Environmental Science & Technology

Critical Review

Cite This: Environ. Sci. Technol. 2019, 53, 13551−13569

pubs.acs.org/est

A Review of Environmental Occurrence, Fate, and Toxicity of Novel Brominated Flame Retardants

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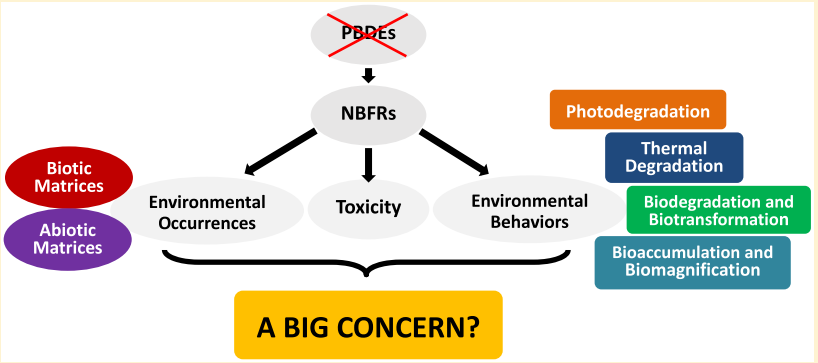
Supporting Information



ABSTRACT: Use of legacy brominated flame retardants (BFRs), including polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCD), has been reduced due to adverse effects of these chemicals. Several novel brominated flame retardants (NBFRs), such decabromodiphenyl ethane (DBDPE) and bis(2,4,6-tribromophenoxy) ethane (BTBPE), have been developed as replacements for PBDEs. NBFRs are used in various industrial and consumer products, which leads to their ubiquitous occurrence in the environment. This article reviews occurrence and fate of a select group of NBFRs in the environment, as well as their human exposure and toxicity. Occurrence of NBFRs in both abiotic, including air, water, dust, soil, sediment and sludge, and biotic matrices, including bird, fish, and human serum, have been documented. Evidence regarding the degradation, including photodegradation, thermal degradation and biodegradation, and bioaccumulation and biomagnification of NBFRs is summarized. The toxicity data of NBFRs show that several NBFRs can cause adverse effects through different modes of action, such as hormone disruption, endocrine disruption, genotoxicity, and behavioral modification. The primary ecological risk assessment shows that most NBFRs exert no significant environmental risk, but it is worth noting that the result should be carefully used owing to the limited toxicity data.

1. INTRODUCTION

Owing to excellent flame retardant properties, brominated flame retardants (BFRs) are used in a variety of consumer products, such as furniture, textiles, carpets, electronics castings, car components, building materials, insulators, etc., to improve their fire resistance.[1,2] However, as mounting evidence shows, BFRs are ubiquitous in the environment,[3−5] and they have potential to accumulate and trigger adverse effects to living organisms[3,6] as well as the capability of long distance transport. Concern about security of these compounds is gradually growing, which leads to strict bans and phase-out of some BFRs.[7] For example, the worldwide use of penta- and octa-BDE has been strictly banned in California, U.S.[7] The use of deca-BDE has also been restricted in Europe in 2008 and was phased out in the U.S. at the end of 2013.[8]

Therefore, as a replacement for the banned and restricted BFRs, some novel BFRs (NBFRs) have been introduced into market. The most common NBFRs are decabromodiphenyl ethane (DBDPE), bis(2,4,6-tribromophenoxy) ethane (BTBPE), and tetrabromobisphenol A bis(2,3-dibromopropyl ether) (TBBPA-DBPE), which are used in place of deca-BDE, octa-BDE, and tetrabromobisphenol A (TBBPA), respectively.[9−11] There are also a number of other NBFRs on the market, typically including 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (TBB or EHTBB), bis(2-ethylhexyl) tetrabromophtalate (TBPH or BEHTBP), hexabromobenzene (HBB), 2,3,4,5,6-

Received: May 27, 2019
Revised: October 28, 2019
Accepted: November 4, 2019
Published: November 4, 2019

DOI: 10.1021/acs.est.9b03159
Environ. Sci. Technol. 2019, 53, 13551−13569

Table 1. Concentrations of NBFRs in Abiotic Matrices (Air, Water, Dust, Sediments, Soil, and Sludge)

	region	date/n[a]	unit	DBDPE	BTBPE	HBB	PBEB	PBT	TBB	TBPH	TBECH	TBBPA-DBPE	ref
Matrix: Air													
air	Madrid, Spain	2013/68	pg/m^3	nd–0.01[c] (14.3%)[d]	nd[e]–2.56 (14.3%)	nd–11.6 (42.9%)	4.89						13
air	BFR production area, China	2013/14	pg/m^3	240[b]		2800	9.7	4000					34
air	The Great Lakes, U.S.	2005–2013	pg/m^3	0.34–2.0		0.08–2.2	0.036–1.8		0.28–4.6	0.39–3.7			14
air	East Greenland Sea	2009/10	pg/m^3		nd–0.06	0.001–0.66		nd–0.02		nd–0.08			23
air	Residential region, China	2007–2008/57	pg/m^3	11	1.1	4.8	0.34	6.1					45
air	Pearl River Delta	2007/4	pg/m^3	1920	30.7							528	48
Matrix: Wastewater													
influent	Harbin, China	2009–2016/64	ng/L	22.3	2.2								55
effluent				4.7	0.4								
WWTP	Norway	2009	ng/L			0.40–1.82	nd	nd					33
incoming water	Norway	2009/9	ng/L	nd–5.1	nd						1.2–5.3	nd–18	40
outgoing water	Norway	2009/9	ng/L	nd	nd						0.6–2.1	nd	40
Matrix: Water													
lake	The Great Lakes, U.S.	2011–2012	pg/L	0.25–10.8		0.23–0.70	0.25–32.0		1.3–7.9	0.27–10.4			60
urban watershed	Singapore	2014–2015/56	ng/L		0.04–5.22	0.0039–0.49		0.0016–0.0097			0.099–0.47		62
seawater	Bohai Sea, China	2015/20	ng/L		0.03–0.15	1.23–9.43					0.81–6.69		61
seawater	Singapore	2011–2012/51	ng/L		nd–0.062	nd–0.965							59
Matrix: Dust													
indoor dust	Antwerp, Belgium	2008/81	ng/g	<20–2470	<0.5–1740				<2–436	<2–6180		<20–9960	15
indoor dust	Barcelona, Spain	NA/14	ng/g	nd–4430 (64.3%)	nd–217 (57.1%)	nd–750 (7.1%)		nd–24 (14.3%)	nd–62.1 (28.6%)	nd–508 (92.9%)			16
indoor dust	Egypt	2013/31	ng/g		0.2–2.4	0.05–0.2			0.8–7.1	0.09–0.6			64
indoor dust	Melbourne, Australia	2016/45	ng/g	2400	nd–98	1.9	nd	nd–9.0	66				65
fire station dust	California, U.S.	2010–2011/27	ng/g	161	28.4	9.4			2690	2080			67
Matrix: Sediments													
urban watershed	Singapore	2014–2015/16	ng/g dw		1.73–4.46 (20%)	0.018–0.23 (26.7%)		nd			0.43–2.33 (40%)		62
surficial sediments	South Africa	2011/45	ng/g dw	171	34				545	96			76
surface sediment	Dongjiang River, China	2006/4	ng/g dw	247	1.32							858	48
leachate ponds	Gauteng, South Africa	2013/18	ng/g dw		51				10	11			80
seepage sediment	Metal recycling area, Norway	2009	ng/g dw			0.077	0.028	0.032					33

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Table 1. continued

	region	date/n[a]	unit	DBDPE	BTBPE	HBB	PBEB	PBT	TBB	TBPH	TBECH	TBBPA-DBPE	ref
Matrix: Soil													
farmland soil	Pearl River Delta, China	2007/4	ng/g dw	28.1	0.05							39.0	48
urban soil	Melbourne, Australia	2014/30	ng/g dw	30.0	4.79	3.52		nd−90.9 (7%)	nd−90.9 (1%)				86
soil	Guiyu, China	2009	ng/g dw	0.53−153	0.13−15	0.041−3.3	nd−0.0019						89
Matrix: Sludge													
sewage sludge	Pearl River Delta, China	2007/5	ng/g dw	1180	0.88							4530	48
primary sludge	Catalonia, Spain		ng/g dw	354	nd				nd	446			57
secondary sludge	Catalonia, Spain		ng/g dw	434	3.6				7.2	695			57
sewage sludge	China	2010−2013/62	ng/g dw	52.2	0.95	0.68	0.04	0.07					93
dewater sludge	Harbin, China	2011−2016/24	ng/g dw	255.8	19.8		0.3	3.5	5.3	160	24.3		55
aerobic sludge	Harbin, China	2012−2013/6	ng/g dw	303	4.41	7.55	1.11	10.3	6.03	172			92
dewatered sludge	Harbin, China	2012−2013/6	ng/g dw	316	42.5	3.59	0.27	6	15.9	242			92

[a]Date/n: sampling date and number. [b]Mean or median value. [c]Concentration range. [d]Detection frequency. [e]nd = not detected.

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pentabromoethylbenzene (PBEB), 2,3,4,5,6-pentabromotoluene (PBT), and 1,2-dibromo-4-(1,2-dibromoethyl) cyclohexane (TBECH) (Supporting Information (SI) Figure S1).[7,12]

Recently, there have been many studies involving the occurrence of several NBFRs in various environmental matrices, including air,[13,14] dusts,[15,16] sewage sludge,[17,18] and sediments,[19,20] as well as human serum.[21,22] It is worth noting that NBFRs have also been found in the Arctic, which indicates that these compounds can undergo a long-range atmospheric transport (LRAT), just as the restricted and banned traditional BFRs.[23] Bioaccumulation potential and adverse effects of NBFRs have been documented,[24,25] which is worthy of attention because they may have the same properties as the restricted and banned BFRs, particularly considering their physical and chemical similarities to traditional BFRs.

Reviews on environmental occurrence, fate, and toxicity of NBFRs are very limited, and few reviews involve aspects such as analytical methods or environmental occurrence.[7,12,26−28] To our best knowledge, there is only one comprehensive review summarizing the analysis, environmental fate, and behavior of NBFRs.[7] This review article was published nearly 10 years ago, and there are many new papers concerning NBFRs coming up in recent years. Additionally, the review article did not involve toxicity of NBFRs. This review article summarized research that has been conducted so far on this class of chemicals in a comprehensive and concise manner, with emphasis on including new information on NBFRs, mainly derived from studies in recent years. Literature was selected via google scholar using key search terms such as NBFRs, DBDPE, BTBPE, HBB, PBEB, PBT, etc., and the publication date was mainly between January 2009 and March 2019. The aims of this review are (1) to gather the latest information about environmental occurrence and distribution of a group of select NBFRs; (2) to summarize environmental behaviors and toxicity of these NBFRs; and (3) to put forward directions for further studies.

2. PHYSICOCHEMICAL PROPERTIES AND PRODUCTION/USAGE OF NBFRS

2.1. Physicochemical Properties of NBFRs. The molecular weights, CAS number, melting points, boiling points, vapor pressures, water solubility, and log K_{ow} values of NBFRs have been summarized in SI Table S1: part of experimental data were from http://www.chemspider.com and https://pubchem.ncbi.nlm.nih.gov/, and part of calculated data were from http://www.chemspider.com (generated using the ACD/Laboratories Percepta Platform-PhysChem Modula), SciFinder originating from calculated properties (ACD/laboratories Software V9.04), and http://www.chemspider.com (generated using the U.S. Environmental Protection Agency's EPISuite) (see SI for details).

2.2. Production/Usage of NBFRs. NBFRs have been produced in large amount worldwide. The estimated production of DBDPE and BTBPE is usually between several thousands and 10s of thousands of tons per year, which is generally higher than those of other NBFRs (see SI for details).[29−41] As replacements for traditional BFRs, NBFRs are widely used as additive flame retardants in various textile, plastic, polyurethane foam, electrical cable coating, and other applications.[7,35,42−44] Since NBFRs are not chemically bound to polymeric substrates, they can leach into various environmental matrices, including air, water, dust, and sediment, during their production, use, and disposal.

3. ENVIRONMENTAL OCCURRENCES

3.1. Abiotic Samples. *3.1.1. Air.* Owing to the low vapor pressures, the select NBFRs are not easily volatilized into the air. Therefore, these substances are generally present in the air at low concentrations (Table 1). For example, DBDPE was only found at concentration of 0.01 pg/m^3 in two winter air samples in Madrid, Spain.[13] In air from Stockholm and the Great Lakes, the mean concentrations of DBDPE were 1.4 and 0.34−2.0 pg/m^3, respectively,[14,29] which were a little lower than those found in airs from a typical residential region of Harbin, China (mean: 11 pg/m^3)[45] and from the northern shore of Taihu Lake, China (23 pg/m^3).[46] Much higher concentrations of DBDPE have been found in air from a BFRs production area in Weifang, northern China (240 pg/m^3),[38] an e-waste recycling site (209 pg/m^3) and a rural site (158 pg/m^3) in southern China[47] and the Pearl River Delta, southern China (1916 pg/m^3) (Table 1).[48] The relatively high concentrations of DBDPE in air from China may be related to the high usage of DBDPE.

BTBPE was not found in air from northeast Greenland,[49] while relatively low concentrations of BTBPE were detected in air from the East Greenland Sea (range: nd−0.06 pg/m^3),[23] and a typical residential region of Harbin (<0.017−9.1 pg/m^3) (Table 1).[45] BTBPE was reported to occur in air (mean: 2.97 pg/m^3) from a rural site in southern China,[47] and higher concentrations of BTBPE were found in air from the Pearl River Delta (mean: 30.7 pg/m^3)[48] and an e-waste site in southern China (mean: 78.7 pg/m^3).[47]

Yu et al. reported that HBB, PBEB, and PBT were found in air in the western sub-Arctic, Canada, and the mean concentrations were 0.024, 0.013, and 0.084 pg/m^3, respectively,[50] which were 1−2 orders of magnitude lower than those found for a typical residential region of Harbin (4.8, 0.34, and 6.1 pg/m^3, respectively).[45] These results are similar to those found in air from the Great Lakes.[14,51,52] Comparable concentrations of HBB (range: 0.001−0.66 pg/m^3) and PBT (nd−0.02 pg/m^3) were detected in air from the East Greenland Sea.[23] Elevated levels of HBB, PBEB, and PBT were found in air from a BFRs production area in Weifang, China (mean: 2800, 9.2, and 3100 pg/m^3, respectively)[38] and an e-waste recycling site in southern China (138, 41.0, 21.8 pg/m^3, respectively) (Table 1).[47]

Occurrence of TBB and TBPH in air from the Great Lakes was reported (Table 1).[14,40,51] Higher concentrations of TBB and TBPH were found in air from urban areas, such as Chicago (mean: 4.8 and 6.2 pg/m^3) and Cleveland (5.7 and 14 pg/m^3), than those in remote areas, such as Eagle Harbor, Sturgeon Point, and Sleeping Bear Dunes (mean: 0.57−0.97 and 0.90−1.1 pg/m^3 for TBB and TBPH, respectively). This distribution pattern of TBB and TBPH is probably related to their high application in urban areas.[40] Low concentrations of TBB and TBPH have been detected in air from Nunavut, Canada (mean: 0.74 and 0.80 pg/m^3) and Tibet, China (0.54 and 0.38 pg/m^3).[53] High concentration of TBBPA-DBPE (mean: 528 pg/m^3) was found in air from the Pearl River Delta (Table 1).[48] Relatively low concentrations of TBBPA-DBPE (geometric means: 0.19−1.3 pg/m^3) were found in air samples from the Great Lakes, North America.[54]

3.1.2. Wastewater and Water. 3.1.2.1. Wastewater. Wastewater treatment plant (WWTP) is an important source of

DOI: 10.1021/acs.est.9b03159
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NBFRs, and there are some studies concerning the occurrence of NBFRs in wastewaters in WWTPs. Since NBFRs undergo a series of transformations in WWTPs and can be adsorbed and accumulated in sludge, it is no wonder that higher concentrations of NBFRs are found in influent than effluent.[55,56] In the biggest WWTP in Harbin, China, the concentrations of DBDPE were 22.3 ng/L in influent and 4.7 ng/L in effluent and the similar pattern was found for BTBPE (influent: 2.2, effluent: 0.4 ng/L) (Table 1).[55] This result was consisted with DBDPE concentrations in influent (26 ng/L) and effluent (0.022 ng/L) of a WWTP in Stockholm, Sweden.[56] In main municipal WWTPs in Norway, concentrations of HBB and TBECH ranged from 0.40 to 1.82 ng/L and 0.6 to 5.3 ng/L, respectively (Table 1).[37,43] Relatively high concentrations of TBPH (range: 52−130 ng/L) were detected in influent samples from five WWTPs close to Barcelona, Spain.[57]

3.1.2.2. Water. There are also some research about the occurrence of NBFRs in natural water, including river,[58] lake,[59] and seawater.[23] Since a higher volume of NBFRs are produced and used in urban areas than in remote areas, the concentrations of NBFRs in natural waters in urban areas were generally higher than that in remote areas. DBDPE was found at median concentration of 13 pg/L in Dongjiang River, China, which was comparable with those found for Lake Ontario (10.8 pg/L) and Lake Superior (6.7 pg/L) (Table 1).[58,60] BTBPE was detected in seawater in the Bohai Sea, with concentrations ranging from 0.03 to 0.15 ng/L,[61] which was higher than that detected in coastal water of Singapore (range: nd−0.062 ng/L),[59] but 1 order of magnitude lower than that in an urban watershed of Singapore (0.040−5.22 ng/L).[62] The HBB concentration in seawater of Bohai Sea ranged from 1.23 to 9.43 ng/L,[61] which was higher than that detected in the coastal water of Singapore (range: nd−0.965 ng/L),[59] an urban watershed of Singapore (0.0039−0.49 ng/L),[62] the Great Lakes (nd−0.70 pg/L)[60] and the Atlantic and Southern Ocean (nd−0.02 pg/L).[63] PBT and PBEB were infrequently found in natural waters, and the detection rates were generally less than 28.1%.[23,60,62,63] In the Great Lakes, concentrations of TBB and TBPH ranged from 1.3 to 7.9 pg/L and 0.27 to 10.4 pg/L, respectively.[60] Higher TBB concentrations (0.81−6.69 ng/L) were found in the seawater of the Bohai Sea.[61] Concentrations of TBECH in an urban watershed of Singapore ranged from 0.099 to 0.47 ng/L (Table 1).[62]

3.1.3. Dust. Numerous studies have investigated the occurrence of NBFRs in dust to assess human exposure. In different indoor environmental dusts from Egypt, concentrations of NBFRs (BTBPE, HBB, TBB, TBPH, and TBECH) in workplace dust (mean: 38.9 ng/g) were generally higher than in home (30 ng/g) and car (24.2 ng/g) dusts (Table 1).[64] McGrath et al. also found that concentrations of NBFRs (DBDPE, BTBPE, HBB, PBEB, PBT, and TBB) in office dust (mean: 3400 ng/g) were higher than in home (2000 ng/g) and vehicle dusts (2200 ng/g) in Melbourne, Australia.[65] However, NBFRs (DBDPE, HBB, TBB, and TBPH) were found to be more abundant in car dust (mean: 21800 ± 5990 ng/g) than in office (4160 ± 823 ng/g) and public microenvironment (6010 ± 1720 ng/g) dusts in Nanjing, China.[66] The higher concentrations of NBFRs in car dust than in office and public microenvironment dusts are partly attributed to the limited ventilation and higher temperature inside the car, which enhances the release of NBFRs.[66] As for the somewhat different phenomenon observed in Egypt and Melbourne, it may be attributed the different NBFRs measured (DBDPE, which usually accounts for the highest proportion, was not measured in dust from Egypt) in dust samples between Nanjing and Egypt, and the different usage of DBDPE between Nanjing and Melbourne since DBDPE accounts for the highest proportion (>90%) among the NBFRs measured. As important flame retardants, it is not surprising that higher median concentrations of NBFRs were found in fire station dust (DBDPE: 161, BTBPE: 28.4, HBB: 9.4, TBB: 2690, TBPH: 2080 ng/g) than in house dust (DBDPE: 82.8, BTBPE: 22.3, HBB: 1.85, TBB: 337, TBPH: 186 ng/g) in California (Table 1).[67]

Mean concentrations of DBDPE, BTBPE and TBPH in home dust from different areas were compared (SI Figure S2).[15,16,65,68−71] The higher concentrations of DBDPE in home dust from Melbourne, Australia (mean: 2000 ng/g) and Barcelona, Spain (1157 ng/g) compared with those from other countries (6.8−512 ng/g) reflect that Melbourne and Barcelona have a greater consumption of DBDPE or a higher substitution proportion of BDE-209 by DBDPE.[16,65] Mean concentrations of TBPH in home dust from Bloomington (2540 ng/g) and Toronto, Canada (2650 ng/g) are obviously greater than those from other places (15−212 ng/g), which indicates a higher usage of TBPH in North America compared with other regions.[71] BTBPE in home dust is generally at low level, as compared to DBDPE and TBPH.

There are some studies concerning the occurrence of NBFRs in dust from e-waste recycling sites.[72−74] DBDPE was found at mean concentration of 1300 ng/g in dust from electronic waste storage facilities in Thailand,[72] which was far lower than those found in e-waste recycling sites in China, where mean concentrations of DBDPE were 4 8000, 63 000, 42 000, and 39 000 ng/g in Taizhou, Guiyu, Dali, and Qingyuan, respectively.[73] Generally, concentrations of NBFRs in dust from e-waste recycling site are undoubtedly higher than those from home, office or other places, since NBFRs, as a replacement of PBDEs, are widely used in electronic equipment.[75] Therefore, more attention should be paid to the contamination of NBFRs in e-waste recycling regions.

3.1.4. Sediments and Soil. Owing to low water solubility, NBFRs tend to distribute in sediment when they enter into aquatic system. Concentrations of DBDPE in surface sediments from different areas were compared (SI Figure S3).[19,48,76−79] Mean concentrations of DBDPE in sediments from Pearl River Delta, China (247 ng/g dry weight (dw)) and eThekwini metropolitan municipality, South Africa (171 ng/g dw) were obviously higher than those from other places (1.75−2.96 ng/g dw), which may be explained by the fact that both Pearl River Delta and eThekwini metropolitan municipality are highly industrialized and urbanized.[48,76] BTBPE was found at mean concentration of 34 ng/g dw with a detection rate of 13% in sediment from eThekwini metropolitan municipality in 2011 (Table 1).[76] Comparable concentration of BTBPE was found in sediment in Gauteng Province, South Africa in 2013 (mean: 51 ng/g dw),[80] whereas relatively low concentrations of BTBPE were found in sediments from Dongjiang River in 2006 (0.05−2.07 ng/g dw)[48] and an urban watershed in Singapore in 2014−2015 (1.73−4.46 ng/g dw) (Table 1).[62] Concentrations of TBB and TBPH were found at mean values of 545 and 96 ng/g dw, respectively, in sediment from eThekwini metropolitan municipality in 2011,[76] which are higher than those (mean: 10 and 11 ng/g dw, respectively)

DOI: 10.1021/acs.est.9b03159
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Table 2. Concentrations of NBFRs in Biotic Matrices (Birds, Fishes, Human Serum, and Others)

	region	date/n[a]	unit	DBDPE	BTBPE	HBB	PBEB	PBT	TBB	TBPH	TBECH	TBBPA-DBPE	ref
Matrix: Birds													
black guillemot egg	East Greenland	2012/4	ng/g ww	0.10[b]	0.015				0.076	0.061			49
Peregrine falcon egg	Southern Germany	2014/11	ng/g lipid			0.7−26	0.2−3.9	0.3−14					96
five bird species	Qingyuan County, China	2005−2007/29	ng/g lw		nd−11[c]		1.6−54	nd−16					99
pectoral muscle	waste-recycling region, China	2010/22	ng/g lw	12	7.7								101
Matrix: Fishes													
shad and whitefish	Lake Maggiore, Italy	2011−2012/123	ng/g lw	nd	0.1−25	nd−2.4	nd[e]−0.9						105
fish	France	2014−2016/114	pg/g ww		nd−10 (17%)[d]	0.363	nd−0.17 (6%)	0.174	nd−10 (10%)			nd−300 (19%)	107
carp	Illinois, U.S.	2013−2014	ng/g lw			5.8			1.2	nd−64			109
largemouth bass	Illinois, U.S.	2013−2014	ng/g lw			3.2			1.5	nd−122			109
prey fish	waste-recycling site, China	2010/29	ng/g lw	15−227	2.2−6.7								101
Matrix: Human Serum													
male serum	Beijing, China	2016/12	pg/g lw	nd−43900 (25%)	326	nd−<50 (8.3%)	nd−<50 (8.3%)	nd−373 (58.3%)					110
maternal serum	Sherbrooke, Canada	2008−2009/102	ng/g lw	nd−123 (5.9%)	nd−16 (3.9%)				5.4	nd−164 (16.7%)			112
resident serum	Weifang, China	2014−2015/942	ng/g lw				nd	0.5−1.4					21
Matrix: Others													
ringed seal	Greenland	2012/9	ng/g ww	<0.12−0.3	<0.063−0.21				<0.064−1.46	<0.14			49
ringed seal	Canadian Arctic	1998−2013/477	ng/g lw		nd−0.3 (10.3%)	nd−0.55 (31%)	0.003−0.12 (4%)						117
chicken, beef, and mutton	BFR production area, China	2013/6	pg/g ww	100	0.8	0.1	0.5						34
chicken	China	2011	pg/g ww		20.1−80.9	nd−4.3	nd	nd−48.7					120
human milk	three European countries	2003−2012/458	ng/g lw		0.01−0.03	0.036−0.048		0.028−0.049	0.02−0.13	0.31−0.99			121
mollusk	Bohai Sea, China	2011/84	ng/g dw									0.15	41

[a]Date/n: sampling date and number. [b]Mean or median value. [c]Concentration range. [d]Detection frequency. [e]nd = not detected.

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DOI: 10.1021/acs.est.9b03159

found in sediment from solid waste landfill sites in Gauteng Province in 2013.[80] The TBBPA-DBPE concentrations in sediment from the Dongjiang River in 2006 ranged from 148 to 2300 ng/g dw with a mean value of 858 ng/g dw, which is markedly higher than those (<1.5−190 ng/g dw) detected in 2002, indicating increase in usage of TBBPA-DBPE in this region (Table 1).[48] In bottom sediment from an urban watershed in Singapore in 2014−2015, the TBECH concentrations ranged from 0.43 to 2.33 ng/g dw.[62] Occurrence of HBB, PBEB, and PBT in sediment was investigated in several studies, and detection rates of these compounds were generally less than 42% and concentrations were <LOD−1.33 ng/g dw.[20,37,62,81] In sediment cores collected from the North American Great Lakes in 2007, the concentrations of DBDPE, BTBPE, and TBECH in surface layers were 0.11−2.8, 0.13−8.3, and 0.05−1.4 ng/g dw, respectively. The time trends showed increasing concentrations of DBDPE and BTBPE with doubling times of 3−5 and 7 years in Lake Michigan, and 7 and 5 years in Lake Ontario, respectively.[82] Interestingly, the doubling times of DBDPE concentration in sediment in Arkansas, U.S. were 2.8−4.3 years during approximately the same time period. The faster doubling time of DBDPE in Arkansas may be due to the closer distance to production area where the production activities are the major source, whereas in relatively remote areas, the input may be controlled by release of DBDPE from products.[83] An increasing trend in the DBDPE concentration was also observed in sediment cores collected from Lake Maggiore, Italy and Daya Bay, China.[84,85] Compared with the North American Great Lakes and Arkansas, a higher doubling time of DBDPE was observed in Daya Bay with the value over 55 years, which indicates that the increasing rate of DBDPE was much slower in Daya Bay.

There are some studies concerning the occurrence of NBFRs in soil. McGrath et al. reported that mean concentrations of $\sum_{5}$NBFR (sum of PBT, HBB, EH-TBB, BTBPE, and DBDPE) were 36.0, 83.6 ng/g dw and not detectable (nd) in soil from manufacture area, waste disposal area, and nonindustrial area in Melbourne, Australia, respectively (Table 1).[86] Concentrations of NBFRs in rhizosphere soil and nonrhizosphere soil in Guiyu, China ranged from 11.6 to 70.8 and 8.98 to 144 ng/g, respectively,[87] which were lower than those reported in agricultural soil around a BFR-manufacturing region in north China (mean: 111 ng/g).[88] Concentrations of BTBPE in soil from background site, e-waste disposal area, and an adjacent town in Guiyu were 0.13−0.17, 0.43−15, and 0.47−5.3 ng/g, respectively (Table 1).[89] The concentration of BTBPE in soil from an e-waste disposal area in Guiyu was similar to or higher than those found for other e-waste disposal areas in China.[48,87,90]

3.1.5. Sludge. Sludge can be applied to land use, so it is a potential source of NBFRs in the environment. In sludges from three WWTPs in Catalonia, mean concentrations of DBDPE were 590 ng/g dw in the primary sludge and 723 ng/g dw in the secondary sludge,[57] which were comparable to those found in sludges from different WWTPs in Korea,[91] Harbin,[55,92] Guangzhou City, China,[48] and the U.S.,[18] with mean values ranging from 237 to 1180 ng/g dw, and 1 order of magnitude higher than those found in sludges from municipal WWTPs in China,[93] 31 WWTPs in Spain,[94] and 17 WWTPs in Catalonia,[95] with mean values ranging from 47.0 to 81.0 ng/g dw (Table 1). BTBPE was found in sludge from the biggest WWTP in Harbin, China (mean: 4.41 and 42.5 ng/g dw in aerobic and dewatered sludge, respectively) (Table 1).[92] Nevertheless, BTBPE was only found in the secondary sludge (mean: 18 ng/g dw) from one WWTP among five WWTPs in Catalonia, Spain.[57] Concentrations of DBDPE and BTBPE in nationwide sludge samples from four countries were compared (SI Figure S4).[18,91,93,94] Mean concentrations of DBDPE in sludge from the U.S. (485 ng/g dw) and Korea (237 ng/g dw) are obviously higher than those from China (52.5 ng/g dw) and Spain (47.0 ng/g dw), indicating a widespread use of DBDPE in the U.S. and Korea.[18,91] The mean BTBPE concentration in sludge from the U.S. (1960 ng/g dw) is 3 orders of magnitude higher than those from China (0.95 ng/g dw) and Korea (1.97 ng/g dw), which suggests that BTBPE may be largely used in the U.S.[18]

Low concentrations of HBB, PBEB, and PBT were found in sludge from municipal WWTPs in China,[93] 17 WWTPs in Catalonia, Spain,[95] and one WWTP in Drammen, Norway,[37] with the highest mean values of 0.55 ng/g dw for HBB, 0.25 ng/g dw for PBEB and 0.06 ng/g dw for PBT, respectively. Elevated levels of HBB (mean: 7.55 ng/g dw), PBEB (1.11 ng/g dw), and PBT (10.3 ng/g dw) were found in aerobic sludge from the biggest WWTP in Harbin (Table 1).[92] Generally, the concentration of TBPH in sludge was higher than that of TBB.[55,57] In the primary and secondary sludges from Catalonia, Spain and sludge from the biggest WWTP in Harbin, China, mean TBPH concentrations were 446, 695, and 160 ng/g dw, respectively, and mean TBB concentrations were nd, 7.2, and 5.3 ng/g dw, respectively. Mean concentrations of α-TBECH and β-TBECH were 15.5 and 8.8 ng/g dw, respectively in sludge from the biggest WWTP in Harbin.[55] High concentration of TBBPA-DBPE (mean: 4530 ng/g dw) was found in sludge from Guangzhou City, China (Table 1).[48]

3.2. Biota Samples. *3.2.1. Birds.* There are relatively few studies concerning the occurrence of NBFRs in birds. DBDPE, BTBPE, TBB, and TBPH were found at mean concentrations of 0.10, 0.015, 0.076, and 0.061 ng/g wet weight (ww), respectively, in black guillemot eggs from East Greenland (Table 2), which indicated the long-range transport of NBFRs.[49] Higher concentrations of HBB, PBEB, and PBT were found in eggs of peregrine falcons (range: 0.7−26, 0.2−3.9, and 0.3−14 ng/g lipids, respectively) than those in other prey birds (range: nd−12, nd, nd−11 ng/g lipids, respectively) from southern Germany (Table 2), which indicated the bioaccumulation of these compounds in peregrine falcons.[96] PBEB was only detected in two of 15 bald eagle plasma samples from the Great Lakes region, at an average level of 0.11 ng/g ww.[97] The concentrations of TBBPA-DBPE ranged from nd to 42.8 ng/g ww in herring gull egg pools from Laurentian Great Lakes of North America in 2001 to 2017. Retrospective analysis showed higher concentrations of TBBPA-DBPE in egg pools collected in more recent years, which indicates increased TBBPA-DBPE exposure to the gulls.[98]

The distribution of NBFRs in birds has been investigated and NBFRs were prone to distribute in kidney and liver compared with muscle.[48,99] In birds from an e-waste area in southern China, relatively higher concentrations of NBFRs were found in liver (DBDPE: 13.7−54.6, BTBPE: 0.27−2.41 ng/g lipid weight (lw)), and kidney (24.5−124, 0.12−0.83 ng/g lw), as compared to those in muscle (9.6−16.3, 0.07−0.39 ng/g lw).[48] Similar pattern was found for BTBPE, PBT, and PBEB in five bird species from Qingyuan county, China.[99]

DOI: 10.1021/acs.est.9b03159
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In pectoral muscle of birds from different areas in south China, concentrations of DBDPE were found in decreasing order from urban (median: 37−51 ng/g lw), suburban (8.2−23 ng/g lw), to rural areas (3.4−10 ng/g lw), which indicated that local industry activities were the major source of DBDPE in the studied areas.[100] DBDPE and BTBPE were also found in pectoral muscles of common kingfishers in an e-waste-recycling region in south China, with median values of 12 and 7.7 ng/g lw, respectively (Table 2).[101] The BTBPE concentration ranged from nd to 0.5 ng/g dw in tail feathers of Pakistani predatory bird species.[102] Mean concentration of TBPH in liver of ring-billed gull from a highly industrialized area of the St. Lawrence River, Canada reached to 2.16 ng/g ww.[103]

3.2.2. Fishes. To evaluate the bioaccumulation of NBFRs, some studies have investigated the occurrence of NBFRs in fishes. DBDPE was reported to occur in fishes from Dongjiang River (a highly polluted river), China at concentrations of 26−230 ng/g lw,[58] which were similar to or somewhat higher than those found in fishes (range: 15−227 ng/g lw) from an e-waste-recycling region in south China (Table 2).[101] However, the DBDPE concentrations were below the detection limit in fishes from Daugava River, Venta River, Latvia, and Lake Maggiore, Italy,[104,105] which are obviously lower than those from Dongjiang River and the e-waste-recycling region, suggesting that industry activities are important source of DBDPE.

BTBPE in fishes from Lake Maggiore, Italy ranged from 0.1 to 25 ng/g lw,[105] which were comparable with those found in fishes (range: 2.2−6.7 ng/g lw) from an e-waste recycling region in south China (Table 2).[101] Nevertheless, extremely low concentrations of BTBPE (almost all below the limit of detection) were found in fishes from Daugava River and Venta River, Latvia[104] and Qingyuan county, China[105] and France.[106]

Low concentrations of HBB and PBEB were found in fishes from Lake Maggiore, Italy and France, with the highest values of 2.4 ng/g lw for HBB and 0.9 ng/g lw for PBEB, respectively (Table 2).[105,107] Relatively high concentration of HBB (range: 0.8−240 ng/g lw) was detected in four fish species from fish ponds in an e-waste recycling site in Qingyuan county, China, which was possibly related to the release of e-wastes. In the same samples, the PBT concentration ranged from nd to 1.8 ng/g lw,[106] which was 3−4 orders of magnitude higher than that detected in fishes (median: 0.174 pg/g ww) from France.[107] The PBEB concentrations ranged from nd to 0.091 ng/g ww with the detection frequency of 56.9% in six fish species from the Laurentian Great Lakes, Canada.[108] TBB and TBBPA-DBPE in fishes from France ranged from <LOD to 10.0 and <LOD to 300 pg/g ww, with detection rates of 10% and 19%, respectively.[107] In carp and largemouth bass from streams and lakes across the state of Illinois, median concentrations of TBB were 1.2 and 1.5 ng/g lw, respectively, while median concentrations of TBPH were below the detection limit (Table 2).[109]

3.2.3. Human Serum. Few studies are available on the occurrence of NBFRs in human serum. DBDPE was found at concentrations of 9100 to 43 900 pg/g lw in 3 of 12 male sera from Beijing, China (Table 2).[110] High DBDPE concentration (mean: 125 ng/g lw) was detected in serum from dismantling workers in a rural e-waste region in Wenling, China, whereas the mean DBDPE concentrations dropped to 56.1 and 13.8 ng/g lw in serum from nonoccupational residents in the rural e-waste area and urban residents, respectively.[111] The result indicates that e-waste recycling activities are an important potential source of DBDPE. DBDPE was rarely (detection rates less than 5.9%) found in human sera from other places as reported in earlier studies.[112−114]

Relatively higher concentrations of BTBPE were found in human sera from electronics stores (mean: 0.5 ng/g lw), as compared to those from university (0.2 ng/g lw) and clothing stores (0.1 ng/g lw).[115] Comparable BTBPE concentrations were found in human sera from Norway (range: nd−0.99 ng/g lw)[114] and Beijing, China (nd−2.56 ng/g lw) (Table 2).[110] Some other studies have also detected the concentrations of BTBPE in human serum and the detection rates were less than 3.9%.[112,113,116]

PBT was found at concentration of 109−373 pg/g lw in 7 of 12 serum samples in Beijing, whereas HBB and PBEB were only found in one sample with levels lower than 50 pg/g lw.[110] Similar pattern was found in 20 human serum samples from Weifang, China where the PBT concentration ranged from 0.50 to 1.4 ng/g lw, whereas HBB was only detected in three samples and PBEB was not detected.[21] TBB and TBPH in maternal sera from Sherbrooke, Canada ranged from nd to 68 and nd to 164 ng/g lw, respectively (Table 2).[112] TBB was also found at concentrations of 50 pg/g lw in human cord blood from Belgium.[113]

3.2.4. Others. Mean DBDPE concentrations in skin, muscle, liver, spleen, and kidney of adult Chinese alligators were 55.4, 30.2, 4.74, 49.9, and 192 ng/g lw, respectively, and they dropped to 1.10 and 0.16 ng/g lw in neonate alligators and alligator eggs, respectively, which suggests that the maternal transfer potential of DBDPE is limited in Chinese alligators.[33] TBBPA-DBPE was found at concentrations ranging from <0.008 to 1.41 ng/g dw (mean: 0.15 ng/g dw) in 32% mollusk samples from the Bohai Sea, China (Table 2).[44]

NBFRs were reported to occur in biota from remote areas, indicating long-range transport potential of these compounds.[49,117] HBB (detection rate: 31%), BTBPE 10.5%, TBB (23%) and TBPH (19%) were infrequently found in blubber of ringed seals collected from the Canadian Arctic during 1998−2013, and the highest concentrations were 0.55, 0.30, 0.36, and 0.34 ng/g lw, respectively.[117] DBDPE, BTBPE, and TBB were found at a concentration range of <0.12−0.30, < 0.063−0.21, and <0.064−1.46 ng/g ww in blubber of ringed seals from Greenland, respectively (Table 2).[49] Mean concentrations of PBEB and HBB in male belugas collected from the St. Lawrence Estuary, Canada in 1997−2013 were 2.26−9.04 and 6.47−31.8 ng/g lw, respectively. The temporal trends showed that the HBB concentrations decreased while the PBEB concentrations did not vary over the study period, which suggests that there were continuous inputs of PBEB to the estuary.[118] PBEB was found at concentrations ranging from <0.34 to 35 ng/g ww in harbor porpoise blubber from the UK.[119]

Occurrence of NBFRs in food has been investigated. Mean concentrations of DBDPE, HBB, PBT, and PBEB were 100, 0.8, 0.5, and 0.1 pg/g ww in three types of meat (chicken, beef, and mutton), respectively.[38] The concentrations of HBB, PBT, and BTBPE in chicken from four different places of China (Sichuan, Fujian, Jilin, Henan) were in the range of nd−4.3, nd−48.7, and 20.1−80.9 pg/g ww, respectively (Table 2).[120] In human milk from three European countries (Norway, The Netherlands, Slovakia), mean concentrations of HBB and PBT were 0.036−0.048 and 0.028−0.049 ng/g lw, respectively, and PBEB were rarely found (detection rate in human milk: Norway 2%, The Netherlands 0%, Slovakia 3%) (Table 2).[121]

DOI: 10.1021/acs.est.9b03159
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4. ENVIRONMENTAL BEHAVIORS

4.1. Photodegradation. The photodegradation of DBDPE involves formation of subsequent debrominated products, and matrixes play an important role in the photolysis process.[34,122] The photodegradation of DBDPE and deca-BDE, both are incorporated into high-impact polystyrene, was investigated. Deca-BDE degraded with a half-life of 51 days while no obvious loss of DBDPE was observed throughout the experimental period of 224 days.[123] However, in another study, DBDPE degraded a little faster than deca-BDE, with half-lives of 16.6 and 18.1 min in *n*-hexane under ultraviolet light, respectively.[34] In other matrixes under ultraviolet light, the half-lives ($t_{1/2}$) of DBDPE were in the order of tetrahydrofuran ($t_{1/2}$ = 6.0 min) > humic acid/water (30 < $t_{1/2}$ < 60 min) > silica gel ($t_{1/2}$ = 75.9 min) > methanol/water ($t_{1/2}$ > 240 min). However, the matrixes had little effect on the degradation products of DBDPE where several similar debrominated intermediates were identified under photolysis process with different matrixes (SI Figure S5).[34]

For BTBPE, both ether bond cleavage and debromination are considered to be the main photodegradation pathways (SI Figure S5).[124] In addition, debromination on the positions ortho to the ether oxygen bonds compared with the para position is considered to be easier. Notably, some highly toxic degradation products, such as 2,4,6-tribromophenol and 2,4-dibromophenol, were identified, and release of these degradation products into the environment may enhance the potential risk of BTBPE. PBT and PBEB in raw hospital wastewater exhibited 14.2% and 15.9% removal rates within 45 min under UV light irradiation. When 0.25 g/L nano-CeO_2 was added, the photodegradation rates rose to 77% for PBT and 75% for PBEB. The higher photodegradation rates were attributed to the generated hydroxyl radicals owing to the addition of nano-CeO_2.[125]

In three kinds of matrixes (toluene, methanol, tetrahydrofuran) under sunlight, di- and tribrominated analogues of TBB and TBPH were identified as the most dominant photodegradation products, and sequential reductive debromination was the dominant photodegradation process (SI Figure S5).[126] Half-lives in toluene, methanol, and tetrahydrofuran were 162, 94.6, and 85.7 min for TBB and 147, 220, and 168 min for TBPH, respectively. The quantum yield value of TBBPA-DBPE in polystyrene films (0.84) was significantly higher than that in tetrahydrofuran (0.19), which could be attributed to a higher hydrogen donor capacity of polystyrene or π-π stacking between polystyrene and NBFRs. Successive debromination, ether bond cleavage, H-abstraction, C−C scission, or oxidation, occurs in the process of photodegradation. Hydroxylated and ether bond ruptured products are formed from oxidation of the phenyl side of primary debrominated intermediates.[127]

4.2. Thermal Degradation. Thermal degradation products of BTBPE are found to depend on their removal rates from hot reaction zone. Two main degradation products, tribromophenol and vinyl tribromophenyl ether, are formed through the cleavage of the aliphatic C−O bond at 340 °C. It is noteworthy that high toxic compounds, such as dibenzodioxins, were produced in the case of slow removal from the hot reaction zone.[128] Therefore, high temperature may lead to the generation of high toxic compounds in the presence of BTBPE or other NBFRs, making a more serious environmental hazard. In another study, two potential debromination products of DBDPE were found, which were probably attributed to the thermal degradation during instrumental analysis.[58]

4.3. Biodegradation and Biotransformation. Though there was no direct study concerning microbial degradation of NBFRs by specific bacteria or fungi, there were two studies about the degradation of several NBFRs in soil, which was attributed to the microbial process.[129,130] Biodegradation of NBFRs is tightly related to the oxygen condition which plays an important role in the activity of microorganisms. Nyholm et al. found that the half-life of HBB was 22 days in aerobic soil, and it rose to 120 days in anaerobic soil. Half-lives of TBECH were 21, 36, and 23 days in aerobic soil spiked with 0.5% (w/w) of activated sludge, aerobic soil spiked with 0.5% (w/w) of digested sludge and anaerobic soil spiked with 0.5% (w/w) of activated sludge, respectively.[129] In another study, biodegradation process of TBECH was divided into two phases (fast degradation in 0−90 days and slow degradation in 90−360 days). Half-lives were 63, 617 days for α-TBECH and 68 and 614 days for β-TBECH during the two phases, respectively.[130] The different half-lives of TBECH in the two studies may be ascribed to the difference in microorganisms in soil and the added sludge.

Unlike the photodegradation of DBDPE, recent studies indicated that debromination to lower brominated DBDPEs was not the primary biotransformation pathway for DBDPE.[131,132] No evidence showed simply debrominated metabolites of DBDPE in liver microsomes from various mammals, although greater depletion of DBDPE (44−74% of 90 pmol) occurred. Formation of two phenolic was observed.[131] After orally administrating with corn oil containing 100 mg/kg body weight (bw)/day of DBDPE to male rats for 90 days, seven unknown compounds, whose relative retention times were not consistent with debrominated products of DBDPE, were observed in rats. Through gas chromatograph/electron impact-mass spectrometer analysis, two compounds were momentarily considered as $MeSO_2$-nona-BDPE and $EtSO_2$-nona-BDPE (SI Figure S6).[132]

After exposure of BTBPE for 42 days, dibromophenol was found in fathead minnows and it mirrored the fate of BTBPE in vivo, which suggested that dibromophenol was formed from metabolism rather than accumulation from the environment.[133] This could be confirmed by the study of Hakk et al, where biotransformation of BTBPE in rats included a series of debrominations, oxidations, and ether cleavages, which accounted for the formation of dibromophenol from BTBPE.[10] In another dietary exposure study, no metabolism of BTBPE was observed in juvenile rainbow trout (*Oncorhynchus mykiss*), which may be ascribed to the minor biotransformation or storage of BTBPE-metabolites or the greater debromination ability of cyprinids than salmonids.[133,134]

In human and rat tissues, 2,3,4,5-tetrabromobenzoic acid (TBBA), formed via cleavage of the 2-ethylhexyl chain, was detected as a metabolite of TBB. And carboxylesterase was considered responsible for the metabolism of TBB. Mono (2-ethylhexyl) tetrabromophthalate, as a metabolite of TBPH, was formed in purified porcine carboxylesterase, although no metabolites of TBPH were detected in rat and human tissues (SI Figure S6).[135] As a urine biomarker of the Flame Retardant Mixture Firemaster 550 (FM550, TBB is the major component), TBBA was significantly increased in urine of FM550-exposed rats, which indicated that TBBA was rapidly formed from metabolism of FM550.[136] De Joudan et al. have

DOI: 10.1021/acs.est.9b03159
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exposed BZ-54 (mixture of TBB and TBPH) to fathead minnows and found a lack of consistent accumulation of TBB and TBPH in fishes, with several brominated transformation products detected.[133]

The biotransformation of NBFRs may undergo different pathways in different microsomes. Through rat liver microsome, monohydroxy-TBECH (OH-TBECH) and dihydroxy-TBECH ($(OH)_2$-TBECH) were identified while no debrominated TBECH metabolites were identified, which suggested that debromination of TBECH via cyctochrome P450 catalysis did not occur.[137] However, in human liver microsome, besides OH-TBECH and $(OH)_2$-TBECH, mono- and dihydroxylated TriBECH were also identified, which showed that the biotransformation of TBECH included cyctochrome P450-catalyzed debromination in human liver microsome.[138] Monohydroxylated TriBECH was formed by direct debromination of OH-TBECH or through hydroxylation of debrominated TBECH.

TBBPA-DBPE was poorly absorbed in gut lumen after oral administration (20 mg/kg) to male fischer-344 rats and the absorbed was rapidly sequestered in liver, with slow metabolism.[139] Fathead minnow was found to accumulate TBBPA-DBPE and TBBPA was measured in its body, which can be the result of biotransformation of TBBPA-DBPE (SI Figure S6).[133]

4.4. Bioaccumulation and Biomagnification. NBFRs are lipophilic and have a potential of bioaccumulation and biomagnification. Evidence shows that NBFRs can bioaccumulate and biomagnify in specific species, which should be a concern owing to their potential environmental risks.[58,140] Bioaccumulation factors (BAFs) of DBDPE were between 6.1 and 7.1 in three fish species (*Cirrhina molitorella*, *Tilapia nilotica*, and *Hypostomus plecostomus*) from Dongjiang River, China.[58] DBDPE was found to be bioavailable to oligochaete *Lumbriculus variegatus* with a biota-sediment accumulation factor (BSAF) of 0.0192 g organic carbon/g lipid.[141] However, in another study, DBDPE was below the detection limit in all studied biological samples including *Dreissena polymorpha* and *Rutilus rutilus*, in spite of high concentration in sediments.[134] Biomagnification factors (BMFs) of DBDPE calculated from common kingfishers (*Alcedo atthis*) and their prey fish were 0.10−0.77, suggesting that no biomagnification of DBDPE occurred in the kingfishers.[101] But in a Lake Winnipeg (Canada) food web, except a BMF value of 0.2 derived from white fish/emerald shiner (predator/prey), the BMF values of DBDPE ranged from 1.6 to 9.2 in other predator/prey pairs, which showed the biomagnification of DBDPE within the food web.[140] The different BMFs of DBDPE may be ascribed to the different types of consumers and the different composition of the predators' diet.[101]

BAFs of BTBPE ranged from 3.32 to 6.08 in two aquatic invertebrates, three fish species and one reptile.[142] From common kingfishers (*Alcedo atthis*) and their prey fish, the calculated BMFs ranged from 1.90 to 3.60 in the kingfishers,[101] which were similar to those calculated from several predator/prey pairs, such as emerald shiner/zooplankton (BMF = 2.5) and walleye/whitefish (BMF = 2.4) in the Lake Winnipeg (Canada) food web,[140] as well as juvenile rainbow trout (BMF = 2.3) exposed to environmentally relevant concentration of BTBPE via their diet.[134] This suggested that biomagnification of BTBPE occurred in these species. Nevertheless, BMFs of BTBPE ranged from 0.1 to 0.9 in several other predator/prey pairs in the Lake Winnipeg (Canada) food web, indicating no biomagnification in these species.[140]

Trophic magnification factor (TMF) of HBB in an aquatic food chain (invertebrates and fish) in south China was 2.1.[106] PBT and PBEB exhibited the biomagnification potential in waterbirds from south China.[99] BAFs were greater than 3.7 for HBB and 3.3 for PBEB and PBT in most of the investigated aquatic species from a natural pond in south China, showing the bioaccumulation potential in these species.[142] Nyholm et al. have examined the bioaccumulation potential of HBB in earthworms (*Eisenia fetida*) and found that level of HBB, degree of soil aging and soil types affected the bioaccumulation of HBB.[143]

Metabolic rates in organisms can exert a significant influence on the bioaccumulation and biomagnification of NBFRs. In an aquatic food web of Lake Taihu, China, TBPH was found to biomagnify in the food web (TMF = 2.42), while β-TBECH did not biomagnify or underwent trophic dilution (TMF = 0.39).[144] The reason for this phenomenon was that TBPH showed no significant metabolism while β-TBECH exhibited a rapid metabolism in the fish species. After exposure to BZ-54 (mixture of TBB and TBPH), fathead minnows exhibited a limited accumulation of TBB and TBPH,[133] which may also be ascribed to the rapid metabolism of these compounds in fathead minnows.

5. TOXICITY

5.1. In Vitro Studies. In vitro effects of NBFRs have been investigated. Although no overt signs of toxicity were observed in chicken embryo treated with even up to the highest exposure dose (0.2 μM), DBDPE up-regulated the expression of CYP1A4/5 to a maximum of 29- and 53-fold at 0.1 and 0.2 μM, respectively, and up-regulated the expression of DIO1 mRNA to a maximum of 1.9-fold at 0.1 μM.[145] In another study, DBDPE was found to cause the induction of ethoxyresorufifin-O-deethylase (EROD) activity at low test concentrations (0−0.0129 μM) in rainbow trout hepatocyte, whereas the EROD activity started to decrease immediately at the lowest test concentration in brown trout hepatocyte.[9] Through inhibiting formation of 3,3′,5-triiodothyronine and 3,3′-diiodothyronine from deiodination of 3,3′,5,5′-tetraiodothyronine, with median inhibitory concentration (IC_{50}) of 0.16 μM in human liver microsome, DBDPE was found to be the first nonhydroxylated contaminant inhibiting thyroid hormone deiodinase activity.[146]

BTBPE induced CYP1A4/5 mRNA level in chicken embryonic hepatocyte up to a maximum of 115- and 18-fold at ≥0.03 and 0.1 μM, respectively, which may be ascribed to structural resemblance of BTBPE to dioxin-like compounds (a traditional indicator of CYP1A induction).[145] Meanwhile, BTBPE inhibited DIO3 expression in a concentration-dependent manner, which may be related to a similar hepatic response to the presence of a thyroid hormone-like compound.[145] In another study, BTBPE was found to reduce β-galactosidase production by about 12.2% at concentration of 14.5 μM in β-galactosidase assay, and to inhibit yeast luminescence by 31% at concentration of 12.1 μM in luminescent assay, suggesting that BTBPE may possess antiestrogenic effects.[147]

HBB was found to activate aryl hydrocarbon receptor (AhR) at weaker potency as compared to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). PBT was found to stimulate AhR transformation into a DNA binding form in gel retardation

DOI: 10.1021/acs.est.9b03159
Environ. Sci. Technol. 2019, 53, 13551−13569

Table 3. Summary of Toxicity Data and PNECs of NBFRs[a]

compounds	cell line/species	assay	exposure route/duration/end points	concentration	$PNEC_{WATER}$	$PNEC_{SEDIMENT}$	ref
DBDPE	rabbits		dermal, −, acute toxicity LD_{50}	>2000 mg/kg bw			150
	rats		oral, 90 days, LD_{50}	>5000 mg/kg bw			150
	Daphnia magna		−, 48 h, EC_{50}	19 μg/L	0.019 μg/L[c]		9
	Chironomus riparius		−, 28 days, development rates NOEC	5000 mg/kg		100 mg/kg dw[b]	162
BTBPE	rats		inhalation, −, 4 h, LC	>36.7 g/m^3			150
	rabbits		dermal, −, lethal dose	>10 g/kg			150
HBB	rats		intraperitoneal, −, LOAEL	150 mg/kg bw			150
	zebrafish		−, embryo mortality, LC_{50}	10.7 mg/L	10.7 μg/L[c]		164
PBEB	rabbits		−, −, LD_{50}	>8 g/kg			150
PBT	rats		oral, 91 days, NOAEL	0.35 mg/kg/d			150
TBB	MDA-kb2 cell line	AR reporter gene assays	−, −, antiandrogenic activity IC_{50}	43.5 μM			151
	MDA-kb2 cell line	GR reporter gene assays	−, −, antiglucocorticoid activity IC_{50}	1.9 μM			151
	zebrafish		−, embryo mortality, LC_{50}	7.0 mg/L	7.0 μg/L[c]		164
TBPH	MDA-kb2 cell line	AR reporter gene assays	−, −, antiandrogenic activity IC_{50}	0.1 μM			151
	MDA-kb2 cell line	GR reporter gene assays	−, −, antiglucocorticoid activity IC_{50}	0.3 μM			151
	Daphnia magna		−, 48 h, LC_{50}	0.91 mg/L	0.91 μg/L[c]		167
TBECH	HepG2	Receptor binding-assay	−, bind tightly to the receptor, IC_{50}	163 nM			149
	HepG2	AR activation assay	−, −, androgenic activity IC_{50}	42.7 nM			149
Penta-BDE	*Daphnia magna*		−, 48 h, mortality NOEC	5.3 μg/L	0.53 μg/L		175
BTBPE/PBEB/PBT					0.53 μg/L[d]		
penta-BDE	*Lumbriculus variegatus*		flow through, 28 days, survival/reproduction NOEC	3.1 mg/kg dw		1.55 mg/kg dw	175
BTBPE/HBB/PBEB/PBT/TBB						1.55 mg/kg dw[d]	
octa-BDE	*Lumbriculus variegatus*		flow through, 28 days, survival/reproduction NOEC	≥1270 mg/kg dw		≥127 mg/kg dw	176
TBPH						≥127 mg/kg dw[d]	

[a]−: not available from the literature. [b]$PNEC_{SEDIMENT}$ of DBDPE is adopted from ref 162. [c]$PNEC_{WATER}$ of DBDPE, HBB, TBB, TBPH are calculated through dividing the lowest acute toxicity value (EC_{50} or LC_{50}) by a safety factor of 1000. [d]$PNEC_{WATER}$ of BTBPE, PBEB and PBT refer to $PNEC_{WATER}$ of penta-BDE; $PNEC_{SEDIMENT}$ of BTBPE, HBB, PBEB, PBT and TBB refer to $PNEC_{WATER}$ of penta-BDE; $PNEC_{SEDIMENT}$ of TBPH refers to $PNEC_{SEDIMENT}$ of octa-BDE.

assay, but was not or weakly active in chemically activated luciferase expression (CALUX) assay.[148] In another study, HBB was not able to activate human androgen receptor (AR) at 100 μM in human hepatocellular liver carcinoma cell.[149] No mutagenic activity was observed for PBEB and PBT according to the *Salmonella typhimurium* assay.[150]

TCDD-like effect or agonistic effect were not observed for TBB and TBPH at tested concentrations (0−0.91 μM for TBB and 0.0425−2120 μM for TBPH, respectively), while 0.91 μM exposure of TBB caused a maximal antiestrogenic effect of 62% in the yeast estrogen screen assay and 425 μM exposure of TBPH produced a maximal antiandrogenic effects of 74% in the yeast androgen screen assay.[39] Using the luminiscence assay and the sensor strain *S. cerevisiae* BMAEREluc/AR, no estrogenic and androgenic activities of TBPH were observed even at the highest test concentration (2.8 μM).[147] Through the luciferase reporter gene assay, IC_{50} of TBB and TBPH were identified to be 1.9 and 0.3 μM for antiglucocorticoid activity, 43.5 and 0.1 μM for antiandrogenic activity, and 37.5 and 0.1 μM for antithyroid hormonal activity, respectively (Table 3).[151] TBB and TBPH were also found to exert significant effects in the H295R steroidogenesis assay where 0.091 μM exposure of TBB and 21.2 μM exposure of TBPH resulted in a 2.8- and 5.4-fold increase in concentrations of 17-β-estradiol, respectively.[39] Based on the transactivation assay in HepG2 cell, potent agonist activity and antagonist activity on pregnane X receptor (PXR) were found for TBPH, with median effect concentration (EC_{50}) and IC_{50} of 5.5 and 13.9 μM, respectively, and both TBB and TBPH were found to significantly up-regulate expression of CYP3A4 via PXR activation, which would initiate endocrine disruption effect.[152] Through primary porcine testicular cell, TBB (0.009−0.91 μM) was found to not affect sex-steroid production and TBPH at the greatest concentration (21 μM) induced production of sex hormones including testosterone and estradiol.[153]

Tight binding to androgen receptor (AR) was observed for TBECH in human hepatocellular liver carcinoma cell, with an IC_{50} of 163 nM, and relevant androgenic activity was observed in AR activation assay test, with an IC_{50} of 42.7 nM, which indicates that TBECH can activate the human AR (Table 3).[149] Another study found that TBECH-γ and δ were more potent activators of human AR than TBECH-α and β.[154] AR

DOI: 10.1021/acs.est.9b03159
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agonistic effects of isomers of TBECH in chicken LMH cell line were examined. TBECH-β did not result in any activation and TBECH-γ and TBECH-δ at 10 μM resulted in 15% induction of AR activation by reference to the testosterone level.[155] TBECH was identified as a weak activator of zebrafish AR in comparison with being activator of human AR, and for both zebrafish AR and human AR, β-isomer was the weakest activator among the TBECH isomers.[156] The phenomenon may be attributed to the different sequence between ARs from different species.[155]

5.2. In Vivo Studies. Acute toxicity was not observed for DBDPE in rat and rabbit, with median lethal doses (LD_{50}) greater than 5000 and 2000 mg/kg bw, respectively (Table 3).[150] Although no overt toxicity was observed in male rat after oral administration of 100 mg/kg/d DBDPE for 90 days and in Balb/C mouse after oral administration of DBDPE with highest dose of 200 mg/kg/d for 30 days, DBDPE was found to have activity on endocrine disruptors and alter thyroid hormone homeostasis, which leads to a series of adverse effects.[24,132]

No mutagenicity was observed for BTBPE in *Salmonella typhimurium* strain and *Saccharomyces cerevisiae* strain test.[150] Lethal concentrations of BTBPE were greater than 36.7 g/m^3 for rat after inhalation for 4 h and 10 g/kg for rabbit after dermal exposure, accompanying with nutritional and metabolic changes (Table 3).[150] In a epidemiologic study, the level of total 3,3′,5-triiodothyronine in serum of adult men was positively associated with concentrations of BTBPE and TBPH in house dust, which indicated high levels of BTBPE and TBPH may cause thyroid hormone disruption.[157]

Although no histopathological changes in mouse administered with 20−90% of lethal doses were found for HBB, increased malondialdehyde levels in liver and gamma-glutamyltransferase activity in serum as well as declining liver glutathione levels were observed.[158] Intraperitoneal exposure to HBB in rat induced biochemical effects on liver, with the lowest observed adverse effect level (LOAEL) reported at 150 mg/kg bw.[150] Oral exposure to HBB in quail and chicken induced change of enzyme activity in blood and tissues, with the LOAEL values reported at 1.5 g/kg/15 days and 52.5 g/kg/12 weeks, respectively (Table 3).[150] Administration to different doses (15, 75, and 375 mg/kg HBB) in female rat for 28 days increased excretion of coproporphyrin and 5-aminolevulinic acid and elevation of microsomal P450 level, which suggests that HBB has porphyrogenic activity in female rat.[159] No observed adverse effect level (NOAEL) was determined as 0.35 mg/kg/d in rat after oral administration of PBT at different doses (from 0.003 to 40 mg/kg/d) for 91 days. The lethal concentration of PBT in fish was greater than 5 mg/L and acute toxicity of PBEB has been tested in rabbit, with LD_{50} values greater than 8 g/kg (Table 3).[150]

Dietary exposure to different technical TBECH doses (0−5000 mg/kg) in rat for 28 days altered serum triiodothyronine and thyroxine levels in female and serum testosterone levels in male.[160] After exposure of 0.239 ng β-TBECH/g/d to kestrel by diet, androgen-dependent behaviors including copulation and aggression in male were increased.[42]

5.3. Ecotoxicity in Aquatic Organisms. There have been some studies examining the toxicity of NBFRs in aquatic organisms. Exposure of DBDPE at different doses (10, 50, and 100 mg/kg) evoked oxidative stress in *Carassius auratus* with longer exposure time.[161] Acute toxicity of DBDPE to water flea was tested, with a 48 h EC_{50} value of 19 μg/L, and DBDPE exposure (12.5 and 25 μg/L) raised mortality of hatched larvae and reduced the hatching rate of zebrafish egg (Table 3).[9] However, no marked acute toxicity was observed for DBDPE in fish, algae and *Daphnia magna* even treated with 110 mg/L.[162] In another study, DBDPE was found to pose low neurotoxicity to embryo-larval zebrafish, although malformation and mortality of zebrafish were not affected even at the highest concentration tested (1000.0 μg/kg dry sediment).[163]

After environmentally relevant concentration (46.2 ng/g lw) exposure of BTBPE to rainbow trout for 49 days, no obvious change in circulating thyroid hormone concentration, thyroid glandular histology and liver deiodinase enzyme activity was observed, which suggests that BTBPE was not a potent thyroid axis disruptor for rainbow trout.[134] Waterborne exposure to HBB in zebrafish embryo caused the embryo mortality with LC_{50} reported at 10.7 mg/L.[164] Intraperitoneal exposure to HBB and PBT at different doses (10 and 100 mg/kg) in fish (*Carassius auratus*) evoked oxidative stress.[165]

Acute genotoxicity of TBB and TBPH was evaluated in fathead minnow and DNA damage in liver cell was observed in fathead minnow after oral exposure to 1 mg/fish/day of Firemaster 550 and Firemaster BZ-54, two brominated formulations (both contain TBB and TBPH).[166] Acute toxicity of Firemaster 550, Firemaster BZ-54 and TBPH to freshwater crustacean *Daphnia magna* was examined, with 48 h LC_{50} values of 0.486, 0.5, and 0.91 mg/L, respectively (Table 3), which shows that these substances were highly toxic to aquatic organisms according to regulation of the USEPA (chemical with LC_{50} values of 0.1−1 mg/L is defined as highly toxic).[167] Another study reported that TBB exposure induced mortality and malformation in zebrafish embryo with LC_{50} at 7.0 mg/L (Table 3), while no adverse effect was observed for TBPH in zebrafish embryo even at the highest concentration (20 mg/L).[164]

No apparent effect on liver or gonad development in juvenile brown trout (*Salmo trutta*) was observed for β-TBECH even at the highest dietary exposure dose of 118.4 ± 3.1 pmol/g. However, thyroid axis disruption in juveniles was observed for β-TBECH. During the uptake phase, significant reduction in total plasma thyroxine in the high dose group (118.4 ± 3.1 pmol/g) and marked increase in mean thyroid epithelial cell height in all dose groups were observed.[31,168] Androgenic activity and adverse effects of TBECH on zebrafish physiology were illustrated by delayed hatch at 0.428 and 4.28 mg/L doses and morphological abnormalities and juvenile mortality at 4.28 mg/L doses in zebrafish.[156] Developmental toxicity, immunotoxicity and locomotor behavioral toxicity of TBECH on early life zebrafish were also observed through continuously waterborne exposure at different doses (0.004-4.280 mg/L).[169]

5.4. Ecological Risk Assessment. Owing to the ubiquitous occurrence in various environmental matrices and the potential toxicity to diverse organisms, it is important to conduct an ecological risk assessment for NBFRs. Here, the assessment of environmental risk is based on the risk quotient (RQ), which is calculated as a quotient of measured environmental concentration (MEC) and predicted no effect concentration (PNEC).[170] PNEC can be calculated as a quotient of toxicological relevant concentration and a safety factor which ranges from 1 to 1000. The accuracy of PNEC depends on the availability of dose−effect data for all environmental compartments and the sufficient number of species tested.[171] In this study, PNEC values of NBFRs are

DOI: 10.1021/acs.est.9b03159
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adopted from literature first. When there are no available data, the PNECs are calculated by dividing the lowest acute toxicity value (EC_{50} or LC_{50}) by a safety factor of 1000, which has been used in ecological risk assessments.[172] The calculated RQs can be divided into several grades that indicate different ecological risks: RQ < 1.0 indicates no significant risk; 1.0 ≤ RQ < 10 indicates little potential for adverse effects; 10 ≤ RQ < 100 indicates significant potential for adverse effects; RQ ≥ 100 indicates that potential adverse effects should be expected.[170]

Hardy et al. have calculated PNECs of DBDPE for microorganisms in sewage treatment plant ($PNEC_{STP}$), soil-dwelling organism ($PNEC_{SOIL}$) and sediment organism ($PNEC_{SEDIMENT}$) and the values were 2500, 156, and 100 mg/kg, respectively.[162,173] $PNEC_{WATER}$ of DBDPE, HBB, TBB, and TBPH are calculated through dividing the relevant EC_{50} or LC_{50} values (48 h EC_{50} of water fleas: 19 μg/L, LC_{50} of zebrafish embryo: 10.7 mg/L, LC_{50} of zebrafish embryo: 7.0 mg/L, 48 h LC_{50} of *Daphnia magna*: 0.91 mg/L) by a safety factor of 1000, and the resulting $PNEC_{WATER}$ of DBDPE, HBB, TBB, and TBPH are 0.019, 10.7, 7.0, and 0.91 μg/L, respectively. In "Statlig program for forurensningsovervåking", owing to limited toxicity data, the PNECs of NBFRs were set according to the similar structures to PBDEs.[174] By referring to the PNEC value of pentaBDE,[175] the $PNEC_{WATER}$ values of BTBPE, PBEB, and PBT were set at 0.53 μg/L (derived from no observed effect concentration (NOEC) of *Daphnia magna*) and the $PNEC_{SEDIMENT}$ values of BTBPE, HBB, PBEB, PBT, and TBB were set at 1.55 mg/kg dw (derived from NOEC of *Lumbriculus variegatus*). The $PNEC_{SEDIMENT}$ of TBPH was set at ≥127 mg/kg dw (derived from NOEC of *Lumbriculus variegatus*), which was referred to the PNEC value of octaBDE (Table 3).[176]

With the summary of measured environmental concentration data and PNECs, the RQs of NBFRs were evaluated. The highest RQ of NBFRs is 0.01 for BTBPE which is a quotient of MEC (5.22 ng/L) and $PNEC_{WATER}$ (0.53 μg/L). Most RQs calculated from the MEC and $PNEC_{SEDIMENT}$ of NBFRs are far less than 1.0, indicating no significant risk. In the worst scenario, the RQ calculated from the highest MEC (13 900 ng/g dw) and $PNEC_{SEDIMENT}$ (1.55 mg/kg dw) is 8.97 for TBPH, which indicates little potential for adverse effects. From the preliminary results, it can be seen that the select NBFRs have little ecological risk. However, it should be noted that owing to the limited toxicity data, the accuracy of PNECs are debatable. In addition, there is evidence that NBFRs can bioaccumulate and biomagnify in organisms through the food chain, which can increase their potential environmental risks. Therefore, more data on the toxicity, environmental occurrence and behaviors of NBFRs are needed for better assessing their environmental risks.

6. CONCLUSIONS AND FURTHER RESEARCH

Available data show that as replacements of traditional BFRs, NBFRs are ubiquitous in various environmental matrices (air, dust, water, soil, sludge, fishes, birds, and human tissue). Concentrations of NBFRs in samples collected from e-waste recycling sites and manufacture areas are generally higher than those from other places. Special attention should be paid to environmental issues in e-waste recycling sites and manufacture areas owing to the greater environmental risks of NBFRs. However, the data concerning spatial and temporal trend in concentrations of NBFRs are scarce. More attention should be paid to this aspect in further studies in order to better evaluate their potential risks. In addition, although there have been studies on occurrence of NBFRs in different environmental compartments, transportation of NBFRs between environmental compartments is rarely studied, which is vital for understanding the environmental fate of NBFRs. Therefore, further studies are also needed in this field.

Environmental behaviors of NBFRs summarized in this review show that NBFRs generally degrade to corresponding debromination products along with some others through photodegradation and biodegradation. Unfortunately, current studies concerning photodegradation of NBFRs are mainly performed in an artificial environment instead of a natural environment, and the degradation mechanisms and influence factors are not fully understood. Further studies can be focused on these aspects for better understanding of the environmental fate of NBFRs. The degradation products/metabolites should also be worthy of attention as these compounds may possess persistent, bioaccumulative, and toxic characteristics that will cause potential environmental risks.

Although there have been a few studies concerning biodegradation of NBFRs in soil, no information about the specific bacteria or fungi that can biodegrade the NBFRs is available. Effort should be made to screen and identify specific bacteria or fungi, which can be used in terms of removal of NBFRs from soil or other environmental matrices. To the best of our knowledge, there is only one study with respect to removal of PBT and PBEB from hospital wastewater. More studies are needed to investigate removal of NBFRs from different environmental matrices.

The toxicological data of NBFRs summarized in this review suggest that these compounds can cause adverse effects through different action modes (hormone disruption, endocrine disruption, neurotoxicity, DNA damage, etc.). Nevertheless, the toxicities of NBFRs are usually tested at high exposure doses in a short period, which are significantly higher than real environmental concentrations of such contaminants. Further studies should be focused on chronic toxicities of NBFRs at environmentally relevant concentrations. More toxicity data of NBFRs derived from different species are needed for better understanding their health impacts. It is also greatly valuable if there are more epidemiological data since they can truly reflect the toxicities of NBFRs to human.

In the future, when we select new alternatives for traditional chemicals, it is important to conduct a comprehensive assessment for the alternatives, which not only includes the aspect of toxicity, but also involves the aspect of environmental behaviors (persistence, migration, and biodegradation). In this way, it can better determine whether the alternatives are suitable choices.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.9b03159.

Additional information as noted in the text (one table and six figures) (PDF)

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DOI: 10.1021/acs.est.9b03159
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■ ACKNOWLEDGMENTS

This study was jointly supported by the National Natural Science Foundation of China (21677167 and 21806172), National Key Research and Development Program of China (2018YFC1801600), and Thousand Young Talents Program of China.

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