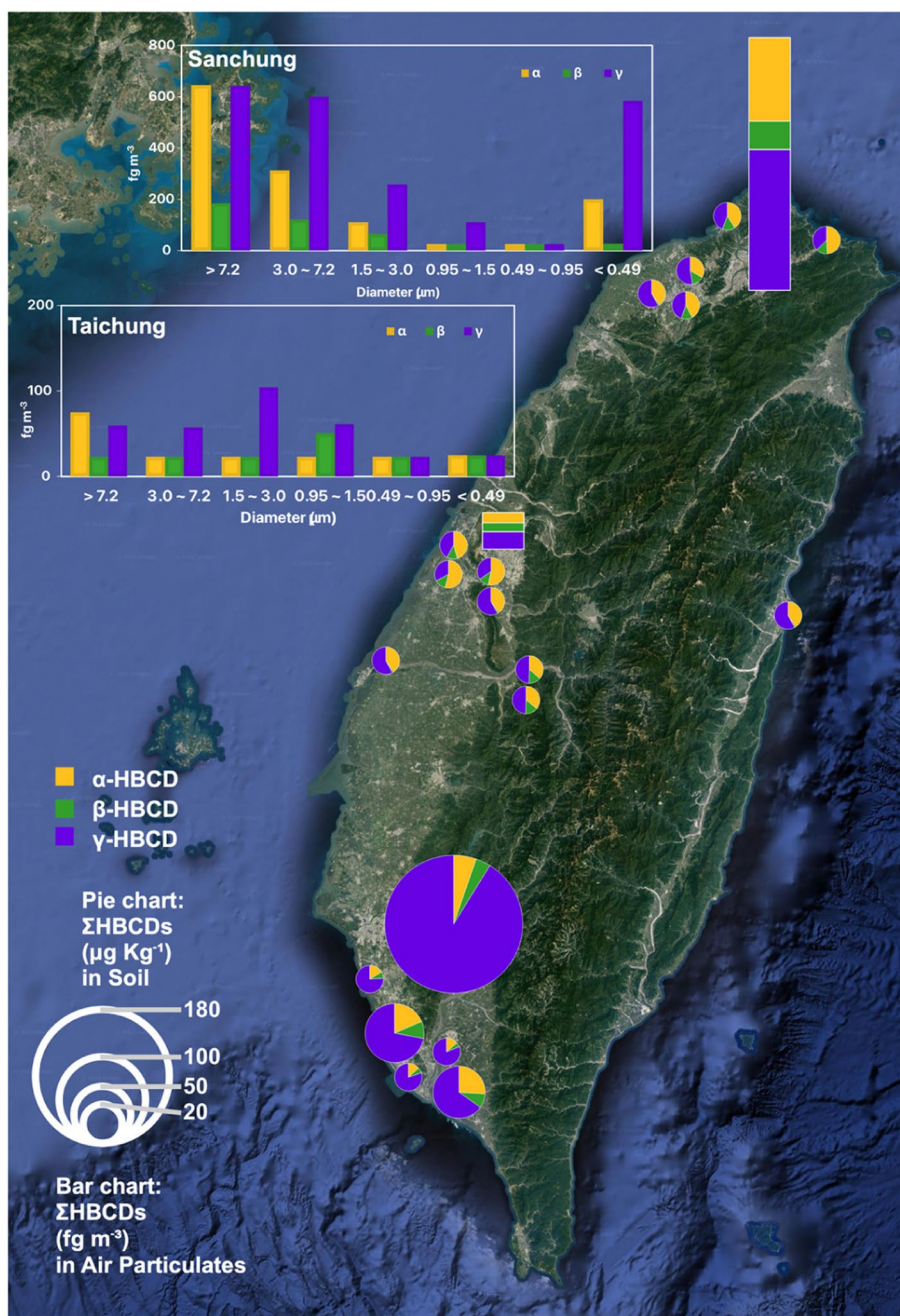
Fig. 2 The average concentrations of HBCDs in soil (pie) and the average concentrations of HBCDs (histogram)

concentrations of HBCDs in soil samples were increased with decreasing distance from the extruded polystyrene-producing plant, and the HBCD concentrations ranged from 140 to 1300 μg kg^{-1} [10]. The soil samples collected near China's largest HBCDs manufacturing factory were 11,700 μg kg^{-1} [5]. In a Korean study, the concentrations of HBCDs ranged from 0.95 to 27.35 μg kg^{-1}, with a median value of 2.18 μg kg^{-1}. Table 1 shows that the five soil

samples in grassland with higher HBCDs were obtained from samples near polystyrene-producing plants in southern Taiwan, and other samples collected from sites near car tyre, PVC, Nylon and carrier tape plants which also produced plastic products were almost had the similar HBCD level as ones collected from sites without factory nearby. These results suggested that the environmental HBCDs primarily originated from industrial emissions
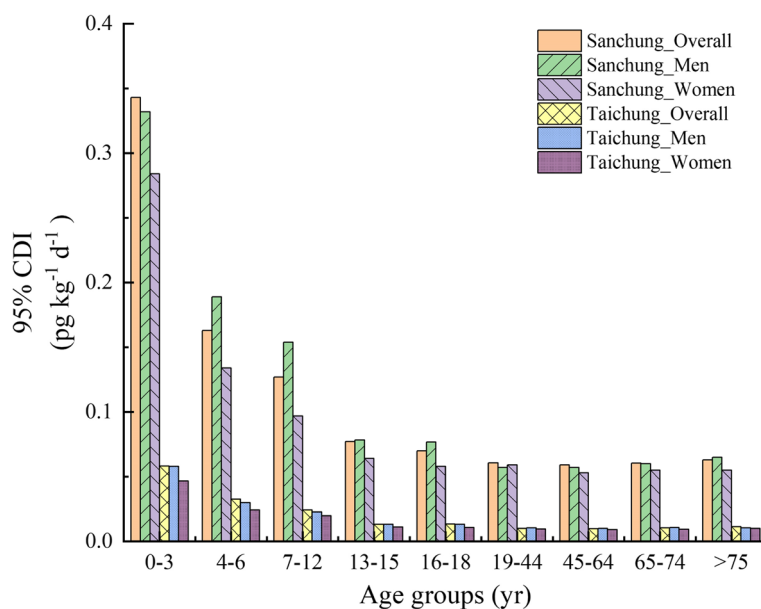
Table 2 Concentrations of HBCD (pg m⁻³) and proportions of isomers (%) in particulate samples

	March 22, 12:00 p.m. to March 24, 12:00 p.m				March 24, 1:00 p.m. to March 26, 1:00 p.m				March 26, 2:00 p.m. to March 28, 2:00 p.m			
Sanchung	α	β	γ	ΣHBCD	α	β	γ	ΣHBCD	α	β	γ	ΣHBCD
> 7.2 μm	34.2	13.8	52.0	2.2	52.0	8.7	39.3	1.1	55.0	13.6	31.4	1.1
3.0 − 7.2 μm	29.0	11.8	59.2	2.6	40.1	-	59.9	0.4	-	-	-	N.D
1.5 − 3.0 μm	24.5	12.2	63.3	1.1	-	-	-	N.D	-	-	-	N.D
0.95 − 1.5 μm	-	-	100.0	0.3	-	-	-	N.D	-	-	-	N.D
0.49 − 0.95 μm	-	-	-	N.D	-	-	-	N.D	-	-	-	N.D
< 0.49 μm	39.3	-	60.7	0.3	52.4	-	47.6	0.5	12.9	-	87.1	1.5
Sum	29.3	11.5	59.3	6.6	49.8	4.7	45.5	2.0	30.8	5.8	63.3	2.6
Taichung	α	β	γ	ΣHBCD	α	β	γ	ΣHBCD	α	β	γ	ΣHBCD
> 7.2 μm	-	-	100.0	0.1	-	-	-	N.D	100.0	-	-	0.2
3.0 − 7.2 μm	-	-	-	N.D	-	-	100.0	0.1	-	-	-	N.D
1.5 − 3.0 μm	-	-	100.0	0.3	-	-	-	N.D	-	-	-	N.D
0.95 − 1.5 μm	-	43.4	56.6	0.2	-	-	-	N.D	-	-	-	N.D
0.49 − 0.95 μm	-	-	-	N.D	-	-	-	N.D	-	-	-	N.D
< 0.49 μm	-	-	-	N.D	-	-	-	N.D	-	-	-	N.D
Sum	16.4	-	83.6	0.6	-	-	100.0	0.1	100.0	-	-	0.2

Fig. 3 Chronic daily intake (CDI) of total HBCDs in inhalation pathway

Table 3 Dermal absorbed dose of HBCDs based on the worst case by age groups

95% DAD (pg kg^{-1} d^{-1})	The worst case in this Study (pg kg^{-1} d^{-1})	U.S. EPA (2020) [36] (pg kg^{-1} d^{-1})
0–12	588	1.4–4.6
13–75 up	151	0.18–0.34

and polystyrene products [6]. The isomer distribution of HBCDs can reflect the environmental fate of the assessed sample. The degradation rate of HBCDs may vary because of the isomer conformation and the different affinities for the debrominating enzymes. For example, α-HBCD has two equatorial bromine atoms, and γ-HBCD has two axial bromine atoms. Therefore, dibromoelimination can occur more easily for γ-HBCD than α-HBCD, decreasing γ-HBCD concentrations in biological samples, this phenomena was also reported by others [7–9]. Based on previous reasons, the conformation of HBCDs was a key factor for persistence in organisms and the environment. The negative relationship between the fractions of α-HBCD and γ- HBCD, the higher R^2 (0.8976) and spearman correlation (-0.91, *p*-value < 0.05) supported the conclusions that the degradation rate of γ-HBCD is higher than α-HBCD by biotransformation [7, 9]; and the samples with higher HBCD concentrations (dash circle in Fig. 4) were dumped recently or have continuous inputs, whereas the others with α type dominant (solid circle in Fig. 4) may have been retained in soil for a long time. For the park sample in

Table 4 95% Margin of exposure (MOE) estimation from the three exposure pathways in Taiwan

Inhalation			Dermal		Diet		
Age group	Sanchung	Taichung	Age group	Worst case	Age group	Revised[a]	Origin
0–3	2.0×10^9	1.2×10^{10}	0–12	1.2×10^6	0–3	1.5×10^5	672
4–6	4.2×10^9	2.1×10^{10}			4–6	2.8×10^5	1198
7–12	5.4×10^9	2.9×10^{10}			6–12	3.0×10^5	1294
13–15	8.9×10^9	5.3×10^{10}			12–16	4.6×10^5	1990
16–18	9.8×10^9	5.3×10^{10}	13–>75	4.6×10^6	16–18	5.1×10^5	2209
19–44	1.1×10^{10}	6.9×10^{10}			19–65	5.1×10^5	2239
45–64	1.2×10^{10}	6.9×10^{10}			>65	6.8×10^5	2942
65–74	1.1×10^{10}	6.9×10^{10}					
>75	1.1×10^{10}	6.3×10^{10}					

[a] Re-calculate MOE from C.C. Lee's study, 2019 [29]

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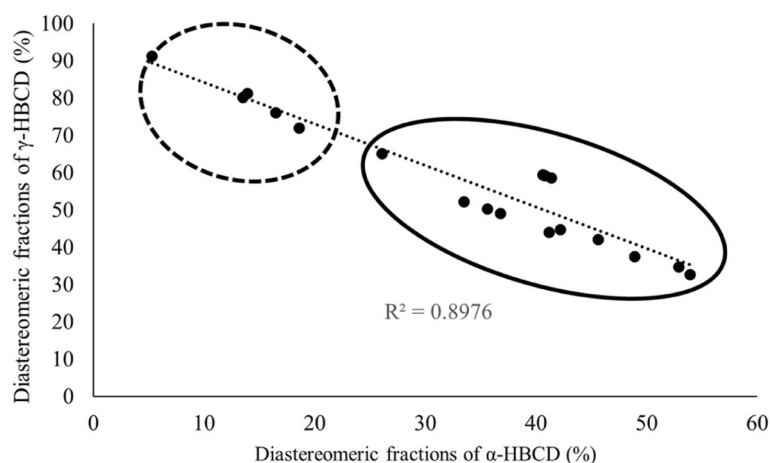**Fig. 4** The relationship between α- and γ-HBCD in soil samples

southern Taiwan, the HBCD concentrations were slightly higher (2.5 μg kg^{-1}) than those samples collected from non-polystyrene plant sites (0.63 to 1.37 μg kg^{-1}). Moreover, the proportion of γ-HBCD was 65%, it implied that HBCDs in this park were newly imported. We found the distance between the park and the highest concentrations of sampling site (187 μg kg^{-1}) was around 400 m, indicating that the soil in this park could be contaminated from this plant via air deposition.

4.2 Comparison and characteristics of HBCDs in particulate matter samples

Several studies showed that the HBCDs are major in particle phase during gas-particle partition [11]. In this study, we focused on the HBCDs analysis in particulate matter. Our data showed similar concentration ranges with those reported in US (0.16 to 11 pg m^{-3}) [12], Sweden (N.D. to 0.54 pg m^{-3}) [10] and Canada (N.D. to 4.69 pg m^{-3}) [13] but was lower than Czech (6.2 to 53.2 pg m^{-3}) [19], UK (mean value of 100 pg m^{-3}) [14] and China (8.69 to 85.3 pg m^{-3})]. In a study from the UK [15], concentrations of HBCDs near the city centre were slightly higher than those collected at other sites. However, a study from Czech indicated that the abundance of HBCDs in rural sites was higher than in urban sites [19]. Results from both studies elucidated that sampling sites near buildings can have higher concentrations of HBCDs, so the surrounding environmental conditions around the sampling site could be one of the crucial factors affecting the abundance of HBCDs. Compared with the sampling site in Taichung, the sampling site in Sanchung was closer to the city centre and crowded buildings and higher concentrations of HBCDs were detected. Wet deposition can scavenge pollutants adsorbed on particulate matters or in the gas phase [14]. Hence, HBCD concentrations dropped drastically between the first and the second period because of the precipitation before the second period (Precipitation in Sanchung and in Taichung is shown in Fig. 5, 26 mm and 22 mm of precipitation in the first period, and 0 mm and 0.5 mm of precipitation in the combining second and third period). Lower elevated HBCDs between the second and the third period may result from the stable atmospheric condition (the average wind speed in the third period was 1 m s^{-1} in Sanchung and 2 m s^{-1} in Taichung).

We observe the variation of concentrations in size-segregated particles. Larger than 1.5 μm particles with HBCDs dominated in two sites and the concentrations in Sanchung was higher than in Taichung. In this fraction, particles could be formed during grinding. Due to the heavy automobile transportation near the sampling site in Sanchung, abrasion from vehicle tires may contribute to the rubber particles and microplastics on the road. The γ-HBCD with the highest concentrations in the first sampling period dominants in all size-segregated particles, it implies the original products were broken into small particles during mechanic process on the road surface. It also implies that microplastics may exist in the atmospheric environment.

HBCDs can induce reactive oxygen species (ROS) production when they enter circulation and the mitochondrial pathway [38, 39]. Particulate matter with diameters less than 2.5 μm can enter the respiratory tract and probably reach the alveoli. In addition, the overall high surface area of the fine particles may cause greater delivery doses of HBCD compared to the particles with larger sizes. The internal doses of inhaled chemicals vary based on different physical and chemical
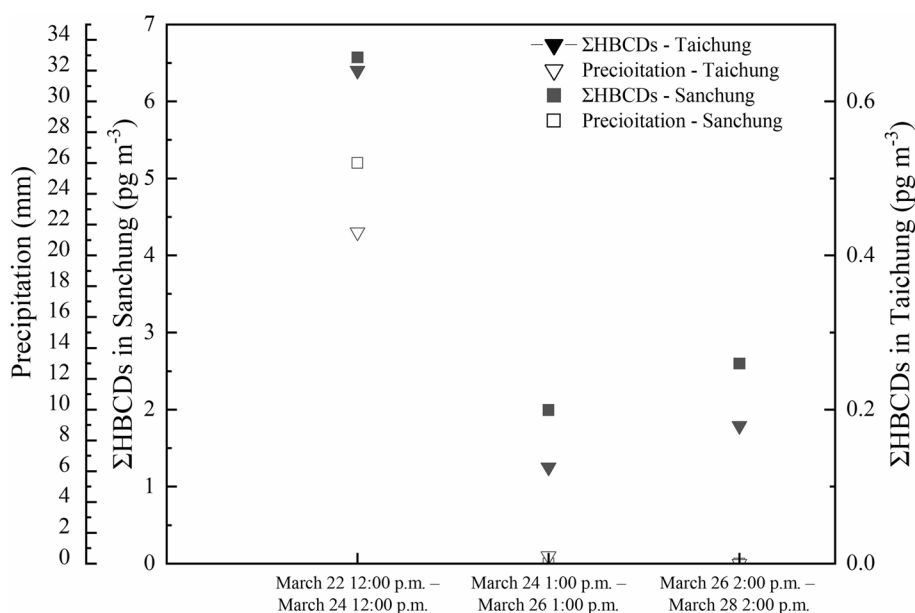
Fig. 5 Concentrations of HBCDs and the precipitation in both sampling sites

properties, such as solubility, log K_{ow}, and partition coefficient between particle and respiratory tract. The combination of the fine particles and POPs is likely to develop synergistic effects [30], which raise health concerns for humans in general.

4.3 Health risk from exposure risk to HBCDs through three pathways in Taiwan

We assumed that all exposure parameters were the same between the two cities. The higher CDI in Sanchung can be expected in the inhalation pathway due to its higher concentrations of HBCDs. Interestingly, males had a greater CDI than females, which probably resulted from the greater exposure time in males. The relatively high exposure and health risk in infants and toddlers were likely due to the lower BW compared to age groups.

For the dermal exposure pathway, the $DAD_{soil-dermal}$ value reported in this study was relatively higher than those in the U.S. EPA report [37], as the worst-case concentration estimate of 187 μg kg^{-1} was used in this study (Table 3). U.S. EPA reported the central tendency of 1.4×10^{-3} μg kg^{-1} and the high-end estimate of 3.0×10^{-3} μg kg^{-1} for the HBCD concentration in soil samples. Using the worst-case concentration estimate for risk evaluation would potentially overestimate the HBCD-induced health risk via the dermal route. The ingestion route is the most crucial, while the inhalation and dermal pathways are less critical for HBCD exposures. The high lipophilicity leads to the ubiquitous

presence of HBCDs in different food matrices, such as oils, fish, and baby food [25]. Regardless of the exposure routes, children tend to receive greater HBCD exposure because of their relatively low BW. HBCDs can affect multiple organ systems, including liver, endocrinological, and developmental systems. Therefore, selecting the most appropriate POD values is crucial to the risk assessment of HBCD. The European Food Safety Authority derived the reference dose (RfD) of HBCDs from a LOAEL of 0.9 mg kg^{-1} d^{-1} and an additional uncertainty factor of 3 to extrapolate from LOAEL to non-observed NOAEL, and an absorption efficiency of 83% in mice with the worst-case estimate in the half-life of 219 days, leading to a RfD of 0.003 mg kg^{-1} d^{-1} [2]. However, LOAEL may underestimate the real POD values, where the benchmark dose approach has been preferred for performing the dose–response assessment in the past decades [36]. In this study, the HED of the POD associated with a 10% extra risk of inducing an effect on primordial follicles in F1 adult rats (0.689 mg kg^{-1} d^{-1}) was used for MOE calculation [29, 37]. Infants, toddlers, and children remain the most susceptible population because of the low BW and monotonous food consumption (e.g., baby food). The primary exposure pathway was oral ingestion via diet (from 79.4 to 90.5% among age groups), followed by dermal exposure (from 9.1 to 20.1% among age groups), and inhalation exposure (from 0.4 to 0.7% among age groups) (Fig. 6). These data were similar to those reported in Fromme's literature review [19].
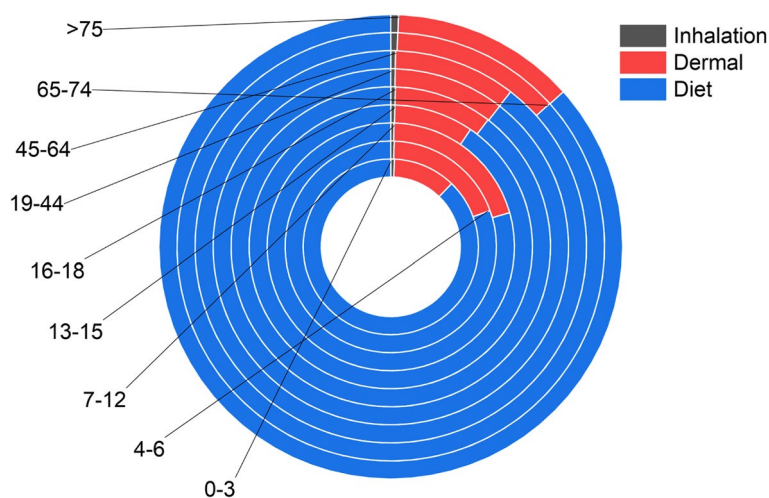
Fig. 6 Doughnut plot for the proportion of three exposure pathways across age groups (Unit: yr)

4.4 Limitation

We note that this study has some limitations. First, the results of soil and particulate matter samples are difficult to compare due to the different sampling locations. A synchronized sampling plan would result in a more relevant comparison between soil and particulate matter samples. Second, the emission profile of adjacent industrial plants is scarce. Therefore, we could not verify the postulated pollution sources solely based on the data from this study. Additional environmental monitoring in adjacent plastics plants and discharge pipes may construct the exposure scenario from the source to receptors. Third, seasonal effects could significantly affect inhalation exposure to HBCD. Meteorological factors such as temperature, wind direction, and humidity are varied with seasonal change, and these factors could influence the exposure routes for residents. Finally, this study only reported the outdoor concentrations of HBCD. The indoor exposure to HBCD remains unclear. Using outdoor HBCD concentrations for the overall exposure assessment is likely to underestimate the inhalation exposure, as the indoor HBCD concentrations may be greater than the outdoor concentrations [10, 16]. These limitations notwithstanding, we present a comprehensive risk assessment of HBCD from three major exposure pathways for the general population. The potential health concern of HBCDs with sub-micrometer particulate matters is highlighted, and more studies are warranted to fill this critical knowledge gap for a refined risk assessment of HBCDs.

5 Conclusions

We found that the higher concentrations of HBCD in soil were near polystyrene production plants, revealing that HBCDs could be spilled from specific plants and contaminated adjacent areas. HBCDs were also found in particulate matter, especially in the sub-micrometer particles with busy transportation, which may exacerbate the HBCD-induced effects in respiratory systems. Evaluating the risk from three exposure pathways, the diet was significant for HBCD. Our assessment indicates a lower risk of gross HBCD exposure in the general population.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s42834-023-00172-z.

Additional file 1: Table S1. Gradient elution for HBCD isomers analysis. **Table S2.** Detailed multiple reaction monitoring (MRM) parameter for HBCD isomers analysis. **Fig. S1.** Air sampler working in situ (a) Sanchung (b) Taichung. **Fig. S2.** Chromatograms for blank sample (a) full chromatograms (b) α-HBCD (c) β-HBCD (d) γ-HBCD.

Authors' contributions
Shih-Lin Lo provided conceptualization, validation, formal analysis and writing—original draft. Ren-Der Wang provided methodology. Yi-Ju Chen provided data curation. Yuan-Cheng Hsu provided supervision and project administration. Yu-Syuan Luo provided visualization, writing—review & editing. Gen-Shuh Wang provided writing—review & editing. All authors read and approved the final manuscript.

Availability of data and materials
All data analyzed during this study are available from the corresponding author upon reasonable request.

Declarations

Competing interests
The authors declare they have no competing interests.

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