



# A review of sources, environmental occurrences and human exposure risks of hexachlorobutadiene and its association with some other chlorinated organics<sup>☆</sup>

Haiyan Zhang<sup>a, b</sup>, Yanting Shen<sup>a</sup>, Wencong Liu<sup>a</sup>, Zhiqiao He<sup>a</sup>, Jianjie Fu<sup>c</sup>,  
Zongwei Cai<sup>b, \*</sup>, Guibin Jiang<sup>c</sup>

<sup>a</sup> College of Environment, Zhejiang University of Technology, Hangzhou 310014, China

<sup>b</sup> State Key Laboratory of Environmental and Biological Analysis, Department of Chemistry, Hong Kong Baptist University, Hong Kong, China

<sup>c</sup> State Key Laboratory of Environmental Chemistry and Ecotoxicology, Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences, Beijing 100085, China

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## ABSTRACT

Research on hexachlorobutadiene (HCBD) has increased since its listing in the Stockholm Convention on Persistent Organic Pollutants in 2011. However, thorough reports on recent data regarding this topic are lacking. Moreover, potential associations between HCBD and some chlorinated organics have usually been ignored in previous research. In this review, possible formation pathways and sources, current environmental occurrences and human exposure risks of HCBD are discussed, as well as the association with several organochlorine compounds. The results reveal that unintentional production and emission from industrial activities and waste treatments are the main sources of HCBD. Similar precursors are found for HCBD and chlorobenzenes, indicating the presence of common sources. Although recent data indicates that levels of HCBD in the environment are generally low, risks from human exposure to HCBD, together with other pollutants, may be high. More attention in the future needs to be paid to the mixed contamination of HCBD and other pollutants from common sources.

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## 1. Introduction

Today, a vast number of pollutants are released into the environment, giving rise to adverse effects on the eco-environment and human health. Persistent organic pollutants (POPs) have become one of the major problems and attract global concern due to their persistence, toxicity, bioaccumulation, and long-range transport properties (Wania and MacKay, 1996). In order to control the contamination from POPs, the Stockholm Convention on Persistent Organic Pollutants (SCOPs) has been ratified by 181 countries and one regional economic integration organization (Stockholm Convention, 2019). Hexachlorobutadiene (HCBD) is a man-made chlorohydrocarbon and was proposed as a POPs candidate in 2011. After researching and considering the evidences for its POPs characteristics, HCBD was added as a new controlling POPs to

Annex A (for intentional production control) and Annex C (for unintentional formation and emission control) of the SCOPs in 2015 and 2017, respectively. In recent years, HCBD has received increasing attention.

Some studies on volatile organic compounds (VOCs) or organochlorine compounds have involved HCBD as one of the targets (Fang et al., 2017, 2018; Georgieva et al., 2015; Li et al., 2018; Monclús et al., 2018; van Drooge et al., 2018). It should be noted that HCBD can often be detected alongside several substances such as pentachlorobenzene (PeCB) and hexachlorobenzene (HCB) (Fang et al., 2017, 2018; Zhang et al., 2014). PeCB and HCB are two typical POPs that were also included in Annex A and Annex C of the SCOPs. Apart from the similarity in chemical properties and characteristics, the formation pathways and sources of HCBD may also be similar to these compounds. However, previous reviews have rarely considered the relationship between HCBD and other compounds. Moreover, the last comprehensive reviews concentrating on the sources, occurrences and risks of HCBD in the environment were published more than a decade ago (Euro Chlor, 2002; IPCS, 1994; Lecloux, 2004). Since HCBD was proposed as a

<sup>☆</sup> This paper has been recommended for acceptance by Eddy Y. Zeng.

\* Corresponding author.

E-mail address: [zwcai@hkbu.edu.hk](mailto:zwcai@hkbu.edu.hk) (Z. Cai).

POPs candidate and became a contentious issue, HCBd has been monitored and the data continuously updated. Timely summary on recent data regarding this substance should be provided.

In this review, we discussed the formation pathways and sources and investigated environmental incidents and human exposure risks of HCBd in details. The possible association between HCBd and other chlorinated compounds were also included with the following goals: (1) to explore the common sources; (2) to gain a clearer understanding of general levels of HCBd contamination; (3) to recognize the regions to be further investigated.

## 2. Formation pathways and possible sources

### 2.1. Formation pathways

In the past, HCBd was prepared by the chlorination and dehydro-chlorination of hexachlorobutene, and the chlorination of hexyl iodide, polychlorobutanes, or butadiene (HSDB, 2001; IPCS, 1994). Besides, it can be unintentionally produced in lots of processes such as the manufacture of chlorinated solvents. Under appropriate conditions, many hydrocarbons can lead to the generation of HCBd as well as chlorobenzenes (CBs) and polychlorinated dibenzo-*p*-dioxin and dibenzofuran (PCDD/Fs) via a series of chlorination, oxidation, and polymerization reactions. Three possible pathways for HCBd formation from hydrocarbons are summarized in Fig. 1 (i, ii, and iii), where  $C_2/C_4$  olefin and aetylenes are likely to be the important intermediates (Heindl and Hutzinger, 1987; Sherry et al., 2018; Tirey et al., 1990; Wehrmeier et al., 1998; Zhang et al., 2018b). HCBd yields from these pathways depend on the temperatures of reactions, the amounts of chlorine sources, the addition of metal catalysts and so on.

- (i) Chloromethanes are conventionally produced by hydrochlorinating methanol with HCl in industrial processes, and carbon tetrachloride ( $CCl_4$ ) can be generated after subsequent chlorination reactions. Then tetrachloroethylene ( $C_2Cl_4$ ) could be generated through the co-reaction of  $CCl_4$ , methane and chlorine. The trichlorovinyl radical ( $C_2Cl_3$ ) resulting from the rupture of carbon-chlorine (C–Cl) bond of  $C_2Cl_4$  may react with another  $C_2Cl_4$  to form HCBd through converted Cl displacement from the chemically activated adduct at 750–900 °C. The yield of HCBd from  $C_2Cl_4$  reached the highest level (0.07 mol %) at 850 °C.
- (ii) Acetylene or trichloroethylene can be converted to dichloroacetylene ( $C_2Cl_2$ ) via chlorination or HCl-elimination. Dimerization of  $C_2Cl_2$  will lead to form metalacyclic intermediate in the presence of metal catalysts. Chlorinated metallacyclopentadiene would be converted to HCBd and HCB via oxidative chlorination action with  $CuCl_2$  or an insertion of  $C_2Cl_2$ . The addition of HCl and strong metal catalyst such as  $CuCl_2$  could increase the product yields. Maximum product yields were detected at 300 °C. HCB could be also formed from trimerization of  $C_2Cl_2$ . In addition, HCB can be further converted to pentachlorophenolate via a substitution reaction to finally form PCDD.
- (iii) Benzene can likewise convert to HCBd in the presence of  $Cl_2$  and  $O_2$ : (1) H atom of benzene is replaced by O atom under oxygen attack, and then converted to cyclopentadienyl, cyclopentadienonyl and 1,3-butadienyl radicals. Cl radicals can abstract H atoms of 1,3-butadienyl radicals to form HCBd; (2) phenyl is generated from the rupture of C–H bond in benzene, the molecular vacancy of which will be filled by Cl atom to form chlorinated benzene. CBs can be oxidized to chlorophenoxy, which are the precursors of PCDD/Fs. Chlorinated cyclopentadiene might convert to HCBd through

further oxidation. In this pathway, HCBd was detected at 600 °C, whereas no HCBd could be found at higher temperatures (700 °C). In addition to these compounds, some other pollutants such as octachlorostyrene, octachloronaphthalene and polycyclic aromatic hydrocarbons (PAHs) can be simultaneously formed (not shown here).

### 2.2. Possible sources

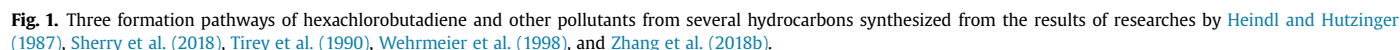
HCBd can be used as scrubbers for removing chlorine containing contaminants from gas streams, hydraulic fluids and lubricants, isolation fluids in electrotechnical practices and heat-transfer liquids. It can also be used for the production of aluminum and graphite rods, and as a solvent for polymers, a heavy diluent for the extractant during spent nuclear fuel reprocessing, a vineyard fumigant, a pesticide and as a herbicide in agricultural activities (Belova et al., 2017; Cristofori et al., 2015; Euro Chlor, 2002; Lava et al., 2014; WWF, 2005). Some applications of HCBd have been stopped because of its ecotoxicity (Euro Chlor, 2002). HCBd has no natural sources. A considerable amount of HCBd was produced as a result of its wide industrial and agricultural application in the 1980s. However, the commercial production of HCBd cannot presently be found in China, the USA, Canada and other United Nations Economic Commission for Europe regions (Wang et al., 2018). Current emissions of HCBd mainly occur during its unintentional production, usage as a by-product, disposal as waste and historical stockpile. Well-known sources are shown below.

#### 2.2.1. Industrial activities

**2.2.1.1. Organochlorine production.** The synthesis of various chlorinated hydrocarbons is usually carried out at high temperatures (Heindl and Hutzinger, 1987) and in some cases metal catalysts are added to promote the reaction at relatively low temperatures (Zhang et al., 2015). This makes the radical reactions for HCBd formation probable. Chlor-alkali plants and other chemical plants producing trichloroethylene (TCE), tetrachloroethylene (TeCE), carbon tetrachloride (CTC), chloromethane, hexachlorocyclopentadiene (HCCP) and/or pesticides such as chlortoluron, are the typical sources of HCBd. The HCBd formed from TCE and TeCE production accounted for 73.0% and 24.5% of the total unintentional production (about 2871.5 metric tons per year) in China in 2016, respectively. It is predicted that the unintentional production of HCBd will increase with the development of the chlorinated hydrocarbon industry in China (Wang et al., 2018). While HCBd emissions from this part decrease with the phase-out or strict control of the manufacture and use of TCE, TeCE and CTC in some other nations (POPRC, 2016).

Parts of these unintentionally produced HCBd may be reused or incinerated and the rest will be directly discharged into the environment. The emission of HCBd from these plants has been confirmed by monitoring the ambient atmosphere and soil (Fang et al., 2018; van Drooge et al., 2018; Zhang et al., 2014).

**2.2.1.2. Other industrial activities.** Magnesium production by electrolysis methodology, cement production, and plastics material and resin production are all considered as potential sources of HCBd. HCBd from these sources is relatively slight. According to a national priority chemicals trends report by the United States Environmental Protection Agency (USEPA, 2010), the percentage of HCBd generated from plastics material and resin manufacturing was only 0.2% in total quantity in 2007, while that from organic chemical manufacturing was 99.8%. Nonetheless, the contributions of various sources to HCBd emission may differ from one country to another, and change with the development of technology.



The re-use of HCBD by-products in downstream industrial plants inevitably gives rise to the emission of portions of HCBD. It is estimated that HCBD emitted from its consumption as solvents in oil paint, waterproof plastic and rubber production, and chemical reagents in laboratories, increased in China from 2004 to 2012 and decreased after 2012, after which time oil-based paint production was the main contributor (Wang et al., 2018). Paper-making processes were also indicated as potential sources of HCBD in China because it was recently detected in wastewater from a pulp and paper factory in Shandong Province (Gong et al., 2017). Some researchers have found that several promising substitutes for ozone depleting substances such as 1,2-dichlorotetrafluorocyclobutene and Z-1,1,1,4,4,4-hexafluoro-2-butene can be synthesized from the catalytic fluorination of HCBD (Zhang et al., 2016; Zhou et al., 2017). The low cost and high efficiency of these synthetic routes and the prospect of the wide application of these substitutes might

High volumes of wastes containing large amounts of HCB and HCB were generated from organochlorine production. For example, approximately 15,000 tons of such waste from Kalush factories in the Ukraine were landfilled in a polygon waste disposal site near Kalush between 1973 and 2001. HCB have been detected in water and soil samples near the site (Lysychenko et al., 2015). Similar

events have occurred in other countries. After the disposal of chemical wastes from chemical plants in Runcorn to two stone quarries near Weston village in England between 1920 and the 1970s, high contaminations of HCBd were discovered in the gases of some bore holes near houses and inside two houses in Weston in 1999–2000 (Barnes et al., 2002).

**2.2.2.2. Wastewater treatment.** Wastewater treatment is currently used to decrease the pollutants in wastewater before it is returned to the water cycle. Due to the easy adsorption of HCBd in sewage sludge and incomplete treatment (Gong et al., 2017; Schröder, 1987), wastewater treatment plants (WWTPs) become secondary sources of HCBd with the re-use or disposal of sewage sludge and treated waters. HCBd at different levels have been detected in sludges from numerous WWTPs in China and the USA (Jacobs et al., 1987; Zhang et al., 2014). The investigation of HCBd in sewage sludge from 37 WWTPs in China revealed that higher concentrations of HCBd were found in sewage sludge from WWTPs located in coastal areas with more developed industries such as Shandong, Shanghai, and Zhejiang (Zhang et al., 2014). While HCBd could not be detected in the influent and effluent from six WWTPs in Hong Kong (Feng et al., 2019). This is expected due to the fact that HCBd-related industrial activities are the main sources of HCBd in wastewater.

**2.2.2.3. Waste incineration.** Incineration is a major method for managing wastes containing HCBd in some countries. In the USA, facilities incinerated an estimated 682,140 pounds of HCBd (41.5% of total) in 2007 (USEPA, 2010). A total of 29,445 tons of wastes and soil containing HCBd from a waste disposal polygon site were removed to EU states (UK, France and Poland) for destruction by incineration between 2010 and 2013 (Lysyuchenko et al., 2015). Although high-temperature incineration could eliminate a large part of HCBd, HCBd emissions might occur due to (1) the poor quality and lengthy time of storage sites, and (2) incomplete destroying techniques. For instance, high concentrations of HCBd were found near the rotary kiln and storage areas for wastes from the tire industry in Turkey (Bakoğlu et al., 2004).

The potential formation and emission of HCBd during the waste incineration cannot be ignored. Several laboratory studies have showed that HCBd could be generated during the metal-catalyzed combustion of carbon, brown paper or acetylene (Larson et al., 1994; Lenoir et al., 2001; Luijk et al., 1994). HCBd was also detected as one of the products during the thermal decomposition of PeCB, HCB, octachlorostyrene, 1,3-dichloropropene and TeCE at 600–900 °C (Ahubelem et al., 2015; Klusmeier et al., 1988; Tirey et al., 1990). The emission of HCBd from waste incineration has been confirmed through the determination of HCBd in real waste incineration fly ashes from Eastern China (Zhang et al., 2018a). Indeed, an investigation on waste gasification and combustion in a pilot plant showed that municipal waste with 4% polyvinyl chloride (PVC) or 6% polyester addition resulted in more than twenty times higher concentrations of HCBd than those of the standard waste (Wienecke et al., 1992).

Inductively-coupled thermal plasmas (IC-TPs) with extremely high temperatures (8000–12,000 K) and strong UV radiation has been increasingly applied in waste treatment to reduce toxic by-products such as dioxins. However, the formation of HCBd could still be observed in the decomposition of PVC in IC-TPs in oxidative conditions (Fazekas et al., 2016).

### 2.2.3. Possible sources speculated from related pollutants

The investigation of other possible sources of HCBd is necessary to provide a wholly integrated emission inventory for controlling

the contamination. Identification of specific sources by means of monitoring HCBd in the environmental matrix is workable but very laborious because of the various and numerous types of industrial processes. From the formation pathways in Fig. 1, it can be speculated that HCBd may have some common sources with other organochlorines such as CBs. In fact, unintentionally produced POPs including HCBd, PeCB, HCB, polychlorinated naphthalene (PCNs), polychlorinated biphenyls (PCBs), and PCDD/Fs have been simultaneously found in the methanol-based production of chlorinated methane (Zhang et al., 2015). In addition to chloromethanes production, the abovementioned HCBd sources involving magnesium production and waste incineration have also been reported as unintentional sources of PeCB and HCB (Liu et al., 2018). In this case, the release of HCBd may also occur in other sources identified for PeCB and HCB such as thermal wire reclamation, e-waste recycling, and open and domestic coal and biomass burning. These potential common sources are of priority to be identified in the future.

## 3. Environmental occurrence and human exposure

### 3.1. Environmental occurrence of HCBd

HCBd may be released into the surrounding environment during production, usage of HCBd by-products, waste treatments and other processes. Due to its high volatility (Henry's law constant of  $1044 \text{ Pa m}^3/\text{mol}$  at 25 °C) and hydrophobicity ( $\log K_{ow}$  of 4.78), HCBd released at sites can migrate to other places and transfer among different medias through volatilization, absorption, deposition and bioaccumulation (Environment Canada, 1999). Tables S1–S5 summarize the concentrations of HCBd and several other pollutants in the atmosphere, water, sediment, top soils and biota from recent scientific literatures. The global occurrences of HCBd have decreased in recent years due to the ceased or restricted commercial production and usage in many countries (POPRC, 2016). Nevertheless, HCBd levels in some places increase with the release from historical residues or emission from ongoing unintentional production.

#### 3.1.1. Atmosphere

HCBd contamination in the atmosphere is generally minor. HCBd was not found in indoor air from a child care center located in Kansas City in the USA (Vu et al., 2018) or indoor dust from public places such as high schools, museums, and libraries, or in private spaces such as houses and cars in the metropolitan area of Barcelona (Velázquez-Gómez et al., 2019). HCBd concentrations were under the detection limit of 0.5 ppb in air samples from a rural western Colorado area (Colborn et al., 2014) and less than 2.23 ng/m<sup>3</sup> in air around a factory producing organochlorine pesticides in Jiangsu and a closed factory formerly producing organochlorine pesticides in Chongqing in China (Fang et al., 2017, 2018). Levels of HCBd in the ambient air surrounding a chlor-alkali plant located in the Catalonia region of Spain were relatively high, with the detection frequency being 77% and average concentration being 0.21 µg/m<sup>3</sup> (van Drooge et al., 2018).

HCBd in air in some regions is of concern. Juang et al. (2010) detected high levels of HCBd (mean value: 225.8 µg/m<sup>3</sup>; maximum value: 716.5 µg/m<sup>3</sup>) in air samples collected from areas near a heavily polluted river named Fong Shan Stream from August 2004 to July 2005. Cheng et al. (2019) found the geometric mean value of HCBd reached to  $8.7 \times 10^3 \text{ µg/m}^3$  in the air of a belt conveyor area and stacking workshop at a compost plant in the southwest boundary of Shanghai in China. In most cases, a large portion of HCBd is estimated to finish up in the atmosphere (Environment Canada, 1999; SYKE, 2012). In-lab hydroponic



exposure experiments also showed that nearly 99% of HCBd volatilized from the water phase to the air after 4 days (Hou et al., 2017) and field monitoring at and around a closed factory formerly producing organochlorine pesticides showed levels of HCBd in air samples that were higher than those in top soils (Fang et al., 2017). Therefore, once there are HCBd contamination accidents, air monitoring may be advisable.

### 3.1.2. Water, sediment and aquatic organism

**Water.** HCBd may enter the water from (1) deposition from the contaminated air, (2) direct discharge of wastes from agricultural and industrial sources, (3) rain and runoff from highway junctions, gas stations and other contaminated sites, and (4) secondary release from sediments or soils (Li et al., 2018; Moeck et al., 2016; Santolaria et al., 2015).

Liu and Zhou (2011) analyzed VOCs in 152 water samples from drinking water sources (reservoir or lake, river and ground water) in 28 provinces in China in 2006. HCBd was barely detectable in ground waters, while relatively high levels of HCBd (0.08–0.37 µg/L) were observed in surface waters, indicating surface waters were more easily contaminated by HCBd due to atmospheric migration and deposition. The increase in the current production and emission of HCBd in China is demonstrated by the increasing contamination of HCBd in source waters. The range of HCBd concentrations in 48 drinking source water samples from five major river basins in China in 2013 increased to 0.10–1.23 µg/L, of which HCBd concentrations at three sites (0.76–1.23 µg/L) exceeded the regulated value of 0.6 µg/L (Chen et al., 2015b). The contamination of HCBd in river water in China is comparable with that in Saudi Arabia (0.46–0.81 µg/L) (Nuhu et al., 2011) but more serious than that in Korea (0.029–0.067 µg/L) (Cho et al., 2014). However, HCBd contamination in groundwater and reclaimed waters from Gran Canaria in Spain was negligible, with the highest concentration being  $0.8 \times 10^{-3}$  µg/L and the detection frequency being only 3.7% (Estevez et al., 2016).

It is worth noting that secondary releases of HCBd from sediments or soils in some contaminated areas can be the main sources. A dense non-aqueous phase liquid containing HCBd was generated from a leakage of chlorinated organic compounds in France in the late 1960s, then migrated into 10 m deep soil and released over a long time into groundwater (Maire et al., 2015). Moeck et al. (2016) mentioned that concentrations of HCBd in the groundwater from north-western Switzerland ranged from 0.01 to 3 µg/L, the origin of which was traced back to remobilization of HCBd from the quarternary Rhine sediments.

Cirque glacial lakes or tarns are sensitive indicators of long-range and local airborne pollution due to their remoteness and isolation from most direct human activities. HCBd in waters of the Sabocos tarn, a cirque glacial mountain lake located in the Spanish Pyrenees, during 2011–2012 were at the levels of  $3.3\text{--}5.3 \times 10^{-5}$  µg/L and not detected in 2014 samples (Santolaria et al., 2015).

**Sediment.** Pinto et al. (2016) analyzed HCBd in surface sediment samples (0–2 cm) and a 50 cm long sediment core from the upper part of Óbidos Lagoon in Portugal. Concentrations of HCBd were detected in eight of the 14 stations and ranged from 0.3 to 11.1 ng/g dry weight (ng/g dw). Relatively high levels of HCBd in the core below 12 cm reflects historical extensive use of products containing HCBd. In a study of riverine contamination from an industrial point source in Germany (Berger and Schwarzbauer, 2016), HCBd was not detected in sediments from the upper stream of the Mulde River where there is little industrial impact, while it was detectable (6–15 ng/g dw) in sediments from highly contaminated water downstream of the Mulde River. These results provided clear

evidences that HCBd in the sediments was strongly affected by the industrial-related sources.

**Aquatic biota.** Aquatic biotas usually respond to chemical changes in their living environment. Water quality monitoring carried out by the Environment Agency of England found that HCBd in 136 water samples collected from sites along the Thames and Welland Rivers from 2006 to 2012 were all lower than the detection limit of 3 ng/L (Jürgens et al., 2013). As expected, little contamination of HCBd ( $<0.2$  µg/kg wet weight (µg/kg ww)) was detected in fishes from English rivers (Jürgens et al., 2013). Recent studies also failed to find HCBd in freshwater fishes from other European rivers such as the Rhone River near Lyon and the Seine River in France (Azimi and Rocher, 2016; Miège et al., 2012), main streams in Germany (Fliedner et al., 2016) and Lakes Varna and Beloslav in Bulgaria (Georgieva et al., 2015). A long-term study found HCBd in only one (3.9 µg/kg ww) of 150 eel samples collected from 30 sites across Scotland during 2004–2008 (Macgregor et al., 2010). Lava et al. (2014) collected 28 fishes (*Silurus glanis*) in the Flix Reservoir of the Ebro River in Spain in 2010–2011. With the exception of one fish that was highly contaminated by HCBd (393.7–935.6 µg/kg ww in head and tail, respectively), HCBd was under the detection limit of 4.7 µg/kg ww in most of the samples.

A contamination survey of the Niagara River was conducted at sites on the Canadian and American sides of the river by the Ontario Ministry of the Environment (Richman et al., 2011). There are many contaminant sources near the American side such as the Hyde Park and 102nd Street hazardous waste disposal sites. Due to leaching from these waste stockpile sites into the tributaries of the Niagara River, HCBd was frequently detected at variable concentrations in freshwater mussels from several American sites over the period 1987 to 2009. The mean concentration of HCBd in mussels from the Gill Creek tributary in 2009 was 95 µg/kg ww.

### 3.1.3. Soils and terrestrial plants

**Soil.** HCBd may enter to the soil environment due to (1) the atmospheric migration and deposition from the point sources such as chlor-alkali plants, (2) historical or current use of organochlorine pesticides containing a small amount of HCBd as impurities, and (3) disposal or accidental leakage of waste containing HCBd (Maire et al., 2015; Tang et al., 2014; Zhang et al., 2014).

HCBd was widely detected in the soil samples in China, although the contamination levels were generally low. Concentrations of HCBd (range: 0.07–8.47 ng/g dw) in top soils of farmlands in the Yangtze River Delta in China were similar to or slightly lower than those ( $<0.02\text{--}9.26$  ng/g dw) in top soils surrounding chemical factories possibly producing unintentional HCBd. Relatively high concentrations of HCBd (27.9 ng/g dw) were observed in soils in a factory in a study whereas no difference of HCBd levels in soils were observed between the sites within factories and the surroundings in another two investigations (Fang et al., 2017, 2018; Sun et al., 2018; Tang et al., 2014, 2016; Zhang et al., 2014). According to the Hazardous Substances Data Bank (HSDB, 2001), HCBd has slight to no mobility in soil due to its high adsorption (based on the high Koc value). Conversely, a report by Environment Canada (1999) mentioned that HCBd was found to be mobile in sandy soils in a dune infiltration study. Recently, Feng et al. (2018) extended the application of a coarse-grained soil organic matter (SOM) model to assess the interaction of SOM with contaminants. The diffusion coefficient of HCBd calculated by the model was similar to that of HCB, indicating their similar behavior in SOM. The accumulation and mobility of HCBd in soil was therefore predicted because HCB has been demonstrated to accumulate in soil and may reach deeper layers by downward transport.

Berger and Schwarzbauer (2016) measured organic compounds

in soil layer samples from a riverine floodplain near the Bitterfeld Wolfen in Germany, where industrial activities before 1990 were the specific sources of HCBd. HCBd was detected in 0–30 cm deep soils, but concentrations decreased with increasing soil depth. Concentrations of HCBd in upper soil layers taken in 2012 (12–22 ng/g dw) were more than six times higher than those in samples taken in 2004 (2 ng/g dw). Similar trends were found for other detectable compounds. These results indicate that environmental contamination with pollutants, especially the persistent organic pollutants from former production are continuing and even increasing.

**Terrestrial plants.** Terrestrial plants may accumulate HCBd from contaminated air through leaves and stems, and from the contaminated soil through adsorption/absorption, and translocation by roots. In-lab hydroponic exposure experiments showed that the latter pathway through roots was the main source of HCBd for exposed pumpkin (Hou et al., 2017). Berry-Spark et al. (2003) demonstrated an uptake of HCBd by carrots and lettuces from sand or clay soils with different concentrations of HCBd added (29–10,000 ng/g) in the laboratory. Bioaccumulation of HCBd in terrestrial plants was also found in several field studies. Relatively high concentrations of HCBd (0.03–24.6 µg/kg dw) were detected in terrestrial plants, even when the concentrations in the soil medium were low (<0.02–4.27 ng/g dw). Different species of biotas showed different accumulation abilities for HCBd (differences in bioconcentration factors and bioaccumulation factors) (POPRC, 2012). Higher levels of HCBd were determined in some species such as paper mulberry and zoysia, implying the interspecies differences in the bioaccumulation capacities for HCBd (Tang et al., 2016). Bioaccumulation factors of HCBd in carrots, lettuces, rice and pumpkin crop plants from suburban farms in Taicang in Eastern China ranged from 8.5 to 38.1 (Tang et al., 2014).

### 3.1.4. Other biotic samples

As well as aquatic biotas and terrestrial plants, mammals, birds, insects and other animals are also often used as bioindicators of environmental contamination. Tang et al. (2014, 2016) confirmed HCBd in various farm animals such as grasshoppers, locusts, worms, butterflies, crickets, muscle tissue of chickens and Chinese toads. Levels of HCBd in samples from the farmland adjacent to a former pesticide plant in Chongqing (1.65–3.80 µg/kg lipid weight (µg/kg lw)) were comparable with or slightly lower than those in samples from suburban farms in Taicang (1.30–8.20 µg/kg lw) in China. Zapata et al. (2018) found that levels of HCBd in gull eggs from parks in Spain and Portugal were in the range of <0.003–0.11 µg/kg ww with a mean value of 0.04 µg/kg ww. Monclús et al. (2018) used interscapular feathers of red kites as bioindicators. Concentrations of HCBd in the feathers of free-living kites (mean/median 0.25/0.21 µg/kg dw) from northern Europe were comparable with those in captive kites born in a rehabilitation center in Spain (0.23/0.21 µg/kg dw).

HCBd was considered to have a strong potential for long-range atmospheric transport (POPRC, 2012), resulting in occurrences in biotas from some background sites. Vorkamp et al. (2004) found HCBd in terrestrial animals (maximum value: 4.9 µg/kg lw), seabirds (3.4 µg/kg lw), marine invertebrates (0.57 µg/kg lw) and mammals (0.80 µg/kg lw) collected from Greenland during the period of 1997–2001. A recent study also found HCBd in moose from the southern Northwest Territories of Canada. Concentrations of HCBd in the moose livers were in the range of 0.003–0.014 µg/kg ww (0.05–0.24 µg/kg lw), which were positively correlated with % lipid (Larter et al., 2017). Whereas another report for Arctic biotas showed that HCBd was below the detection limit in the fat and liver samples of polar bears from Hudson Bay (<16.6 µg/kg ww) (Letcher et al., 2018), which might be partly due to the relatively high

detection limit.

### 3.2. Human exposure risk from HCBd

HCBd may enter the human body and have adverse effects on human health directly or by metabolism. Nephrotoxicity of HCBd has been confirmed in animal experiments, having caused necrosis of the *pars recta* of the renal proximal tubule (Ishmael et al., 1982), down-regulation of regucalcin (Chiusolo et al., 2008), up-regulation of kidney injury molecule-1 (Chiusolo et al., 2010) and lipid peroxidation in renal cells (Sadeghnia et al., 2013). Kidney degeneration of male rats could be observed at HCBd doses of as low as 10 mg/kg (Swain et al., 2012). The formation of S-(1,2,3,4,4-pentachloro-1:3-butadienyl)-L-glutathione from HCBd in liver and its final metabolism (a nephrotoxic thioketene) in kidneys are the keys for HCBd nephrotoxicity (Birner et al., 1998). The genotoxicity and carcinogenicity of HCBd have remained inconclusive. However, based on the evidence of adenomas and adenocarcinomas of the kidney induced by HCBd (Kqciba et al., 1977), the carcinogenic potential of HCBd should not be ignored.

Human exposure risk can be measured directly by assessing the levels of HCBd in human blood and tissues and HCBd has been detected in human liver samples (5.7–13.7 ng/g wet weight) (IPCS, 1994). Whereas there are few available data of HCBd in human body in recent times. More commonly, exposure risk is estimated indirectly based on monitoring HCBd occurrence data in the environment. One method is to compare the measured concentrations of HCBd with the suggested standards that are inferred from threshold effects concentrations in toxicity experiments for animals such as rats and mice and epidemiological studies. Environmental quality standards for HCBd in different media have been recommended by some organizations (Table 1). Current concentrations of HCBd reported in the most studies were generally under these limits, indicating the low risk of HCBd affecting the safety of biota. As relevant environmental quality standards are central to risk assessment procedures, it is necessary to establish and unify environmental standards for HCBd in different countries.

Another method is to compare the exposure risk index estimated by using risk calculation models with the reference values. HCBd was classified as Group 3 (not classifiable as to its carcinogenicity to humans) by International Agency for Research on Cancer (IARC, 1999) and Group C (possible human carcinogen) by the USEPA (1987), respectively. The risk assessment for HCBd includes a health hazard assessment for noncarcinogenic effects and carcinogenicity assessment for lifetime exposure. A simple model of hazard coefficient calculation (POPs toolkit, 2019) can be used for preliminary risk assessment. Exposure ratios including Hazard Quotients (HQs) for non-carcinogens and Incremental Lifetime Cancer Risk (ILCR) for carcinogens are calculated using Equations (1) and (2), respectively. The WHO (2003) has derived a tolerable daily intake (TDI) of 0.2 µg/kg/day for HCBd. The cancer slope factor for HCBd is 78 (µg/kg/day)<sup>-1</sup> (USEPA, 1987). Pathways via accidental soil ingestion, water ingestion, food ingestion, inhalation of contaminated particles and dermal contact with contaminated soil are of most concern. Details of calculation equations and parameters for the exposure dose of each pathway are shown in Table S6 in the Supporting Information.

$$HQ = \frac{\text{Estimated exposure dose } (\mu\text{g/kg/day})}{\text{Tolerable daily intake } (\mu\text{g/kg/day})} \quad (1)$$

$$ILCR = \text{Estimated exposure dose } (\mu\text{g/kg/day}) \times \text{Cancer slope factor } (\mu\text{g/kg/day})^{-1} \quad (2)$$

**Table 1**  
Environmental quality standards for HCBd in different medias set by some organizations.

Matrix		Limits of HCBd	Origin
Air	Workplaces	210 µg/m <sup>3</sup>	Occupational safety and hygiene regulation in Taiwan (Juang et al., 2010)
	Residential exposure	0.6 ppb (~6 µg/m <sup>3</sup> )	Committee on Toxicity (COT, 2000)
Water	Drinking water	0.6 µg/L	World Health Organization (WHO, 2003)
	Surface water	0.6 µg/L	European Commission (EC, 2013)
Biota	Such as fish, molluscs, and crustaceans	55 µg/kg ww	European Commission (EC, 2008)
Soil	Agricultural coarse-grained soil	6.7 ng/g	Saskatchewan Ministry of Environment, Canada (SME, 2011)
	Agricultural fine-grained soil	10 ng/g	
	Uncontaminated soil	1 µg/g	State Environment Protection Agency of China (SEPAC, 2007)
Solid waste	Biosolid for land application	600 µg/g dw	United States Environmental Protection Agency (USEPA, 1995)

For the risk index calculated from Eq. (1), if a HQ for a single pathway is greater than 0.2 or the total of HQs for all pathways is greater than 1.0, potential adverse effects are likely; if a HQ is equal to 0.2 or the total HQs is equal to 1.0, the HCBd alone is not likely to cause a health risk; if a HQ is less than 0.2 or the total HQs is less than 1.0, adverse effects from the HCBd are not likely.

From the risk index calculated from Eq. (2), if the ILCR is no more than  $1 \times 10^{-5}$  ( $ILCR \leq 1 \times 10^{-5}$ ), cancer risk is considered essentially negligible, while if the ILCR is greater than  $1 \times 10^{-5}$ , potential adverse effects are likely and risk management measures may need to be taken.

We have applied this model to assess the risk of human exposure to HCBd through the soil within a chemical plant in China, the estimated exposure dose of which was  $8.1 \times 10^{-6}$  µg/kg/day (Zhang et al., 2014). Fernandes et al. (2019) determined HCBd in commonly consumed dietary (bread, cereals, eggs, poultry, fish, milk, vegetables, fruit, meat and meat products, etc.) collected between 2012 and 2015 in the UK. The estimated intake (97.5th percentile) through food ingestion was  $7.3 \times 10^{-4}$  µg/kg/day for adult and  $2.04 \times 10^{-3}$  µg/kg/day for children (4–6 years), respectively. The results of risk assessments based on the HQs for these two studies showed acceptable risks while cancer risks potentially exist according to the ILCR results. The dietary exposure values for UK people might be overestimated because HCBd was not detectable in most foods and the limit of detection value was used for the calculation. Moreover, the above risk calculation model is only for preliminary quantitative risk assessment, refined assessments for the cancer risk of HCBd are needed in future studies. In addition, other pathways such as dermal absorption from contaminated water adhered to exposed skin and inhalation of air (Fang et al., 2017; Wang et al., 2014) cannot always be ignored, especially at sites with serious air pollution. Comprehensive risk assessments of human exposure to HCBd via multi-pathways are encouraged.

### 3.3. Association with other pollutants

Some studies showed significantly positive correlations between the concentrations of HCBd and HCB, dichlorodiphenyltrichloroethane (DDT) in the environment (Sun et al., 2018), whereas some did not find such a relationship. Whether or not they came from the same sources, HCBd was usually found together with some legacy pollutants. From Tables S1–S5, it can be seen that levels of these pollutants such as PCBs, PeCB and HCB were generally higher than HCBd, which reflects the more extensive use of legacy pollutants.

In addition to other POPs, HCBd might be transformed to dechlorinated products under anaerobic conditions (Booker and Pavlostathis, 2000; Bosma et al., 1994). In the ambient air surrounding a chlor-alkali plant located in Catalonia, Spain, 1,3-butadienes with 3–5 chlorine substituents were qualitatively detected. This may have partly been a result of the reductive

dichlorination of HCBd in the contaminated water reservoir and subsequent volatilization to the atmosphere during dragging operations for river restoration (van Drooge et al., 2018). As with HCBd, tetrachloro-1,3-butadienes (TeCBD) and pentachloro-1,3-butadienes can also induce chromosome aberrations. Besides, 1,1,3,4-TeCB and 1,2,3,4-TeCBD were positive in the Ames test, indicating their mutagenicity (Brüschweiler et al., 2010). Furthermore, James et al. (2008) reported that non-specific bacteria from activated sludge can dechlorinate HCBd to 1,3-butadiene, which is a level 1 carcinogen recognized by IARC (2012). These transformation of HCBd will bring greater risks to the ecosystem and human health.

In view of such a prodigious amount of pollutants that are formed from common sources and are accompanied by HCBd, emitted to the environment and finally enter the human body and other biota, to only assess the exposure risk from individual compounds is inadequate. It is recommended to add the exposure ratios (HQs or ILCRs) calculated from each pollutant together for the risk assessment when the pollutants have a similar mechanism of action and similar target organ (Health Canada, 2010). Therefore, more toxicity tests for HCBd are needed to make sure the hazard characterization and classification. In addition, previous toxicity tests for HCBd focus on the reaction from this single compound. However, mixtures of many pollutants have showed combined (additive, synergistic or antagonistic) toxic effects (Chen et al., 2015a). Possible combined toxic effects from HCBd and other co-existing pollutants should be taken into consideration to avoid underestimate or overestimate the exposure risk where mixed contamination occurs. The exposure experiment by using animals, target organs, or cells dealt with different doses of multi-component mixtures is an available method to determine the combined toxic effects.

### 4. Conclusions

This review summarizes the possible formation pathways, sources, and environmental levels of HCBd, as well as potential human health risks associated with the exposure to HCBd in isolation and in combination with other commonly co-existing organochlorines. The global contamination of HCBd is generally slight, with concentrations mostly under current environmental standards. Whereas relatively high levels of HCBd were found near the point sources in some cases. HCBd contamination in the environment mainly results from industrial activities and waste treatments, some of which are also the sources of other pollutants such as CBs. The co-emission of HCBd and other pollutants may largely increase the exposure risk to the surrounding ecosystem and human. Therefore, recognition of their common sources should be a high priority. Subsequent risk assessment and pollution control are also indispensable. The toxicity of HCBd, especially the combined toxicity with other pollutants are still not well known. More efforts



need to be made in this area to improve the accuracy of risk assessments. In addition, similar formation pathways of HCBd and co-existing organochlorines indicate the synergistically controlling the contamination is possible via reducing the production of precursors such as TCE or controlling the reaction conditions such as temperatures.

## Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

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