Assessment of the occupational and environmental risks of hexabromocyclododecane (HBCD) in China

Shan Yi^{a, b}, Jian-Guo Liu^{a, *}, Jun Jin^c, Jing Zhu^a

^a State Key Joint Laboratory for Environmental Simulation and Pollution Control, College of Environmental Sciences and Engineering, Peking University, 100871 Beijing, China

^b Beijing Tongzhou District Environmental Protection Bureau, 101100 Beijing, China

^c College of Life and Environmental Sciences, Minzu University of China, 100081 Beijing, China

Abstract: In 2013, hexabromocyclododecane (HBCD) was listed in the Stockholm Convention on Persistent Organic Pollutants obligated to be phased out worldwide. China is a major producer and user of HBCD. Based on Chinese HBCD production and processing conditions, we classified the existing 599 HBCD production and processing plants into six occupational exposure scenarios. We also used occupational environmental monitoring and occupational health risk assessment models to estimate exposure levels. Occupational internal exposure levels for HBCD in China were estimated to range from 0.61 to 840 g·kg⁻¹·d⁻¹, which suggests that approximately 453–840 workers, or 72% of all workers in this industry, may have occupational exposure risk. As such, the occupational risks of HBCD should not be ignored. In our study area, HPLC-MS/MS revealed HBCD concentrations ranging from 0.11 to 560 ng g dry weight (dw)⁻¹, 20.4 to 24.2 ng g dw⁻¹, and 166 to 1964 ng g lipid weight (lw)⁻¹ in soil, sediment, and biological samples, respectively, consistent with previous monitoring results. These data suggest potential risk to marine environments due to sustained and large-scale HBCD production and processing. Thus, timely measures to control HBCD-related risk are necessary and may bring significant occupational health and environmental benefits in areas where HBCD is prevalent.

Key words: Hexabromocyclododecane (HBCD), Exposure simulation, Occupational risk, Environmental risk, HPLC-MS/MS

1. Introduction

Hexabromocyclododecane (HBCD) is the world's third most prominent brominated flame retardant, second only to decabromodiphenyl ether (decaBDE) and tetrabromobisphenol A (TBBPA) (Zegers et al., 2005). HBCD is mainly used in exterior building insulation materials, such as expanded polystyrene (EPS) and extruded polystyrene (XPS), and is also added into electrical equipment, high impact polystyrene (HIPS), and textile coatings (POPRC, 2011). A series of studies have shown that HBCD is environmentally persistent, bioaccumulates, and induces reproductive, liver, and thyroid toxicity (Ema et al., 2008; Eriksson et al., 2006; Van der Ven et al., 2006, 2009). Thus, HBCD was listed in the Stockholm Convention on Persistent Organic Pollutants in 2013, with the intention of eliminating its use worldwide. Existing risk assessments indicate that HBCD risk exists primarily in occupational settings, occurring during the production of HBCD and flame-retarded EPS and XPS (Environment Canada and Health Canada, 2013; Managaki et al., 2009; NICNAS, 2011; Swedish Chemicals Agency, 2008; US EPA, 2013). One hour of occupational HBCD exposure is equivalent to that experienced by the general population over a period of 1–3 months (Kuo et al., 2014; Zhang et al., 2012). In addition, higher HBCD concentrations are observed in the areas surrounding HBCD production and processing plants, which may result in local environmental risks (Rememger et al., 2004; van der Ven et al., 2006).

Based on industry surveys, there are 14 HBCD production plants and approximately 65 EPS and 520 XPS plants (BIT, 2011; Wang et al., 2011; Zhang and Li, 2005), and China is the world's largest producer and user of HBCD. Furthermore, due to the recent implementation of improved energy efficiency and fire safety standards in China, the production and use of HBCD in China continues to grow. However, there is a lack of long-term occupational and environmental risk assessment for HBCD in China.

In this study, we constructed occupational exposure scenarios using survey data describing HBCD production and processing in China, along with environmental monitoring data from areas surrounding factories and risk assessment modeling. This

is the first study using such an approach to assess occupational and environmental HBCD risks in China. As such, the data provided here may serve as a baseline for policy makers in China seeking to comply with the Stockholm Convention recommendations and make related decisions on HBCD production and use, thereby contributing to global HBCD risk control.

2. Methods

2.1 Sampling and monitoring methods

In this study, HBCD-related production and processing plants and their surrounding areas were included in the study area. These sites were primarily located in Weifang City, Shandong Province. Samples were collected in September 2013 and May 2014 at the sites shown in Figure 1. The total number of samples included 16 air particulate samples collected inside factories, 25 surface soil samples, and 2 sediment samples. We also bought or collected biological samples from a number of organisms found in the local environment, including *Macra veneriformis*, short-necked clam (*Ruditapes philippinarum*), mantis shrimp (*Oratosquilla oratoria*), Japanese sea bass (*Lateolabrax japonicus*) and eggs.

Air particulate samples were collected at HBCD production and processing plants using quartz fiber filters and air samplers. Soil samples were collected from topsoil (0–5 cm) and then quartered, from this procedure approximately 50 g of soil were retained. Sediment samples, due to the environmental conditions of the study area, were collected from surface marine sediments (0–5 cm) at low tide; approximately 100 g of sediment were retained. Biological samples consisted of a mixed sample of the edible portions of the organism and weighed approximately 50 g. All samples were placed in a portable refrigerator at –4°C for transport to the laboratory.

After pre-treatment (described in Supporting Information), samples were spiked with 20 ng of $^{13}\text{C}_{12}$ - α -HBCD (Cambridge Isotope Laboratories, USA) as an internal standard and extracted using a Soxhlet extraction (300 mL of *n*-hexane and acetone mixed at a ratio of 1:1, volume/volume [v/v]) for air particulate and biological samples and an accelerated solvent extractor (ASE 300, Dionex, USA; *n*-hexane

and acetone mixed at a ratio of 3:1, v/v) for soil and sediment samples. Extracts were then purified via chromatography using a silica gel column composed of the following (bottom to top): 6 g neutral silica gel, 3 g acidic silica gel (44%), and 3 g anhydrous sodium sulfate. The samples were then concentrated to 100 L by rotary evaporation under a nitrogen atmosphere and stored for further analysis.

In the next step, samples were analyzed via high-performance liquid chromatography (HPLC) using an Agilent 1200 series liquid chromatograph (Agilent Technologies, Palo Alto, CA, USA) with an octadecylsilyl (ODS or C₁₈) column (5 m, 4.6 mm i.d. × 150 mm L., Shimadzu, Japan), coupled to an Agilent XL triple quadrupole mass spectrometer (MS/MS, Agilent Technologies) in negative electrospray ionization mode. The mobile phase during HPLC consisted of a solution of methanol/acetonitrile/water (80%:4%:16%, v/v/v; see Supplementary Information).

Three parallel blank samples were matrix spiked with α -, β -, γ -HBCD (Cambridge Isotope Laboratories, USA) at 100 ng/g. The recoveries of these three isomers and Σ HBCD were $113 \pm 1.7\%$, $103 \pm 3.8\%$, $104 \pm 3.4\%$, and $105 \pm 3.7\%$, respectively, while the relative standard deviations (RSD) of these samples were less than 25%, which satisfied the requirements of quantitative analysis. Native HBCD standard mixtures at five concentration levels were used to obtain a calibration curve. During analysis, a procedural blank (anhydrous Na₂SO₄) and a quality control standard were run every five samples. Method detection limits were defined as signal to noise(S/N)=3/1 in procedural blanks, which for the three isomers were 0.2 ng g⁻¹, 0.5 ng g⁻¹, and 0.1 ng g⁻¹ respectively. A quantitative standard curve of five known concentrations was plotted every 20 samples. The RSD of repeated analyses of the same samples (n = 3 replicates each) ranged from 0.81–7.21%, which satisfied the requirements of quantitative analysis. All isomers were baseline separated, and HBCD in all blank samples was below the limit of detection.

2.2 Construction of occupational exposure scenarios

Occupational exposure to HBCD occurs primarily in the packaging sector, after the

finished product dries, as well as the point at which HBCD is fed into the production of flame-retarded EPS, XPS and XPS masterbatch. Based on the scale of HBCD production and typical working conditions in China, the HBCD production and processing plants were classified into six occupational exposure scenarios (Table 1).

2.3 Occupational exposure assessment

Chemical exposure assessments are usually approached in one of two ways. The first approach is to use environmental monitoring data to calculate emission loads or concentrations of harmful substances. The second approach involves the use of specific occupational exposure assessment modeling tools (Zhang et al., 2012).

a) Calculating internal exposure due to inhalation

Occupational HBCD inhalation exposure was calculated based on monitoring data for HBCD particles detected in representative workshops, as shown in Formula 1:

$$IEL_I (\text{g kg}^{-1} \text{d}^{-1}) = (C \times V \times t) / BW \quad (1),$$

where, IEL_I = internal exposure level due to inhalation ($\text{g kg}^{-1} \text{d}^{-1}$); C = concentration of HBCD in the particle phase of air samples collected in the workshop ($\mu\text{g m}^{-3}$), based on the assumption that 100% of particles collected could be absorbed via inhalation due to their small size ($\leq \text{PM}_{10}$); V = individual breathing rate ($\text{m}^3 \text{h}^{-1}$); t = exposure time in the workplace (h d^{-1}); BW = average body weight of workers (kg).

b) Calculating internal exposure due to dermal absorption

A widely used occupational risk assessment model, the Estimation and Assessment of Substance Exposure (EASE) model, was selected to assess occupational dermal exposure to HBCD in China. The EASE model relies on a database consisting of process research and monitoring data. It can be used to estimate occupational dermal exposure levels for specific substances using basic physical properties, operating conditions, protective measures, and other information on the substance.

The dermal absorption of HBCD varies as a function of particle size. For granular HBCD (particle size, 650–2400 µm), dermal absorption is assumed to be approximately 2% for workers. For powdered HBCD (particle size, ≤ 150 µm), dermal absorption is approximately 4% (Roper et al., 2007). Dermal exposure levels were estimated as described in Formula 2:

$$IEL_D \text{ (mg kg}^{-1} \text{ d}^{-1}\text{)} = (C_{\text{dermal}} \times A \times IE_D) / BW \quad (2),$$

where IEL_D = internal exposure level due to dermal absorption ($\text{mg kg}^{-1} \text{ d}^{-1}$); C_{dermal} = dermal concentration of HBCD estimated using the EASE model (mg cm^{-2}); A = dermal area potentially in daily contact with HBCD ($\text{cm}^2 \text{ d}^{-1}$); IE_D = the weighted internal exposure proportion via dermal exposure.

c) **Characterizing occupational risk**

Given the lack of toxicological test data for HBCD on human health, the margin of safety (MOS), a non-threshold-based parameter, was chosen to characterize HBCD risk (Swedish Chemicals Agency, 2008). The MOS describes the relationship between a selected reference or exposure dose and the degree of absorption or internal exposure to the toxicant. The MOS is calculated as shown in Formula 3:

$$MOS = POD / IEL \quad (3),$$

where, POD = point of departure for a given toxicity parameter, which can be represented by a number of effect measures, including the median lethal dose (LD_{50}), the no observed adverse effect level (NOAEL), the lowest observed adverse effect level (LOAEL), the benchmark dose level (BMDL), or other toxicity parameters; IEL = internal exposure level for HBCD. The reference MOS (RMOS) is the inherent degree of uncertainty for existing data in specific areas extrapolated to the overall situation. When comparing MOS with RMOS, ratios < 1 indicate that the substance in question poses a risk for a given toxicity parameter that subsequently needs to be managed and controlled. Ratios > 1 indicate that the risk is acceptable.

Based on previous toxicity studies of HBCD, four toxicity parameters—repeated dose toxicity, reproductive toxicity, developmental neurotoxicity, and the risk of reduced bone mineral density in female offspring—were examined (see Supporting Information).

2.4 Environmental risk assessment

The environmental risk of HBCD exposure was characterized using the hazard quotient (HQ) method (Zhang et al., 2014), which was calculated as shown in Formula 4:

$$HQ = EEC/PNEC \quad (4)$$

where, EEC = estimated environmental concentration (mg kg dry weight [dw]⁻¹); PNEC = predicted no effect concentration (mg kg dw⁻¹). An HQ value > 1 indicates elevated risk due to HBCD exposure. Previous studies have reported that the PNEC for HBCD is 5.9 mg kg dw⁻¹ in soil and 0.17 mg kg dw⁻¹ in marine sediments (Betrò et al., 2011; Swedish Chemicals Agency, 2008).

3. Results and Discussion

3.1 Occupational risk

Drawing from the literature and field research, 599 plants were included in the six occupational exposure scenarios, and the total number of workers potentially exposed to HBCD ranged from 614–1213 individuals (Table 1).

Based on samples collected using personal samplers at representative workshops for each of the six exposure scenarios, the range of HBCD concentrations detected in workshop air was 3.72–35.5 µg m⁻³ (ranges of α-HBCD, β-HBCD, γ-HBCD were 1.11–7.94 µg m⁻³, 0.40–4.13 µg m⁻³, and 2.03–35.5 µg m⁻³, respectively). IEL_I values for workers inhaling HBCD in workshop air ranged from 0.61–6.09 µg kg bw⁻¹ d⁻¹. In contrast, IEL_I values for the general population were approximately 93.2 pg kg bw⁻¹ d⁻¹ in a previous study (Ni and Zeng, 2013), representing a difference of approximately 5–6 orders of magnitude.

Based on a worst-case scenario, the area of skin exposed to HBCD was assumed to be 2020 cm². Considering HBCD particle emissions observed during actual HBCD

production in a Chinese facility, the weighted exposure ratio for HBCD was calculated to be 0.58%. Concentrations of HBCD exposure via dermal absorption, as estimated by the EASE model, ranged from 0–0.84 mg kg bw⁻¹ d⁻¹.

Overall, total HBCD internal exposure levels for Chinese workers ranged from 0.61–840 µg kg bw⁻¹ d⁻¹ (Table 2). Internal exposure levels under scenario I were the highest, whereas those under exposure scenarios II–IV were fairly moderate, and those under exposure scenarios V and VI were minimal. Compared to HBCD exposure levels among the general population (0.05–81 ng d⁻¹; Hong et al., 2013; Knutsen et al., 2008; Roosens et al., 2009), the values obtained in the present study in an occupational setting were 5–7 orders of magnitude higher.

For each of the toxicity parameters, occupational risk differed according to the exposure scenario (Figure 2). For the risk of repeated dose toxicity, MOS/RMOS ratios were > 1 for all exposure scenarios. For reproductive risk, MOS/RMOS ratios were < 1 only under the most severe occupational exposure scenario (scenario I) and > 1 for scenarios II–VI. For the risk of developmental neurotoxicity, MOS/RMOS ratios were < 1 under scenario I and slightly less than 1 for scenarios II–IV. Finally, for the risk of reduced bone mineral density in female offspring, MOS/RMOS ratios were < 1 for all six occupational exposure scenarios, although these ratios were only marginally < 1 for exposure scenarios V and VI.

Assuming that the distribution of workers fit a normal distribution, workers exposed to HBCD in this Chinese setting had no significant risk of repeated dose toxicity, whereas approximately 9–11 workers, accounting for 0.90–1.34% of all workers, might encounter reproductive toxicity risk. Similarly, approximately 117–226 workers, accounting for 18.6–19.1% of all workers, might carry risk of developmental neurotoxicity, and 453–840 workers, accounting for 69.2–73.6% of all workers, might carry a risk of reduced bone mineral density in female offspring. There were some uncertainties in the occupational risk assessment, which were mainly due to scenario uncertainty, model uncertainty, and parameter uncertainty.

3.2 Local environmental risk

In this study, 17 soil samples (SS1–SS17) were collected on-site at HBCD production and processing plants, and concentrations ranged from 96.1–560.4 ng g dw⁻¹ (ranges of α -HBCD, β -HBCD, γ -HBCD were 17.1–129 ng g dw⁻¹, 7.50–34.9 ng g dw⁻¹, and 70.3–397 ng g dw⁻¹, respectively) (see Supporting Information). Although HBCD concentrations decreased with increasing distance from the workshop, no significant correlation was observed between HBCD concentration and distance. HBCD concentrations in soil samples from the study area (Figure 3) were comparable to those detected at other domestic industrial sites, but were 1–2 orders of magnitude lower than those previously observed in overseas production and processing plants (Jin et al., 2009; Petersen et al., 2004; Remberger et al., 2004; Tang et al., 2014; Zhu et al., 2014).

In addition to the on-site soil samples, eight samples (SS18–SS25) were collected at distances of 3, 5, 6, 7, 10, and 30 km from the workshops. Off-site soil concentrations ranged from 0.11–31.1 ng g dw⁻¹ (ranges of α -HBCD, β -HBCD, γ -HBCD were 0.02–5.59 ng g dw⁻¹, 0.01–4.34 ng g dw⁻¹, and 0.08–21.2 ng g dw⁻¹, respectively). At a distance of ≥ 5 km, off-site soil concentrations were < 10 ng g dw⁻¹, which are comparable to those reported in previous non-point source studies of HBCD contamination, meaning that the soil environment had not been directly impacted by the production and processing of HBCD (Covaci et al., 2009; Eguchi et al., 2009; Gao et al., 2011; Heeb et al., 2005; Ilyas et al., 2011; Song et al., 2012). The proportions of each of the three HBCD isomers in soil samples were comparable to those observed in industrial products, and also comparable to those observed in previous domestic and international studies (see Supporting Information) (Eguchi et al., 2013; Li et al., 2012; Meng et al., 2011; Tang et al., 2014).

In the marine sediment samples, HBCD concentrations ranged from 20.4–24.2 ng g dw⁻¹ (ranges of α -HBCD, β -HBCD, γ -HBCD were 3.37–4.35 ng g dw⁻¹, 2.10–2.30 ng g dw⁻¹, and 14.7–17.7 ng g dw⁻¹, respectively). These data were consistent with values observed in both domestic and European waters, but higher than those observed in North America and Japan (Figure 4; Drage et al., 2015; Harrad et al., 2009; Letcher et al., 2009; Minh et al., 2007; Verslycke et al., 2005; Yang et al., 2012). In this study,

the most prevalent isomer in sediments was γ -HBCD, accounting for more than 70% of total HBCD. This amount was similar to the proportion of γ -HBCD in industrial products and the values were consistent with the findings of previous studies examining domestic industrial plants, whereas values observed in foreign studies were lower (see Supporting Information). These data indicated that the study area was affected by HBCD production and processing activities, and that the rate of contamination exceeded the rate of HBCD degradation, migration, or conversion, leading to accumulation in the environment (Feng et al., 2012; Guardia et al., 2013; Jeong et al., 2014; Klosterhaus et al., 2012; Li et al., 2013; Marvin et al., 2006).

HBCD concentrations in biological samples collected near industrial areas ranged from not detected (NR)–1964 ng g lipid weight (lw)⁻¹ (ranges of α -HBCD, β -HBCD, γ -HBCD were NR–403 ng g lw⁻¹, NR–382 ng g lw⁻¹, and NR–1179 ng g lw⁻¹, respectively) (Figure 5). These values were 1–2 orders of magnitude higher than those observed in other non-point source studies; the data were similar to those observed in foreign industrial studies and slightly higher than data collected in other domestic industrial studies (Schlabach, 2004; Shaw et al., 2009; Takahashi et al., 2010). These data indicated that organisms in the study area had been contaminated by HBCD production and processing activities. Previous studies have suggested that HBCD affects metabolic rates and the capability of organisms to mediate the migration and transformation of pollutants, and it was generally found that α -HBCD levels were greater than those of γ -HBCD (Shaw et al., 2009; Takahashi et al., 2010; Meng et al., 2012; Schechter et al., 2012). However, in the present study, some biological samples showed γ -HBCDs levels greatly in excess of the other two isomers (see Supporting Information), suggesting that some organisms in the study area were contaminated as a result of HBCD production and processing activities and that the rate of contamination exceeded the ability of these organisms to metabolize the pollutant (Jeong et al., 2014; Meng et al., 2012; Schechter et al., 2012; Xian et al., 2008). Human and animal toxicological studies have shown that the toxicity of HBCD isomers decreases in the order of γ -HBCD > β -HBCD > α -HBCD (Swedish Chemicals Agency, 2008). Qualitative analyses examining roughly equivalent HBCD

exposure levels showed that organisms containing more γ -HBCD suffered more severe toxic effects, produced more severe toxic effects in their predators and humans who consumed them, and overall posed a greater ecological risk.

HQs calculated for soil and marine environments in the study area were all < 1 (see Supporting Information), indicating that HBCD levels did not pose a significant risk to soil and marine environments. Despite this, the proportion of γ -HBCD was high in some organisms, which may pose a risk to the marine environment and should be monitored.

4. Conclusion

HBCD concentrations in the particulate fraction of indoor workplace air ranged from 3.72 to 35.5 g m^{-3} . Combined with our simulation generated using the EASE model, occupational internal exposure to HBCD was estimated to be in the range of 0.61–840 $\mu\text{g kg bw}^{-1} \text{d}^{-1}$. Regarding the overall occupational risk posed by HBCD exposure, the number of workers potentially exposed to increased health risks ranged from 453–840 individuals or approximately 72% of all workers in HBCD-related industries in China, indicating that occupational exposure to HBCD may have widespread negative health impacts. The risk of reduced bone mineral density in female offspring was the most significant among the four health risk endpoints.

In environmental samples, HBCD concentrations ranged from 0.11–560 ng g dw^{-1} in soil samples, 20.4–24.2 ng g dw^{-1} in sediment samples, and 166–1964 ng g lw^{-1} in biological samples. Using the HQ method to characterize environmental risk in the study area indicated that HBCD does not pose a significant environmental risk to nearby soil and marine environments. However the high proportion of γ -HBCD may be a sign that HBCD has created a potential threat to marine environments, which might in turn affect human. Our data suggest that improved controls on HBCD production and processing may have significant health benefits and further reduce environmental risk.

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