Annex XV report

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE OF VERY HIGH CONCERN ON THE BASIS OF THE CRITERIA SET OUT IN REACH ARTICLE 57

Substance Name: 1,1'-[ethane-1,2-diylbisoxy]bis[2,4,6-tribromobenzene]

EC Number: 253-692-3

CAS Number: 37853-59-1

Submitted by: Spain

Date: August 2022

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TABLES

ABBREVIATIONS

AOP: adverse outcome pathway
ASE: accelerated solvent extraction
B: bioaccumulative
BAF: bioaccumulation factor
BCF: bioconcentration factor
BFRs: brominated flame retardants
BMF: biomagnification factor
BSAF: biota-sediment accumulation factor
CA: competent authority
COD: chemical oxygen demand
CTD: characteristic travel distance
DOC: dissolved organic carbon
DT50 : disappearance time 50; time in which half of the test item disappears
ED: endocrine disrupting
GC-ECNI-MS: gas chromatography - electron capture negative-ion mass spectrometry
GC-IRMS: gas chromatography - isotope ratio mass spectrometer
GC/MS: gas chromatography/ mass spectrometry
HL: half-life
HPLC: high performance liquid chromatography
K_{oa}: octanol-air partition coefficient
K_{oc}: organic carbon-water partition coefficient

K_{ow}: octanol-water partition coefficient
LC_{50}: median lethal concentration; concentration that is lethal for 50% of the test animals
LOD: limit of detection
LOAEL: lowest observed adverse effect level
LOEC: Lowest Observed Effect Concentration
LOQ: limit of quantification
LRTP: long-range environmental transport potential
MDL: method detection limit
MoA: mode of action
NBFRs: Novel brominated flame retardants
NO(A)EL: no observed (adverse) effect level
OECD: Organisation for Economic Cooperation and Development
OH-PBDEs: hydroxylated polybrominated diphenyl ethers
P: persistent
PAS: passive air sampler
PBDE: polybrominated diphenyl ether
POP: persistent organic pollutant
P_{OV}: overall persistence
PUF: polyurethane foam
QSAR: Quantitative structure–activity relationship
RAC: Committee for Risk Assessment
ROS: reactive oxygen species
SEv: substance evaluation
SVHC: substance of very high concern
T: toxic
TE: transfer effiency
TG: test guideline
TH: thyroid hormone
TLC: thin layer chromatography
TMF: trophic magnification factor
UV: ultra-violet
vB: very bioaccumulative
vP: very persistent
WoE: weight of evidence
ww: wet weight
WWTP: wastewater treatment plant

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE OF VERY HIGH CONCERN ON THE BASIS OF THE CRITERIA SET OUT IN REACH ARTICLE 57

Substance name: 1,1'-[ethane-1,2-diylbisoxy]bis[2,4,6-tribromobenzene] (BTBPE)

EC number: 253-692-3

CAS number: 37853-59-1

- It is proposed to identify the substance as very persistent and very bioaccumulative (vPvB) according to Article 57 (e) of Regulation (EC) No 1907/2006 (REACH).

Summary of how the substance meets the criteria set out in Article 57 of the REACH Regulation

A weight-of-evidence determination according to the provisions of Annex XIII of REACH has been used to identify the substance as vPvB. All available relevant information (such as the results of standard and non-standard tests, monitoring and modelling, and (Q)SAR results) was considered together in a weight-of-evidence approach.

Persistence:

BTBPE had negligible degradation in a non-standard biodegradation screening study that used pre-adapted inoculum, inoculum:test substance concentration ratio similar to an inherent test and extended duration. According to ECHA Guidance Chapter R.11, lack of degradation (<20% degradation) in an inherent biodegradability test equivalent to the OECD TG 302 series may provide sufficient information to confirm that the P-criteria are fulfilled without the need for further simulation testing for the purpose of PBT/vPvB assessment. The conditions of the test with BTBPE were not completely equivalent to OECD TG 302 tests and limited information on the test is available, and hence, its reliability cannot be fully assessed. Nevertheless, the very low degradation observed in the test vessels with conditions similar to an inherent test and pre-adapted microorganisms suggests that BTBPE may be at least persistent (P). Biowin QSAR predictions are consistent with the experimental data for BTPBE showing that the substance screens for potentially persistent (P) or very persistent (vP).

BTBPE was found to be persistent in soil treated with biosolids in a mesocosms study (reliable with restrictions). The study was run over three years and the BTBPE concentrations were found to be stable over the whole study period. Other higher brominated flame retardants, such as polybrominated diphenyl ether (PBDE) congeners from penta- to deca-BDE, as well as hexabromobenzene (HBB) and pentabromoethylbenzene (PBEB) also remained stable in the study, while some of the less brominated tested substances like di- and tri-BDEs showed decreasing concentrations over time. These observations are in line with other available data on the biodegradation of these substances and the soil mesocosms experiment appears to represent realistic environmental conditions. The study therefore shows clearly that the half-life of BTBPE in soil is higher than the 120 days set in Annex XIII of REACH as criterion for a persistent substance and also higher than the criterion of 180 days for a very persistent substance.

Negligible degradation of BTBPE was also observed in sediment phase in a water-sediment mesocosms study (reliable with restrictions). There is some uncertainty whether or not the high organic carbon content (10%) in the water-sediment mesocosms study influenced the biodegradation/bioavailability of BTBPE. However, sediments with organic carbon content above 10% are found in Europe, and hence, the study is considered to reflect environmentally relevant conditions. Furthermore, the available monitoring data from sediment core studies indicate that BTBPE has been found in 20-40 year old sediment layers in Lake Ontario and Lake Michigan in the USA and a saltwater lake in Korea. These findings, suggest that the degradation in the environment may be slow and provide indirect evidence that BTBPE can persist in sediments for more than two-four decades. Based on the weight of the evidence available and considering the substance is very persistent in the soil compartment, BTPBE is concluded to meet the P/vP criteria of REACH Annex XIII in the sediment compartment (degradation half-life in sediment > 180 days).

Monitoring data for BTBPE support the above conclusions, as the substance has been detected in remote areas, e.g., in air and snow pits in the Norwegian and Canadian Arctic, respectively. These findings further strengthen the conclusion that BTBPE is very persistent in the environment.

Based on a weight-of-evidence approach and considering assessment information in accordance with REACH Annex XIII Section 3.2.1.(d), it is concluded that BTBPE meets both the 'persistence' (P) (degradation half-life in sediment or soil > 120 days) and 'very persistent' (vP) criteria of REACH Annex XIII (degradation half-life in sediment or soil > 180 days) in accordance with Annex XIII, points 1.1.1 and 1.2.1, of the REACH Regulation.

Bioaccumulation:

Based on the predicted log Kow values in the range of 7.88-9.39, which are considered more reliable than the available measured log Kow value of 3.14, BTBPE screens B/vB (log Kow >4.5).

In a non-standard laboratory dietary bioaccumulation in fish study (reliable with restrictions), a low depuration rate constant of 0.0128 day^{-1} (indicative of a BCF > 5000) and a long depuration half-life of 54 days for muscle tissue of rainbow trout were determined, indicating very slow depuration of BTBPE in fish. These values are similar or higher than the whole body depuration rates and half-lives in fish determined for substances concluded to be SVHCs due to vPvB properties, e.g. Dechlorane Plus, some of the vPvB congeners of medium chain chlorinated paraffins (MCCP) and vPvB constituent of terphenyl hydrogenated. Furthermore, in this study BTBPE does not seem to be metabolised by fish. Fish BCFs were derived from data generated in the above dietary study with rainbow trout using the 14 models within the OECD TG 305 BCF estimation tool in methods 1 and 2. Based on the 14 models, 11 BCFs predicted were above 5000 thus indicating a high bioaccumulation potential for BTBPE.

A supporting mesocosms study with fathead minnows (low reliability) confirms the findings of the dietary study as no significant decrease of the concentration of BTBPE in the fish was observed after 28 days depuration period.

Field data used as supporting information in the B assessment point towards the bioaccumulation potential of BTBPE and thus confirm the conclusions from experimental data. Several field studies on bioaccumulation indicate that BTBPE has TMF and BMF values above 1 in some of the studied food webs and predator/prey relationships, respectively, which are clear indications that BTBPE is able to biomagnify. According to REACH Guidance Chapter R.11, food chain transfer and secondary poisoning are basic concerns in relation to PBT and vPvB substances, and therefore an indication of a biomagnification potential (BMF and/or TMF > 1) can on its own be considered as a basis to conclude that a substance meets the B or vB criteria.

BTBPE has been detected in human serum, hair and mother milk samples which indicates that BTBPE is absorbed to some extent in humans. In addition, monitoring data demonstrate widespread contamination of wildlife by BTPBE at all trophic levels (including predatory species (e.g., polar bears which are listed on the IUCN red list of threatened species)). BTBPE has also been detected in biota samples from remote regions, including the Arctic. These data provide supporting evidence that BTPBE is taken up by organisms in the environment.

Based on a weight-of-evidence approach and considering assessment information in accordance with REACH Annex XIII points 3.2.2 (a), (b) and (c), it is concluded that BTBPE meets the 'bioaccumulation' criterion (B) and the 'very bioaccumulative' criterion (vB) in accordance with Annex XIII, points 1.1.2 and 1.2.2, of the REACH Regulation.

Conclusion:

In conclusion, BTBPE is proposed to be identified as a vPvB substance according to Article 57(e) of REACH by comparing all relevant and available information listed in Annex XIII of REACH with the criteria set out in the same Annex, in a weight-of-evidence determination.

Registration dossiers submitted for the substance: No

PART I

Justification

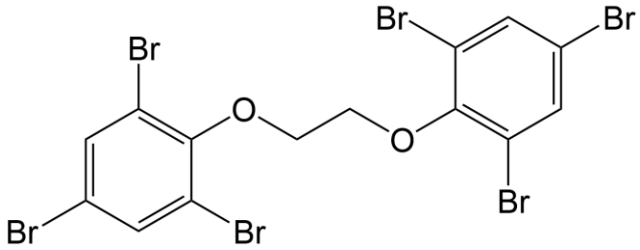
1. Identity of the substance and physical and chemical properties

1.1 Name and other identifiers of the substance

Table 1: Substance identity

EC number:	253-692-3
EC name:	1,1'-[ethane-1,2-diylbisoxy]bis[2,4,6-tribromobenzene]
CAS number (in the EC inventory):	37853-59-1
IUPAC name:	1,1'-[ethane-1,2-diylbisoxy]bis[2,4,6-tribromobenzene] 1,2-Bis(2,4,6-tribromophenoxy)ethane 1,3,5-tribromo-2-[2-(2,4,6-tribromophenoxy)ethoxy]benzene
Index number in Annex VI of the CLP Regulation	-
Molecular formula:	C14H8Br6O2
Molecular weight range:	687.64 g/mol
Synonyms:	

Structural formula:



1.2 Composition of the substance

Name: 1,1'-[ethane-1,2-diylbisoxy]bis[2,4,6-tribromobenzene]

Substance type: mono-constituent

Degree of purity: As the substance is not registered under REACH, no information on

concentration ranges is available. As BTBPE is a monoconstituent substance, it has a purity of ≥80%.

Table 2: Constituents other than impurities/additives

Constituents	Typical concentration
1,1'-[ethane-1,2-diylbisoxy]bis[2,4,6-tribromobenzene] EC 253-692-3	≥ 80% w/w

1.3 Physicochemical properties

Table 3: Overview of physicochemical properties

Property	Description of key information	Value [Unit]	Reference/source of information
Physical state at 20°C and 101.3 kPa		Solid, white powder	PubChem
Melting/freezing point	Measured, Directive 84/449/EEC, A.1	224 °C	(Kirk-Othmer Encyclopedia of Chemical Technology, 1993, cited in GLCC, 2002)
			Kuramochi *et al*. (2014b)
		227 °C	EPISUITE (v4.11)
	Measured, non-guideline study		
	MPBPVP v1.43	214 °C	
Boiling point	Estimated	566 °C	ACD/labs Software V9.04, from SciFinder, cited in Covaci *et al.* (2011)
			EPISuite (v.4.11)
	MPBPVP v1.43	502 °C	
Vapour pressure	Measured, non-guideline study	2.26E−11 Pa at 25 °C	Kuramochi *et al.* (2014b) SciFinder, cited in Covaci *et al.* (2011)
	ACD/labs Software V9.04	3.88E−10 Pa at 25 °C	EPISuite (v.4.11)
	MPBPVP v1.43	3.17E−08 Pa	Kuramochi *et al.* (2014a)
	SPARC	2.09E−11 Pa	
Water solubility	Shake flask method, non-guideline study	200 µg/l at 25 °C	Yu and Atallah (1978), cited in GLCC 2002
			SciFinder, cited in Covaci *et al.* (2011)
	ACD/labs Software V9.04	19.0 µg/l at 25 °C	EPISuite (v.4.11)
	WSKOW/WATERNT		Kuramochi *et al.* (2014b)
	UNIFAC[1]	0.22/6.55E−04 µg/l	Kuramochi *et al.* (2014a)
	SPARC		ACD/Percepta 14.2.0
	ACD/LogS	2.79E−04 µg/l	

		5.47E−04 µg/l 0.03 µg/l	
Subcooled liquid solubility in water	COSMOtherm 19.0.1	0.032 µg/l	
Partition coefficient n-octanol/water (log Kow)	Shake flask method[2] ACD/labs Software V9.04 KOWWIN v1.68 SPARC ACD/Consensus LogP COSMOtherm 19.0.1 Not stated	*3.14* *7.88* *9.14* *9.39* *7.65* ***8.16*** *8.31*	Velsicol Chemical Corp. 1977, cited in GLCC 2002 SciFinder, cited in Covaci *et al*. (2011) EPISuite (v.4.11) Kuramochi *et al.* (2014a) EFSA (2012)
Partition coefficient n-octanol/air (log Koa)	*SPARC* *KOAWIN* *COSMOtherm 19.0.1*	*15.0* *15.7 (using a log kow of 9.15)* *13.6*	Harju *et al*. (2009) EPISuite (v.4.11)

[1] *extended for* brominated aromatic compounds *by Kuramochi et al. (2007)*
[2] *following Leo et al. (1971). Partition coefficients and their uses. Chem. Rev., 71:537-8*

There are few experimental data for the physico-chemical properties of BTBPE. The vapour pressure and the melting point were measured by Kuramochi *et al*. (2014b).

A measured log Kow of 3.14 for BTBPE from a shake flask study conducted in 1977 (Velsicol Chemical Corp. 1977, cited in GLCC, 2002) is also available. The method described by Leo *et al.* (1971) was followed. Information on the procedure can be found at GLCC (2002). There were some deviations from the current OECD TG 107, which raise some uncertainty regarding the reliability of the study.

Furthermore, according to OECD TG 107 and ECHA Guidance R.7a (ECHA, 2017a), the shake flask method is applicable only for measuring log Kow up to 4. The method is prone to artifacts due to transfer of octanol microdroplets into the aqueous phase. With increasing values of log Kow the presence of these droplets in the aqueous phase leads to an increasing overestimation of the concentration of the test substance in the water. The log Kow values predicted by KOWWIN, ACD/Lab and CosmoTherm QSAR models are much higher, in the range of 7.88-9.39, than the available measured value of 3.14.

Moreover, Stieger *et al*. (2014) plotted the log K_{OW} values of some brominated aromatic compounds as a function of the molecular weight and showed that the log K_{OW} of BTBPE is very likely much higher than 4 (see **Figure 1**). The structurally closely related hexa-BDE congener BDE-153 (CAS No. 68631-49-2) also has a higher partition coefficient based on a study by Schenker *et al.*, (2008). In this study independent literature values for physico-chemical properties of various BDE congeners were collected and final adjusted values using a least-squares adjustment method were derived. For BDE-153 (the only hexa-BDE included in the set) the log K_{OW} obtained was 7.36, i.e., well above the experimental value reported for BTBPE in the shake flask study from year 1977.

Hence, based on the available QSAR estimations and information on log Kow values of similar

substances, the log Kow of BTBPE is expected to be well above 4. Consequently, shake flask method is not applicable for measuring the log Kow of the substance, and the available measured log Kow of 3.14 is not considered reliable. COSMOtherm has been shown in the past to outperform SPARC and EPISuite (Glüge *et al.*, 2013; Stenzel *et al.*, 2014). Therefore, log Kow (8.16) predicted by COSMOtherm has been used in this document where necessary.

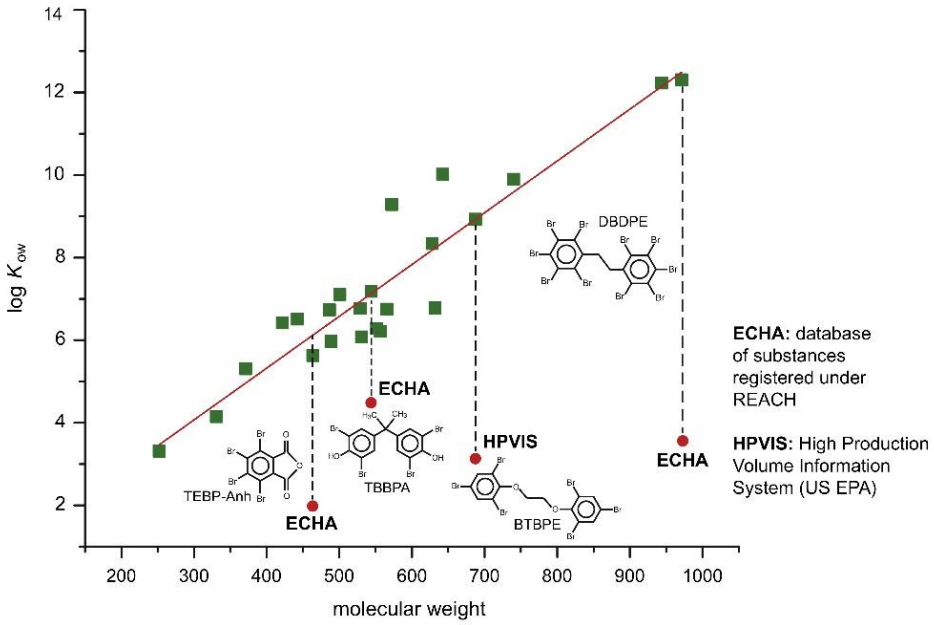


Figure 1. log K_{OW} of brominated aromatic compounds as a function of molecular weight. Red dots indicate values where the deviation from the linear relationship is well over 2 log units. Figure taken from Stieger *et al.* (2014).

Regarding water solubility, measured values of 160 µg/L at 15°C and 200 µg/L at 25°C are reported for BTBPE in a shake flask study (Yu and Atallah, 1978 cited in GLCC 2002). However, there are some uncertainties in these values and they may overestimate the real solubility of the substance. The water solubility values of BTBPE estimated by QSARs are in the range of $2.8 \cdot 10^{-4}$ to 19 µg/L. The experimental study did not follow any standard guideline and some deviations from the current OECD TG 105 could result in higher solubility values. ^{14}C-radiolabelled test substance was diluted with toluene to achieve the appropriate specific radioactivity. Toluene was removed from the test tubes through a gentle stream of nitrogen, but no confirmation of total removal is provided. Distilled water was added to the tubes with the test substance, and the tubes were placed in a water bath and shaken overnight at 35°C. The tubes were then centrifuged for one hour at 15°C, 25°C or 35°C (two tubes per each temperature), and after centrifugation duplicate 2 ml of the solution were taken for radioassay. According to ECHA Guidance Chapter R.7a (ECHA, 2017a), a shake flask method with fast stirring techniques (300-400 rpm) is applicable for substances with relatively high water solubility (> 10^{-2} g/L), and for poorly soluble substance either slow-stirring techniques (<100 rpm) or column elution method should be used. The intensity of shaking of the test vessels in the Yu and Atallah (1978) study is not known. Considering that the estimated water solubility values of BTBPE are low, in the range of $2.8 \cdot 10^{-4}$ to 19 µg/L, if too vigorous shaking was used in the test, formation of micro-droplets or emulsions that may have led to overestimation of water solubility cannot be excluded. Furthermore, for the similar substances BDE-153 and BDE-154 water solubility of 0.9 µg/L has been experimentally determined in a column elution study (Tittlemier *et al.*, 2002).

In conclusion, the measured water solubility values of BTBPE are not considered fully reliable, and the real water solubility of the substance is expected to be much lower.

2. Harmonised classification and labelling

None.

3. Environmental fate properties

3.1 Degradation

3.1.1 Abiotic degradation

3.1.1.1 Hydrolysis

Hydrolysis is not expected to occur at a significant rate in neutral water at ambient temperatures, because BTBPE has a very low solubility in water, and does not possess functional groups readily subject to hydrolysis. HYDROWIN (v2.00) QSAR model cannot be used to estimate the hydrolysis rate for the substance as it does not contain any of the functional groups included in the model.

3.1.1.2 Oxidation

The atmospheric oxidation mechanism and kinetics of BTBPE initiated by OH was investigated by a combined quantum chemical calculations and kinetics modelling *(*Yu *et al.*, 2017). The authors stated that the initial oxidation proceeded via the OH addition and hydrogen abstraction pathways to form intermediates, which were able to further react with O_2 to finally form peroxy radicals and OH-BTBPE. The calculated overall reaction rate constant (k_{OH}) was 1.0 x 10^{-12} cm^3 per molecule per second. The authors translated this into an atmospheric lifetime in the gas-phase, τ, of 11.8 days ($\tau = 1/(k_{OH} \cdot [OH])$, [OH] = $9.7 \cdot 10^5$ molecules cm^{-3}). However, Yu *et al.* (2017) stated also that atmospheric particles will affect the overall atmospheric lifetime of BTBPE, because the chemical is semi-volatile and thus partly particle-bound. According to the calculations in Annex III, 99% of BTBPE is particle-bound at 25 °C, with a higher fraction at lower temperatures. This is in good agreement with the results of the AEROWIN (v1.00) QSAR models which predict the fraction sorbed to airborne particulates to be in the range 97-100%. Monitoring data in air as reported in section 3.2.4 (DeCarlo, 1979; Zweidinger *et al.*, 1979a) and section 3.3.1 (Davie-Martin *et al.* 2016; Möller *et al.,* 2011a and Salamova *et al.* 2014) confirm the presence of BTPBE in the particle phase of atmosphere.

For the conversion of the overall reaction rate constants into half-lives in the OECD P_{OV}-LRTP Tool, an OH radical concentration of $7.5 \cdot 10^5$ molecules cm^{-3} is assumed. Also, the equation ($\tau = \ln(2)/(k_{OH} \cdot [OH])$ is used for the conversion. With these two adjustments, a gas-phase half-life of 256.7 hours or 10.7 days instead of 11.8 days is obtained. Considering that the substance is predicted to be particle-bound in air and this is confirmed by monitoring data in air, the estimated atmospheric half-life for the gas-phase may underestimate its persistence in air.

3.1.1.3 Phototransformation/photolysis

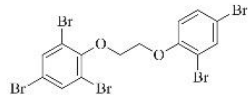
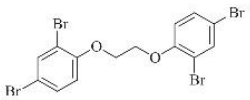
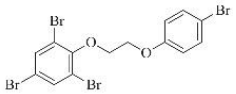
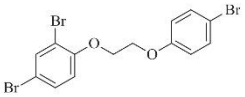
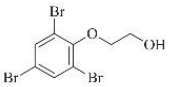
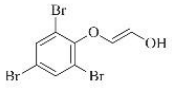
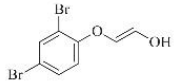
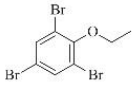
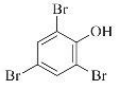
Zhang *et al.* (2016) investigated the photochemical behaviour of five brominated flame retardants (BFRs), including BTBPE, dissolved in hexane or methanol. The experiment was performed in an XPA-1 merry-go-round photochemical reactor with a 500 W mercury lamp equipped with 290 nm filters to mimic the UV-A and UV-B portions of sunlight. Quartz tubes containing the photolysis solutions with a stopper (including dark controls) were placed in the reactor for light irradiation. Quantum yields (ϕ) were measured using *p*-nitroanisole/pyridine as the chemical actinometer. Photolysis followed first-order kinetics ($r^2 > 0.999$) and no remarkable concentration decrease was observed in the dark controls. Direct photolysis half-

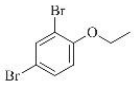
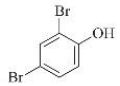
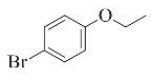
lives (t1/2) relevant with solar irradiation in surface waters were estimated based on the determined ϕ. The rate constant in surface water were obtained based on the linear regression of $\ln(C_t/C_0)$ vs. time (t). The estimated direct photolysis half-life with solar irradiation in surface water at 40° N latitude (represents e.g., Southern Europe) was 2.5 days in spring, 1.5 days in summer, 4.7 days in autumn, and 17.1 days in winter.

However, Zhang *et al.* (2016) stated that higher half-lives than the reported ones should be expected in nature due to weather conditions (e.g., cloudy weather) that reduce the solar irradiation and due to the light absorbance of the water matrix. Moreover, photolysis is only relevant for the upper most water layer. Thus, the half-life of BTBPE in e.g., a lake would be much longer than 17 days. The large variation in the light availability is also the reason that photolysis data are not generally recognised for persistence assessments (European Chemicals Agency, 2017).

Zhang *et al.* (2016) identified 13 phototransformation products for BTBPE as shown in **Table 4**. The evolution profiles of the identified products of BTBPE are shown in **Figure 2** and the proposed phototransformation pathways are shown in **Figure 3**.

Table 4 Identified photoproducts of BTBPE and their structures, as published by Zhang *et al.* (2016)

No.	Products of BTBPE	Structure
P1	1-(2,4,6-tribromophenoxy)-2-(2,4-dibromophenoxy) ethane	
P2	1,2-bis(2,4-dibromophenoxy) ethane	
P3	1-(2,4,6-tribromophenoxy)-2-(4-bromophenoxy)-ethane	
P4	1-(2,4-dibromophenoxy)-2-(4-bromophenoxy)ethane	
P5	2-ethanol-2,4,6-tribromophenoxy ether	
P6	2-ethenol-2,4,6-tribromophenoxy ether	
P7	2-ethenol-2,4-dibromophenoxy ether	
P8	ethyl-2,4,6-tribromophenoxy ether	
P9	2,4,6-tribromophenol (2,4,6-TBP)	

P10	vinyl-2,4,6-tribromophenyl ether	
P11	ethyl-2,4-dibromophenoxy ether	
P12	2,4-dibromophenol	
P13	ethyl-4-bromophenoxy ether	

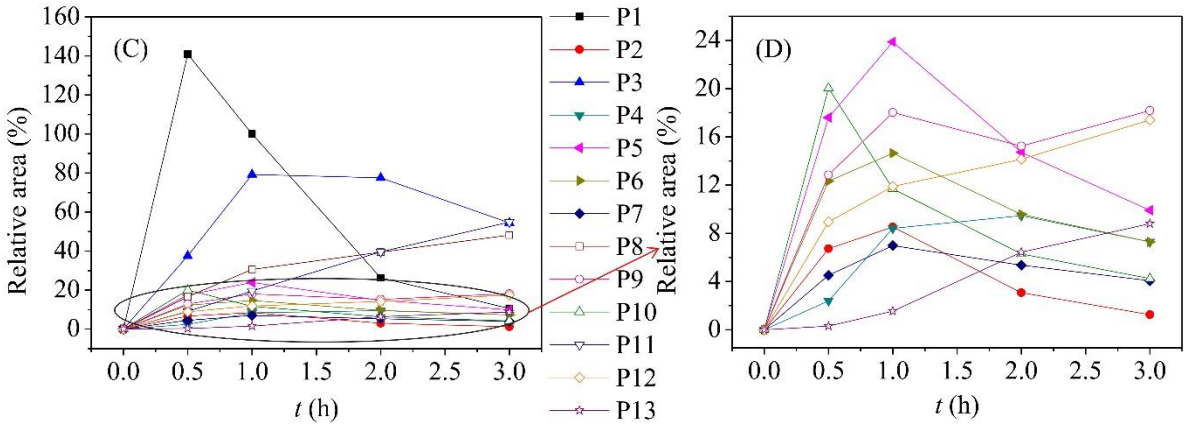


Figure 2 (C) Evolution profiles of the identified products from phototransformation of BTBPE in hexane as shown in Zhang *et al.* (2016). (D) maximized rounded area (Relative areas were calculated with the area of product 1 at 1 h as the reference)

The evolution profiles of the BTBPE products, generated by Zhang *et al.* (2016) showed big peak areas for products 1 and 3 (debrominated products) and products 8 and 11 (ether bond cleavage products), implying that both debromination and ether bond cleavage are main phototransformation pathways of BTBPE. Product 3 is generated by the removal of two bromine atoms on one phenyl (Zhang *et al.* 2016). The authors considered debromination on the ortho position to be easier than on the para position. 2,4,6-tribromophenol (2,4,6-TBP; product 9) and 2,4-dibromophenol (product 12) were also detected as photoproducts of BTBPE. Their relative areas after 3 hours were 17% and 18%, respectively. Bromophenols, especially 2,4,6-TBP, may have harmful effects on human health and aquatic ecosystems (see Annex II, and Norwegian Environmental Agency, 2016). Furthermore, Liu *et al.* (2011) and Lin *et al.* (2014) reported that bromophenols may transform to more toxic hydroxylated polybrominated diphenyl ethers (OH-PBDEs) in the environment. Hence, the transformation of BTBPE leading to formation of bromophenols enhances the potential risk of BTBPE in the environment.

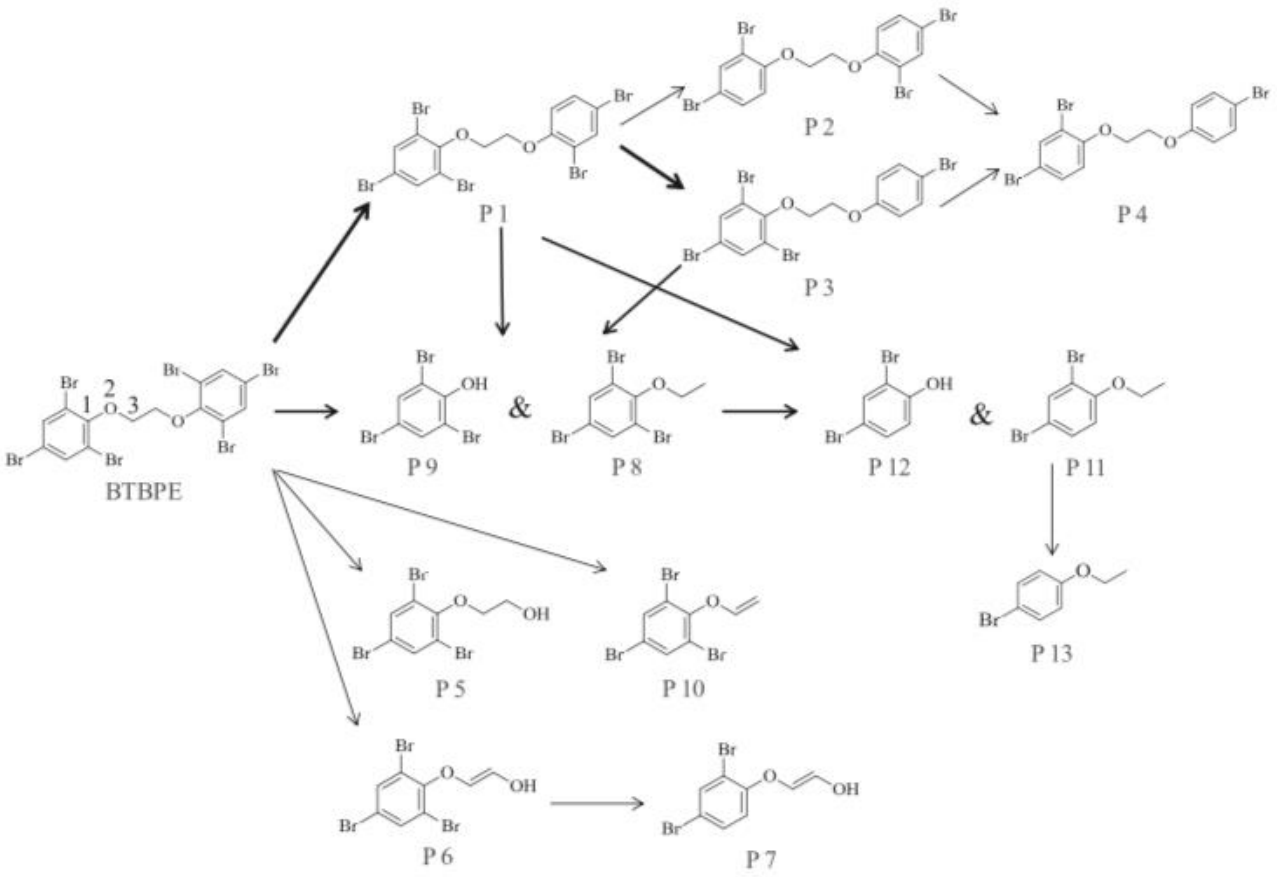


Figure 3 Proposed phototransformation pathways of BTBPE by Zhang *et al.* (2016). Bold arrows represent the dominating pathways.

Cao *et al.* (2022) explored the phototransformation behaviour of BTBPE and the similar legacy flame retardant BDE-155 in water under UV-irradiation. The test solutions contained BTBPE at a concentration of 3.0 mg/L in a THF/H_2O (6/4) solution (pH 7.5–7.6). The irradiation experiments were performed with a photochemical reactor equipped with a water-refrigerated 100 W mercury lamp. A water-cooling system was applied to ensure a steady temperature around 27 ± 2°C. The reaction solution (25 mL) was filled in Pyrex tubes (outer diameter, 20 mm; inner diameter, 16 mm) positioned circularly around the lamp. The Pyrex was used to filter the part of ultraviolet light with wavelengths less than 290 nm. Dark controls were included and treated in the same way but with the tubes wrapped in foil. All the experiments were conducted in at least triplicate. Samples were taken from the reaction vessels at fixed intervals and then directly used for HPLC analysis to measure the parent substances. To identify the photoproducts and measure the stable carbon isotope composition, a Pyrex tube was withdrawn periodically and the extracts were analysed with GC-MS and GC-IRMS.

BTBPE was shown to be more persistent than BDE-155, with nearly four times slower photodegradation rate constants (0.0120 min^{-1} and 0.0447 min^{-1}, respectively) (**Figure 4**). 18 transformation products were identified for BTBPE: 13 debromination photoproducts, three C–O cleavage products (including 2,4,6-tribromophenol) and two of their derived debrominated products. Hence, Cao *et al.* (2022) observed similar transformation products as Zhang *et al.,* (2016), with the exception of products formed by the cleavage of the phenoxy bond that were not detected in the study by Cao *et al.* (2022).

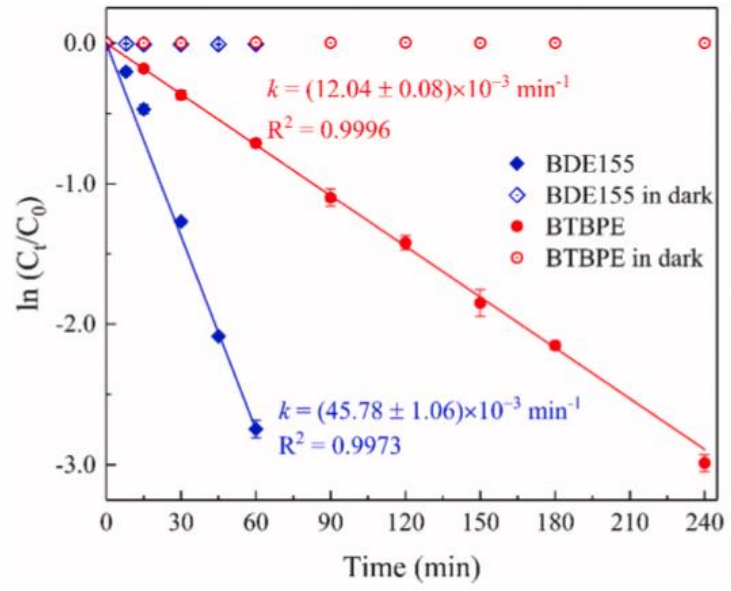


Figure 4 The phototransformation kinetics of BTBPE and BDE155 observed in the study by Cao *et al.* (2022). Figure taken from Cao *et al.* (2022).

Another photodegradation study is included in the dossier of the Great Lakes Chemical Corporation (Yu 1979, cited in GLCC 2002). ^{14}C-labelled BTBPE was irradiated with UV light on a silica gel surface and the degradation was studied. Initially the substance decreased rapidly with a half-life of about 0.4 days. After 1 day of UV exposure; however, the degradation rate decreased. The half-life of the second phase was determined to be 1.7 days. After 10 days of exposure, 37% of the ^{14}C was recovered. According to the study report author, some of the test substance and degradation products probably volatilised from the plate surface. At least 4 transformation/degradation products were detected by TLC analysis. Only one of them was positively identified by mass spectra to be 2 -(2',4',6'-tribromophenoxy)ethanol, which comprised 0.5 to 6% of the applied radiocarbon. One of the unidentified transformation/degradation products, which was assumed to be polymerised product, reached a maximum concentration after one day of 48% of applied radioactivity.

3.1.1.4 Other abiotic transformation routes

Balabanovich *et al*. (2003) investigated the pyrolysis of BTBPE and showed that BTBPE evaporates mostly at 240 °C. The decomposition products at 340 °C depend on the rate of their removal from the hot reaction zone. Main primary decomposition products found in case of rapid removal are 2,4,6-tribromophenol and vinyl 2,4,6-tribromophenyl ether. Balabanovich *et al.* (2003) proposed two possible pathways of formation. One is mutual disproportionation of BTBPE, the other a chain process involving β-scission of radical A and hydrogen abstraction from original BTBPE by radical B.

Prolonged contact with the heating zone leads to secondary reactions and the formation of hydrogen bromide and ethylene bromide in the gas phase. 2,4,6-tribromophenol and vinyl 2,4,6-tribromophenyl ether, tribromophenyl bromovinyl ethers, polybrominated phenoxy phenols, and polybrominated dibenzo-*p*-dioxins were the major products in the condensed phase. These results are in accordance with later experiments of Balabanovich *et al.* (2004). The formation pathways are explained in detail in Balabanovich *et al.* (2004) and in Altarawneh and Dlugogorski (2014).

This information is not relevant for the persistence assessment under environmentally relevant conditions. However, it can be relevant when assessing fate of the substance during e.g., waste-handling and recycling activities of products containing BTBPE.

3.1.1.5. Summary on abiotic degradation

BTBPE can be degraded by oxidation and photolysis in the environment. The use of photolysis data is not generally recognised for persistence assessment due to the large variation in the light available in different environmental compartments. Moreover, data for oxidation in the gas-phase are very uncertain due to the semi-volatile nature of BTBPE, i.e., its adsorption to particles. Therefore, no conclusion on the persistence of BTBPE can be drawn based on the abiotic degradation data.

The formation of 2,4,6-tribromophenol observed in the available studies on photodegradation and oxidation enhances the potential risk of BTBPE in the environment as this transformation product may have harmful effects on human health and aquatic ecosystems (see Annex II, and Norwegian Environmental Agency, 2016). Bromophenols were also formed during thermolysis, which might occur during recycling activities of polymer materials contained, e.g., in waste of electrical and electronic devices.

3.1.2 Biodegradation

3.1.2.1 Biodegradation in aqueous media or aqueous environment

3.1.2.1.1 Estimated data

According to the ECHA guidance Chapter R.11 (ECHA, 2017b), a substance is considered to screen for potential P/vP if EPISuite Biowin models give the following combinations of results:

- BIOWIN 2: does not biodegrade fast (probability < 0.5), and BIOWIN 3: ≥ months (value <2.25), or
- BIOWIN 6: does not biodegrade fast (probability <0.5), and BIOWIN 3: ≥ months (value <2.25).

The results of the Biowin 2, 3 and 6 models for BTBPE are "does not biodegrade fast" (0.000), "recalcitrant" (0.7473) and "does not biodegrade fast" (0.0130), respectively. Therefore, BTBPE screens for potential P/vP properties based on the Biowin predictions. Biowin 2 and 3 models recognise the aromatic bromide and aromatic ether fragments of the substance. Biowin 6 model includes in addition to these two fragments also fragments for aromatic H and linear CH2. The datasets used for validation and training of the BIOWIN 6 model include similar substances, e.g., deca-BDE, dibromobiphenyl and several brominated phenols, including 2,4,6-TBP. The datasets used for deriving the BIOWIN 2 and 3 models include less similar brominated substances but they do contain brominated phenols and benzenes, e.g., 2,4,6-TBP and 2,4-dibromophenol, and hexabromobiphenyl for BIOWIN 2. These predictions are considered to be reliable.

EAWAG-BBD Pathway Prediction System (PPS) predicts microbial catabolic reactions using substructure searching, a rule-base, and atom-to-atom mapping. The system is able to recognise organic functional groups found in a compound and to predict transformations based on biotransformation rules. The biotransformation rules are based on scientific literature on reactions that have been fed into the EAWAG-BBD PPS database. A likelihood is assigned for each biotransformation rule based on an assessment of an expert panel. The likelihood indicates the probability that the reaction will occur under aerobic conditions, exposed to air, in soil (moderate moisture) or water, at neutral pH, 25 °C and without the presence of other competing or toxic compounds. For aerobic biodegradation, EAWAG-BBD PPS predicts that

BTBPE will be degraded to 2,4,6-TBP and (2,4,6-tribromophenoxy)acetic acid with neutral likelihood (**Figure 5**). According to EAWAG-BBD PPS, (2,4,6-tribromophenoxy)acetic acid will also be degraded to 2,4,6-TBP. Hence, 2,4,6-TBP seems to be the major degradation product of BTBPE according to EAWAG-BBD PPS. For anaerobic conditions, EAWAG-BBD PPS predicts that BTBPE could additionally be degraded to 1-(2,4,6-tribromophenoxy)-2-(2,4-dibromophenoxy) ethane or 1-(2,4,6 -tribromophenoxy)-2-(2,6-dibromophenoxy) ethane. However, the anaerobic pathways to both metabolites are unlikely.

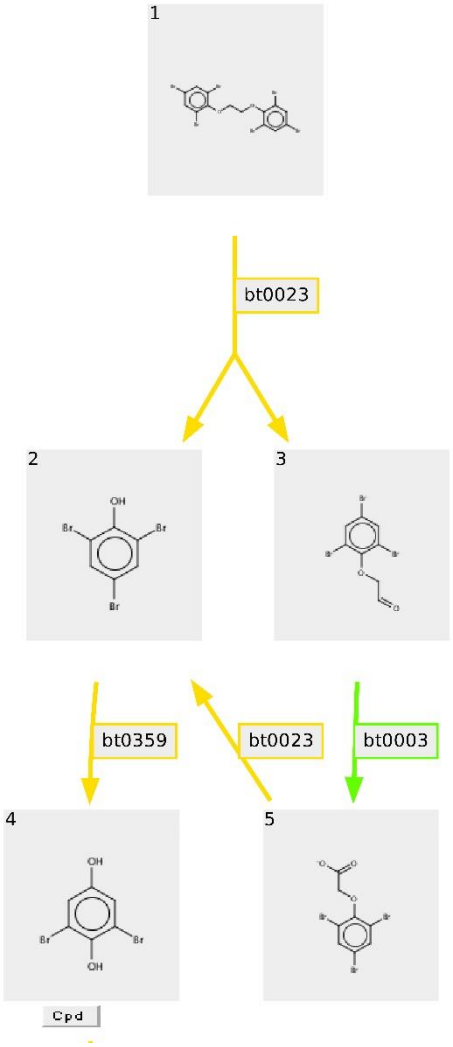


Figure 5 Aerobic biodegradation pathways predicted by EAWAG-BBD-PPS. Pathways in green are likely, pathways in yellow have a neutral likelihood.

3.1.2.1.2 Screening tests

One biodegradation screening test with BTBPE (MC-680) is available (Calandra, 1976 from GLCC 2002). No standard test guideline was followed. In the test the extent of degradation was monitored by measuring the amount of $^{14}CO_2$ liberated after addition of three different concentrations of ^{14}C-labeled test material (1.0 ppm, 0.01% and 1.0%) in microbial medium. Concentrations used were based on a preliminary study that showed that 10% test material was toxic, and that 1.0 % was not. It is not indicated whether the concentrations refer to weight/weight, volume/volume or weight/volume concentrations. However, as BTBPE is solid and the microbial medium is liquid, it could be expected that the 1 ppm, 0.01 % and 1.0 % concentrations refer to weight/volume concentrations, in which case they would be equivalent of 1, 100 and 10000 mg/L, respectively.

The inoculum contained microorganisms from fresh settled sewage and garden soil, which were pre-adapted to the test substance before the definitive test. Prior to testing, the microorganisms were pre-adapted to non-labelled MC -680 (10 mg added on Day 1 and 100 mg added on Day 7) at 20 °C in the dark. The contents were mixed and well aerated every other day. At various intervals during pre-adaptation, samples were taken and tested for microbial activity against ^{14}C-labeled glucose. The final test medium (microbial medium) contained 50 ml of supernatant from the pre-adapted microbes plus 10 mL of settled fresh sewage diluted to 500 ml with a minimum salt and vitamin solution. Hence, a concentration of 120 ml inoculum/L test medium was used. pH of this medium was adjusted to 7.1 at the beginning of the study. Medium used in all experiments with 0.01% and 1.0% test substance contained microorganisms that had been pre-adapted for 18 days, and medium used in experiments with 1 ppm test substance contained microorganisms that had been pre-adapted for 46 days.

The test material was weighed directly into each 125 ml erlenmeyer flask containing 30 ml of medium and the pre-adapted bacteria (for 0.01 and 1.0%) or dissolved in ethylacetate (1.0 ppm) and transferred quantitatively. Two drops of Tween-80 surfactant were added to aid in dispersion of 1.0% test material. Four replicates were prepared per test concentration. Two positive control flasks contained ^{14}C-labeled D-glucose and one negative control contained ^{14}C-labelled test material plus $HgCl_2$ (50 mg/l) in distilled water. It is not indicated whether the same pre-adapted inoculum used for the BTBPE test vessels was also used for the positive control. But as no mention on other inoculum is made, it is assumed that it was the same.

Each reaction vessel was equipped with a small center cup containing filter paper and 1.0 ml of 0.5 N KOH for absorption of the respired $^{14}CO_2$. Flasks were incubated at 19 to 23 °C in the dark under continuous shaking (85 cycles/min). Each flask was purged with a 70:30 O_2/N_2 mixture at least once per week. Liberation of $^{14}CO_2$ was monitored daily for the first 3 days, every 1 to 4 days up to 21 days, and then weekly thereafter.

Tests with 0.01% and 1.0% test material were terminated after 211 days and with 1 ppm after 183 days. Total ^{14}C -activity, liberated as $^{14}CO_2$, was 1.11% in flasks containing 0.01% test material and 0.53% in flasks containing 1.0% test material after 211 days. For the system containing 1 ppm ^{14}C-labeled test material, the total activity recovered as $^{14}CO_2$ was 1.41% of the initial amount after 183 days. 71% of radioactivity from the positive control (glucose) was recovered as $^{14}CO_2$ after 28 days. Hence, very low degradation was observed even though the inoculum was pre-adapted to the test substance and prolonged test duration was used.

It is noted that the concentration of inoculum was quite high (120 ml inoculum/L mineral medium) and the concentration of test substance was quite low in the 1 ppm treatment. This inoculum-test substance ratio seems to be more comparable to conditions of inherent tests than ready biodegradation tests. E.g., in OECD TG 302C an inoculum concentration of 100 ppm (w/v) and a test substance concentration of 30 ppm (w/v) are used. In OECD TG 302B tests, the concentrations of the test substance and inoculum should be 50-400 mg DOC/l (100-1000 mg COD/l) and 0.2-1.0 g dry matter/l, respectively, and it should be ensured that the ratio

between inoculum and test compound (as DOC) lies between 2.5:1 and 4:1. In contrast, in the OECD TG 301 A, B, C and F ready biodegradation tests, the concentration of inoculum should not be higher than 30 mg suspended solids/L and the test substance concentrations are 100 mg/L or 10-40 DOC/L. In OECD TG 301 D test 0.05-5 ml of effluent filtrate per litre of test medium is used, and the test substance concentration should be 2-5 mg/L, while in the OECD TG 301E only 0.5 ml of effluent is added to a litre of test medium and the test substance concentration is 10-40 mg DOC/L. There is no information on the suspended solids concentration or inoculum DOC/L concentration in the test with BTBPE. However, based on the volume of supernatant from the pre-adapted microbes and of settled fresh sewage included in the test medium, the inoculum concentration appeared to be relatively high. Therefore, especially in the test vessels with BTBPE concentration of 1 ppm, the conditions (inoculum:test substance ratio, pre-adapted inoculum) could be considered to be similar to an inherent test. The test vessels with 0.01 % and 1.0 % had higher test substance concentration more similar to a ready biodegradation test. However, considering the high inoculum concentration, at least in the case of 0.01 % test vessels, the inoculum:test substance ratio may still be more similar to conditions of an inherent test than a ready biodegradation test. According to ECHA Guidance Chapter R.11 (ECHA, 2017b), lack of degradation (<20% degradation) in an inherent biodegradability test equivalent to the OECD TG 302 series may provide sufficient information to confirm that the P-criteria are fulfilled without the need for further simulation testing for the purpose of PBT/vPvB assessment. The conditions of the test with BTBPE were not completely equivalent to OECD TG 302 tests and limited information on the test is available, and hence, its reliability cannot be fully assessed. Nevertheless, the very low degradation observed in the test vessels with conditions similar to an inherent test and pre-adapted microorganism suggests that BTBPE may be at least P.

3.1.2.1.3 Simulation tests

3.1.2.1.3.1 Biodegradation in water

No data available.

3.1.2.1.3.2 Biodegradation in sediment

No standard simulation tests in sediment are available for BTBPE.

An aquatic outdoor mesocosm experiment was conducted by de Jourdan *et al.* (2013) to assess the persistence of several novel brominated flame retardants (NBFRs), including BTBPE. The aim of the study was to provide useful information regarding environmental fate and behaviour of the NBFRs under environmental conditions. The study was carried out over a period of two years, with the mesocosms being established in May 2008, and treated in July 2008, and again in July 2009, with year 1 serving for method development purposes. The microcosm facility, located at the Guelph Turfgrass Institute of The University of Guelph (Ontario, Canada), consisted of 30 artificial mesocosms of approximately 12,000 L each. The mesocosms had a depth of 1.2 m and a diameter of 3.9 m and were filled with water to a depth of approximately 1 m. The water supply for the mesocosms was an irrigation pond supplied by a well located on site. Sediment trays (52.1 x 25.4 x 5.7 cm) containing organics-rich soil (1:1:1 mixture of topsoil:manure:compost) were added to each mesocosm such that >50% (ca. 12 m^2) of the bottom surface of the mesocosm was covered. The sediment used in the mesocosms had high organic content, with 11.6% dry total C, 1.6% dry inorganic C, and 10.0% dry organic C. It is not stated why a composition of topsoil, manure and compost and not pure sediment was used in the study, but the emphasis on organics-rich soil indicates that a high content of organic matter was desired. Such a high organic matter content might not have been achieved with pure sediment. Water was circulated from the central irrigation pond into all mesocosms for three weeks to decrease heterogeneity of water chemistry, zooplankton, and algal assemblages. Circulation was discontinued one week prior to treatment.

BTBPE was applied to three separate, randomly selected mesocosms with the target to achieve a concentration of 500 ng BTBPE/g sediment in the upper 5 cm on partitioning into the sediment. Treatment of the mesocosms involved subsurface injection of the substance (300 mg commercial BTBPE dissolved in 125 ml dimethylsulfoxide (DMSO) and an equal volume of solvent for the control treatment, representing 0.001% solvent (v/v)) into a stream created by a paint mixer attached to a handheld drill. Five injections of 25 ml were made at several locations in the mesocosms in an effort to achieve homogeneous distribution of the substance. During the following year, two of the three mesocosms were re-treated with BTBPE at the same concentration, but no additional water was added.

Water-column samples (ca. 4 L) and sediment samples in triplicate were collected after the re-treatment on day 1, 4, 7, 14, 28, 42, and 70. Please note that for unknown reasons the sampling at day 70 was either not performed or was not included in the results. Based on **Figure 6** (bottom), the authors did, however, another sediment sampling at day 56 or 57. Sediment samples were collected using copper tubes (100 mm length, 15 mm internal diameter) to core the upper 3 cm of the sediment. Separate sediment trays (33 x 18 x 10cm) with floats attached by rope were deployed for sediment sampling, because they could be raised to the surface for sample collection with minimal risk of disturbance and resuspension of sediments. On sampling days, two sediment samples were collected from one sediment tray, and the third sample was collected from a tray on the opposite side of the mesocosm.

The identification and quantification of the NBFRs were performed using a GC/MS operated in the electron capture negative ionisation mode. BTBPE was monitored using the characteristic mass fragment at m/z 330 and was quantified by monitoring the bromine ion (m/z 79 and 81). Full-scan mass spectra (m/z 60–800) were also recorded for each sample using electron-capture negative-ion mode. Selected samples were also run in full-scan electron ionisation (EI) mode to elucidate further the structures of degradation products.

The authors reported that standards of PBDEs were analysed by the same method to determine whether any of the observed peaks in the samples were due to field or laboratory contamination with PBDE congeners. The stock solution and technical products used to treat the mesocosms were evaluated for impurities. Matrix spikes were performed by adding 200 ml of the test compounds at a concentration of 100 ng/ml to the diatomaceous earth prior to extraction. The recovery (which is particularly important for biodegradable compounds) and breakdown of the compounds throughout the experiment were assessed and modifications to the method (i.e., reduced acidification of the silica gel) were made to maximise recovery and minimise degradation. The mean recovery of the method for BTBPE was 79% (range 63%–93%). It is noted that according to OECD TG 308, the recovery immediately after the addition of the test substance to the test system should range from 70% to 110% for non-labelled substances. Hence, as the lowest recoveries of the method were below 70%, the measured concentrations of BTBPE might have been slightly underestimated in the study.

Method (pre-ASE (accelerated solvent extraction)) and procedural (post-ASE) blanks were run with every batch of samples (8–10) and were extracted in a manner identical to that of the samples. The analysis showed that the test compounds were not detected in the laboratory nor in the method blanks.

Measured concentrations of BTBPE in the sediment compartment showed almost constant concentrations over time (**Figure 6**, bottom). The calculated regression line suggested no significant decrease in the sediment compartment. Measured concentrations in the particulate phase showed larger fluctuations, but also no statistically significant decrease (**Figure 6**, top). Dissipation DT50 values of 33 days (95% CI 13–54 days) and 187 days (95% CI 67–305 days) for BTBPE in particulates and sediment, respectively, are reported in the study but these are not considered reliable as the data fitted poorly to first order kinetics and the regressions were not statistically significant. The authors mention that a number of physical (e.g., burial, degradation, sediment-to-water diffusion and resuspension), experimental (e.g., homogeneous distribution of the compounds in the mesocosms), and analytical (e.g., matrix interference in

the sediments) factors likely contributed to the level of uncertainty in determining the dissipation times of the substances in the study.

Degradation products were present in the particulate phase, but not in the sediment compartment. However, the concentration of the degradation products were 2 to 3 orders of magnitude lower than the concentration of the parent compound in the particulate phase (**Figure 7**). This shows that only minor biodegradation occurred. One of the degradation products in the particulate matter was identified as 2,4,6-TBP. In the sediment samples 2,4,6-TBP was not detected. However, de Jourdan *et al.* (2013) did not state if and how many other degradation products have been identified in the mesocosms with BTBPE.

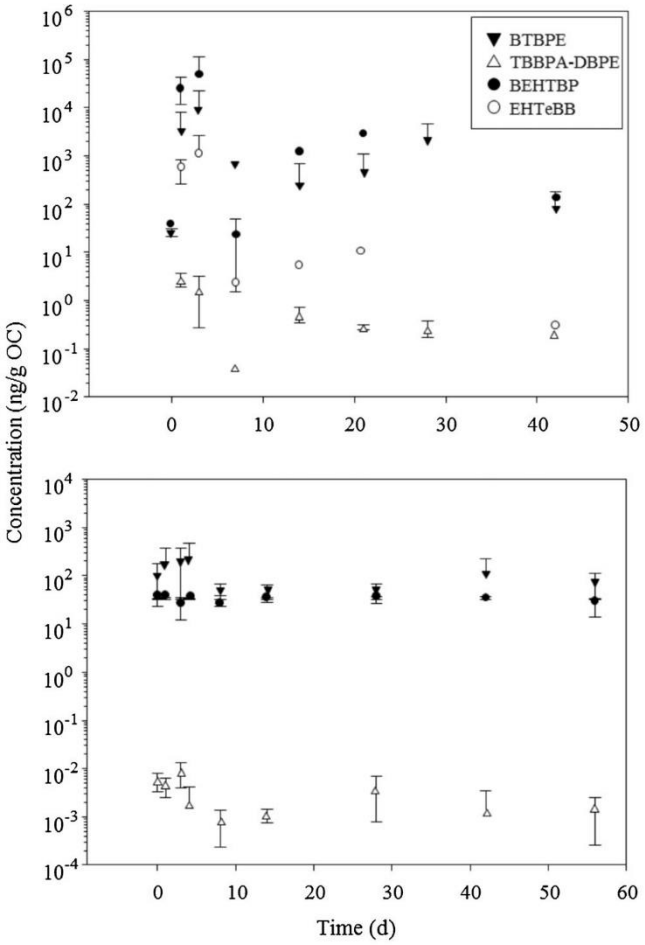


Figure 6 Concentrations over time of the NBFRs in the particulates (top) and sediment (bottom) compartment in the study of de Jourdan *et al.* (2013). From the four investigated chemicals (BTBPE, tetrabromobisphenol A bis(2,3-dibromopropyl ether) (TBBPA-DBPE), bis(2-ethylhexyl) tetrabromophthalate (BEHTBP), and 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (EHTeBB)), only EHTeBB showed a significant decline over time.

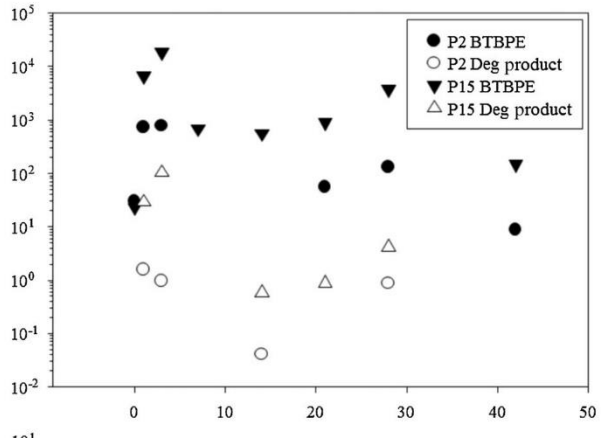


Figure 7 Concentration (ng/g OC) over time (days) of BTBPE and the BTBPE degradation products in the particulates over 42 days as shown in de Jourdan *et al.* (2013). P2 and P15 refer to pond 2 and 15, respectively.

It could be argued that the use of topsoil/manure/compost instead of pure sediment may have influenced the results of the study. However, if there had been an influence (e.g., adaptation of the microorganisms to the chemicals before the experiment), this would have led to faster degradation. The influence of the high organic carbon content (10%) of the sediment used in the study is, otherwise, not so straightforward. A higher organic carbon content of the sediment leads to a higher particle-bound fraction of BTBPE in the sediment, which might have led to a lower bioavailability. On the other hand, the OECD TG 308 for aerobic and anaerobic transformation in aquatic sediment systems (OECD, 2002) mentions that a decrease of the organic carbon content of the sediment may possibly result in a decrease of the microbial activity. It is currently not possible to clarify this point. However, an influence of the organic carbon content on the half-life cannot be ruled out. It is noted that in OECD TG 308 studies two sediments should be used, one with a high organic carbon content (2.5-7.5%) and the other one with a low organic carbon content (0.5-2.5%). Hence, the organic content of the sediment in the de Jourdan *et al.* (2013) study was a bit higher than the upper limit value indicated in the OECD TG 308. However, based on published literature, sediments with organic carbon content above 10% are found in Europe (e.g., Niemirycz *et al.* 2006, Karjalainen *et al.* 2000). Therefore, the de Jourdan *et al.* (2013) study can be considered relevant for assessing persistence in relevant environmental conditions in Europe. Based on the above considerations, this study is considered to be reliable with restrictions.

3.1.2.2 Biodegradation in soil

3.1.2.2.1 Simulation tests in soil

No standard simulation tests in soil are available for BTBPE.

Venkatesan and Halden (2014) analysed archived samples from outdoor mesocosms experiments performed over three years (2005−2008), in Baltimore, Maryland. The purpose of the original study was to understand the fate of pharmaceuticals and personal care products (PPCPs) in biosolids-amended soils (Walters, McClellan and Halden, 2010). After analysis of PPCPs, the remaining samples were stored at −20 °C for future analysis. Venkatesan and

Halden (2014) used the archived samples to investigate the persistence of BFRs in agricultural soil amended with sewage sludge. The biosolids for the original mesocosm study were obtained from a full-scale activated sludge treatment plant located in Baltimore, the mid-Atlantic region of the U.S. Agricultural soil was obtained from the United States Department of Agriculture – Agricultural Research Service from plots at a depth of 0–20 cm. Larger objects like plant debris and rocks were removed before use. The soil consisted of 20% clay, 27% silt, 53% sand, organic carbon content of 1.7% and a pH of 5.6. Biosolids and soil were mixed at a volumetric ratio of 1:2, which is high compared to the typical land application rate of biosolids (e.g., 1:10 after mixing). Venkatesan and Halden (2014) stated that this application rate was chosen to enable the potential observation of multiple half-lives of biosolids-borne compounds in soils and to facilitate the detection of degradants of relatively low abundance.

Biosolids/soil mixtures and control soils were seeded with tomatoes, bell peppers, and green salads in 30 plastic containers made from polyvinyl chloride 25 cm in depth, 30 cm in width and 30–80 cm in length. Mesocosms were seeded one time and left fallow after harvesting of crops at the end of the first growing season. The bottom of the containers was perforated to allow drainage of excess water; no attempts were made to collect the leachate from these vessels during long-term incubation. The containers were exposed to outdoor ambient weather conditions in Baltimore, Maryland without providing shelter or artificial irrigation. The 3-year average monthly precipitation was reported to be 91 mm and the 3-year average air temperature was 14°C. Moisture content of the soils varied between 14.6 and 35.1% from random sampling over the course of the experiment.

Samples were collected from the top 20 cm using a soil coring device, on days 57, 115, 520, 859, and 995. Each sampling event consisted of sampling three containers with unamended control soils and three containers holding soils that had received a biosolids application at the beginning of the experiment. Three cores were obtained per container and pooled per sampling round. Pooled cores were thoroughly homogenised, and stored at −20 °C until the chemical analysis was performed (Walters *et al.*, 2010).

Analysis batches consisted of a maximum of 20 samples, one procedural blank and one spiked matrix sample for ongoing precision and recovery (OPR) determination. Clean sand was used as the matrix for procedural blanks and OPR. A duplicate was analysed for every analysis batch that had to agree to within ±20% of prior measurements on identical samples. The recovery for BTBPE in the spiked matrix was 76%. BTBPE was detected neither in any of the lab blanks nor in the control samples of soil that did not receive sewage sludge.

Out of the 35 BFRs detected in the mesocosms, ten compounds (di-BDE, tri-BDE and 2 out of 7 tetra-BDE congeners) featured a loss from soil during the course of three years. The higher brominated PBDEs as well as pentabromoethylbenzene (PBEB), hexabromobenzene (HBB) and BTBPE persisted over the period of the three years in the mesocosm (**Figure 8**), indicating that neither degradation, volatilisation, leaching nor plant uptake was able to affect their concentrations in the soil/sludge mixture. As the soil was amended with biosolids (at high a volumetric ratio of 2:1) originating from WWTP that contained BTBPE and several other brominated flame retardants, the microorganisms present in the biosolids are considered to have been pre-adapted to BTBPE. The authors of Venkatesan and Halden (2014) point out that the number and volume of samples for the mesocosm study were limited and replicate samples were not always available for each sampling event. They also speculate that storage of the samples for extended periods of time prior to analysis may have allowed chemical degradation of labile chemicals. This latter point could lead to underestimation of the real concentrations. Therefore, there is some uncertainty in the results. However, the study is considered to be reliable with restrictions.

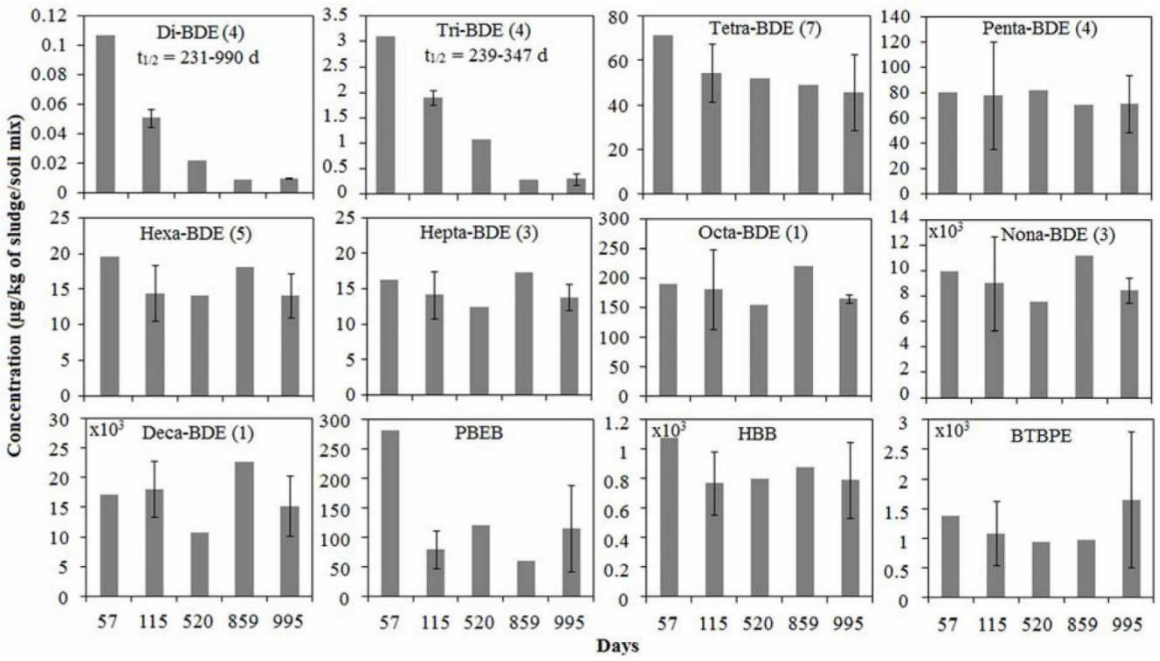


Figure 8 Concentration of BFRs over time in soil amended with sewage sludge from Venkatesan and Halden (2014). The y-axis scale of nona-BDE, deca-BDE, HBB, and BTBPE is in thousands. Error bars represent minimum and maximum concentrations. Numbers in round brackets indicate the number of congeners of which the total concentration is shown.

The results for BTBPE and other BFRs by Venkatesan and Halden (2014) were benchmarked using other available experimental data on degradation. The POPs Review Committee (POPRC) of the Stockholm Convention concluded based on available literature data that commercial penta-BDE (covering tetra- and penta-BDE), commercial octa-BDE (covering hexa- to nona-BDE) and deca-BDE are persistent in the environment (POPRC 2006, 2007, 2014). Tetra-, penta-, hexa-, hepta- and deca-BDEs were later added to Annex A of the Stockholm Convention. In the Stockholm Convention the screening criteria for persistence include degradation half-lives of 2 months for water and 6 months for sediment and soil. Hence, the substances identified as POP substances under the convention can be considered to fulfil the criteria for vP under REACH. The Agency for Toxic Substances and Disease Registry in its literature review concluded that tetra-, penta-, hexa-, octa- and deca-BDE are not readily biodegradable in water (ATSDR, 2017). On the other hand, the biodegradation of PBDEs is strongly dependent on the degree of bromination under aerobic conditions, i.e. lower brominated PBDEs including di- and tri-BDEs are more readily degraded (Zhao *et al.*, 2018). There is no or very few information available on the degradation of PBEB and HBB, but they are likely persistent. Overall, the results of the study by Venkatesan and Halden (2014) correspond well to other available information on the persistence of the investigated substances (**Table 5**). As BTBPE showed in the study of Venkatesan and Halden (2014) a similar pattern of degradation as other known vP/POP substances, it can be concluded that BTBPE is also likely to be vP.

Moreover, the half-lives in soil were estimated for BTBPE and other BFRs included in Venkatesan and Halden (2014) following calculations indicated in Rorije *et al.* (2011). This consisted of first converting the results of EPI Suite v.4.11 BIOWIN3 to half-lives in water using the equation

$$half\text{-}life_{water} = 7300 \cdot e^{(-2 \cdot \text{BIOWIN3 score})}$$ [1] [SEP],

and then calculating the half-life in soil using the following equation

$$half\text{-}life_{soil} = 2 \cdot half\text{-}life_{water}$$.

As indicated in Rorije *et al.* (2011) the Biowin3 model gives an estimate of the time required for 'complete' ultimate biodegradation in the aquatic environment, as estimated by a panel of experts. This model does not give a direct estimate of half-life, but a value between 1 and 5, which should be interpreted as 5 - hours; 4 - days; 3 - weeks; 2 - months; 1 - longer. It should be noted that the ratings are only semi-quantitative and are not half-lives. However, for the purpose of comparing trends in the estimated half-lives and observed degradation in the Venkatessen and Halden (2014) study, the calculations presented in the Rorije et al (2011) were used to estimate half-lives based on the BIOWIN 3 results.

As shown in **Table 5**, (i) the trend in the data of Venkatesan and Halden (2014) of increasing half-lives in soil with increasing number of bromine for the PBDEs is in line with the calculated half-lives based on BIOWIN3 predictions and equations by Rorije et al. (2011); (ii) that the half-lives in soil estimated based on BIOWIN 3 results are longer than 3 years for penta-, hexa-, hepta-, octa-, nona- and deca-BDE and shorter than 3 years for di-, tri- and tetraBDEs.

Table 5 Benchmarking of the results by Venkatesan and Halden (2014) using other available information on persistence of the substances.

Substance(s)	**Significant degradation over 3 years in Venkatessen and Halden (2014)?**	**Estimated $t_{½}$ in soil (equations by Rorije *et al.*, 2011)**	**Conclusion concerning persistence**	**References**
Di-BDE (n=4)	Yes (HL* 231–990 d)	0.5 years	Lower brominated PBDEs clearly less persistent under aerobic conditions	Zhao *et al.*, (2018)
Tri-BDE (n=4)	Yes (HL 224–495 d)	1.0 years		
Tetra-BDE (n=7)	Yes (2 congeners, HL > 770 d) No (5 congeners)	1.9 years	POP	POPRC (2006)
Penta-BDE (n=4)	No	3.5 years	POP	POPRC (2006)
Hexa-BDE (n=5)	No	6.6 years	POP	POPRC (2007)
Hepta-BDE (n=3)	No	12.2 years	POP	POPRC (2007)
Octa-BDE (n=1)	No	22.8 years	Likely similar or higher persistence as penta-, hexa- and hepta-BDEs due to structural similarity and higher bromination	ATSDR (2017), POPRC (2007), ECB (2003)
Nona-BDE (n=3)	No	42.3 years	Likely similar or higher persistence as penta-, hexa- and hepta-BDEs due to structural similarity and higher bromination	POPRC (2007)
Deca-BDE (n=1)	No	78.7 years	POP	POPRC (2014)
PBEB	No	2.8 years	No empirical	EFSA (2012)

			data available; judged as highly persistent	
HBB	No	5.5 years	Likely persistent, but very few studies; brominated derivative of POP HCB	Kondo *et al.*, (1988), JCheck (undated)
BTBPE	No	9.0 years	[target substance]	

* HL=Half-life

This shows that the data from Venkatesan and Halden (2014) showing decreasing concentrations over time for di- and tri-BDEs and stable concentrations for penta-, hexa-, hepta-, octa-, and deca-BDEs are very reasonable. Most of the substances that were expected (due to their BIOWIN 3 data) to degrade did degrade and those substances that were not expected to degrade did not. The only exception is tetra-BDEs. Their estimated half-life in soil is close to 2 years, while 5 of its 7 congeners did not show a significant decrease in the concentrations in the study of Venkatesan and Halden (2014). Bearing in mind that the half-lives from BIOWIN 3 are estimated, these data agree very well with the experimental results. Since BTBPE was found not to degrade in the study of Venkatesan and Halden (2014) and has an estimated half-life in soil of around 9 years, which is significantly higher than the ones of some of the POP-BDEs, the weight-of-evidence suggests that BTBPE is very persistent in soil.

3.1.2.3 Summary and discussion on biodegradation

Biowin QSAR predictions indicate that BTPBE screens as potentially persistent (P) or very persistent (vP).

BTBPE had very low degradation in a non-guideline biodegradation screening study (Calandra, 1976 from GLCC 2002) that used pre-adapted inoculum, inoculum:test substance concentration ratio similar to an inherent test and extended duration. According to ECHA Guidance Chapter R.11 (Version 3.0, June 2017), lack of degradation (<20% degradation) in an inherent biodegradability test equivalent to the OECD TG 302 series may provide sufficient information to confirm that the P-criteria are fulfilled without the need for further simulation testing for the purpose of PBT/vPvB assessment. The conditions of the test with BTBPE were not completely equivalent to OECD TG 302 tests and limited information on the test is available, and hence, its reliability cannot be fully assessed. Nevertheless, the very low degradation observed in the test with conditions similar to an inherent test and pre-adapted microorganisms suggests that BTBPE may be at least P.

Further mesocosms studies (reliable with restrictions) showed that BTBPE is (very) persistent in sediment (de Jourdan et al., 2013) and also in soil amended with biosolids (Venkatesan and Halden, 2014). There is some uncertainty whether or not the high organic carbon content (10%) in the study of de Jourdan *et al.* (2013) has influenced the biodegradation/bioavailability of BTBPE. However, sediments with organic carbon content above 10% are found in Europe (e.g., Niemirycz *et al.* 2006, Karjalainen *et al.,* 2000), and hence, the study of de Jourdan *et al.* (2013) is considered to reflect possible relevant environmental conditions in Europe. The study of Venkatesan and Halden (2014) was run over three years and the BTBPE concentrations were found to be stable over the whole study period. This clearly shows that the half-life of BTBPE in soil is higher than the 120 days set in Annex XIII of REACH as criterion for a persistent substance and also higher than the criterion of 180 days for a very persistent substance.

3.1.3 Field data

Wang *et al.* (2020) investigated the concentrations, behaviours and removal efficiencies of BTBPE and six other NBFRs in wastewater and biosolids samples collected from a wastewater treatment plant (WWTP), treating mainly domestic wastewater, in Beijing, China. The WWTP was designed to treat 400,000 m^3/d of wastewater and provides services to approx. 814,000 people. The inverted anoxic/anaerobic/aerobic (iA^2/O) biological treatment process is adopted in the WWTP. The influent is first treated in an aerated grit chamber as the primary clarifier. The primary sludge is then pumped for dehydration. After the iA^2/O treatment process, it then enters the secondary sedimentation tank, and finally treated wastewater is discharged into the receiving river. Part of the activated sludge from the secondary sedimentation tank and the aerobic bioreactor is returned to the anoxic bioreactor, while the rest is pumped for dehydration as excess sludge.

Samples from each location of the WWTP were taken on 16, 18 and 19 May 2017. The sludge-liquid and biosolid samples were taken at the end of each treatment unit. Each sludge-liquid sample was pooled from samples collected at three locations close to outflow of each unit. Twenty-four hour composite samples of influent, primary effluent and secondary effluent were collected every day using flow proportional samplers (cooled to 4°C), with a sampling interval of 2 h. After sealing without headspace, the samples were transported to the laboratory within 2 h of collection for analysis. During the sampling period, the water temperature was 23-25°C in the biological treatment unit.

The target NBFRs were determined in the extracts of the water and solid samples using GC-ECNI-MS. BTBPE levels were quantified relative to the internal standard 6′-MeO-BDE17. The recoveries were calculated by subtracting the amounts of the analytes detected in the nonspiked samples from those measured for the fortified recovery samples. Recoveries for BTBPE were 73±18 and 76±17% in wastewater and solid samples, respectively. Method detection limits (MDLs) were set at three times the standard deviation of the procedural blanks. The MDLs for BTBPE were 27 pg/L in wastewater and 1.4 pg/g dw in biosolid samples.

BTBPE was detected in all samples collected at various stages of the WWTP (**Figure 9**). The dissolved concentration of BTBPE in influent was 0.14±0.06 ng/L and in the primary effluent 0.11±0.04 ng/L. The authors state that the concentrations of BTBPE in the treatment units of the iA^2O processes decreased only slightly suggesting that the substance is recalcitrant to biodegradation in wastewater. The concentration of disolved BTBPE in the secondary effluent was 0.10±0.05 ng/L. The concentrations of adsorbed BTBPE in biosolids and suspended particles were in the range of 0.52–0.98 ng/g dw.

The authors also compared the dissolved and overall masses of the five NBFRs in influents and secondary effluents in order to estimate the average aqueous removal efficiencies. The overall removal efficiency for BTBPE is stated to be 25±33%, suggesting that the BTBPE was relatively persistent in the treatment processes. To assess the contribution of biodegradation and sorption to the removal efficiency in the WWTP, a mass balance was conducted. The authors considered the mass flows in the influent to contain dissolved and adsorbed phases as the import (100%), and the export then consisted of (i) effluent, (ii) biosolid, and (iii) the mass lost during the process. The mass fractions of BTBPE contained in biosolid and effluents were 68% and 21 %, respectively, and the mass fraction lost due to biodegradation was 11%.

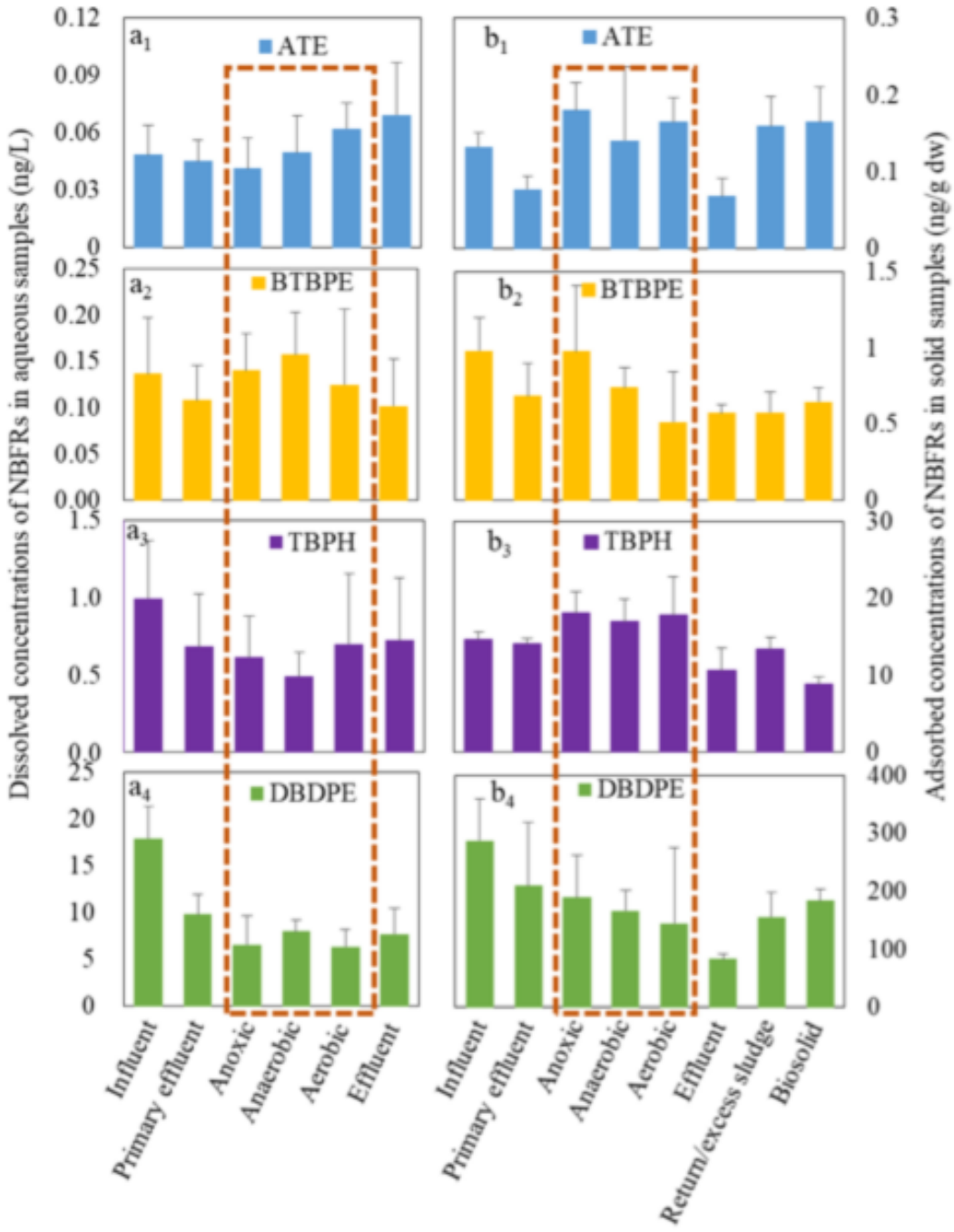


Figure 9 BTBPE and other NBFR concentrations measured in the a) wastewater (dissolved, ng/L) and b) biosolid samples (adsorbed, ng/g dw) from different treatment units in the WWTP in the study by Wang *et al.* 2020. Figure taken from Wang *et al.* (2020).

Qiu *et al.* (2007) detected BTBPE in a sediment core from Lake Ontario. BTBPE was detected in all layers from the early 1980 to the surface layer from 2000 (**Figure 10**). An increased trend was observed in the concentrations with the maximum concentration of 6.7 ng g^{-1} d.w. measured in the surface layer. The samples were taken from station 403 in Lake Ontario (43.59° N, 78.23° W) in July 2004. Subcores were taken by inserting a tube into the sediment box, and each subcore was extruded and cut into 1 cm intervals. Another core, which was collected at the same location in July 2006, was used for determining the sedimentation rate by measuring the specific activities of ^{210}Pb using the polonium distillation procedure. The samples were analysed with GC/MS using highly purified helium as the carrier gas.

Several quality control criteria were used to ensure the correct identification and quantitation of the target compounds: (a) The GC retention times matched those of the standard compounds within ±0.1 min. (b) The signal-to-noise ratio was >5:1. (c) The isotopic ratios for selected ion pairs were within ±15% of the theoretical values. The recovery for the matrix spiked sample was 96±1% for BTBPE. BTBPE was not detected in the blanks.

There are different possibilities to explain the increasing trend from the early 1980s until the 2000s. One possibility is that production volumes have increased since the beginning of the 1980s (BTBPE was first produced in the mid-70s) and that the increasing concentration in the sediment core reflects this increase in the production. There are no annual production figures from the years 1980 to 2000, which is why this hypothesis is difficult to prove. The other possibility to explain this trend is that BTBPE was degraded over time and that the lowest concentrations are therefore found in the oldest layers. Most likely is a combination of both explanations. However, the fact that BTBPE was found in 20 year old sediment layers shows that it is degraded very slowly in anaerobic sediment layers.

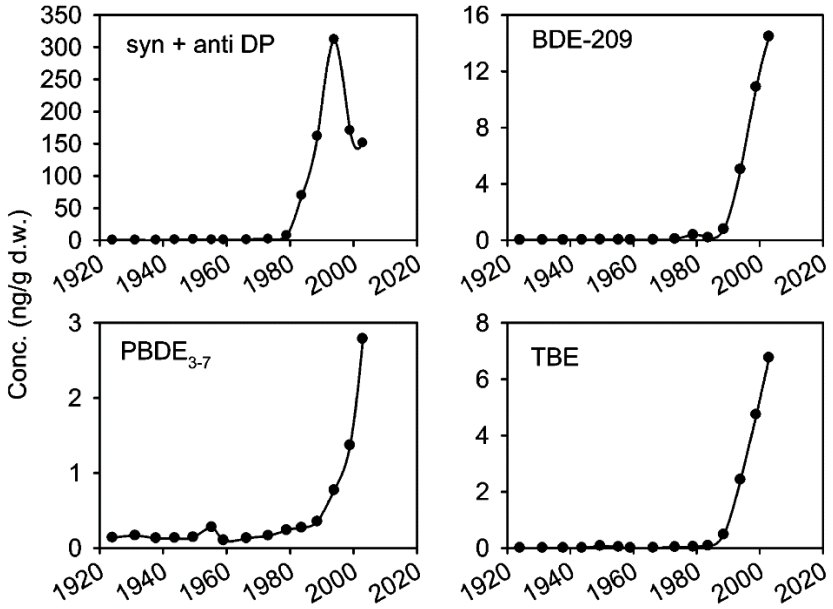


Figure 10 Concentration of BTBPE (TBE) and other brominated flame retardants in a sediment core from Lake Ontario as a function of year of deposition. Figure from Qiu *et al.* (2007).

BTBPE has also been detected in a second sediment core in the US (Hoh *et al.*, 2005, Figure 11). The authors analysed a sediment core from Lake Michigan, which was taken at the end of April 2004 at site MI (45.18° N, 86.38° W). A box core (30 cm × 30 cm × 52 cm depth) was taken aboard of the U.S. EPA's ship, the R/V Lake Guardian. Once the box core was back on the deck, several subcores were taken by inserting subcorer tubes. Care was taken to avoid distortion of the sediment. The cores were cut into 0.5 cm subcorer tubes down to 10 cm depth and into 1 cm slices below 10 cm. One of the subcores was used for dating by measuring the specific activities of the isotopes ^{137}Cs and ^{210}Pb. BTBPE was identified using GC/MS operating in the full-scan electron ionization (EI) and electron capture negative-ionization (ECNI) modes.

Three quality control criteria were used to ensure the correct identification of the target compounds: (a) The GC retention times matched those of the standard compounds within ±0.3 min. (b) The signal-to-noise ratio was greater than 3:1. (c) The isotopic ratio between the ion pairs was within ±15% of the theoretical value. Either a procedural blank or a spike recovery sample containing PBDEs was run with each batch of eight samples. BTBPE was not detected in the blank samples.

BTBPE first appeared in the sediment core at a depth corresponding to 1973 (**Figure 11**). The levels increased rapidly after 1973, with a doubling time of ~2 years until 1985. The BTBPE concentrations were relatively constant after that time. BTBPE was not found in the core's top layer representing 1993–2004. As also mentioned above for the study by *Qiu et al.* (2007), the increasing trend of BTBPE concentrations between 1973-1985 observed in Hoh *et al.* (2005) might also be explained either by increase in production or by degradation of BTBPE in the sediment over time leading to lowest concentrations being found in the oldest layers, or by a combination of both factors. But, also here, BTBPE was found in 20 to 30 year old sediment layers, which confirms the slow degradation of BTBPE in anaerobic sediment layers.

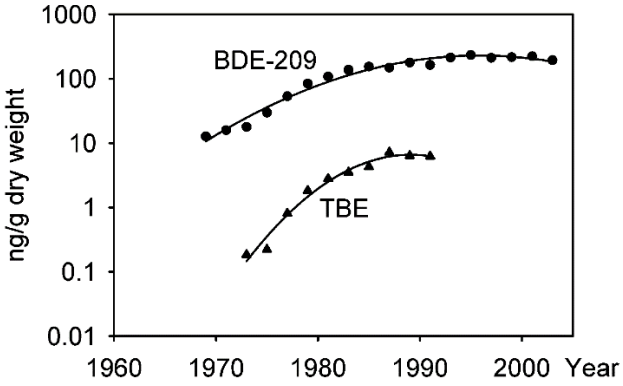


Figure 11 Concentration of BTBPE (TBE) and BDE-209 as a function of depth in the Lake Michigan sediment core. Figure from Hoh *et al.* (2005).

Lee *et al.* (2022) found BTBPE in sediment cores from a highly industrialised saltwater lake in Korea. Sediment cores of approx. 60 cm in length were collected from two sites in Lake Shihwa which is a 49-km^2 artificial lake created by the construction of a sea-dike. The sea-dyke (length: 12.7 km) was constructed in 1994 to supply water for agriculture and the hinterlands. The sediment cores were cut into 2 cm subcores. The sediment subcores were dated based on measurements of ^{210}Pb and ^{226}Ra. BTBPE was measured using GC-MS/MS using the electron impact ionization and multiple reaction monitoring mode. Procedural blanks, treated as real samples were included in the study. The instrumental limits of quantification (iLOQ) were calculated with standard deviations for eight replicate injections at the lowest acceptable calibration points. Recoveries of surrogate standards were 72% ± 15% (mean ± standard deviation), 71 ± 19%, and 89 ± 21% for CBs 103, 198, and 209, respectively.

BTBPE was detected in >90% of all depth sediments, in the range of <LOQ–59.1 ng/g dry wt (**Figure 12**). The highest concentrations were found in the subcores corresponding to years 1975-1990. After that the concentrations decreased. In the article it is indicated that the current consumption of BTBPE is not known but in the 1990s the consumption was 1700-2020 tonnes of BTBPE. It is further stated that the consumption dropped to 280 tonnes in 2004. The time trends in BTBPE in the sediment subcores matched the information on its consumption. The authors also state that the construction histories of the industrial complexes around the lake are reflected in the BTBPE concentrations.

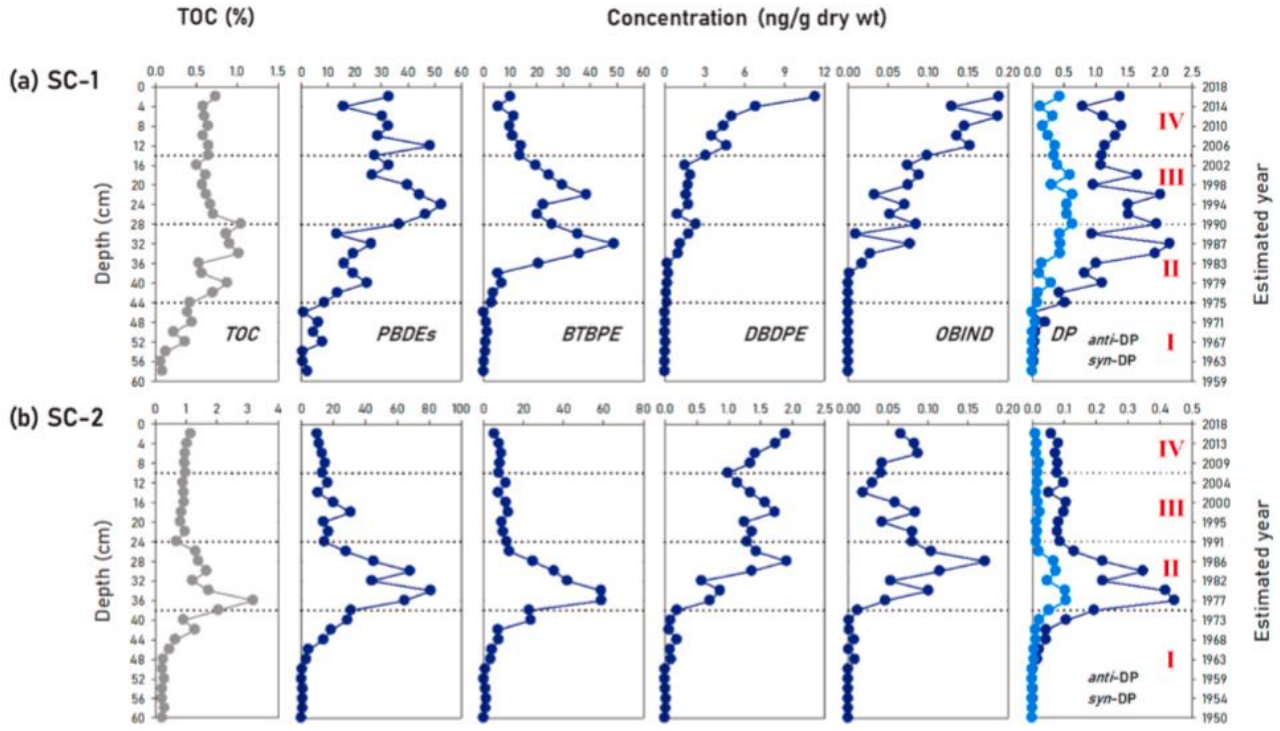


Figure 12 Vertical distributions of the concentrations of BTBPE as well as of Total organic carbon (TOC) and other halogenated flame retardants in sediment cores from Lake Shihwa, Korea. Sediment cores from (a) SC-1 and (b) SC-2 were collected near the mouth of creeks and the sea-dike of the lake Shihwa in Korea, respectively. Figure taken from Lee *et al.* (2022).

Monitoring data in themselves cannot demonstrate persistence because the presence of a substance in the environment is dependent on a range of factors other than degradation rates, namely emission and distribution rates. However, the fact that BTBPE has been found in 20-40 year old sediment layers shows that it is degraded very slowly (if at all) in anaerobic sediment layers. It should be noted that data on anaerobic degradation in sediment cores may only be used as part of a broader Weight of Evidence in the persistence assessment (ECHA, 2017b). Based on the monitoring data it cannot be excluded that degradation occurs in aerobic layers of sediments, but it seems that it is not sufficiently rapid to fully remove the substance before the anaerobic conditions are formed thus supporting the evidence of the persistence of BTBPE in sediments.

The Wang *et al.* (2020) study on fate of BTBPE in WWTP does not employ relevant environmental conditions for assessing the persistence of the substance in the compartments relevant for the PBT/vPvB assessment, i.e.: natural surface water, sediment or soil. However, the study can be used as a part of a weight-of-evidence approach. It seemed that BTBPE had only slow degradation in the WWTP, where microorganisms pre-adapted to the substance are present. This supports the conclusion of persistence of BTBPE.

3.1.4 Summary and discussion of degradation

BTBPE can be degraded by oxidation (Yu *et al.* 2017) and photolysis (Zhang *et al.* 2016) in the environment. The use of photolysis data is not generally recognised for persistence assessment due to the large variation in the light available in different environmental compartments. Moreover, data for oxidation in the gas-phase are very uncertain due to the semi-volatile nature of BTBPE, i.e., its adsorption to particles. Therefore, no conclusion on the persistence of

BTBPE can be drawn based on the abiotic degradation data.

BTBPE had very low degradation in a non-guideline biodegradation screening study (Calandra, 1976 from GLCC 2002) that used pre-adapted inoculum, inoculum:test substance concentration ratio similar to an inherent test and extended duration. According to ECHA Guidance Chapter R.11 (Version 3.0, June 2017), lack of degradation (<20% degradation) in an inherent biodegradability test equivalent to the OECD TG 302 series may provide sufficient information to confirm that the P-criteria are fulfilled without the need for further simulation testing for the purpose of PBT/vPvB assessment. The conditions of the test with BTBPE were not completely equivalent to OECD TG 302 tests and limited information on the test is available. Hence, its reliability cannot be fully assessed. Nevertheless, the very low degradation observed in the test vessels with conditions similar to an inherent test and pre-adapted microorganisms suggests that BTBPE may be at least P. Biowin QSAR predictions are consistent with the experimental data for BTPBE showing that the substance screens for potentially persistent (P) or very persistent (vP).

Further tests in mesocosms (reliable with restrictions) showed that BTBPE is persistent in sediment (de Jourdan *et al.,* 2013) and also in soil amended with biosolids (Venkatesan and Halden, 2014).

Sediment: There is some uncertainty whether or not the high organic carbon content in the study of de Jourdan *et al.* (2013) has influenced the biodegradation/bioavailability of BTBPE. However, sediments with organic carbon content above 10% are found in Europe (e.g., Niemirycz *et al.* 2006, Karjalainen *et al.,* 2000), and hence, the study of de Jourdan *et al.* (2013) is considered to reflect possible relevant environmental conditions. Furthermore, the available monitoring data from sediment core studies indicate that BTBPE has been found in 20-40 year old sediment layers in Lake Ontario (Qiu *et al.*, 2007) and Lake Michigan (Hoh *et al.*, 2005) in the USA and in an artificial saltwater lake in Korea (Lee *et al.*, 2022). These findings, suggest that the degradation in the environment may be slow and provide indirect evidence that BTBPE can persist in sediments for more than two-four decades. Based on the weight of the evidence available and considering the very persistence of the substance in the soil compartment, BTPBE is concluded to meet the P/vP criteria of REACH Annex XIII in the sediment compartment (degradation half-life in sediment > 180 days).

Soil: The study of Venkatesan and Halden (2014; reliable with restrictions) was run over three years and the BTBPE concentrations were found to be stable over the whole study period. The same was true for higher brominated PBDEs as well as for HBB and PBEB. Other tested compounds like BDE-17, BDE 28 or BDE-37 showed decreasing concentrations over time. This is in line with other available data on the biodegradation of these substances and thus demonstrates that the soil mesocosms experiment did represent realistic environmental conditions. The study therefore shows clearly that the half-life of BTBPE in soil is higher than the 120 days set in Annex XIII of REACH as criterion for a persistent substance and also higher than the criterion of 180 days for a very persistent substance.

Monitoring data for BTBPE support the above conclusions, as the substance has been detected in remote areas, e.g., in air and snow pits in the Norwegian and Canadian Arctic, respectively (see section 3.3.1). Furthermore, according to ECHA Guidance Chapter R.11 (Version 3.0, June 2017), if monitoring data as a part of a Weight-of-Evidence analysis show that a substance is present in remote areas (i.e., long distance from populated areas and known point sources, e.g., arctic sea or Alpine lakes), it may be possible to conclude a substance as P or vP.

Therefore, using a weight-of-evidence approach, it is concluded that BTBPE degrades very slowly in sediments and soils and fulfils the criteria for P and vP of REACH Annex XIII (degradation half-life in sediment or soil > 180 days).

3.2 Environmental distribution

3.2.1 Adsorption/desorption

BTBPE has a high logarithmic octanol−water partition coefficient (predicted log Kow in the range of 7.88-9.39) and also a high logarithmic octanol−air partition coefficient (predicted log Koa 13.6-15.7). KOCWIN (v2.00) QSAR model predicts log Koc values of 4.65 (MCI method) and 6.10 (Log Kow method). Hence, BTBPE has high affinity to bind to organic material in soil, sediment and water as well to particles in the atmosphere.

3.2.2 Volatilisation

HENRYWIN (v3.20) QSAR model predicts Henry's Law Constants of 7.42 x 10^{-4} Pa-m^3/mole (bond estimation method) and 4.31 x 10^{-2} Pa-m^3/mole (group estimation method) for BTBPE. Therefore, the substance is expected to have low volatilisation.

3.2.3 Distribution modelling

Mackay Level III fugacity modelling included in EPI Suite (version 4.11) was performed for BTBPE with default values of environmental emission rates (assuming equal emission rates to air, water, and soil). The model predicted that most of the substance partitions to soil (94.4 %), with some partitioning to water (5.1 %) and very little to sediment (0.41 %) and air (0.07 %).

3.2.4 Field data

Covaci *et al.* (2011) published a comprehensive review about novel brominated flame retardants (NBFRs) in 2011. The following subsections are reproduced from the review. Additional studies published after 2011 are mentioned as well.

Sediment

As indicated in Section 3.1.3, BTBPE has been found in sediment layers in Lake Ontario (Qiu *et al.*, 2007) and in Lake Michigan (Hoh *et al.*, 2005). In 1977, Zweidinger *et al.* (1979b) found detectable levels of BTBPE in sediments from streams near a production site in Arkansas. BTBPE concentrations ranged from not detected to 466 µg/kg.

The maximum concentration of BTBPE in sediments from southern China was 22 µg/kg dw (Shi *et al.*, 2009). Surface sediments (n=4) from Dongjiang River from China in 2006 showed concentrations of BTBPE between 0.05 and 2.07 µg/kg dw (Shi *et al.*, 2009). Leonards, Lopez, and De Boer (2008) reported concentrations of three NBFRs in sediments from two locations in the Western Scheldt. The maximum concentration of BTBPE was 0.3 µg/kg dw.

More measurements of BTBPE in sediment are available in Chen *et al.* (2013); Chokwe *et al.* (2019); Ganci *et al.* (2019); La Guardia *et al.* (2013); López *et al.* (2008; 2011); Klosterhaus *et al.* (2012); Liu *et al.* (2014); Poma *et al.* (2014b); Schlabach *et al.* (2011); Stiehl *et al.* (2010); Wang *et al.* (2011); Wang and Kelly (2017); Wu *et al.* (2010); Yang *et al.* (2012); Zhang *et al.* (2015); and Zhang *et al.* (2019).

Soil

In the 1970s, BTBPE was identified, but not quantified in soil samples taken near the Great Lakes Chemical Corporation (Chemtura) production facility in El Dorado, Arkansas, USA (DeCarlo, 1979). More recently, BTBPE was found in soil samples taken from two areas in southern China, one in the Pearl River Delta (PRD) and one near an e-waste processing area in the agricultural area of Qingyuan City, north of the PRD (Shi *et al.*, 2009). Soil samples

collected from farmland near Guangzhou City, PRD, had a mean BTBPE concentration of 0.05 µg/kg dw, whereas the soils from the e-waste area had higher concentrations (1.98 µg/kg dw) (Shi *et al.*, 2009). Outdoor dust samples collected from the ground surface near the e-waste workshops had a mean BTBPE concentration of 107 µg/kg dw, indicating that these workshops are probably a source of emissions to the nearby farmland. The BTBPE concentrations were lower than for PBDEs in the PRD samples, but were similar to pentaBDE concentrations at the e-waste site. (Shi *et al.*, 2009).

More measurements of BTBPE in soil are available in Ilyas *et al.* (2011); Hartmann *et al.* (2016); McGrath *et al.* (2017, 2018b); German Environmental Specimen Bank (2022); and Xu *et al.* (2017).

Air

In 1977, BTBPE was identified in the atmospheric particulate samples collected using high-volume samplers on the grounds of a production site in El Dorado, Arkansas at concentrations up to 183 ng/m^3 (DeCarlo, 1979; Zweidinger *et al.*, 1979a). Low concentrations of BTBPE (0.025–70 pg/m^3) were detected in outdoor air samples from five sites in east-central U.S. with the highest levels in Arkansas, near the abovementioned production site (Hoh and Hites, 2005). Likewise, median concentrations of BTBPE in outdoor air samples collected at five sites around the Great Lakes ranged between 0.5±0.3 and 1.2±0.3 pg/m^3 in Eagle Harbor and Chicago, respectively (Venier and Hites, 2008). By comparison, concentrations in four outdoor air samples taken in Guangzhou, China ranged between 3.8 and 67 pg/m^3 (average=30.7 pg/m^3) (Shi *et al.*, 2009).

Lee *et al.* (2016) conducted a retrospective analysis on air samples that were collected in 2005 and 2006 under the Global Atmospheric Passive Sampling Network. The target analytes were 16 non-PBDE BFRs including BTBPE. Polyurethane foam (PUF) disk passive air samplers (PAS) were deployed at approximately 40 sites in 2005 and 2006. Prior to field deployment, PUF disks were pre-cleaned and spiked with depuration compounds. The PUF disk PAS were installed mainly at background sites away from local emission sources. Some sites were situated in agricultural, rural and urban locations. Samples were collected every three months between March 2005 and March 2006. The samples were extracted and the extracts analysed initially for PCBs, and organochlorine pesticides in year 2006/2007. Extracts were stored in a freezer bank prior to analysis of the flame retardants, which was carried out in 2009. All samples and field blanks (n=24) were quantified for the 16 target analytes. The instrumental analysis was performed by gas chromatography negative-ion mass spectrometry with helium as the carrier gas and methane as the reagent gas.

For BTBPE, the concentrations in the atmosphere ranged from <0.2 to 19 pg/m3 (**Figure 13**). The highest concentration was measured in Canada but in general the concentrations were higher in Asia and Southeast Asia compared to the sites in the other regions. Lee *et al.* (2016) stated that BTBPE had the highest frequency of detection (85%) on a global basis and that BTBPE (together with hexabromocyclododecane) was also the most abundant non-PBDE BFR in the global atmosphere (**Figure 14**). It is indicated that the derived concentrations in air for the new flame retardants should be considered as semi-quantitative due to uncertainties related to e.g. estimation of PUF disk sampling rates and possible effect of the long storage time of the samples.

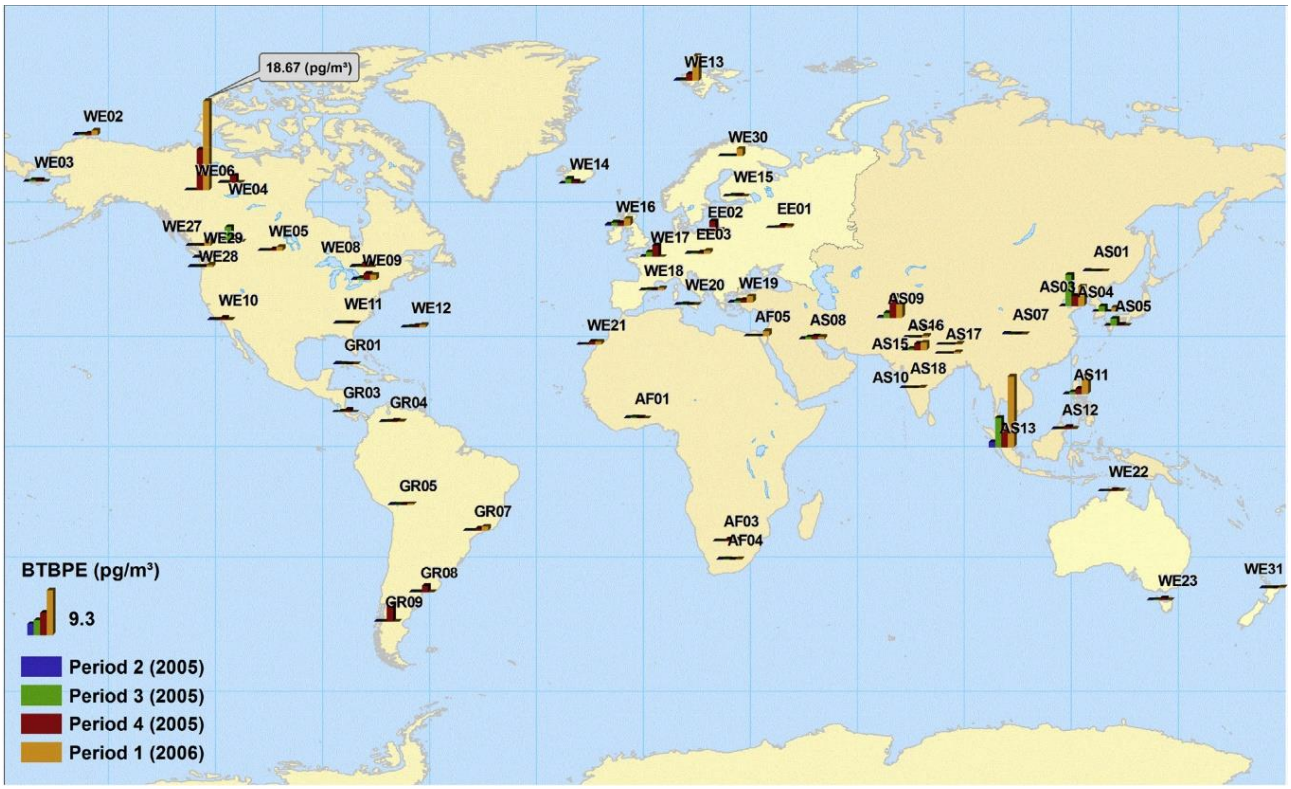


Figure 13 BTBPE concentrations (pg/m³) in the global atmosphere over four consecutive three-month deployment periods (March 2005 – March 2006). Figure from Lee *et al.* (2016).

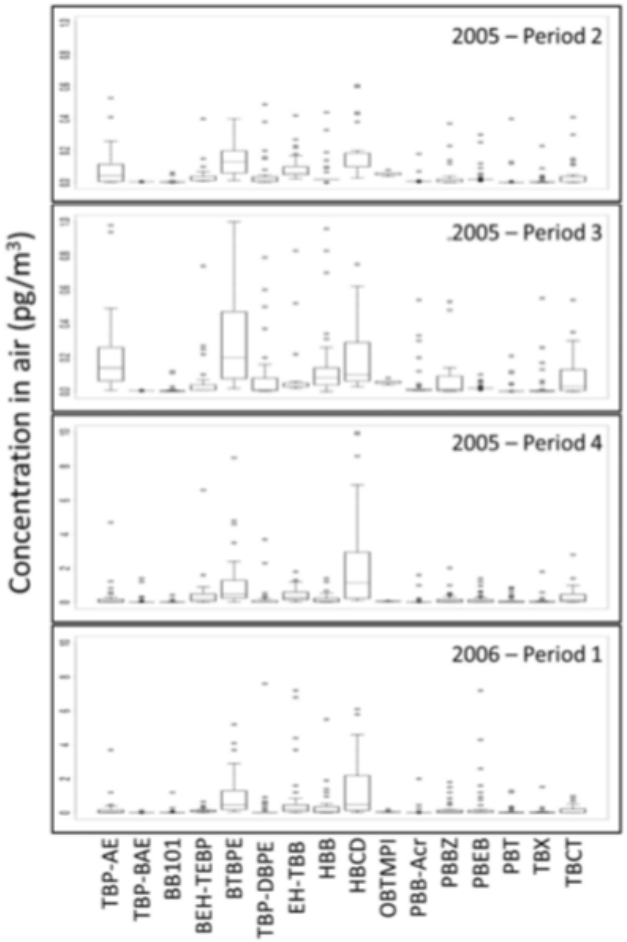


Figure 14 Box-and-whisker plot of the concentrations of the non-PBDE flame retardants detected in the global atmosphere. The four charts contain the data of four consecutive three-month deployment periods for each flame retardant (March 2005 to March 2006) as shown by Lee *et al.* (2016).

More measurements of BTBPE in the atmosphere are available in Arinaitwe *et al.* (2014); Davie-Martin *et al.* (2016); Iqbal *et al*. (2017); de la Torre *et al.* (2018); Liu *et al.* (2016); Ma *et al.* (2013); Ma et al. (2012); Möller *et al.* (2011a); Möller *et al.* (2012); Möller *et al.* (2011b); Qi *et al.* (2014); Qiu *et al.* (2010); Robson *et al.* (2013); Salamova *et al.* (2014); Salamova and Hites (2011); Shoeib *et al.* (2014); Shunthirasingham *et al.* 2018; Tian *et al.* (2011); Vorkamp *et al.* (2015); Xiao, *et al.* (2012a, 2012b); and Yu *et al.* (2015).

Indoor dust

BTBPE has been found in indoor dust in several studies, e.g. in Al-Omran and Harrad (2016, 2018), Ali *et al.* (2011, 2012, 2014); Besis *et al*. (2017); Brown *et al.* (2014); Cao *et al.* (2014); Cequier *et al.* (2014, 2015); Coelho *et al.* (2016); Cristale *et al.* (2016); Dodson *et al.* (2012); Fan *et al.* (2016); Fromme *et al.* (2014); Goosey *et al.* (2009); La Guardia and Hale (2015); Hassan and Shoeib (2015); Hsu *et al.* (2018); Johnson *et al.* (2013); Karlsson *et al.* (2007); Khairy and Lohmann (2018); Kuang *et al.* (2016); Kurt-Karakus *et al.* (2017); Leonards *et al.* (2008); McGrath *et al.* (2018a); Newton et al. (2015); Niu *et al.* (2019); Nkabinde *et al.* (2018); Peng *et al.* (2017); Sahlström *et al.* (2015); Sawal *et al.* (2008); Schreder and La Guardia (2014); Shi *et al.* (2009); Shoeib *et al.* (2012); Sjödin *et al.* (2001); Stapleton *et al.* (2008, 2009); Stuart *et al.* (2008); Sun *et al.* (2018); Tang *et al.* (2019); Tue *et al.* (2013); Venier *et al.* (2016); Yadav *et al*. (2019); and Zheng *et al.* (2015)

Biota

Tree bark can be considered as a surrogate matrix for assessing outdoor concentrations. BTBPE and DBDPE were detected in tree bark from the north east region of the US with concentrations ranging from not detected (ND) to 0.62 µg/kg and from ND to 0.73 µg/kg, respectively (Zhu and Hites, 2006; Qiu and Hites, 2008). Qiu and Hites (2008) also analysed tree bark samples from Canada, Europe and Asia. BTBPE was not detected in the sample from the Northwest Territories in Canada. Germany and Italy had BTBPE concentrations of 0.11 and 1.3 µg/kg lipid, respectively. BTBPE concentrations were much higher in tree bark from South Korea (56 µg/kg lipid), and 3 sites in China (3.1–38 µg/kg lipid). The highest concentration in China was found in Shenzheng, which is located in the PRD.

BTBPE has also been found in animals inhabiting different areas, which indicates that the substance is widely present in the environment. Information on the presence of BTBPE in wild animals is included in Section 3.4.3 on bioaccumulation and in Section 3.3.1 (presence in remote areas). Here some additional information not cited in the above-mentioned sections is included.

In a monitoring programme of organisms in a marine food web of the Inner Oslofjord, BTBPE has been detected in cod livers and herring gull eggs and blood at concentrations ranging from some pg/g ww to several hundreds of pg/g ww in years 2018 and 2019 (Ruus *et al.* 2019, 2020). In another monitoring programme in Norway (Jartun *et al.* 2021), BTBPE was detected in all studied species except in zooplankton, i.e., in the planktonic opossum shrimp *Mysis relicta*, and the fish species vendace (*Coregonus albula*), European smelt (*Osmerus eperlanus*), and brown trout (*Salmo trutta*) in Lake Mjøsa, which is a large lake highly impacted by human activities, and in the top predator brown trout from Lake Femunden, which is a pristine lake with limited impact from human activities. The concentrations were mostly very low, in the range of some tens of pg/g ww or lower.

Marler *et al.* (2022) measured concentrations of BTBPE and other flame retardants in four shark species, including shortfin mako shark (*Isurus oxyrhinchus*; n = 26), porbeagle (*Lamna nasus*; n = 4), sandbar shark (*Carcharhinus plumbeus*; n = 6), and common thresher (*Alopias vulpinus*; n = 4), from coastal and offshore waters of the western North Atlantic Ocean. BTBPE was detected in more than 80% of the samples. The median concentrations of BTBPE by species ranged from 0.7 to 16.7 ng/g lw.

A food web study in Lake Winnipeg included samples of zooplankton, mussels (*Lampsilis radiata*) and six species of fish, including predatory fish such as burbot (*Lota lota*) and walleye (*Stizostedion vitreum*) (Law *et al.*, 2006). Mean BTBPE concentrations were 0.37 µg/kg lipid weight (lw) in zooplankton, 1.3 µg/kg lw in mussels and from 0.13 to 0.95 µg/kg lw in the different fish species, which were much lower than for HBCD and PBDEs. Maximum BTBPE and DBDPE concentrations (in fish and mussels) were 3.7 and 3.3 µg/ kg lw, respectively.

Concentrations of pentabromoethylbenzene (PBEB) and BTBPE were determined in lake trout from Lake Ontario between 1979 and 2004 (Ismail *et al.*, 2009). Concentrations of PBEB showed no overall trend, while BTBPE concentrations peaked around 1993 and then declined Peak concentrations were around 300 and 2.5 µg/kg lw for PBEB and BTBPE, respectively. Interestingly, the variation in the BTBPE concentrations in lake trout did not follow the variation in Lake Ontario sediment (Qiu *et al.*, 2007) which showed a continuous increase (see Section 3.1.3).

The maximum concentration of BTBPE in fish from southern China was 0.15 µg/kg lw, while DBDPE and TBBPA-DBPE were not detected (Shi *et al.*, 2009). *Munschy et al*. (2007) reported concentrations of BTBPE in muscle tissue of common sole from French waters. The maximum concentrations was 2.2 µg/kg lw.

Ding *et al.* (2022) measured concentrations of BTBPE in several insect species and six amphibian species from an abandoned e-waste recycling site in South China. BTBPE had low deteciton frequencies and the mean concentrations ranged from non-detected to 226 ng/g lw in the amphibians and from non-detected to 108 ng/g lw in the insects.

Maximum concentrations of BTBPE and DBDPE in watercock from southern China were 2.4 (liver) and 124 (kidney) µg/kg lw (Shi *et al.*, 2009). Both BFRs were detected at relatively higher concentrations in the liver and kidney than in muscles. In Northern fulmar eggs from the Faroe Islands, BTBPE was measured at concentrations up to 0.11 µg/kg lw (Karlsson *et al.*, 2006). Egg pools of herring gulls collected in 2004 from six sites in the Great Lakes were considered in two studies (Gauthier *et al.*, 2007, 2009). Maximum concentrations of BTBPE in the two studies were 0.7 and 1.8 µg/kg ww, respectively.

Tomy *et al.* (2007a) analysed several BFRs including BTBPE in blubber from Canadian Arctic beluga (*Delphinapterus leucas*) collected in 2002–2005 from several sites. BTBPE was found in a few samples with concentrations ranging from 0.1 to 2.5 µg/kg lw. These concentrations were similar to those found for HBCD but lower than for PBDEs.

More measurements of BTBPE in fish are provided in Munschy *et al.* (2011); Poma *et al.* (2014c); Poma *et al.* (2014a); Sawal *et al.* (2011); Schlabach *et al.* (2011); Strid *et al.* (2013); Umweltbundesamt (2016); Wolschke *et al.* (2015); Wu *et al.* (2010); and Zhang *et al.* (2010).

More measurements of BTBPE in birds are provided in Abbasi *et al.* (2016, 2017); Fernie *et al.* (2017); Guerra *et al.* (2012); Herzke *et al.* (2003); Jin *et al.* (2016); McKinney *et al.* (2006); Peng *et al.* (2015); Sun *et al.* (2014); Verreault *et al.* (2005); Vorkamp *et al.* (2015, 2018); and Zhang *et al.* (2011).

More measurements of BTBPE in mammals are provided in Dam *et al.* (2011); Houde *et al.* (2017); Verreault *et al.* (2005); Vorkamp *et al.* (2015); and Zhu *et al.* (2014).

3.2.5 Summary and discussion of environmental distribution

Based on the available information, BTBPE is ubiquitously present in the environment. It is found in sediments, soils, air and biota. Due to its low water solubility and high adsorption capacity, in surface waters BTBPE is expected to be mostly present in the suspended particles. In air, it is expected to be mainly present in the particle phase (see also Annex III).

3.3 Data indicating potential for long-range transport

3.3.1 Measured concentrations in remote regions without local sources

Detection of contaminants in remote regions is evidence of their persistence and capability for long-range transport (LRTP) (Newton *et al.*, 2014). The following studies show that BTBPE has been found in remote regions and is able to undergo long-range transport.

Davie-Martin *et al.* (2016) investigated BTBPE concentrations in air at Toolik Lake, Arctic Alaska (68.627 ° N, -149.598° E) during the Northern Hemisphere summer of 2013. The concentrations at Toolik Lake were measured with a high-volume air sampler. BTBPE was only detected in association with atmospheric particles, with concentrations ranging from 0.02 to 0.15 pg/m^3. BTBPE was not detected in any of the blanks. The estimated detection limit (EDL, 2.5 times signal to noise ratio) for BTBPE was 0.01 pg/m^3. BTBPE was detected in 38% of the measurements above EDL. Measurements of BTBPE and other BFRs along a transect extending away from the field station showed that the BFR concentrations did not originate from local emissions of the Toolik Field Station.

BTBPE has also been detected in air samples collected using a super high volume air sampler in Alert, Nunavut, Canada (82.202° N, −55.546° E) (Xiao *et al.* 2012a). The concentrations of BTBPE (not corrected for field blanks nor adjusted for recoveries) ranged between 0.16 and 1.9 pg/m^3. The method detection limit (MDL, mean field blank values plus 3 times the standard deviation) was 3.0 pg/m^3. None of the measurements was above the MDL and only five of the 14 measurements were above the blank level of 0.76 pg/m^3. Thus, at the 99% confidence level, the ambient concentrations are not significantly higher than the blanks. The measured concentrations are therefore not reliable.

In another study by Xiao *et al.* (2012b) BTBPE was also detected in air samples in Alert, Nunavut, Canada (82.202° N, −55.546° E). Air samples were taken both with a flow-through sampler (FTL) and a super high volume air sampler (SHV) during 2007 and 2008. The concentrations of BTBPE (corrected for field blanks but not for recoveries) ranged between non-detectable to 1.2 pg/m^3.

BTBPE has also been detected in air samples at Little Fox Lake, in Canada's Yukon Territory (61.35° N, 135.63° W) (Yu *et al.*, 2015). Air samples were taken with a flow-through sampler containing a PUF plug. One PUF was collected as field blank for every sample, while solvent blanks were analysed for every two samples. Field blanks and solvent blanks were extracted and analysed in the same manner as PUF samples. BTBPE was not detected in the solvent blanks. In the field blanks a concentration of 0.008 pg/m^3 was detected. Recovery determined by spiking a clean PUF sample with working standard was 129 %. The MDL (mean field blank values plus 3 times the standard deviation) for BTBPE was 0.02 pg/m^3. The measured concentration of BTBPE in the PUF samples ranged between 0.024 and 0.22 pg/m^3. BTBPE was detected in 23.8% of the samples above MDL. No blank-correction or recovery adjustment was made. No temperature dependence of the BTBPE air concentrations was found.

Lee *et al.* (2016) found BTBPE in their retrospective analysis in Barrow, Alaska (71.32° N,

156.58° W). The concentrations ranged between 0.2 and 1.0 pg/m^3. However, BTBPE was also detected in the field blanks at a concentration of 0.6 pg/m^3. The MDL (mean field blank values plus 3 times the standard deviation) would thus be 1.1 pg/m^3 and the measured concentrations below the MDL.

Lee *et al.* (2016) found BTBPE also in their retrospective analysis in St. Lawrence Island, Alaska (63.7° N, −170.48° W) at a concentration of 0.33 pg/m^3. There was no deployment of field blanks.

Möller et al. (2011a) measured BTBPE in air samples from the East Greenland Sea. Air samples were taken with a high-volume air sampler. BTBPE concentrations up to 0.02 pg/m^3 were measured in the particulate phase and up to 0.06 pg/m^3 in the gaseous phase. BTBPE was not detected in any of the field blanks. The MDL (mean field blank values plus 3 times the standard deviation) was 0.02 pg/m^3. BTBPE was detected above MDL in 70% of the particle phase samples and in 22% of the gaseous phase samples. All sampling locations were located in the East Greenland Sea, far away from local sources.

In another study, Möller *et al.* (2011b) measured marine boundary layer air on a polar expedition cruise from the East China Sea to the Arctic (33.23-84.5°N). Air samples (1-2 days, 17 samples) were taken via a high-volume air sampler placed in the front of the ship's upper deck. BTBPE was not detected in any of the field blanks. The MDL (3 times signal to noise ratio) was 0.031 pg/m^3. In the 8 samples from the stations north of 60°N, BTBPE was detected once above the MDL at a concentration of 0.17 pg/m^3.

The LRTP and deposition of BTBPE was also confirmed by the presence of BTBPE in an ice-core from Svalbard, Norway (79.13° N, 13.27° E) (Hermanson *et al.*, 2010). The sampling location of the ice-core was about 40 km northeast of Ny-Alesund on the west coast of Spitsbergen. Ice core subsampling for analysis included combining contiguous sections of the core from the upper 34 m into 6 distinct samples with liquid volumes of 11-15 L each. This depth was estimated to cover a period from 1953 to 2005. The analysis of BTBPE (and other BFRs) yielded net ng/L units. They were converted to a flux (pg cm^{-2} yr^{-1}) by dividing the amount of BFR by the surface area of the core (86.6 cm^2) and the years represented in the core segments analysed. To account for possible background contamination from transport, storage, and other handling, including in the laboratory, two deeper ice core segments representing the pre-BFR period from about 1900 to 1914 at depths of 52.3 to 59.2m were analysed. The largest BFR concentration in these deep samples represented the procedural detection limit, or background, which was subtracted from amounts in the upper 34 m of the core. The input flux of BTBPE was below background level or not detected until the subcore 1988-1995 where it was about 5.1 pg cm^{-2} yr^{-1} and a similar level (4.3 pg cm^{-2} yr^{-1}) was measured in the top layer of the ice core, representing years 1995-2005.

BTBPE was also detected in snow pits from Devon Ice Cap, Nunavut, Canada (75.34° N, 82.67° W) (Meyer *et al.*, 2012). Snow pits were dug with depths of 5 m in 2005, 6.8 m in 2006, and 7 m in 2008, each located several kilometres upwind from the nearest temporary research site. The MDL (mean field blank values plus 3 times the standard deviation) of BTBPE was 5 pg/L. The measured concentrations of BTBPE ranged from <MDL to 120 pg/L. BTBPE was detected in 20% of the horizons of the snow pits (representing 1992 to 2006) above MDL but the concentration patterns did not show clear deposition time trends.

Biota

BTBPE has been detected in the Canadian Arctic in approximately 20% of the ringed seal samples (NCP, 2013). The exact concentrations are not stated, but the detection limit was 0.02 ng/g ww, meaning that the ringed seals had concentrations higher than 0.02 ng/g ww. BTBPE was also detected in wolf (*Canis lupus*) in concentrations ranging from 0.008 to around 0.2 ng/g ww (NCP, 2013; AMAP, 2017).

BTBPE was also detected in about 25% of polar bear samples analysed from the Canadian Arctic, but was undetectable in polar bear samples from Alaska, Hudson Bay and the European Arctic (McKinney *et al.*, 2011). No concentrations were given.

Furthermore, BTBPE was found in Greenland sharks accidentally caught in waters around Iceland between 2001 and 2003. BTBPE was detected in 10 out of 15 liver samples above the MDL (0.16 ng/g fat) with concentrations ranging from 1.6 to 8.1 ng/g fat (median concentration 0.61 ng/g fat) (Strid *et al.*, 2013). Greenland sharks usually stay in cold areas. The distribution area of this species are the Arctic waters of the North Atlantic. Occasionally they are also found further south. The detection of BTBPE in Greenland sharks shows that BTBPE is present in Arctic waters or biota.

Vorkamp *et al.* (2015) measured BTBPE in samples of black guillemot eggs (n=4), polar bear adipose tissue (n=5), glaucous gull liver (n=4) and blubber of ringed seal (n=5) collected in 2012 from Ittoqqortoormiit, East Greenland (70.485° N, 21.964° W) with additional ringed seal samples (n=4) from West Greenland. Concentrations in black guillemot eggs ranged from 0.013 to 0.017 ng/g ww. All concentrations in the black guillemot eggs were above the MDL of 0.012 ng/g ww. Concentrations in polar bear adipose tissue ranged from 0.065 to 0.27 ng/g ww. 80% of the samples were above the MDL of 0.065 ng/g ww. In addition, the concentration of BTBPE in a single sample of ringed seals and glaucous gulls was above MDL, at 0.21 and 0.022 ng/g ww, respectively. The polar bears and the ringed seals live in Greenland, which has an extremely low human population density. From this study, it seems likely that the polar bears and ringed seals were exposed to BTBPE originating from remote rather than local sources, suggesting long-range environmental transport of the substance. Black guillemots breed in Arctic regions of the Northern Hemisphere and winter south to shores of the Holarctic. The black guillemots could have accumulated the BTBPE concentrations in the Holarctic; however, the bird would in this case transfer the BTBPE to a remote region – which is also problematic and considered a means of long-range environmental transportaccording to Annex D of the Stockholm Convention. The same is true for glaucous gull.

Another study (Verreault *et al.*, 2007) found BTBPE in egg yolk from glaucous gulls sampled in 2006 at Bear Island in the Norwegian Arctic (74.367° N, 19.083° E). The highest measured concentration was 0.96 ng/g ww. In 29% of the samples (n=31 in total) concentration of BTBPE was above the method limit of quantification (MLOQ) of 0.27 ng/g ww. BTBPE was not detected in the blanks. The MLOQ was calculated as 10 times the standard deviation of the noise. BTBPE was detected only in 5 % of the plasma samples of male glaucous gulls (n=19 in total) above the MLOQ of 0.20 ng/g ww. In all plasma samples of female glaucous gulls (n=30 in total) BTBPE concentration was below MLOQ. Regarding the location for the accumulation of the BTBPE, in addition to being exposed to BTBPE in the Norwegian Arctic due to atmospheric deposition of the substance, the glaucous gulls might have accumulated the BTBPE also in other regions, but this would indicate again BTBPE transfer via birds as a migratory species. Bear Island is located midway between the North Norwegian mainland and the Svalbard archipelago, and only a meteorological station is active all-year around at the island. No other human activity besides campaign-based research projects have been reported from the island during recent years, and hence, significant local contamination sources are not expected (Kallenborn *et al.* 2007).

Sagerup *et al.* (2010) detected BTBPE in 40% of Brünnichs' guillemot eggs (n=10 in total) from Svalbard and Bjørnøya (Norway). The concentrations ranged between 0.0005 and 1.125 ng/g ww.

Schlabach *et al.* (2011) detected BTBPE in black guillemot eggs from the Faroe Islands. The eggs were sampled from two locations; 9 eggs were sampled from the island Skúvoy, and 10 eggs from the island Koltur. The eggs were analysed as one pooled sample from each sampling site. BTBPE was detected in both pooled samples with concentrations of 0.019 and 0.024 ng/g ww, respectively. BTBPE was also detected in muscle of Arctic char (collected from 12 fish) from a lake on the Faroe Islands (Schlabach *et al.*, 2011). The pooled sample had a BTBPE

concentration of 0.012 ng/g ww. According to Schlabach *et al.* (2011) the samples of the black guillemot eggs and arctic char were taken from background areas which are mainly exposed to long-range transported contaminants. Possible background levels of BTBPE were subtracted from measured sample values in the study. The limit of quantifications (LOQ) was calculated as a signal 10 times the standard deviation of the blank values. The measured BTBPE concentrations were all above the LOQ.

All studies quoted above are summarised in **Table 6**

Table 6 Overview of the measured concentrations in remote regions without local sources. MDL=method detection limit; LOD=limit of quantification.

Concentrations in air

Study location	Concentration [pg/m^3]	MDL [pg/m^3]	Samples > MDL	Reference
Toolik Lake, Arctic Alaska	0.02 – 0.15	0.01 (LOD)	38 %	Davie-Martin *et al*. (2016)
Alert, Nunavut, Canada	0.16 – 1.9*	3.0	0 %	Xiao, *et al.* (2012a)
Little Fox Lake, Canada	0.02 – 0.22	0.02	24 %	Yu *et al.* (2015)
East Greenland Sea	0.02 – 0.08	0.02	70 %	Möller *et al.* (2011a)
Chukchi Sea	0.03-0.17	0.031	13 %	Möller *et al.* (2011b)

* Only five of the 14 measurements were above the blank level of 0.76 pg/m^3. None of the measurements was above the MDL. Thus, at the 99% confidence level, the ambient concentrations are not significantly higher than the blanks. Therefore, the measured concentrations are not reliable.

Concentrations in ice and snow

Study location	Concentration [pg/L]	MDL [pg/L]	Samples > MDL	Reference
Svalbard, Norway	14.9 – 95.5	n.a.	n.a.	Hermanson *et al.* (2010)
Devon Ice Cap, Nunavut, Canada	5.5 – 120	5.0	19 %	Meyer *et al.* (2012)

Concentrations in biota

Study location	Concentration [ng/g ww]	MDL [ng/g ww]	Samples > MDL	Reference
Canadian Arctic				
Ringed seal	>0.02	0.02	20%	NCP (2013)
Wolf	0.008-0.2	-	-	AMAP (2017)
Iceland				
Greenland sharks	<0.16 – 8.1 ng/g fat	0.16 ng/g fat	67 %	Strid *et al.* (2013)
Ittoqqortoormiit, Greenland				
Black guillemot eggs	0.013 – 0.017	0.012	100 %	Vorkamp *et al.* (2015)
	0.065 – 0.27	0.065	80 %	
Polar bear	0.21**	0.070	11 %	
Ringed seal	0.022**	0.012	25 %	
Glaucous gull				
Bear Island, Glaucous gull eggs	0.27 – 0.96	0.27	29 %	Verreault *et al.* (2007)
Svalbard and Bjørn-øva, Brünnich's guillemot eggs	0.0005-0.024	0.0005	40%	Sagerup *et al*. (2010)
Faroe Islands				
Black guillemot eggs	0.019-0.024	-	100%	Schlabach *et al.* (2011)
Arctic char	0.012	-	100%	

** Only one value was above the MDL

3.3.2. Measured concentrations in (remote) regions with potentially local sources

Lee *et al. (2016)* found BTBPE in their retrospective analysis in Ny-Alesund, Norway (78.9° N, 11.883° E) at concentrations of up to 5.2 pg/m^3. However, this concentration originated from the warmest measurement period (February to May 2006, average temperature 11 °C), whereas the concentrations in the other three measurement periods were much lower (**Table 7**). The measured concentrations might therefore have originated from local sources.

Table 7 Measurement period, average temperature and BTBPE concentration for Ny-Alesund, Norway, from Lee *et al.* (2016).

Measurement period	Average temperature	Concentration (pg/m^3)
March – June 2005	−5 °C	<0.2
June – September 2005	2 °C	<0.2
October – December 2005	−5 °C	1.4
February – May 2006	11 °C	5.2

Salamova *et al.* (2014) measured BTBPE in particle phase atmospheric samples from Longyearbyen on Svalbard (8.22° N, 15.65° E) in the European Arctic from September 2012 to May 2013. The averaged concentrations ranged from 0.01 to 0.09 pg/m^3. However, while located in the Arctic, Longyearbyen is a coal mining community of ~2100 permanent residents (as of 2011). It was established in 1906 and became an incorporated community during the 1970s. Nearly all of the population growth and building construction has occurred since the 1980s. The daily annual mean temperature is −7.5 °C. Therefore, the use of building and pipe insulation and associated flame retardants might be extensive.

BTBPE has also been detected at a remote Chinese research station close to Nam Co Lake, Tibet (30.74° N, 90.988° E) (Xiao *et al.*, 2012a). BTBPE concentrations were below 1 pg/m^3 during most of the year but increased dramatically from below 0.57 to 20 pg/m^3 in May 2007 and then declined after three months. Despite this strong temporal variation, no significant temperature dependence of the BTBPE air concentrations was found at the site. This suggests that there was no significant constant local emission within the vicinity of the sampling site, but it cannot be excluded that temporary local sources or an accidental release occurred at Nam Co.

3.3.3 OECD P_{OV}-LRTP Tool

The OECD P_{OV}-LRTP Tool (Wegmann *et al.*, 2009) is a decision support tool that estimates overall environmental persistence (P_{OV}) and long-range environmental transport potential (LRTP) of substances and compares them with acknowledged POPs. The LRTP metrics predicted by the tool include overall persistence (Pov), characteristic travel distance (CTD, in km) and transport efficiency (TE, in %). CTD indicates the distance from a point source at which the chemical's concentration has dropped to 38% of its initial concentration. TE estimates the percentage of emitted chemical that is deposited to surface media after transport away from the region of release. The input parameters into the Tool are: logarithmic air−water partition coefficient (log K_{AW}), logarithmic octanol−water partition coefficient (log K_{OW}), half-life in air ($t_{1/2}$ in air), half-life in water ($t_{1/2}$ in water), and half-life in soil ($t_{1/2}$ in soil). The input parameter for BTBPE and the reference chemicals are provided in **Table 8**. The results are listed in

Table 9 and shown in **Figure 15** and **Figure 16**.

The input values used in the tool for BTBPE and the reference substances were predicted using EPISUITE v4.11 QSAR models, and the half-lives in water and in soil were calculated based on the result of BIOWIN3 QSAR model and using the following equations from Rorije *et al.* (2011):

$$\text{half-life}_{water}\ [\text{days}] = 7300 \cdot e^{(-2 \cdot \text{BIOWIN3 score})}$$

$$\text{half-life}_{soil} = 2 \cdot \text{half-life}_{water}\ .$$

It is noted that the Biowin3 model gives an estimate of the time required for 'complete' ultimate biodegradation in the aquatic environment, as estimated by a panel of experts. It does not give a direct estimate of half-life, but only a semi-quantitative rating between 1 and 5, which should be interpreted as 5 - hours; 4 - days; 3 - weeks; 2 - months; 1 - longer. Therefore, for example, if the average expert rating for ultimate degradation of a substance is 2.5, it means the experts considered that the substance would biodegrade completely in a time frame somewhere between weeks and months. For the purpose of OECD P_{OV}-LRTP Tool quantitative half-lives for air, water and soil are needed. As reliable experimental half-lives are not available for BTBPE and the reference substances for all compartments, the equations used in the Rorije *et al.* (2011) were used to get comparable estimates for all substances. However, these estimated half-lives have high uncertainty and should be interpreted with caution and used only for comparing the substances with each other, not for comparing the results with any criteria for persistence.

Using the equations of Rorije *et al.* (2011) resulted in calculated half-life in water and soil of 4.5 and 9 years, respectively, for BTBPE. It is noted that in the Venkatesan and Halden (2014) soil mesocosms study BTBPE remained stable in soil during the 3-year study period, and hence, the half-life would have been longer than 3 years.

Several scenarios for BTBPE with different input values were calculated. First, the influence of the partition coefficients (input values of EPI Suite™ v.4.11 vs. COSMOtherm) and second, on the influence of the half-life in air (input value from AopWin v1.92 vs. value of 10.7 days from Section 3.1.1 Oxidation) were looked at. All four scenarios produced very similar results. The half-life in air has a marginal effect in the CTD and TE of BTBPE as the fraction of the substance in the gas phase is predicted to be very small (0.003%) by the OECD P_{OV}-LRTP Tool based on log K_{aw} and log K_{ow}. Therefore, the input parameters from EPI Suite™ v.4.11 for BTBPE were used for the analysis to get a higher comparability with the reference substances.

Using the OECD P_{OV}-LRTP Tool and the input data shown in **Table 8**, the overall environmental

persistence (P_{OV}) of BTBPE is 4720 days, its CTD is 2860 km, and TE is 12.7%. This estimation ranks BTBPE in a position of typical POP-like features as provided by the Tool. For instance, in comparison with several benchmark POPs, such as penta-, hexa-, and heptaBDE, PCB-101 and PCB-180, BTBPE has comparable P_{OV}, CTD, and TE (**Figure 15** and **Figure 16**). This still holds true, even if taking into account the uncertainty of the input parameters and performing a Monte Carlo analysis. The thick black line in each plot defines the maximum LRTP that is possible for a given P_{OV}. Therefore, data points for all chemicals lie on or below this line (Wegmann *et al.*, 2009).

Table 8 OECD P_{OV} LRTP tool input data used for BTBPE and for the reference substances. Values are calculated using EPI Suite™ v.4.11: [a]KOAWIN v1.10, [b]KOWWIN v1.68, [c]AopWin v1.92, [d]BIOWIN3 (BIOWIN v4.10) and calculation from Rorije *et al.*, 2011, and [e](2 × half-life in water) (Rorije *et al.*, 2011).

	MW (g/mol)	log K_{AW}[a]	log K_{OW}[b]	$t_{1/2}$ in air (hours)[c]	$t_{1/2}$ in water (hours)[d]	$t_{1/2}$ in soil (hours)[e]
BTBPE	687.6	−6.52	9.14	17.3	39304	78608
α-endosulfan	406.9	−2.576	3.50	25	50246	100492
α-HCH	290.8	−3.68	4.26	448	8424	16849
Aldrin	364.9	−1.80	6.06	1.95	41735	83469
CCl_4	154.0	0.052	2.44	688000	3515	7031
Hexachlorobuta-1,3-diene	260.8	−0.376	4.72	8544	47377	14753
HBCDD[1]	641.7	−3.51	5.62	76.8	12000	1512
HBCDD[2]	641.7	−2.73	7.74	51.1	3513	7025
HCB	284.8	−1.16	5.86	15192	12250	24500
PCB-101	326.4	−2.43	6.98	767	9679	19357
PCB-180	395.3	−3.39	8.27	2454	30184	60369
PCB-28	257.5	−2.09	5.69	217	3144	6288
Pentachlorobenzene	250.3	−1.54	5.22	4436	6958	13917
tetraBDE	485.8	−3.92	6.77	256	8322	16644
pentaBDE	564.7	−4.32	6.84	467	15480	30959
hexaBDE	643.6	−4.72	8.55	1108	28799	57597
heptaBDE	722.5	−5.11	9.44	1544	53567	107133
octaBDE	801.4	−5.52	10.33	2588	99656	199313
decaBDE	959.2	−6.31	12.11	7621	344856	689713

Table 9 OECD POV LRTP tool generated values for Figure 15 and Figure 16.

	P_{ov} (days)	CTD (km)	TE (%)
BTBPE	4720	2860	12.7
α-endosulfan	628	518	0.08
α-HCH	895	4182	16.3
Aldrin	2803	235	0.0001
CCl_4	18560	1113409	1914
Hexachlorobuta-1,3-diene	559	153085	74.7
HBCDD[1]	378	1391	1.68
HBCDD[2]	422	1131	0.80
HCB	1325	205434	732
PCB-101	1148	10216	28.6
PCB-180	3625	3191	14.2
PCB-28	357	4231	2.25
Pentachlorobenzene	708	71437	194
tetraBDE	997	2704	8.64
pentaBDE	1855	2945	11.9
hexaBDE	3459	2863	12.7

[1] HBCDD using data from the registration dossier (https://echa.europa.eu/en/registration-dossier/-/registered-dossier/15003)
[2] HBCDD using data from EPI Suite™

heptaBDE	6433	2861	12.7
octaBDE	11969	2861	12.7
decaBDE	41417	2861	12.7

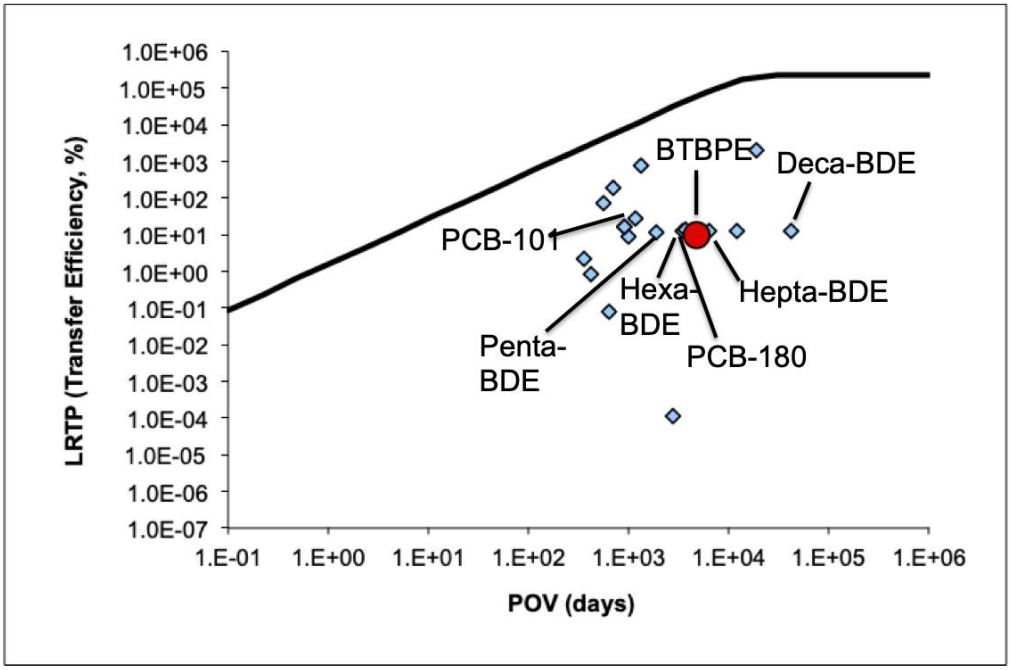


Figure 15 OECD LRTP-P_{OV} tool plot comparing BTBPE (red dot) and benchmark POPs (grey diamonds) for TE, and P_{OV} (Wegmann *et al.* 2009). See Table 9 for input data used in the tool.

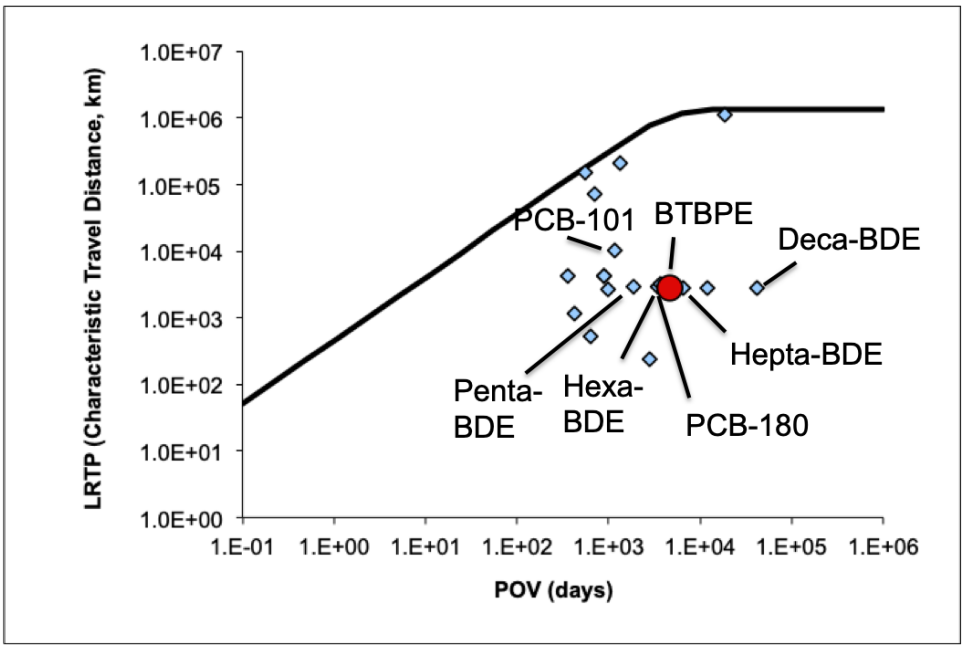


Figure 16 OECD LRTP-P_{OV} tool plot comparing BTBPE (red dot) and benchmark POPs (grey diamonds) for CTD and P_{OV} (Wegmann *et al.* 2009). See Table 9 for input data used in the tool.

3.3.4 Conclusion on long-range transport

As indicated in Section 3.1.1.2, a gas-phase half-life of 10.7 days for atmospheric oxidation initiated by OH is calculated for BTBPE based on the reaction rate determined by Yu *et al.* (2017) using a combined quantum chemical calculations and kinetics modelling. Considering that the substance is predicted to be particle-bound in air the estimated atmospheric half-life for the gas-phase may underestimate its persistence in air. Hence, the atmospheric half-life of BTBPE is expected to be well above 2 days, which is one of the criteria indicated for long-range environmental transport potential in the Annex D of the Stockholm Convention on persistent organic pollutants.

BTBPE has been detected in the atmosphere of some remote regions like Toolik Lake (Arctic Alaska) and the East Greenland Sea. It has also been detected in an ice-core from Svalbard (Norway) and in snow pits from Devon Ice cap (Nunavut, Canada). These measurements show that BTBPE is indeed able to undergo long-range environmental transport. The same conclusion has been drawn by the authors of the Arctic Monitoring and Assessment Programme (AMAP, 2017). They stated: "*The air, snow and ice measurements show that BTBPE is transported to the Arctic and deposited in the Arctic environment.*" It has also been detected in biota, e.g., polar bears and ringed seals, in Greenland.

The model results from the OECD P_{OV}-LRTP Tool show furthermore that BTBPE has an overall environmental persistence, characteristic travel distance and transfer efficiency comparable to benchmark POPs like penta-, hexa-, and heptaBDE as well as PCB-180 and PCB-101.

3.4 Bioaccumulation

3.3.1 Bioaccumulation in aquatic organisms (pelagic & sediment organisms)

3.4.1.1 Screening information

Based on the predicted log Kow values in the range of 7.88-9.39, which are considered more reliable than the available measured log Kow value of 3.14 (see Section 1.3), BTBPE screens B/vB (log kow >4.5).

3.4.1.2 Laboratory studies

The only measured BCF values for BTBPE are from a study (CITI, 1976 cited in GLCC, 2002) where carp (*Cyprinus carpio*) were exposed to the substance for 8 weeks at 25°C via aquatic phase. Two nominal test concentrations were used: 0.3 and 0.03 ppm of BTBPE. Eight fish per test concentration were used. A control group of eight fish exposed to water without the test substance was also included in the test. The test substance was supplied continuously to a mixing tank and then diluted and introduced into each test tank. Fish were fed with pelleted feed 2-3 times daily. Two fish were sacrified and analysed after 2, 4, 6, and 8 weeks of exposure in each exposure group. Concentrations of test material in the water were also measured 2, 4, 6, and 8 weeks after the beginning of the experiment.

In **Table 10** the measured concentrations in water and fish as well as the BCF values are shown for the different sampling times and exposure concentrations. The measured concentrations in water are not reported in the robust study summary (GLCC 2002). However, as the concentrations in fish and the BCF values are reported for each sampling time, the concentrations in water have been calculated based on those values. The test substance concentrations in water seemed to remain stable during the study (**Table 10**). The whole body BCF values at the different sampling times were in the range of 5.2-56.6 L/kg at the exposure concentration of 0.3 ppm and in the range of 11.9-43.6 L/kg at the exposure concentration of 0.03 ppm (**Table 10**). The concentrations in fish and the BCF values had high variation between the different sampling times and they did not show any clear increasing trend and no

plateau indicating steady-state. No statistically significant differences were observed between the two exposure scenarios.

Table 10: Concentrations of Carp exposed to 0.3 and 0.03 ppm of BTBPE for 8 weeks

Exposure Scenario	0.3 ppm							
Week	2	2	4	4	6	6	8	8
Concentration in water (ppm)	0.28	0.28	0.27	0.27	0.27	0.27	0.28	0.28
Concentration in fish (ppm)	16	7.5	2.76	7.47	1.82	1.41	2.38	7.49
BCF	56.6	26.6	10.3	27.9	6.7	5.2	8.6	27.1
Exposure Scenario	0.03 ppm							
Week	2	2	4	4	6	6	8	8
Concentration in water (ppm)	0.025	0.025	0.026	0.026	0.026	0.026	0.026	0.026
Concentration in fish (ppm)	0.474	0.492	0.304	0.954	0.677	0.757	1.13	0.661
BCF	19	19.7	11.9	37.4	26.1	29.2	43.6	25.4

Based on the high variability in the measured BCF values and the high predicted log Kow value of BTBPE (in the range of 7.88-9.39, see Section 1.3 for further information), it may be that steady-state was not reached. According to OECD TG 305, an estimation of the time to reach 80% of the steady-state concentrations can be calculated as:

$$t_{80} = \frac{-\ln(0.20)}{k_2} = \frac{1.6}{k_2} \qquad (1)$$

$$\log k_2 = 1.47 - 0.414 \cdot \log K_{\mathrm{ow}} \qquad (2)$$

Using a predicted log K_{OW} of 8.16 for BTBPE, 80% of the steady-state concentration is reached after 130 days. After 56 days (8 weeks), only 50% of the steady-state concentration is reached. This means that the duration of the available BCF test was too short to calculate reliable steady-state bioconcentration factors (and therefore the BCF may have been higher than 56.6 L/kg). Limited description of the test conditions is available but it seems that the study did not include a depuration phase, and therefore, kinetic BCFs were not calculated.

Furthermore, the exposure concentrations in the test were likely higher than the water solubility of BTBPE. Measured water solubility values of 160 µg/L at 15°C and 200 µg/L at 25°C are reported in a shake flask study (Yu and Atallah, 1978 from GLCC 2002). However, as indicated in Section 1.3, there are some uncertainties in these measured values and they may overestimate the real solubility of BTBPE. The predicted water solubility values are in the range of $2.8 \cdot 10^{-4}$ to 19 µg/L.

In conclusion, considering that the exposure concentrations were likely above the water solubility, small number of fish was tested (n=2 per sampling), there was high variability in the BCF values and steady-state was likely not reached, the study is not considered reliable for concluding on the bioaccumulation of BTBPE in fish.

Tomy *et al.* (2007b) exposed rainbow trout (*Oncorhynchus mykiss*) (initial mean weights 202 g) to an environmentally relevant dose of BTBPE via the diet for 49 days, followed by 154 days of untreated food. The study did not follow any standard guideline. In order to assess its reliability, the study design and results were compared with the current OECD TG 305 dietary study and its validation criteria.

The spiking of the food was done by placing commercial fish food in a blender together with corn oil spiked with BTBPE (500 µL of 50 ng/µL solution in TMP). After 20 min of gentle stirring, an aqueous gelatin binder (40 g of gelatin in 1.5 L of H_2O) was added. Stirring continued until a firm consistency was observed (approx. 20 min). The resulting spiked food was air-dried for 40 min, extruded through a 4 mm diameter noodler, thoroughly dried at 10 °C for 48 h, and crushed into pellets. Control food was prepared in the same manner but without the test substance. Food was stored in the dark at -4 °C to limit the possibility of light-induced degradation of BTBPE. Lipid based concentrations of BTBPE in treated (n=4) and untreated (n=4) food were determined to be 46.2±2.0 (arithmetic mean ± 1 × standard error) and 0.2 ± 0.1 ng/g, respectively. Average lipid content in the food was determined to be 13.6 ±0.5%. According to OECD TG 305, test diets with total lipid content between 15 and 20% (w/w) have commonly been used in the development of this method. However, the guideline points out that fish food with such a high lipid concentration may not be available in some regions. In such cases the guideline recommends that studies could be run with a lower lipid concentration in the food, and if necessary, the feeding rate adjusted appropriately to maintain fish health. The daily feeding rate was equal to 1.0% of the mean weight of the fish, adjusted after each sampling period based on the mean weight of the sub-sample of fish that were sacrificed. Hence, it was in the range recommended by OECD TG 305 and not adjusted higher based on the lower lipid content of the feed. Nevertheless, according to OECD Guidance Document on Aspects of OECD TG 305 on Fish Bioaccumulation (OECD 2017), adjustment is only needed when the lipid content of the food is very much lower than 15%. As in the study by Tomy et al. (*2007b*) the final lipid content of the feed (spiked with corn oil) was 13.6 ±0.5%, it was only slightly below 15%, and hence, it is considered not to have a significant effect on the reliability of the results.

In Tomy *et al.* (2007b) it is stated that the concentrations of BTBPE did not decline in the food from the start of the exposure experiment (day 0) to the end of the depuration phase (day 203). However, there is no detailed information on this, and therefore, it cannot be fully assessed whether the validity criterion of OECD TG 305 stating that the concentration of the test substance in fish food before and at the end of the uptake phase is within a range of ± 20% (based on at least three samples at both time points) was met. Also, there is no information regarding whether there was high degree of homogeneity of BTBE in the treated food, which is one of the validity criteria of the test guideline. Hence, there is some uncertainty regarding the exposure conditions.

51 fish were used for each treatment (exposure and control groups) and each treatment was held in separate 800 L fiberglass aquaria receiving 1.5 L UV and carbon dechlorinated tap water/min (12°C, pH 7.9-9.1). It is noted that this is just below the test water temperature range (13-17 °C) recommended for rainbow trout in the OECD TG 305. Furthermore, according to one of the validity criteria of the OECD TG 305, the water temperature should vary less than ± 2 ºC because large deviations can affect biological parameters relevant for uptake and depuration as well as cause stress to animals. There is no further information on the test water temperature variation in the Tomy *et al.* (2007b), and hence it is not possible to assess whether the validity criterion of the OECD TG 305 was fulfilled. This raises some uncertainty to the study. It is stated that the dissolved oxygen was always at a level of saturation, and thus, the validity criterion of OECD TG 305 regarding this aspect seemed to be met. A 12 h light:12 h dark photoperiod was maintained throughout the experiment. Four fish were sampled from each tank on days 0, 7, 14, 28, and 49 of the uptake phase and on days 7, 14, 28, 56, 112, and 154 of the depuration phase. Sampling was always done 24 h after the previous feeding.

Muscle tissues of the sampled fish were weighed and the lipid content was determined. The concentration of BTBPE in muscle tissue extracts was determined using gas chromatography mass spectrometry analysis (GC/MS). Instrument blanks, used to monitor possible BTBPE contamination between GC injections, were injections of isooctane run after every 5 samples. Method (or procedural) blanks were derived by extraction of control fish muscle tissue and also extraction of Na2SO4. Method blanks were used to monitor the potential for contamination to

occur during extraction and workup of the sample. Method detection limit (MDL) was estimated to be 0.30 pg/g. For calculation of mean concentrations, and for statistical purposes, a concentration of 1/2 of the MDL was assumed in those instances where BTBPE concentrations were below the MDL. In the case of Tomy et al. (2007b) study where the depuration was slow, this may not be advisable, as according to OECD TG 305, in many cases where the chemical concentrations in fish at the end of the depuration phase are very low and may fall below the limit of detection (l.o.d.) it may be advisable to not use these time-points in data analysis. The guideline recommends using a specific value below the l.o.d. (e.g., 0.5 x l.o.d.) only in some cases, e.g. when the depuration is fast and many of the concentrations in fish fall below the l.o.d. In Tomy et al. (2007b) it is also indicated that when detected, concentrations of BTBPE in muscle tissue of control fish were subtracted from that in fish exposed to treated food. However, there is no information on the concentrations or detection frequencies of BTBPE in the control fish. According to OECD TG 305 validity criteria, the test substance should not be detected, or be present only at typical trace levels, in un-spiked food or control fish tissues relative to treated samples. These aspects introduce some uncertainty to the results. Concentrations in fish were also corrected for lipid content and recovery using BDE-71 and BDE-126 which averaged 81 ±2%.

The fish whole body growth rates determined in Tomy *et al.* (2007b) were slightly greater in fish exposed to treated food (0.0051±0.0007 day-1) than those exposed to untreated food (0.0035±0.0008 day-1) suggesting that exposure of fish to BTBPE did not have a negative effect on the growth of the fish ($p > 0.05$). Liver somatic index, which can be used as an indicator of fish health, did not vary between fish exposed to treated and untreated food. The mean lipid content of the muscle samples on days 49 and 203 of the study, which were 0.94±0.02 % and 0.77±0.39 %, respectively, for the exposed group, and 0.96±0.48 % and 0.95±0.48 %, respectively, for the control group. Hence, at the end of the uptake phase there was no difference between the lipid contents of the muscle of the exposed and control fish, while at the end of the study there was a slight difference. However, based on the reported standard errors on day 203, there seemed to be relatively high variation in the lipid contents of the different samples, and therefore, the difference may not be statistically significant. No mortality of the test fish was observed during the study. Therefore, it seems that the validity criteria of OECD TG 305 regarding mortality and other adverse effects were met in the Tomy *et al.* (2007b) study.

Tomy *et al.* (2007b) observed a linear uptake and a first-order depuration kinetics with a depuration rate constant of 0.0128±0.002 day^{-1} and a depuration half-life of 54±8 days. The depuration rate was calculated based on concentrations of BTBPE measured in muscle tissue, corrected for lipid content (see **Figure 17**). The biomagnification factor reported in the study was 2.3±0.9. However, the biomagnification factors reported in Tomy *et al.* (2007b) should be treated with caution and are not used in the assessment, because there are inconsistencies in the data (assimilation efficiencies, mean feeding rates, and BMFs) presented in the published article and it is not clear how the BMF was calculated. However, the depuration rate constant is considered reliable for the assessment.

It is noted that the whole fish depuration rate could differ to some extent from that determined for muscle. The relation between lipid-corrected concentrations in muscle tissue and in whole body is not known for BTBPE in rainbow trout or other fish species. In a study by Gandhi *et al.* (2017) whole body ∑PBDE concentrations (based on wet weight) were 2–5 times higher than muscle concentrations for some fish species. However, the differences in ∑PBDE levels between the two tissue types (i.e., whole body and muscle) were similar to the differences in their lipid content. In a study by Stone *et al.* (2006) the whole body concentrations of PBDEs in salmon trout were 34% higher than in fillet tissues, but no significant difference was found in the lipid-corrected concentrations. Hence, as in the Tomy *et al.* (2007b) the BTBPE concentrations in muscle tissue were lipid-corrected, it can be expected that they may be relatively representative to whole body lipid-corrected concentrations. Nevertheless, it cannot be excluded that depuration (e.g. through metabolism) could differ in other tissues, leading to different whole body depuration rate. Therefore, the lack of whole body measurement raises

some uncertainty to the results of Tomy *et al.* (2007b).

All in all, there are some uncertainties in the Tomy et al. (2007) study due to lack of detailed information or deviations from the conditions recommended in the OECD TG 305. However, the study is considered to be reliable with restrictions.

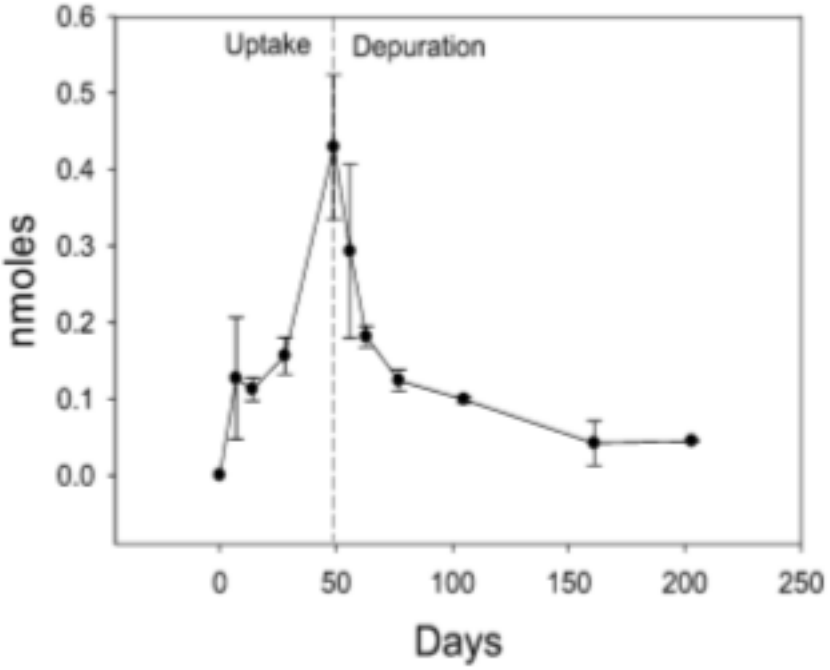


Figure 17. Uptake and depuration curves of BTBPE through dietary exposure in juvenile rainbow trout (*Oncorhynchus mykiss*). Molar amounts are for muscle tissue that have been control and lipid corrected. Each data point represents the arithmetic mean (±1 × standard error) of four fish. Figure taken from Tomy *et al.* 2007b.

The ECHA guidance Chapter R.11 for the PBT/vPvB assessment under REACH (ECHA, 2017b) Chapter R.11.4.1.2.9 gives some guidance on dietary exposure and the depuration rate constant. It is stated that upon prolonged exposure and after internal redistribution of a compound, the rate of elimination is independent of the uptake route: aqueous exposure, dietary exposure or both routes simultaneous as in the field. Besides that, uptake rates in fish are rather similar for neutral organic compounds and dependent on e.g., ventilation rates of gills for aqueous exposure and feeding rate for dietary exposure. So, the elimination rate is a discriminating factor in the bioaccumulation potential of such compounds. For this reason, the half-life has been suggested as a useful metric for the bioaccumulation assessment and some indicative values for depuration rates that can lead to B/vB properties are given. The ECHA Guidance refers to the model of Sijm *et al.* (1995) for estimating an uptake rate, which is then compared to the experimental depuration rate from a dietary study. The model uses the fish weight (W in g) to estimate the uptake rate (k_1) with the following allometric relationship:

$$k_1 = 520 \cdot W^{-0.32} \qquad (3)$$

Using a fish weight of 202 g in the above equation (the initial mean weight at the start of the test in Tomy *et al.* 2007b), a BCF of 5000 would be reached if the depuration rate is lower than 0.019 day^{-1} (BCF = k_1/k_2). The ECHA Guidance Chapter R.11 (ECHA, 2017b) further refers to a study of Brooke and Crookes (2012) where of a limit of 0.085 d^{-1} for the depuration rate corresponding with a BCF of 5000 was reported resulting from a comparison of lipid normalised BCF values with their corresponding depuration rate constants. Hence, the obtained depuration rate constant of 0.0128±0.002 day^{-1} from Tomy *et al.* (2007b) indicates that BTBPE is very bioaccumulative (BCF > 5000).

In the OECD Guidance Document on Aspects of OECD TG 305 on Fish Bioaccumulation (OECD 2017), three methods have been proposed to estimate BCF values based on the results of dietary bioaccumulation studies. The first method consists of several models for estimating uptake rate and calculating BCF based on the estimated uptake rate and the measured depuration rate. The second method relates the measured depuration rate directly to an estimated BCF. The third method correlates dietary BMF with BCF. The first two approaches were used to estimate BCFs based on the depuration rate measured in the study by Tomy *et al.* (2007b) and the log Kow of 8.16 as input. The BCF Estimation Tool version 2 provided by OECD[3] was used for the calculations (see **Table 11**). The BCF values calculated with the models in method 1 were in the range of 1032-120312 L/kg and the median of the values was 13218 L/kg. 10 out of the 13 models included in method 1 estimated BCFs above 5000 L/kg, two models gave BCFs above 2000 but below 5000 L/kg, and one model resulted in a BCF below 2000 L/kg. The method 2 resulted in a BCF of 50873 L/kg.

Table 11 BCF values calculated for BTBPE based on the depuration rate measured in the study by Tomy *et al.* (2007b) using the Methods 1 and 2 included in the OECD's BCF Estimation Tool version 2.

Method 1			
inputs for K1	**K1**	**BCF Est.**	**Ref.**
weight	177.40	13859.0	Hayton and Barron (1990)
weight	291.50	22773.5	Erickson and McKim (1990a)
weight	258.25	20175.7	Barber et al. (1991)
weight	155.89	12178.7	Barber (2003) - observed
weight	294.05	22972.5	Barber (2001)
weight	54.68	4271.6	Streit and Sire (1993)
weight	169.19	13217.6	Erickson and McKim (1990b)
weight	94.63	7392.9	Sijm et al. (1995)
weight	75.83	5924.0	Barber (2003) - calibrated
log Kow	1540.00	120312.3	Tolls and Sijm (1995)
log Kow	1511.89	118116.4	Spacie and Hamelink (1982)
weight, log Kow	33.87	2645.8	Hendriks et al. (2001)
weight, log Kow	13.21	1032.3	Thomann (1989)

Method 2			
input	**Estimated K1**	**BCF Est.**	**Ref.**
K_{2g}	651.18	50873.2	Brookes and Crooke (2012)

Furthermore, a benchmark approach is used in order to compare the depuration rate and half-life determined in Tomy et al. (2007b) for BTBPE with values determined in laboratory studies for substances identified as SVHC based on their vPvB properties (**Table 12**). Dechlorane plus, covering its anti- and syn-isomers, has been concluded as vB based on the long depuration half-life indicative of a BCF > 5000 L/kg (ECHA, 2017c). The growth-corrected depuration half-life determined for Dechlorane Plus in a non-standard dietary study with rainbow trout was

[3] Available at: https://www.oecd.org/chemicalsafety/testing/section-3-environmental-fate-behaviour-software-tg-305.htm

around 36 days for the anti- isomer and 58 days for the syn- isomer. Hence, the depuration half-lives were similar or lower for Dechlorane Plus than for BTBPE (54 days). Also, some of the congeners of medium-chain chlorinated paraffins (MCCP) concluded to be vB have growth corrected half-lives similar to that of BTBPE in Tomy et al. (2007b), while other vB congeners of MCCP as well as D4 and D5 have longer half-lives. o-Terphenyl, which is the vPvB constituent of Terphenyl, hydrogenated (EC 262-967-7) has a depuration half-life well below that of BTBPE. Hence, the benchmark exercise supports the conclusion that based on the depuration rate and depuration half-life determined in Tomy et al. (2007b) BTBPE is very bioaccumulative (>5000 L/kg) in rainbow trout.

Table 12 Comparison of laboratory depuration rates and half-lives in rainbow trout for BTBPE and SVHC substances identified as vPvB.

Substance	Log K_{ow}	Depuration rate constant k_2 (d^{-1})	Growth corrected depuration rate constant K_{2g} (d^{-1})	Growth corrected depuration half-life (days)	Reference
BTBPE	8.16		0.0128 (muscle)	54	Tomy *et al.*, (2007b)
$C_{14}Cl_5$ congener of MCCP	6.32	0.0021		337.9	ECHA, 2021
$C_{14}Cl_6$ congener of MCCP	6.66	0.0230		164.1	ECHA, 2021
$C_{14}Cl_7$ congener of MCCP	6.59	0.0268		86.7	ECHA, 2021
$C_{14}Cl_8$ congener of MCCP	6.66	0.0124		55.7	ECHA, 2021
$C_{14}Cl_9$ congener of MCCP	6.86	0.0104		66.4	ECHA, 2021
$C_{14}Cl_{10}$ congener of MCCP	5.98	0.0096		72.1	ECHA, 2021
$C_{14}Cl_{11}$ congener of MCCP	6.34	0.0116		59.6	ECHA, 2021
D4 (EC 209-136-7)	6.49		0.0066	105	ECHA, 2015 ECHA 2018a
D5 (EC 208-764-9)	8.02		0.0094	74	ECHA, 2018a
o-Terphenyl vPvB constituent of Terphenyl, hydrogenated (EC 262-967-7)	5.52	0.085		8.1	ECHA, 2018b
Dechlorane Plus (EC 236-948-9) (anti-isomer)	≥9		0.017-0.023	30-40	ECHA, 2017c
Dechlorane Plus (EC 236-948-9) (syn-isomer)	≥9		0.010-0.013	50-70	ECHA, 2017c

Tomy *et al.* (2007b) analysed also liver samples of the fish in their study for possible debrominated and hydroxylated metabolites. The ion chromatograms showed peaks that

corresponded presumably to other Br-containing compounds that were present in the fish. The authors state that since the ion intensities of these peaks did not increase as a result of longer exposure periods this suggests that they were likely other Br-based compounds that were unrelated to BTBPE exposure. No hydroxylated metabolites were detected in the liver extracts.

3.4.1.3 Mesocosm studies

De Jourdan *et al.* (2014) continued the aquatic mesocosm experiment of de Jourdan *et al.* (2013) (see Section 3.1.2.1.3.2) and introduced fathead minnows (*Pimephales promelas*) to the mesocosms. 24 fish (approx. 5 cm in length) were introduced to each mesocosm in two mesh enclosures (22 cm diameter, 40 cm long). Three mesocosms were used for BTBPE treatment and three for solvent controls (mixture of DMSO and toluene at a concentration of 0.001 %). Treatments were chosen to reflect concentrations observed in sewage sludge from the San Francisco Bay area, approximately 500 ng BTBPE/g sediment in the upper 5 cm of sediment. Application of the test substance to the mesocosms involved subsurface injection of 300 mg of commercial BTBPE dissolved into 125 mL of dimethyl sulfoxide and 5 mL of toluene. According to de Jourdan *et al.* (2013), this resulted in a nominal concentration in water of approximately 0.3 mg/L, which is well above the water solubility of BTBPE. Fish were allowed to acclimate 10 days prior exposure in their mesocosms. The exposure period was 42 days, followed by 28 days of depuration after transfer to a control mesocosm. The fish were not fed during the test but subsisted on the native zooplankton community of the mesocosms. Samples of water column were taken for analysis to measure the test substance concentration in filtered particulates 4 days prior the test start and during the test at 1h, 4h and on days 1, 2, 4, 7, 14, 21, 28, 35, 42, 49, 56 and 70. However, the results of these measurements are not reported. Water temperature and dissolved oxygen concentration were measured on all working days. Fish were monitored daily during the entire study for signs of stress or illness (e.g., fin erosion, loss of righting ability, exophthalmia) and mortality. Three fish per mesocosm were sampled on days 7, 14, 28 and 42 of the exposure phase and on day 7 and 28 of the depuration phase.

Based on the growth adjusted concentrations of BTBPE in the fish, fathead minnows were observed to accumulate BTBPE (**Figure 18**). The maximum concentration was reached at day 14; however, the concentration was statistically not significantly different to the concentrations measured on day 7, 28 or 42. This indicates a very fast uptake of BTBPE (dissolved in DMSO) in fathead minnows. Substances like BTBPE with a high octanol−water partition coefficient are normally not expected to reach steady-state after 14 days. As calculated in section 3.4.1.2 using the equations indicated in OECD TG 305 and a log Kow of 8.16, 80% of steady-state is estimated to be reached after 130 days. DMSO may have enhanced the biological availability of BTBPE leading to a faster uptake of the substance. The fast uptake is still unexpected and is not in line with the outcome of the above mentioned BCF study by CITI (1976, cited in GLCC, 2022) where steady-state was not reached after 8 weeks of exposure. The fact that De Jourdan *et al.* (2014) have not discussed this fast uptake weakens the study considerably. The study did also not report water concentrations. Only a nominal concentration of 0.3 mg/L is reported, which is well above the water solubility of BTBPE. Measured water concentration would have been important to verify that the fish were exposed to a constant BTBPE concentration during the uptake phase.

No statistically significant decrease in the BTBPE concentration in fathead minnows was observed during the 28 days depuration period, which could suggest a long half-life of BTBPE in the fish. However, the lack of a proper uptake phase observed in the study raises some uncertainty in the reliability of the measurements and in the results of the study.

By day 14, the fathead minnows exposed to BTBPE accumulated 2,6-dibromophenol (2,6-DBP). The concentration of 2,6-DBP followed a similar trend as that of BTBPE in the fish. According to the authors this suggested that 2,6-DBP was formed from metabolism rather than accumulation from the environment. They also mention that DBP was not detected as a degradation product of BTBPE in their environmental fate study conducted in the same

mesocosms in 2009 (de Jourdan *et al.* 2013); however, tribromophenol (TBP) was detected as a degradation product in suspended particulates. Hence, it is possible that the DBP observed in fathead minnows in de Jourdan *et al.* (2014) was the result of accumulation of TBP, followed by a reductive debromination. However, according to the authors, there was no trace of TBP in the fish. For the formation of DBP from BTBPE to occur in fathead minnows, there would need to be ether cleavage and debromination. This metabolic pathway has not been observed in fish but based on the available information on rats (Hakk *et al.,* 2004) and on the metabolism of other similar brominated substances in fish, the authors conclude that it is possible in fathead minnows.

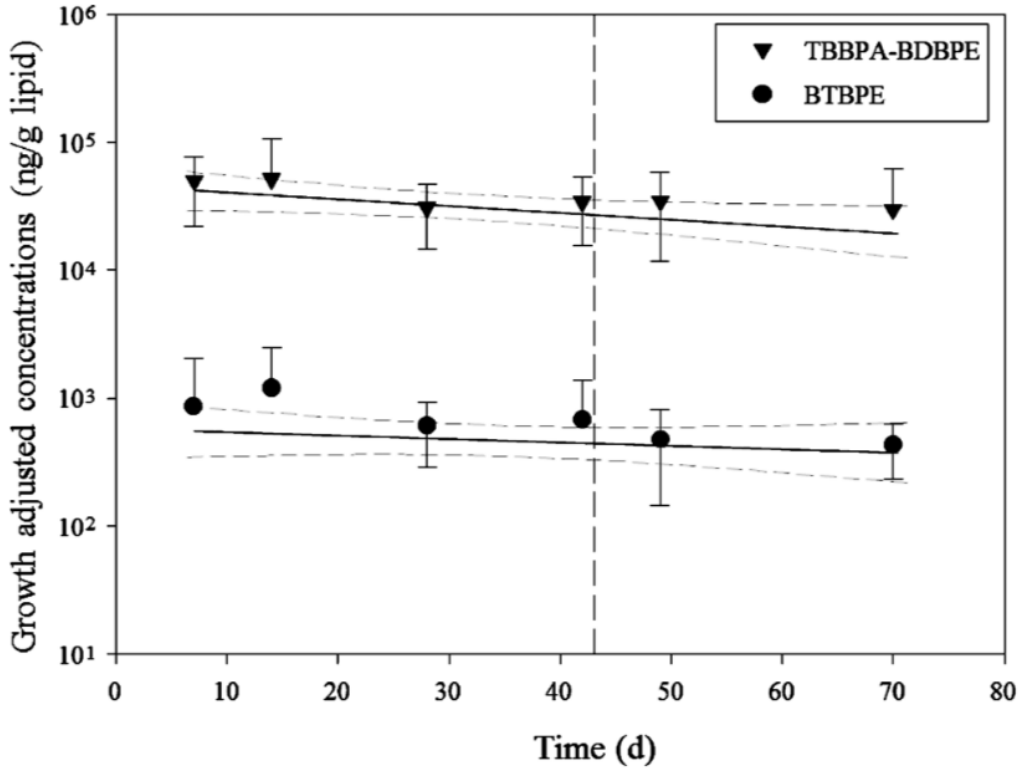


Figure 18 Growth-adjusted, lipid-normalised concentrations of BTBPE (and tetrabromobisphenol A bis(2,3-dibromopropylether, TBBPA-BDBPE) in whole-body fathead minnow extracts. Each point is the mean (BTBPE, n=9) and the standard deviation grouped from each mesocosm. The vertical dashed line separates the uptake period (0–42 d) and the depuration period (42–70 d). The linear regression (solid black lines) and 95% confidence intervals (dashed gray lines) are shown for each compound. Figure taken from de Jourdan *et al.* (2014).

3.4.2 Bioaccumulation in terrestrial organisms (soil dwelling organisms, vertebrates)

There is no information available on the bioaccumulation in terrestrial organisms. Based on the predicted log Koa (≥ 5) and log Kow (≥ 2) values BTBPE screens for potential accumulation in air-breathing organisms according to ECHA Guidance Chapter R.11 (ECHA, 2017b).

Based on the available toxicokinetic studies in rats (See section 4.1), absorption of BTBPE via oral exposure seems to be poor. However, as BTBPE is commonly found in particles in air, exposure via inhalation may be more relevant for air-breathing organisms.

3.4.3 Field data

Several field studies investigating the bioaccumulation of BTBPE have been carried out. It should be noted that there is a lack of agreed guidelines and methodologies for carrying out such studies, and interpretation of such studies encompasses several uncertainties (see section.11.4.1.2.6 of ECHA Guidance Chapter R.11, Borgå *et al.,* 2012). ECHA Guidance document indicates that the results from such field studies should be considered as part of the overall evaluation of the data. However, it should be noted that the Chapter R.11.4.1.2 of the Guidance also indicates that the absence of a biomagnification potential in field studies cannot be used on its own to conclude that the B or vB criteria are not fulfilled. This is because a field BMF only represents the degree of biomagnification in the predatory/prey relationship for which it was measured. Biomagnification will vary between predatory/prey relationships, so a low BMF in one does not mean that it will be low in other predatory/prey relationship. Conversely, evidence of high biomagnification in one predatory/prey relationship is cause for significant concern and it is then in accordance with a cautious approach to assume that biomagnification may also occur in other (unmeasured) predatory/prey relationships.

Trophic magnification factors (TMFs)

Zheng *et al.* (2018) studied the trophodynamics of BTBPE and other BFRs in a food web in Lake Taihu, in the southeast region of China. Lake Taihu, which is the third largest freshwater lake in China, has an approximate area of 2338 km2 and a maximum depth of 1.9 m. The food web consisted of primary producers (seston/plankton) (n=6), four invertebrate species including freshwater mussel (n=6), clam (n=6), crayfish (n=6), and snail (n=6), 12 fish species including ricefield eel (n=6), blunt-snout bream (n=2), whitebait (n=5), crucian, carp (n=3), pipefish (n=3), silver fish (n=6), whitefish (n=6), catfish (n=6), redfin culter (n=7), wolfish (n=3), and yellow-head catfish (n=6). The food web covered more than three trophic levels (TL). Trophic levels and carbon sources for each species were determined based on stable isotopic ratios of carbon ($\delta^{13}C$) and nitrogen ($\delta^{15}N$) measurements. Six replicate spiked samples and one matrix sample were analysed to determine the general recovery rates. The absolute recovery for the spiked simple of BTBPE was 75.5±3.1%. BTBPE was detected in the procedural blanks, and the MDL was set to 43 pg/g ww. A statistically significant positive relationship between trophic levels and lipid-normalised concentrations was found for BTBPE. The calculated trophic magnification factor was 2.83. However, the components of the aquatic food web were collected in August 2014 and May 2015, thus, not the whole food web was collected at the same time. This introduces some uncertainty to the TMF value as it cannot be excluded that the organisms sampled at different times may have been exposed to different environmental concentrations. Consequently, the observed TMF values are considered to have low reliability. Zheng *et al.* (2018) also determined the metabolic rates of several BFRs in crucian (TL = 2.93), carp (TL = 3.86) and yellow-head catfish (TL = 4.3). For BTBPE, they found no significant metabolism after 24 hours incubation with the liver microsomes of the three species, which is consistent with the trophodynamics of BTBPE in the Lake Taihu food web.

Liu *et al.* (2021) studied the presence and trophic magnification of brominated flame retardants, including BTBPE, in marine food webs from Bohai Sea, which is an inland sea in China's northernmost offshore. They sampled seven fish species (*Clupea pallasii* (n=9), *Scomberomorus niphonius* (n=10), *Pneumatophorus japonicas* (n=11)*, Lateolabrax japonicas* (n=9), *Lophius litulon* (n=13), *Collichthys niveatus* (n=15), *Synechogobius hasta* (n=11)), ten invertebrate species (*Squilla orarotia* (n pooled samples of 3 individuals=11)*, Charybdis japonica* (n pooled samples of 3 individuals=9), *Palaemon gravieri* (n pooled samples of 6 individuals =12), *Ruditapes philippinarum* (n pooled samples of 7 individuals =12), *Scapharca subcrenata* (n pooled samples of 7 individuals =11), *Sinonovacula constricta* (n pooled samples of 7 individuals =12), *Omphalus rustica* (n pooled samples of 30 individuals =13), *Crassostrea gigas* (n pooled samples of 5-7 individuals=11)*, Sepia pharaonis* (n=12), *Octopus vulgaris* (n=12)) and plankton (n pooled samples=8) from near shore area in the Northwest of

Bohai Sea in August 2019. Based on the available information in Liu et al. (2021) it seems that all species were collected from a relatively limited area, and hence, spatial variability in the sampling is not expected. Trophic levels and carbon sources for each species were determined based on $\delta^{13}C$ and $\delta^{15}N$ measurements. Similar food web models based on stable carbon and nitrogen isotopes in Bohai Sea have been established and applied to assess the trophic transfer of several other organic substances previously. To reduce the contamination during sampling, treatment and analysis, special care was taken. The acetone rinsed bistoury was used to cut soft tissue from organism, and the samples were stored in solvent-rinsed glass bottles with Teflon lid. Labelled recovery surrogate standards of CB65, CB155 and C13-BDE209 were used to examine the recovery of each sample. Procedure blanks and spike samples were treated for every ten samples to check the contaminations and recoveries, respectively. None of the target compounds were detected in blanks. The recoveries of CB65, CB155 and C13-BDE209 were 79% to 108%, 75% to 103% and 72% to 98%, respectively. In spike samples, the recoveries of BTBPE were 75 ±4.7 %. MDL of BTBPE was 16 pg/g dw. BTBPE was detected in 89% of the samples and the concentrations ranged from non-detectable to 30,000 pg/g lipid (mean 5700 g/g lipid). The species were about 1.9 trophic levels (TL) across, ranging from 1.6 ± 0.2 (in plankton) to 3.5 ± 0.3 (in *Lophius litulon*). Regression analysis showed statistically significant ($p<0.01$) positive correlation between lipid-normalised concentrations of BTBPE and trophic levels. A TMF of 2.3 (95% CI 1.5–3.5), indicating trophic magnification, is reported for BTBPE. The study is considered reliable with restrictions.

In a study by Hou *et al*. (2022), a tropical marine food web from coral reef waters of the Xisha Islands, the South China Sea, was collected and analysed for BTBPE and 10 other NBFRs. The collection of samples is indicated to be done randomly in October and November 2020. All biota samples seemed to be collected from a relatively limited area, and hence, spatial variability in the sampling is not expected. The collected species included five shell species (n=3-6 per species), three sea cucumber species (n=3-4 per species), three crab species (n=4-6 per species) and 18 fish species (n=3-6 per species). The marine shells are largely herbivorous, whereas crabs and sea cucumbers are largely omnivorous; the herbivorous fishes of rabbitfish and parrotfish are lower-order predators, whereas grouper, goatfish, wrasse, and other carnivorous fishes feed at higher trophic levels. Trophic levels and carbon sources for each species were determined based on $\delta^{13}C$ and $\delta^{15}N$ measurements. The whole bodies of invertebrates and muscle tissues of fish were analysed. Surface water and sediment samples were also collected from the area. The concentration of the studied NBFRs in procedural blanks were all below the method detection limit (0.060 ng/g lw for BTBPE). Spike recovery of BTBPE performed on the fish muscle was 82.3±10.8 %. The trophic levels (TLs) of the studied invertebrate species ranged from 2.00±0.14 (hermit crab) to 2.92±0.12 (Xanthid crab) and the TLs of the fish species ranged from 3.02±0.10 (herbivorous Yellowband parrotfish) to 4.14±0.18 (carnivorous Redfin emperor). BTBPE was not detected in the water samples whereas it was detected in 37.5% of the sediment samples. BTBPE was detected in 45.4% of the biota samples with concentrations ranging from non-detected to 0.403 ng/g lipid weight. The highest concentration was measured in wrasse fish while BTBPE was not detected at all or only at mean concentrations below MDL in all crabs and sea cucumbers. No statistically significant positive relationship between the lipid normalised concentrations of BTBPE and TL was found in a nonparametric Spearman correlation analysis. However, a statistically significant positive relationship ($p<0.01$) was found for log-transformed lipid normalised concentrations of BTBPE and TLs, and a TMF of 1.91, calculated as the slope of the regression line, is reported for BTBPE. However, there is some uncertainty in the TMF value as only the muscles of fish were analysed for BTBPE while for invertebrates the whole body was analysed. TMFs should be based on whole body concentrations measured in all organisms in the food web (for both predators and preys). As indicated above in section 3.4.1.2., the concentration of BTBPE in fish muscle may underestimate the concentrations in whole body, although as the concentrations in muscle were lipid corrected, they may not significantly differ from the whole body lipid corrected concentrations.

Wu *et al.* (2010) measured several currently used non-PBDE flame retardants, including BTBPE in a freshwater food web (i.e., a natural pond) in an electronic waste recycling site in South

China. The sampling site was located approx. 50 km north of Guangzhou, a major urban centre in South China. It is estimated that more than 1300 workshops and 80000 workers had been involved in the business of e-waste dismantling and recycling, and approximately 1.7 million tons of e-waste were dismantled annually in this site. Meanwhile, the traditional agricultures including rice-growing and fish-farming were also practiced around the recycling workshops. The sampled food web consisted of six species including two invertebrates species (Chinese mystery snails (n=43) and prawns (n=7)) three fish species (mud carp (n=12), crucian carp (n=18), northern snakehead (n=6)) and one reptile species (water snake (n=2)), spanning two trophic levels (Wu *et al.*, 2011). The samples were simultaneously collected in 2006. The trophic levels of the species were determined based on nitrogen stable isotopes measurements and the results are reported in Wu et al. (2008) in which the same samples as in Wu et al. (2010) were analysed. Quality assurance and quality control included e.g., determining recoveries of surrogate standards, recovery of BTBPE (102.7±1.37%) in spiked samples of ashed anhydrous sodium sulfate and procedural blanks (no BTBPE detected). No statistically significant relationship between trophic levels and lipid-normalised concentrations was found for BTBPE. However, the data indicated trophic dilution with a TMF of around 0.4.

Zhang and Kelly (2018) investigated ninety hydrophobic organic contaminants in seawater, marine sediment, suspended particulate organic matter (mainly phytoplankton) and fish collected in the Singapore Strait between 2011 and 2012. The sampled fish included pike conger eel (*Muraenesox sp.,* n=14), marine catfish (*Arius venosus* and *Hexanematichthys sagor*, n=11), bamboo shark (*Chiloscyllium indicum*, n=3), stingray (*Dasyatis lata*, n=1), snapper (*Lutjanus johnii*, n=3), and grunter (*Pomadasys aurita*, n=5). BTBPE was detected in 25% of the sediment and 6% of the suspended particulate organic matter samples, but not in the dissolved or particulate phase of the seawater nor in any of the fish. This might suggest a low bioaccumulation potential in the investigated species as stated by Zhang and Kelly (2018) or just a too low abundance of BTBPE to be accumulated at sufficiently high levels to be quantified in the fish. The study was omitted here because the reason for not detecting BTBPE in the fish samples is not clear.

Kurt-Karakus *et al.* (2019) determined the trophic magnification of PBDEs and non-legacy halogenated organic compounds in the food web of Lake Ontario, Canada. The food web consisted of net plankton, zooplankton, diaporeia, mysis, rainbow smelt, round goby, alewife, slimy sculpin, and lake trout, spanning three trophic levels. The sampling locations for the different fish and invertebrate species were spread over the lake, which might give some bias to the study as some parts of Lake Ontario might be more contaminated than others. Furthermore, there was temporal variation in the collection of the biota samples; mysis and plankton were collected in July 2006 and 2008 as well as in September-October 2007 and 2008, while fish species and diaporeia were only collected in September and October 2008, respectively. Trophic levels and carbon sources for each species were determined based on $\delta^{13}C$ and $\delta^{15}N$ measurements. TMF was evaluated based on the regressions between log concentration of the BTBPE (on a lipid wt basis) and the trophic levels of the organisms. For BTBPE, significant trophic dilution with a TMF of 0.53 was found. This was mainly caused by the low concentrations of BTBPE found in lake trout. The spatial and temporal variation in sampling raises uncertainty to the results, and hence, the study is considered to be of low reliability.

Law *et al.* (2006) examined the bioaccumulation and trophic transfer of several BFRs including BTBPE in a food web in Lake Winnipeg, Canada. The food web consisted of six species of fish, zooplankton and mussels. The results of this study were omitted, because the $\delta^{15}N$ values and trophic levels reported in Law *et al.* (2006) (and in the erratum to the paper (Law *et al.*, 2007)) did not match and it is unclear, which values were used for the calculation of the TMFs. Furthermore, the coefficient of determination, r^2, for the TMF of BTBPE (in the erratum) is 0.01, indicating no statistically significant correlation between the concentration and the TMF.

Biomagnification factors (BMFs)

Mo *et al.* (2012) investigated the biomagnification of BTBPE and other BFRs in common kingfishers (*Alcedo atthis*) and their prey fish near an electronic waste-recycling site in South China. They stated that kingfishers are one of the most common and widely distributed resident birds in this area and avid eaters feeding mostly (approx. 99%) on small fish species. The biomagnification factors (BMFs) were calculated in the study as a ratio of lipid-normalised concentrations in the muscle of kingfishers to the mean lipid-based whole body concentrations in the prey fish. In the article it is stated that the BMF values of BTBPE were in the range of 1.90-3.60. However, if the BMF values are calculated based on the information on the mean lipid normalised concentrations of BTBPE in kingfishers and the prey fish included in the article, this results in median predator/prey BMFs of 1.51 for kingfisher/paradise fish, 2.26 for kingfisher/mosquito fish, and 1.26 for kingfisher/Chinese hooksnout carp. Hence, there is some inconsistency in the information reported in the article. Nevertheless, all BMFs for BTBPE are above 1, thus indicating biomagnification for BTBPE. However, further uncertainty in the BMF values is raised as only the muscles of predator fish were analysed for BTBPE while for the prey fish the whole body was analysed. BMFs should be based on whole body concentrations measured for both predators and preys.

In the study by Wu *et al.* (2022), concentrations of BTBPE as well as PBDEs and methylmercury (MeHg) were measured in adjacent aquatic and riparian food webs from The Pearl River Delta region in South China. Measurements of stable isotopes of carbon and nitrogen were made to identify the food sources and trophic positions of the studied species. The species were collected from a suburb of Guangzhou City (23◦14′ N, 113◦38′ E), which is among the most developed areas in China. The sampling area covers about a 1 km × 1 km square, including an orchard and paddy fields. The riparian species included locust (*Orthoptera*) (n=3 composite samples, corresponding to 150 individual samples), butterfly (*Lepidoptera*) (n=4 composite samples, corresponding to 200 individual samples), dragonfly (*Odonata*) (n=3 composite samples, corresponding to 180 individual samples), sooty-headed bulbul (*Pycnonotus aurigaster*)(n=5), long-tailed shrike (*Lanius schach*)(n=4), and Eurasian thrush (*Turdus merula*)(n=4). Aquatic species included shrimp (*Macrobrachium*) (n=10 composite samples, corresponding to 300 individual samples), tilapia (*Oreochromis mossambicus*)(n=8), catfish (*Silurus asotus*)(n=8), and water snake (*Enhydris chinensis*)(n=3). Sweep nets and light traps were used to catch insects. Shrimps, fish, water snakes and dead birds were collected by the local farmers. Muscle samples of birds, snakes, and fish were analysed. Due to the small body weight of insect and shrimp species, about 30–50 individuals were mixed as a pooled sample to merit limit of quantification of target pollutants. The blank corrected and lipid normalised concentrations of BTBPE ranged from non-detected to 126 ng/g lw. The highest concentration was measured in tilapia, and in the terrestrial organisms in Eurasian thrust. The BMF values reported for tilapia/shrimp, snake/shrimp and Eurasian thrust /insects are 48.9, 44.0 and 41.7, respectively. The diet of the Eurasian thrust was estimated to consist of 33% terrestrial insect (Locust and Butterfly) and 67% aquatic insect (Dragonfly) based on the δ13C values. No BMFs were calculated for the other predator/prey pairs in the case of BTBPE. No TMF is reported for BTBPE and it is indicated that a statistically significant TMF was only observed for MeHg. There is no exact information on when the species were collected, it is only indicated that it was done in 2018 and 2019. This raises some uncertainty regarding the BMF values as it is not known whether the samples of the predator/prey pairs were collected at the same time.

De Wit *et al.* (2020) studied the presence and bioaccumulation of BTBPE and other halogenated organic compounds in species from different trophic levels in the Baltic Sea. The studied species representing benthic food web included blue mussel (*Mytilus edulis*), viviparous eelpout (*Zoarces viviparus*), and common eider (*Somateria mollissima*). Species belonging to the pelagic food web included Atlantic herring (*Clupea harengus*), common guillemot (*Uria aalge*), white-tailed eagle (hereafter sea eagle), grey seal, harbor seal (*Phoca vitulina*), and harbor porpoise (hereafter porpoise). The concentrations of BTBPE were measured in whole body for mussels, in muscle for fish, in blubber for the mammals, in eggs for the birds and also

in liver for common eider. Samples used for analysis were collected in 2015 or 2016, except for harbor seal (2012–2016), grey seal (2006–2010), porpoise (2006–2012) and one pooled herring sample (2014). The sampling sites were background monitoring sites spread in a relatively extended area, primarily in the Baltic Proper, including Swedish, Danish, and German coastal area. BTBPE was detected in all species except in mussel, eelpout and porpoise. The mean lipid normalised concentrations ranged from 0.036 (for Atlantic herring) to 5.5 ng/g lw (for grey seal). It is noted that for grey seal very high concentration (11 ng/g lw) of BTBPE was detected only in one pooled sample, while in the other BTBPE was below LoQ. Also, for herring and harbour seal BTBPE concentrations above LoQ were detected only in one pooled sample. The following predator/prey pair BMFs are reported for BTBPE: 3.1 for harbour seal/herring, 9 for sea Eagle/guillemot, 10 for guillemot/herring and 20 for sea Eagle/eider. However, as indicated above, the predator and prey species were not collected at the same time nor at the same site and therefore both spatial and temporal bias in the results is possible. Furthermore, the trophic positions of the species were not investigated in the study. Therefore, there is high uncertainty in the BMF values.

Tao *et al.* (2019) investigated the biomagnification of BTBPE and other BFRs in northern snakehead (*Channa argus*) (n=15) and their prey from the same electronic waste recycling site in South China as Wu *et al.* (2011). The potential prey species included mud carp (*Cirrhinus molitorella*; n = 18), Chinese bitterling (*Rhodeinae*, n = 6), crucian carp (*Carassius auratus*, n = 7), tilapia (*Oreochromis spp*, n = 9), shrimp (*Neocaridina denticulata,* n = 108), dragonfly larvae (*Aeshnidae rambur*, n = 18), and water beetles (*Sternolophus inconspicuus*, n = 16). Tao *et al.* (2019) used fatty acid signatures to investigate the diet composition of the predator and assess the sources of pollutants in the predator. For BTBPE in northern snakehead, they found trophic dilution with a mean lipid normalised BMF of 0.4. However, the authors of the study state that the abundance of various prey species in the bond may affect the prey, and consequently BFRs (including BTBPE), consumed by the northern snakeheads, which may influence the observed biomagnification. They also point out that the BMF may be 2–5 times underestimated, because levels of BFRs were determined using the dorsal muscle of the predator, while the entire organism was used as a sample for its potential prey. Based on literatures findings (Gandhi *et al.,* 2017 and Stone, 2006) cited in Tao *et al.* (2019) for PBDEs, a factor of 2–5 might be expected between whole-body and muscle concentrations in fish. However, it is noted that in Gandhi *et al.* (2017) and Stone (2006) no significant difference was found in the lipid-corrected concentrations of PBDEs for muscle and whole body.

The study of Poma *et al.* (2014a) evaluated the concentrations of BTBPE and other BFRs in pelagic zooplankton and zooplanktivorous fish from Lake Maggiore, Italy. Zooplankton and fish (shad and whitefish) were sampled in four different seasons and the carbon isotopic signatures were checked in each season to determine whether pelagic food was the main food source to the fish. Poma *et al.* (2014a) found that both fish species are strictly zooplanktivorous during spring and summer, but not in autumn and winter. Therefore, only the values from spring and summer were used for the calculation of the biomagnification factor. In the calculation, the mean concentration of BTBPE in fish muscle in spring and summer was used, and the BMFs were calculated separately for young (1-3 years) and old (≥3 years) fish. The authors calculated a trophic level normalised BMF_{TL} of 0.3 for BTBPE in shad/zooplankton and a trophic level normalised BMF_{TL} of 0.30 and 0.60 (young and old, respectively) for BTBPE in whitefish/zooplankton based on lipid normalised concentrations of BTBPE in the fish and zooplankton. It is noted that if BTBPE is slowly depurated from the fish, as observed in rainbow trout in Tomy *et al.* (2007b) and in fathead minnows in de Jourdan *et al.* (2014), the diet consumed in winter may also contribute to the concentrations of BTBPE measured in the fish in spring and summer. Therefore, there is uncertainty in the BMF values determined in the study. Further uncertainty is caused again by measuring the BTBPE concentrations only in the fish muscle tissue as it may underestimate the concentration in the whole body.

Kurt-Karakus *et al.* (2019) also determined biomagnification factors in their study (mentioned above). Lipid and trophic level normalised BMF_{TL} reported in the study for BTBPE were 0.03 for trout/plankton, 0.32 for trout/alewife, 0.002 for trout/smelt, 0.02 for trout/sculpin, 0.91 for

sculpin/diaporeia, 3.50 for sculpin/mysis, 33.8 for smelt/mysis, 8.78 for smelt/diaporeia, 0.11 for alewife/plankton, and 0.001 for trout/goby. However, it is noted that based on the supplementary information of the study, BTBPE was not detected in Mysis and plankton and it is not explained which values were used in the BMF calculations for these organisms. Hence, the BMF values calculated for predator/prey pairs where these organisms are involved are not considered reliable. Furthermore, as indicated above, the sampling locations for the different fish and invertebrate species in the Kurt-Karakus *et al.* (2019) study were spread over the lake, which raises uncertainty in the biomagnification factors.

Bioaccumulation factors (BAFs)

Wu *et al.* (2010) also determined bioaccumulation factors in their study (mentioned above). Lipid-normalised BAFs of BTBPE for Chinese mystery snail, prawn, mud carp, crucian carp, northern snakehead and water snake were 3360, 2240, 25900, 16150, 86, and 460, respectively. The lowest BAFs (86 and 460) belonged to the two species with the highest trophic levels (northern snakehead (TL 3.6–4.6) and water snake (TL 3.7 and 4.1), demonstrating bioaccumulation in the lower trophic level species but not in the higher trophic level species. Note that the study only analysed two water snakes. The BAF for water snake is therefore highly uncertain.

Biota – sediment accumulation factors (BSAFs)

La Guardia *et al.* (2012) collected sediment, filter-feeding bivalve (*Corbicula fluminea*) and grazing gastropod (*Elimia proxima*) from the Yadkin River 0, 17, 25, and 45 km downstream of a textile manufacturing outfall. They analysed the sediment and biota samples for several flame retardants, including BTBPE. The biota-sediment accumulation factor (BSAF) were calculated based on lipid-normalised concentrations of the substances in the biota and organic carbon normalised concentrations of the substances in sediment. BSAF for BTBPE at the outfall was 0.08 for *Corbicula fluminea* and 0.15 for *Elimia proxima*. BTBPE was also detected in *Corbicula fluminea* 17 km downstream of the outfall. There, the biota-sediment accumulation factor was 0.50 and thus higher than at the outfall. Lower BSAFs at the outfall than further downstream were also observed for the other BFRs with K_{OW} < 10. La Guardia *et al.* (personal communication) reasoned this with a greater bioavailability with distance downstream due to degradation of the BFR associated polymer/fiber over time. It is noted that in ECHA Guidance Chapter R.11 (Appendix R.11—4) (ECHA, 2017), it is indicated that lipid and organic carbon normalized BSAF values of 0.5 and higher determined in bioconcentration studies on benthic and terrestrial invertebrate species are an indication of high bioaccumulation. It is not clear whether it refers to laboratory studies, e.g., studies performed following OECD TG 315 or 3017. As the study by la Guardia et al. (2012) is a field study, the results have more uncertainty and are not directly comparable with laboratory studies, e.g., the overlying water concentrations of BTBPE, and hence, the exposure of the biota through that route, may differ.

Conclusion on the field studies for bioaccumulation

Several field studies on the bioaccumulation of BTBPE have been carried out.

BTBPE is able to undergo trophic magnification in food webs and is also able to biomagnify as shown by Zheng *et al.* (2018) for the food web in Lake Taihu, Liu *et al.* (2021) for a marine food web in Bohai Sea in China and by Mo *et al.* (2012) for common kingfishers near an electronic waste-recycling site in South China. Kurt-Karakus *et al.* (2019) found biomagnification in some of the investigated species, but not in all. Wu *et al.* (2010) did not find trophic magnification for the whole food web in an electronic waste-recycling site in South China, but bioaccumulation in the lower trophic level species was observed. No bioaccumulation of BTBPE was found in fish from Lake Maggiore (Poma *et al.*, 2014a). No biomagnification of BTBPE in northern snakehead and their prey at an e-waste recycling site in South China (Tao *et al.*, 2019) was observed but the authors stated that the biomagnification may have been underestimated as only muscle tissue was sampled for the predator whereas

the entire organism of the prey were analysed. BSAF value determined for grazing gastropod from the Yadkin River does not indicate bioaccumulation while the BSAF determined for a filter-feeding bivalve in the same study may indicate bioaccumulation potential (La Guardia *et al.*, 2012).

In general, it is not surprising that substances magnify in some food web or predator/prey relationship but not in others. Reasons are for example the ability of some organisms to biotransform a substance where other organisms are not able to metabolise it. Furthermore, the relative importance of food versus water exposure for a particular substance and the composition of the food web (only poikilothermic species or poikilothermic and homoeothermic species) will likely influence the magnitude of the TMF in the food web (Borgå *et al.*, 2012). However, the existence of food webs where the substance undergoes trophic magnifications is a clear indication that the substance is able to biomagnify.

As indicated above, there is a lack of agreed guidelines and methodologies for carrying out such studies, and interpretation of such studies encompasses several uncertainties (see section.11.4.1.2.6 of ECHA Guidance Chapter R.11 and Borgå *et al*., 2012). In many of the available field studies for BTBPE uncertainties related to e.g., spatial and temporal variability in sampling of different species, lack of whole body BTBPE concentrations for some species, were identified. However, even if individual data are uncertain, many of the studies point towards biomagnification/bioaccumulation of BTBPE in the food chain so that as part of a weight-of-evidence approach, it can be overall concluded that the field data indicate B/vB properties for BTBPE.

3.4.4 Summary and discussion of bioaccumulation

All available studies quoted above are listed in the below table.

Table 13 Overview of all bioaccumulation studies for BTBPE

Field - Trophic magnification factor (TMF)

Study location	TMF	Statistically significant?	Reference
Lake Taihu, South China	2.83	significant	Zheng *et al.* (2018)
Bohai Sea, China	2.3	significant	Liu *et al.* (2021)
Xisha Islands, South China Sea	1.9	significant	Hou *et al.* (2022)
Electronic waste recycling site in South China	0.4	not significant	Wu *et al.* (2010)
Lake Ontario, Canada	0.53	significant	Kurt-Karakus *et al.* (2019)

Field - Biomagnification factors (BMFs)

Study location and predator	BMF	prey or predator/prey	Reference
Electronic waste recycling site in South China, common kingfisher	1.51 2.26 1.26	Paradise fish Mosquito fish Ch. hooksnout carp	Mo *et al.* (2012)
Suburb of Guangzhou City, the Pearl River Delta region, South China	48.9 44.0 41.7	tilapia/shrimp snake/shrimp Eurasian thrust /insects	Wu *et al.* (2022)
Baltic Sea	3.1*** 9*** 10*** 20***	harbour seal/herring sea eagle/guillemot guillemot/herring and sea eagle/eider	De Wit *et al.* (2020)

Electronic waste recycling site in South China, northern snakehead	0.4*	all predators (with fatty acid signature)	Tao *et al.* (2019)
Lake Maggiore, Italy	0.3** 0.3-0.6**	shad/zooplankton whitefish/zooplankton	Poma *et al.* (2014a)
Lake Ontario, Canada	0.03** 0.32 0.002 0.02 0.91 3.50** 33.8** 8.78 0.11** 0.001	trout/plankton trout/alewife trout/smelt trout/sculpin sculpin/diaporeia sculpin/mysis smelt/mysis smelt/diaporeia alewife/plankton trout/goby	Kurt-Karakus *et al.* (2019)

* BMF may be 2–5 times underestimated, because levels of BRFs were determined using the dorsal muscle of the predator, while the entire organism was used as a sample for its potential prey
** BTBPE was not detected in plankton and Mysis and it is not explained how the BMFs were calculated for these prey species
*** Samples of predator and prey pairs were neither collected at the same time nor at the same site

Field - Bioaccumulation factors (BAFs)

Study location	BAF	Organism	Reference
Electronic waste recycling site in South China	3360 2240 25,900 16,150 86 460	Chinese mystery snail Prawn Mud carp Crucian carp Northern snakehead Water snake	Wu *et al.* (2010)

Field - Biota-sediment accumulation factors (BSAFs)

Study location	BSAF	Organism	Reference
Yadkin River, 0 km from outfall of textile manufacturing plant and 17 km from outfall	0.08 0.15 0.5	filter-feeding bivalve grazing gastropod filter-feeding bivalve	La Guardia *et al.* (2012)

Field – Mesocosms study with fish

Mesocosms and organism	Results	Reference
Water-sediment system Fathead minnow	No statistically significant decrease in the BTBPE concentration in fish during 28 day depuration phase	De Jourdan *et al.* (2013)

Laboratory – Bioconcentration factors (BCFs) in fish

Organism	BCF (exposure concentration)	Reference
Common carp	5.2-56.6 L/Kg (0.3 ppm) 11.9-43.6 L/kg (0.03 ppm)	CITI, 1976 cited in GLCC, 2002

Laboratory –Dietary bioaccumulation in fish study		
Organism and Depuration rate	Calculated BCF	Reference
Rainbow trout 0.0128 ± 0.002 day^{-1}	Calculated BCFs according to OECD Guidance Document on Aspects of OECD TG 305 on Fish Bioaccumulation (2017) and based on the data from the Tomy *et al.* (2007b): Median value with Approach 1: 13218 L/kg (range 1032-120312 L/kg) , Approach 2: 50873 L/kg	Tomy *et al.* (2007b)

Based on the predicted log Kow values in the range of 7.88-9.39, which are considered more reliable than the available measured log Kow value of 3.14 (see Section 1.3), BTBPE screens B/vB (log kow >4.5).

Bioaccumulation in fish data from controlled laboratory experiments are only available from the manufacturer of BTBPE, the Great Lakes Chemical Corporation, (GLCC, 2002) and Tomy *et al.* (2007b). The measured BCF_{SS} values from GLCC (2002) are not considered reliable as the exposure concentrations were likely above the water solubility and steady-state was likely not reached. The BMF values reported from the dietary study of *Tomy et al.* (2007b) should also not be used due to erroneous reported data. However, the obtained depuration rate constant (0.0128 day^{-1}) and depuration half-life (54 days) for muscle tissue from Tomy *et al.* (2007b; reliable with restrictions) can be used for the assessment. These values are similar or higher than the whole body depuration rates and half-lives in fish determined for substances concluded to be SVHCs due to vPvB properties, e.g., Dechlorane Plus, some of the vPvB congeners of medium chain chlorinated paraffins (MCCP) and vPvB constituent of terphenyl hydrogenated. Therefore, the depuration rate and half-life from Tomy *et al.* (2007b) together with the derived BCF values from the OECD TG 305 BCF estimation tool indicate that BTBPE is very bioaccumulative (BCF>5000). A supportive mesocosm study with fathead minnows (De Jourdan *et al.* 2013) indicated that no significant decrease of the concentration of BTBPE in the fish was observed after 28 days depuration period.

Several field studies assessing bioaccumulation of BTBPE are available. In the studies by Zheng *et al.* (2018) and Liu *et al.* (2021) BTBPE was shown to be able to undergo trophic magnification in a freshwater food web (TMF = 2.83) and in a marine food web (TMF = 2.3), respectively. There is another study (Mo *et al.* 2012) showing that BTBPE is able to biomagnify in semi-aquatic predator–prey relationships (lipid normalised BMF common kingfisher/prey = 1.26–2.26). In some studies, biomagnification (Kurt-Karakus *et al.* 2019) or bioaccumulation (Wu *et al.* 2010) of BTBPE was found in some of the investigated species, but not in all. In other studies, trophic dilution occurred (Kurt-Karakus *et al.* 2019) or no biomagnification was observed in the studied species (Tao *et al.* 2019, Poma *et al.* 2014a).

Furthermore, there is a lack of agreed guidelines and methodologies for carrying out field studies on bioaccumulation, and interpretation of such studies encompasses several uncertainties (see section.11.4.1.2.6 of ECHA Guidance Chapter R.11 and Borgå *et al*., 2012). In many of the available field studies for BTBPE uncertainties related to e.g., spatial and temporal variability in sampling of different species, lack of whole body BTBPE concentrations

for some species, were identified. However, even if individual data are uncertain, many of the studies point towards biomagnification/bioaccumulation of BTBPE in the food chain. According to REACH Guidance Chapter R.11 (2017), food chain transfer and secondary poisoning are basic concerns in relation to PBT and vPvB substances, and therefore an indication of a biomagnification potential (BMF and/or TMF > 1) can on its own be considered as a basis to conclude that a substance meets the B or vB criteria. Biomagnification will vary between predatory/prey relationships, so a low BMF in one does not mean that it will be low in other predatory/prey relationship. Conversely, evidence of high biomagnification in one predatory/prey relationship is cause for significant concern and it is then in accordance with a cautious approach to assume that biomagnification may also occur in other (unmeasured) predatory/prey relationships. Therefore, it is concluded that the field data, used as supporting information in the weight-of-evidence B assessment, point towards the bioaccumulation potential of BTBPE and thus confirm the conclusions from the experimental data.

In conclusion, taking into account all the available information in a weight-of-evidence approach and considering especially the very slow elimination of BTBPE in fish in Tomy *et al.* (2007b) (indicative of a BCF >5000) and in de Jourdan *et al.* (2013); the fish BCF values (10 out of 14 BCFs >5000) derived from data generated in the dietary study with rainbow trout by Tomy *et al.* (2007b) using the 14 models within the OECD TG 305 BCF estimation tool in methods 1 and 2, as well as the TMF and field BMF values above 1 observed in some of the available field studies, BTBPE is concluded to fulfil the criteria for B and vB of REACH Annex XIII.

4. Human health hazard assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57 point (e) of REACH, with the exception of toxicokinetic information which can be used for the B assessment. Information related to the T criterion of Article 57 (d) of REACH is presented in Annex I as additional information.

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

Information from four toxicokinetic studies with rats is available for BTBPE.

Nomeir *et al.* (1993) performed a study on the metabolism and depuration of ^{14}C- FF-680 (BTBPE) in rats by gavage. The test substance was administered to rats in feed for 1 day at target concentrations of 0.05, 0.5, or 5% (three groups of four rats each/per dose), and for 10 days at a concentration of 0.05% (five rats). These corresponded to doses of ca. 26.8, 233.5 and 2688.9 mg BTBPE/kg body weight, respectively, for the 1 day exposure groups and a daily dose of approx. 35 mg BTBPE/body weight for the 10-days exposure group. In addition, three rats exposed to ^{4}C-BTBPE concentration of 0.169% (dose 125.8 mg BTBPE/body weight) in feed sticks were used for $^{14}CO_2$ collection, and another group of four rats were given a single oral gavage dose of 200 mg/kg of ^{14}C-BTBPE in corn oil and were used for bile collection. For the 1-day feeding study, urine and feces were collected at 0-18, 18-24, 24-48, 48-72, and 72-96 hr after the start of the administration of BTBPE in the diet. For the 10-day feeding study, urine and faeces were collected daily after the start of the administration of the test substance. At sacrifice blood samples were collected and the rats were dissected into different organs and tissues. Expired CO_2 was collected in 8 M KOH traps at 0- 18, 18-24, and 24-48 hr after the administration of BTBPE. Bile was collected from four cannulated animals at 0-15, 15-30, 30-60, 60-90, 90- 120, 120- 180, 180-240, 240-300, and 300-360 minutes after administration of the substance. Radioactivity in duplicate samples of urine, bile and CO_2 traps was determined using liquid scintillation counting. In feces and tissues (four rats per dose for the 1 day study sacrified after 96 hours of administration, five rats for the 10 day study) radioactivity was determined by oxygen combustion followed by liquid scintillation counting. Urine and extracted faeces samples were also analysed for parent substance concentration using HPLC.

Results showed that 99% of the total excreted ^{14}C was via the faecal route and 1 % was recovered in the urine. In the 1-day exposure group the radioactivity was excreted primarily during the first 48 hours after the administration. After 4 days of the administration, at all doses studied, no radioactivity was detectable in any of the tissues analysed except adipose tissue, skin, and thymus, where low levels were detected in some animals. In rats dosed for 10 days low levels of radioactivity were found in all tissues except the brain of some animals. The adipose tissue contained the highest levels (0.06% of administered dose) (excluding the gastrointestinal tract) followed by kidney, skin and thymus and lowest concentrations in brain, testes and spleen. At the 200 mg/kg gavage dose, very little radioactivity was excreted in bile (ca. 0.04% within 6 hr), and the concentrations were too low to permit HPLC analysis. No radioactivity was detected in the expired air. In HPLC analyses of the faeces only one peak, representing the parent substance, was detected, while in the urine samples no parent substance was detected. The data indicated that FF-680 was very poorly absorbed through the gastrointestinal tract of the rats.

Hakk *et al.* (2004) performed a study where radiolabelled BTBPE dissolved in peanut oil was given to seven conventional and six bile-duct cannulated male rats orally via a stomach tube device at a dosis of 2.0 mg/kg body weight. Urine, faeces, and bile were collected at 24-h intervals for 72 h. After sacrifice of the rats, adrenals, epididymal fat, G.I. tract, heart,

kidneys, liver, lungs, spleen, testes, and thymus were removed. Urine, bile, and blood were assayed for radioactivity by counting aliquots in a liquid scintillation counter (LSC). Lyophilised feces and tissues were combusted in a tissueoxidizer, and the ^{14}C counted by LSC. Faecal, urine and bile extracts were chemically analysed to determine concentrations of parent substance and metabolites.

Most of the radioactivity was excreted during the first 24 hours via faeces (93 and 58 % of the dose for conventional and canulated rats, respectively) and the cumulative faecal excretion after 72 hours was >94%. Only low levels (1.6 and 0.03% of the dose in conventional and canulated rats, respectively) were excreted in urine after 72 hours. Cumulative biliary excretion of BTBPE was only 0.22 % of the dose. Very low concentrations of ^{14}C were found in the tissues (in total 2 % of the dose). Tissues retaining the highest concentrations (>0.5 nmol/g tissue) were thymus, adipose tissue, adrenals, lung and skin.

Most of the extractable ^{14}C in the faeces was parent substance. Seven different, unconjugated metabolite structures in 0–24 h feces extracts were observed, which accounted for 2.7% of the administered dose. The mass spectral results demonstrated that metabolism of BTBPE fell into two general categories. The first category of metabolites arose from multiple oxidations and debrominations of aromatic rings (see **Figure** 19). The second category of metabolites were formed by cleavage on either side of the ether linkage resulting in monoaromatic ring metabolites, including 2,4,6-tribromophenol (see **Figure** 19). Chemical analysis of urine and bile showed only trace amounts of parent compound. In the bile, both conjugated and unconjugated metabolites were found. The authors concluded that limited absorption and metabolism of BTBPE would occur by ingestion in animals.

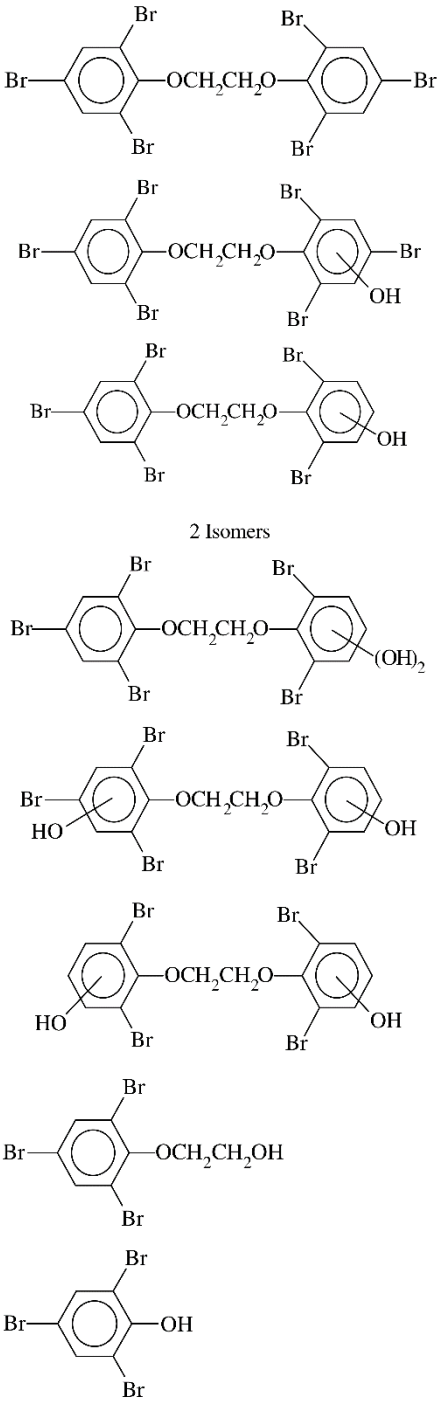


Figure 19 Metabolites observed in the study of Hakk *et al*. (2004). Figure taken from Hakk *et al*. (2004).

Hakk and Letcher (2003) and Nomeir *et al*. (1993) cited two further studies with rats. In the first one (NTP 1987), rats fed a diet containing 100 or 1000 ppm FF-680 (BTBPE) for 28 days showed accumulation of BTBPE in fat, liver, and muscle during the treatment period. However, the substance levels decreased steadily from the tissues and reached background levels after the cessation of dosing. The second cited study (GLCC 1981) was performed by the Great Lake Chemical Corporation. In the study, rats were given a single oral dose of [^{14}C]-FF-680 with unspecified dose and vehicle. It was reported that 80% of the dose were excreted in the faeces and 5% in the urine within 96 hours following dosing. Examinations ten days after dosing showed highest concentration in fat (0.38 ppm), whereas the maximum concentration for other tissues was 0.05 ppm. The highest concentration of 0.58 ppm was observed in blood at

24 h after dosing, which gradually decreased to 0.15 ppm at 96 h. No further information on these studies is available.

4.1.2 Human information (including bioaccumulation in humans)

There are no toxicokinetic studies in humans for BTBPE. However, BTBPE has been detected in human serum of mothers and children from Pakistan (Ali *et al.*, 2013) as well as in human serum of women from Norway (Cequier *et al.*, 2013) and of men and women from Sweden (Haglund *et al.,* 2016). BTBPE has also been detected in breast milk in China (Chen *et al.*, 2019), in mother–toddler cohorts in Sweden (Sahlström *et al.*, 2015) and in human hair in South China (Zheng *et al.*, 2011). Therefore, uptake of BTBPE in humans occurs.

4.1.3 Conclusion on toxicokinetics (and bioaccumulation in humans)

Based on the available toxicokinetic information on rats, absorption of BTBPE via oral route in mammals is poor. However, other routes of exposure may be more relevant for the substance. As indicated in Section 3.2.4, BTBPE is commonly detected in air and in indoor dust, and hence exposure via inhalation is expected. BTBPE is found in human serum, mother milk and hair, which indicates that there is uptake of BTBPE in humans.

Once absorbed, some metabolism of BTBPE seems to occur in mammals, including formation of 2,4,6-tribromophenol.

5. Environmental hazard assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57 (e) of REACH. Information related to the T criterion of Article 57 (d) of REACH is presented in Annex II as additional information.

6. Conclusions on the SVHC Properties

6.1 CMR assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57 (e) of the REACH Regulation.

6.2 PBT and vPvB assessment

6.2.1 Assessment of PBT/vPvB properties

A weight-of-evidence determination according to the provisions of Annex XIII of REACH is used to identify the substance as vPvB. All available information (such as the results of standard and non-standard tests, monitoring and modelling and (Q)SAR results) was considered together in a weight-of-evidence approach.

6.2.1.1 Persistence

BTBPE can be degraded by oxidation (Yu *et al.* 2017) and photolysis (Zhang *et al.* 2016) in the environment. The use of photolysis data is not generally recognised for persistence assessment due to the large variation in the light available in different environmental compartments. Moreover, data for oxidation in the gas-phase are very uncertain due to the semi-volatile nature of BTBPE, i.e., its adsorption to particles. Therefore, no conclusion on the persistence of BTBPE can be drawn based on the abiotic degradation data.

BTBPE had very low degradation in a non-guideline biodegradation screening study (Calandra, 1976 from GLCC 2002) that used pre-adapted inoculum, inoculum:test substance concentration ratio similar to an inherent test and extended duration. According to ECHA Guidance Chapter R.11 (Version 3.0, June 2017), lack of degradation (<20% degradation) in an inherent biodegradability test equivalent to the OECD TG 302 series may provide sufficient information to confirm that the P-criteria are fulfilled without the need for further simulation testing for the purpose of PBT/vPvB assessment. The conditions of the test with BTBPE were not completely equivalent to OECD TG 302 tests and limited information on the test is available, and hence, its reliability cannot be fully assessed. Nevertheless, the very low degradation observed in the test vessels with conditions similar to an inherent test and pre-adapted microorganisms suggests that BTBPE may be at least P. Biowin QSAR predictions are consistent with the experimental data for BTPBE showing that the substance screens for potentially persistent (P) or very persistent (vP).

In a water-sediment mesocosms study (de Jourdan *et al*., 2013; reliable with restrictions) concentrations of BTBPE in the sediment phase showed no decrease during the study period, ca. 57 days from the introduction of the substance in the system, which indicates that very low degradation of the substance occurred in the sediment. There is some uncertainty whether or not the high organic carbon content in the study of de Jourdan *et al.* (2013) has influenced the biodegradation/bioavailability of BTBPE. However, sediments with organic carbon content above 10% are found in Europe (e.g., Niemirycz *et al.,* 2006, Karjalainen *et al.,* 2000), and hence, the study of de Jourdan *et al.* (2013) is considered to reflect environmentally relevant conditions. Furthermore, the available monitoring data from sediment core studies indicate that BTBPE has been found in 20-40 year old sediment layers in Lake Ontario (Qiu *et al.*, 2007) and Lake Michigan (Hoh *et al.*, 2005) in the USA and in an artificial saltwater lake in Korea (Lee *et al.*, 2022). These findings, suggest that the degradation in the environment may

be slow and provide indirect evidence that BTBPE can persist in sediments for more than two-four decades. Based on the weight of the evidence available and considering the very persistence of the substance in the soil compartment, BTPBE is concluded to meet the P/vP criteria of REACH Annex XIII in the sediment compartment (degradation half-life in sediment > 180 days).

BTBPE was also found to be persistent in soil amended with biosolids in a mesocosms study by Venkatesan and Halden (2014; reliable with restrictions). The study was run over three years and the BTBPE concentrations were found to be stable over the whole study period. Other higher brominated PBDEs as well as HBB and PBEB also remained stable in the study, while some of the tested substances like BDE-17, BDE 28 or BDE-37 showed decreasing concentrations over time. These observations are in line with other available data on the biodegradation of these substances, and thus, the soil mesocosms experiment seemed to represent realistic environmental conditions. The study therefore shows clearly that the half-life of BTBPE in soil is higher than the 120 days set in Annex XIII of REACH as criterion for a persistent substance and also higher than the criterion of 180 days for a very persistent substance.

Monitoring data for BTBPE support the above conclusions, as the substance has been detected in remote areas, e.g., in air and snow pits in the Norwegian and Canadian Arctic, respectively. Furthermore, according to ECHA Guidance Chapter R.11 (2017), if monitoring data as part of a Weight-of-Evidence analysis show that a substance is present in remote areas (i.e., long distance from populated areas and known point sources, e.g., in the Arctic sea or Alpine lakes), it may be possible to conclude a substance as P or vP.

Therefore, using a weight-of-evidence approach, it is concluded that BTBPE degrades very slowly in sediments and soils and fulfils the criteria for P and vP of REACH Annex XIII (degradation half-life in sediment or soil > 180 days).

6.2.1.2 Bioaccumulation

Based on the predicted log Kow values in the range of 7.88-9.39, which are considered more reliable than the available measured log Kow value of 3.14 (see Section 1.3), BTBPE screens B/vB (log kow >4.5).

Bioaccumulation in fish data from controlled laboratory experiments are only available from the manufacturer of BTBPE, the Great Lakes Chemical Corporation, (GLCC, 2002) and Tomy *et al.* (2007b). The measured BCF_{SS} values from GLCC (2002) are not considered reliable as the exposure concentrations were likely above the water solubility and steady state was likely not reached. The BMF values reported from the dietary study of *Tomy et al.* (2007b) should also not be used due to erroneous reported data. However, the obtained depuration rate constant (0.0128 day^{-1}) and depuration half-life (54 days) for muscle tissue from Tomy *et al.* (2007b; reliable with restrictions) can be used for the assessment. These values are similar or higher than the whole body depuration rates and half-lives in fish determined for substances concluded to be SVHCs due to vPvB properties, e.g., Dechlorane Plus, some of the vPvB congeners of medium chain chlorinated paraffins (MCCP) and vPvB constituent of terphenyl hydrogenated. Therefore, the depuration rate and half-life from Tomy *et al.* (2007b) together with the derived BCF values from the OECD TG 305 BCF estimation tool indicate that BTBPE is very bioaccumulative (BCF >5000). A supportive mesocosm study with fathead minnows (De Jourdan *et al.* 2013) indicated that no significant decrease of the concentration of BTBPE in the fish was observed after 28 days depuration period.

Several field studies assessing bioaccumulation of BTBPE are available. In the studies by Zheng *et al.* (2018) and Liu *et al.* (2021) BTBPE was shown to be able to undergo trophic magnification in a freshwater food web (TMF = 2.83) and in a marine food web (TMF = 2.3), respectively. There is another study (Mo *et al.* 2012) showing that BTBPE is able to biomagnify

in semi-aquatic predator–prey relationships (lipid normalised BMF common kingfisher/prey = 1.26–2.26). In some studies, biomagnification (Kurt-Karakus *et al.* 2019) or bioaccumulation (Wu *et al.* 2010) of BTBPE was found in some of the investigated species, but not in all. In other studies, trophic dilution occurred (Kurt-Karakus *et al.* 2019) or no biomagnification was observed in the studied species (Tao *et al.* 2019, Poma *et al.* 2014a).

There is a lack of agreed guidelines and methodologies for carrying out field studies on bioaccumulation, and interpretation of such studies encompasses several uncertainties (see section.11.4.1.2.6 of ECHA Guidance Chapter R.11 and Borgå *et al*., 2012). In many of the available field studies for BTBPE uncertainties related to e.g., spatial and temporal variability in sampling of different species, lack of whole body BTBPE concentrations for some species, were identified. However, even if individual data are uncertain, many of the studies point towards biomagnification/bioaccumulation of BTBPE in the food chain. According to REACH Guidance Chapter R.11 (2017), food chain transfer and secondary poisoning are basic concerns in relation to PBT and vPvB substances, and therefore an indication of a biomagnification potential (BMF and/or TMF > 1) can on its own be considered as a basis to conclude that a substance meets the B or vB criteria. Biomagnification will vary between predatory/prey relationships, so a low BMF in one does not mean that it will be low in other predatory/prey relationship. Conversely, evidence of high biomagnification in one predatory/prey relationship is cause for significant concern and it is then in accordance with a cautious approach to assume that biomagnification may also occur in other (unmeasured) predatory/prey relationships. Therefore, it is concluded that the field data, used as supporting information in the weight-of-evidence B assessment, point towards the bioaccumulation potential of BTBPE and thus confirm the conclusions from the experimental data.

Based on the available toxicokinetic information on rats, absorption of BTBPE via oral route in mammals is poor. However, exposure via inhalation may be more relevant for air-breathing animals, especially for humans as BTBPE is commonly detected in air and in indoor dust (Section 3.2.4). BTBPE is found in human serum, mother milk and hair (section 4.1.2), which indicates that there is uptake of BTBPE in humans. Furthermore, the observations on the presence of BTBPE in several animal species (Section 3.2.4), especially in top predators such as sharks (Marler *et al.* 2022, Strid *et al.* 2013) and polar bears (Vorkamp *et al.* (2015)) support the conclusion on bioaccumulation.

In conclusion, taking into account all the available information in a weight-of-evidence approach and considering especially the very slow elimination of BTBPE in fish in Tomy *et al.* (2007b) (indicative of a BCF >5000) and in de Jourdan *et al* (2013); the fish BCF values (10 out of 14 BCFs >5000) derived from data generated in the dietary study with rainbow trout by Tomy *et al.* (2007b) using the 14 models within the OECD TG 305 BCF estimation tool in methods 1 and 2, as well as the TMF and field BMF values above 1 observed in some of the available field studies, BTBPE is concluded to fulfil the criteria for B and vB in Annex XIII of REACH.

6.2.1.3 Toxicity

There is limited experimental information available on the adverse effects of BTBPE in human health and in the environment (see Annex I and II). However, there are indications that BTBPE may potentially be toxic to reproduction and have endocrine disrupting properties both in humans and in the environment.

6.2.2 Summary and overall conclusions on the vPvB properties

A weight-of-evidence determination according to the provisions of Annex XIII of REACH has been used to identify the substance as vPvB. All available relevant information (such as the

results of standard and non-standard tests, monitoring and modelling, and (Q)SAR results) was considered together in a weight-of-evidence approach.

Persistence:

BTBPE had negligible degradation in a non-standard biodegradation screening study that used pre-adapted inoculum, inoculum:test substance concentration ratio similar to an inherent test and extended duration. According to ECHA Guidance Chapter R.11, lack of degradation (<20% degradation) in an inherent biodegradability test equivalent to the OECD TG 302 series may provide sufficient information to confirm that the P-criteria are fulfilled without the need for further simulation testing for the purpose of PBT/vPvB assessment. The conditions of the test with BTBPE were not completely equivalent to OECD TG 302 tests and limited information on the test is available, and hence, its reliability cannot be fully assessed. Nevertheless, the very low degradation observed in the test vessels with conditions similar to an inherent test and pre-adapted microorganisms suggests that BTBPE may be at least persistent (P). Biowin QSAR predictions are consistent with the experimental data for BTPBE showing that the substance screens for potentially persistent (P) or very persistent (vP).

BTBPE was found to be persistent in soil treated with biosolids in a mesocosms study (reliable with restrictions). The study was run over three years and the BTBPE concentrations were found to be stable over the whole study period. Other higher brominated flame retardants, such as polybrominated diphenyl ether (PBDE) congeners from penta- to deca-BDE, as well as hexabromobenzene (HBB) and pentabromoethylbenzene (PBEB) also remained stable in the study, while some of the less brominated tested substances like di- and tri-BDEs showed decreasing concentrations over time. These observations are in line with other available data on the biodegradation of these substances and the soil mesocosms experiment appears to represent realistic environmental conditions. The study therefore shows clearly that the half-life of BTBPE in soil is higher than the 120 days set in Annex XIII of REACH as criterion for a persistent substance and also higher than the criterion of 180 days for a very persistent substance.
Negligible degradation of BTBPE was also observed in sediment phase in a water-sediment mesocosms study (reliable with restrictions). There is some uncertainty whether or not the high organic carbon content (10%) in the water-sediment mesocosms study influenced the biodegradation/bioavailability of BTBPE. However, sediments with organic carbon content above 10% are found in Europe, and hence, the study is considered to reflect environmentally relevant conditions. Furthermore, the available monitoring data from sediment core studies indicate that BTBPE has been found in 20-40 year old sediment layers in Lake Ontario and Lake Michigan in the USA and a saltwater lake in Korea. These findings, suggest that the degradation in the environment may be slow and provide indirect evidence that BTBPE can persist in sediments for more than two-four decades. Based on the weight of the evidence available and considering the substance is very persistent in the soil compartment, BTPBE is concluded to meet the P/vP criteria of REACH Annex XIII in the sediment compartment (degradation half-life in sediment > 180 days).

Monitoring data for BTBPE support the above conclusions, as the substance has been detected in remote areas, e.g., in air and snow pits in the Norwegian and Canadian Arctic, respectively. These findings further strengthen the conclusion that BTBPE is very persistent in the environment.

Based on a weight-of-evidence approach and considering assessment information in accordance with REACH Annex XIII Section 3.2.1.(d), it is concluded that BTBPE meets both the 'persistence' (P) (degradation half-life in sediment or soil > 120 days) and 'very persistent' (vP) criteria of REACH Annex XIII (degradation half-life in sediment or soil > 180 days) in accordance with Annex XIII, points 1.1.1 and 1.2.1, of the REACH Regulation.

Bioaccumulation:

Based on the predicted log Kow values in the range of 7.88-9.39, which are considered more reliable than the available measured log Kow value of 3.14, BTBPE screens B/vB (log Kow >4.5).

In a non-standard laboratory dietary bioaccumulation in fish study (reliable with restrictions), a low depuration rate constant of 0.0128 day^{-1} (indicative of a BCF > 5000) and a long depuration half-life of 54 days for muscle tissue of rainbow trout were determined, indicating very slow depuration of BTBPE in fish. These values are similar or higher than the whole body depuration rates and half-lives in fish determined for substances concluded to be SVHCs due to vPvB properties, e.g., Dechlorane Plus, some of the vPvB congeners of medium chain chlorinated paraffins (MCCP) and vPvB constituent of terphenyl hydrogenated. Furthermore, in this study BTBPE does not seem to be metabolised by fish. Fish BCFs were derived from data generated in the above dietary study with rainbow trout using the 14 models within the OECD TG 305 BCF estimation tool in methods 1 and 2. Based on the 14 models, 11 BCFs predicted were above 5000 thus indicating a high bioaccumulation potential for BTBPE.

A supporting mesocosms study with fathead minnows (low reliability) confirms the findings of the dietary study as no significant decrease of the concentration of BTBPE in the fish was observed after 28 days depuration period.

Field data used as supporting information in the B assessment point towards the bioaccumulation potential of BTBPE and thus confirm the conclusions from experimental data. Several field studies on bioaccumulation indicate that BTBPE has TMF and BMF values above 1 in some of the studied food webs and predator/prey relationships, respectively, which are clear indications that BTBPE is able to biomagnify. According to REACH Guidance Chapter R.11, food chain transfer and secondary poisoning are basic concerns in relation to PBT and vPvB substances, and therefore an indication of a biomagnification potential (BMF and/or TMF > 1) can on its own be considered as a basis to conclude that a substance meets the B or vB criteria.

BTBPE has been detected in human serum, hair and mother milk samples which indicates that BTBPE is absorbed to some extent in humans. In addition, monitoring data demonstrate widespread contamination of wildlife by BTPBE at all trophic levels (including predatory species (e.g., polar bears which are listed on the IUCN red list of threatened species)). BTBPE has also been detected in biota samples from remote regions, including the Arctic. These data provide supporting evidence that BTPBE is taken up by organisms in the environment.

Based on a weight-of-evidence approach and considering assessment information in accordance with REACH Annex XIII points 3.2.2 (a), (b) and (c), it is concluded that BTBPE meets the 'bioaccumulation' criterion (B) and the 'very bioaccumulative' criterion (vB) in accordance with Annex XIII, points 1.1.2 and 1.2.2, of the REACH Regulation.

Conclusion:

In conclusion, BTBPE is proposed to be identified as a vPvB substance according to Article 57(e) of REACH by comparing all relevant and available information listed in Annex XIII of REACH with the criteria set out in the same Annex, in a weight-of-evidence determination.

6.3 Assessment under Article 57(f)

This section is not relevant for the identification of the substance as SVHC in accordance with Article 57 (e) of the REACH Regulation.

Part II

7. Registration and C&L notification status

7.1 Registration status

Not registered under REACH.

7.2 CLP notification status

Table 14: CLP notifications

	CLP Notifications[4]
Number of aggregated notifications	2
Total number of notifiers	30

8. Total tonnage of the substance

BTBPE is not registered under REACH. In the C&L inventory, there are 30 notifications for the substance, and hence, there could be use of the substance at low tonnages (< 1 t/y) in the EU.

BTBPE was included in the 2007 OECD List of high production volume chemicals meaning that it was produced or imported at levels greater than 1,000 tonnes per year in at least one member country/region (OECD, 2009). The substance is also included in the High production volume list in the United States (USEPA, 2022). The Great Lakes Chemical Corporation was the only US producer of BTBPE and production volumes in the USA were 4500–22,500 tons/year between 1986 and 1994 (Covaci *et al.,* 2011), but decreased to 450–4500 tons/year in 1998 (CECBP, 2008, Covaci *et al.,* 2011). The production stayed on this level until at least 2005 (CECBP, 2008). Information on the current production volumes is not available. However, BTBPE is offered online by several suppliers, mostly Chinese (Chembid, 2022, Chemical Book 2022).

According to Lassen *et al.* (2014, citing Eurostat 2012) the average net imports and exports of BTBPE in the EU for years 2006-2007 were 82 t/y and 9.6 t/y, respectively. Based on the information published in the SPIN Database[5], use of BTBPE at low quantities may have occurred in Sweden in year 2018. In the KemiStat[6], which contains data on the chemical products and substances registered in the Swedish Product and Pesticide Registers in years 1993-2016, use of BTBPE is reported only for years 1997-1999 in the range of 2.2 to 6.6 tonnes per year. For years 2009-2016, according to KemiStat one product containing the substance was registered but the tonnage data is claimed confidential.

[4] C&L Inventory database, http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database (accessed 7 June 2022)
[5] http://www.spin2000.net/spinmyphp/
[6] https://apps.kemi.se/kemistat/start.aspx?sprak=e

9. Information on uses of the substance

Based on publicly available information, BTBPE is used as an additive flame retardant (e.g., PubChem, Lassen *et al.* 2014), i.e., it is incorporated to polymeric matrices through physical mixing and does not chemically bind to them. It is marketed for use in in acrylonitrile-butadiene-polystyrene (ABS), high-impact polystyrene (HIPS), thermoplastics, thermoset resins, polycarbonate, and coatings (WHO, 1997) and textiles (Lassen, 2006). BTBPE is especially efficient for applications in which thermal stability at high processing temperatures is important (Lassen, 2006). The applications known are in electric and electronic equipment, such as computers, televisions, and mobile cell phones (Thuresson, 2004), and construction materials (sealant around window frames) available to consumers or in the domestic environment (EBRC, 2011). Furthermore, BTBPE may be available to consumers in preparations that need flame retardancy like adhesives used for construction (EBRC, 2011).

BTBPE belongs to the group of "novel" brominated flame retardants, that have been developed as replacements to "legacy" brominated flame retardants, e.g., polybrominated diphenyl ethers (PBDEs), hexabromocyclododecane (HBCD) and tetrabromobisphenol A (TBBA). BTBPE has been produced since 1970's and it is used as a replacement especially to Octa-BDE (Renner, 2004) in ABS and it can also replace deca-BDE in some applications (Lassen *et al.*, 2006).

10. Information on structure of the supply chain

No information available.

11. Additional information

11.1 Substances with similar hazard and use profiles on the Candidate List

According to publicly available information, BTBPE is used as a replacement especially to Octa-BDE (Renner 2004) in ABS and it can also replace deca-BDE in some applications (Lassen *et al.,* 2006).

11.2 Alternatives

No information available.

11.3 Existing EU legislation

There is currently no EU legislation applying to BTBPE.

11.4 Previous assessments by other authorities/ongoing regulatory activities

No information available.

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Annex I – Human health hazard assessment[7]

4.1 Toxicokinetics

Based on the available toxicokinetic information summarised in Part I, Section 4.1, absorption of BTBPE via the oral route in mammals is poor. Excluding the gastrointestinal tract, adipose tissue contained the highest concentration of BTBPE in biodistribution studies, followed by kidney, skin, and thymus, whereas brain, testes, and spleen contained the lowest concentrations. Once absorbed, some metabolism of BTBPE occur in mammals, including the formation of bromophenols like 2,4,6-TBP. The latter may have endocrine disrupting properties and may cause neurotoxic effects (Norwegian Environmental Agency, 2016) (see also Annex II).

There are no toxicokinetic studies in humans for BTBPE. However, as indicated in Section 3.2.4, BTBPE is commonly detected in air and in indoor dust, and hence human exposure via inhalation is expected. BTBPE is found in human serum, mother milk and hair, which indicates that there is uptake in humans. Martínez et al., (2021) reviews and summarises levels of Halogenated Flame Retardants, including BTBPE, in humans, reviewing also the analytical methods used for measuring in biological samples.

4.2 Acute toxicity

Not relevant for this dossier.

4.3 Irritation

Not relevant for this dossier.

4.4 Corrosivity

Not relevant for this dossier.

4.5 Sensitisation

Not relevant for this dossier.

4.6 Repeated dose toxicity

4.6.1 Non-human information

4.6.1.1 Repeated dose toxicity: oral

A chronic toxicity study in rats over 106 days gave a LOAEL of 8300 mg/kg and a NOAEL of 730 mg/kg in the daily feed (data from 1977 cited in GLCC, 2002). These results were based on histopathologic hepatic changes among most animals in the highest dosed group, increased incidence of mild unilateral or bilateral hypervolemia of the adrenal gland, increased incidence of focal vacuolization of basophils and focal increased of hyperpolasia in the pituitary and increased incidence of focal interstitial lymphoid infiltrations in the pancreas. There were also haematological alterations observed (lower total leukocyte count, haematocrit and haemoglobin level), however the authors stated that the values in treated animals were within

[7] It should be noted that the substance is under testing by NTP. See at https://ntp.niehs.nih.gov/whatwestudy/testpgm/status/ts-m20292.html?utm_source=direct&utm_medium=prod&utm_campaign=ntpgolinks&utm_term=ts-m20292

the range of historical controls.

Authors indicated that the results of the study may be influenced by the presence of pneumonia. Majority of control and high dose treated animals had aggregated of alveolar macrophages in the lungs.
Concentrations of test material in diets were not verified analytically. Limited information on the test is available, and hence, its reliability cannot be fully assessed.

4.6.1.2 Repeated dose toxicity: inhalation

Rats that inhaled air with 5 or 20 mg/L for 21 days (4 hours per day) showed no gross pathological changes; however, unspecified histopathological lesions were observed in the lungs. Authors indicated a slight, dose-dependent decrease in leukocytes in females exposed to 5 mg/L. Males are indicated to exhibit a dose-dependent increase in absolute lung weight compared to controls and also microscopic findings were referred to the lungs of treated animals (data from 1975 cited in GLCC, 2002). The LOAEL was set to 5 mg/L.

The lack of statistical analysis makes it difficult to determine if hematologic changes, blood chemistry or urinalysis were significant and due to toxic effects. No independent evaluation of the robust study has been possible.

4.6.1.3 Repeated dose toxicity: dermal

No data available

4.6.1.4 Repeated dose toxicity: other routes

No data available

4.6.2 Human information

No data available

4.6.3 Summary and discussion of repeated dose toxicity

Information from repeated dose toxicity is available for oral and inhalation studies. A chronic study on rats over 106 days gave a NOAEL of 730 mg/kg in the daily feed. Based on the available information for inhalation a LOAEL of 5 mg/L has been set. However, it should be stressed that due to lack of detailed information makes reliability cannot be fully assessed.

4.7 Mutagenicity

4.7.1 Non-human information

4.7.1.1 In vitro data

The mutagenicity of BTBPE was evaluated in the bacteria Salmonella tester strains TA98, TA100, TA1535, TA1537 and TA1538 (Ames Test) and in the yeast *Saccharomyces cerevisiae* tester strain D4, both in the presence and absence of added metabolic activation by Aroclor-induced rat liver S9 fraction. Based on preliminary bacterial toxicity determinations, BTBPE was tested for mutagenicity in the bacterial and yeast cultures at concentrations up to 50 µg/plate. BTBPE did not cause a positive response in any of the bacterial or yeast tester strains, either

with or without metabolic activation (Zeiger *et al.*, 1987).

4.7.1.2 In vivo data

No data available.

4.7.2 Human information

No data available.

4.7.3 Summary and discussion of mutagenicity

BTBPE did not cause any positive response in *in vitro Salmonella* nor *Saccharomyces* tested strains. However, no information from *in vivo* studies is available and therefore, no firm conclusion on mutagenicity can be drawn.

4.8 Carcinogenicity

No data available.

4.9 Toxicity for reproduction

4.9.1 Effects on fertility

4.9.1.1 Non-human information

Egloff (2011) investigated the concentration-dependent effects of BTBPE in chicken embryonic hepatocytes (CEH) and the dose-dependent effects of BTBPE in chicken embryos following injection into the air cell of eggs prior to incubation. BTBPE was not cytotoxic up to 1.4 µM BTBPE in CEH. Injection doses up to 10 µg/g egg BTBPE had no effect on embryonic hatching success.

Smith-Edwards (2013) studied the effects of BTBPE in mink which were exposed to the chemical via diet. Forty adult female mink were fed one of four diets containing 0, 0.014, 0.13 or 2.3 mg BTBPE/kg feed two months prior to breeding. Females were bred to untreated males. At whelping and at 3 and 6 weeks of age, kits were counted and weighed. At 6 weeks of age, six offspring from each treatment group, as well as the adult females, were necropsied. Samples of plasma, liver, fat, lungs, and feces were processed for chemical analysis and thyroids were processed for histological assessment. Ten offspring per group were maintained on their respective treatments through seven months of age at which time the juvenile mink were necropsied and tissues processed as described above. The results of the study indicated that exposure to BTBPE at dietary concentrations up to 2.3 mg/kg feed had no effect on the reproductive performance of mink and the survival and growth of their offspring.

No studies conducted according to OECD Test Guidelines have been performed.

4.9.1.2 Human information

No data available

4.9.2 Developmental toxicity

4.9.2.1 Non-human information

Thirty-five female Charles River CD rats (approximately 10 weeks old) were administered BTBPE by gavage (constant volume of 25 ml/kg/day) at 30, 100, 300, 1,000, and 3,000 and to the additional group of animals at 10,000 mg/kg/day from days 6, 12 and 15 of gestation (Goldenthal 1978, cited in GLCC 2002). The study finalised up to the 20th gestation day. Survival and clinical signs of toxicity of females and offspring, male to female sex ratios, and number of litters and foetuses with abnormalities were determined. In the study from 1978, no Test Guideline is indicated to be followed and no independent review of the study has been possible as no robust summary was available. Authors indicated that the survival in all groups was 100%. The test material had no effect on body weight gains, appearance or behaviour. One animal in the 1,000 mg/kg/day group delivered 14 viable and one nonviable foetus after 7 days of treatment. Three animals in the 100 mg/kg/day group were nongravid. The decrease in fertility seen in animals treated with 100 mg/kg/day was indicated to be not related to the test material since it was given after mating. The authors attributed the early delivery from one rat treated with 1,000 mg/kg/day to be due to an inaccurate determination of copulation. However, the fact that this was the only animal that had a nonviable foetus suggests that the animal may have aborted. This does not appear to be related to test material, since two higher doses did not induce early delivery or foetal death. According to the authors of the study, the NOAEL (female maternal) is 10 000 mg/kg bw and the NOAEL (foetus) is 10 000 mg/kg bw.

4.9.2.2 Human information

No data available

4.9.3 Summary and discussion of reproductive toxicity

No studies conducted according to OECD Guidelines have been performed. Only information from one non-guideline study is available for the assessment of reproductive toxicity. The study administered concentrations of BTBPE from day 6 to 15 of gestation. The study finalised up to 20 day of gestation. Test conditions results in clear deviations from the current guidelines resulting lack of relevant information which make difficult to drawn a clear conclusion.

4.10 Endocrine disruption (Human Health)

Smythe *et al*. (2017) investigated the inhibitory effects of BTBPE on thyroid hormone deiodinase (DIO) and sulfotransferase (SULT) activity. Enzymatic activity was measured by incubating active human liver subcellular fractions with thyroid hormones and measuring changes in thyroid hormone concentrations. The results indicate that BTBPE does not exhibit inhibitive properties in DIO or SULT.

An epidemiologic study correlated the levels of brominated flame retardants in dust to serum hormone levels (Johnson *et al.*, 2013). They found that the level of total 3,3',5-triiodothyronine (T3) in serum of adult men was positively associated with the concentration of BTBPE in house dust. This suggests that high levels of BTBPE may cause thyroid hormone disruption.

See also section 5.7 of Annex II. Some of the information on potential endocrine disrupting properties of BTBPE and its metabolite/degradation product 2,4,6-TBP observed in the available studies for the environment could also be relevant for human health. However, no firm conclusion can be drawn based on the available information although concerns are

identified (Hamers et al., 2006; Norwegian Environmental Agency, 2016).

4.11 Summary and discussion of human health hazard assessment

BTBPE does not have a harmonised classification according to Regulation EC/1272/2008 (CLP) for any human health hazard. It is notified in the classification inventory as Skin Irrit. 2, Eye Irrit. 2 and STOT SE 3 for respiratory irritation. However, there is limited experimental information available. Therefore, no conclusion can be drawn on most of the human health hazard endpoints.

It is noted that in a recently adopted RAC opinion (ECHA, 2020) it was concluded that ammonium bromide has adverse effects on sexual function and fertility; adverse effects on development and adverse effects on or via lactation that warrant classification as Repr. 1B, H360 FD and H362. It was also concluded that ammonium bromide warrants classification as STOT SE 3, H336 (narcotic effects) and STOT-RE 2; H372 (nervous system). These adverse effects are caused by the bromide ion, and most of the evidence is from studies on sodium bromide or potassium bromide.

Hence, the presence of the bromine may indicate a potential for neurotoxicity, developmental neurotoxicity and reproductive toxicity either due to potential metabolism that would release bromide within the body or because of direct action of the substances passing the blood brain barrier. BTBPE contain bromine and therefore bromide could potentially be released *in vivo*. In the non-standard tests mentioned above in chicken embryonic hepatocytes, mink and rats no toxic effects on reproduction were observed. However, as there are no standard tests on reprotoxicity available for BTBPE, there is a concern for potential reproductive toxicity and neurotoxicity, but the uncertainty is if and how fast bromine is released under physiological conditions. The structurally similar octabromodiphenyl ether (EC 251-087-9) has a harmonised classification as Repr. 1B for developmental toxicity.

Furthermore, BTBPE is metabolised in the body to 2,4,6-TBP. The results of an available screening study (OECD TG 422) for 2,4,6-TBP are indicative of increased liver and kidney weights, decrease of thymus weight, atrophy of thymus and hypertrophy of adrenals , which suggests potential ED properties. 2,4,6-TBP has been self-classified by one notifier with Reproductive Toxicity cat. 2 and Specific Target Organ Toxicity, Repeated Exposure (STOT RE 2). The Norwegian Competent Authority has concluded after a substance evaluation (SEv) on this substance that the substance may induce reproductive toxicity (Norwegian Environmental Agency, 2016). The main concern is related to perinatal development and developmental neurotoxicity. In addition, it is concluded in the SEV Conclusion Document that no studies regarding endocrine disruption in mammals due to 2,4,6-TBP exposure were found, but the available *in vitro* studies (Hamers et al., 2006; Smythe *et al*. 2017) and MoA (Stinckens et al., 2018) indicate a potential for endocrine disruption that is relevant for humans. However, further *in vivo* studies would be needed to firmly conclude.

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Annex II – Environmental hazards assessments

5.1 Aquatic compartment (including sediment)

5.1.1 Fish

5.1.1.1 Short-term toxicity to fish

Acute aquatic toxicity studies are only available for fish. The Great Lakes Chemical Corporation (GLCC, 2002) tested the acute toxicity (96 hours) of BTBPE in two fresh water fish species (*Lepomis macrochirus* and *Oncorhynchus mykiss*). All tests were performed with concentrations well above the water solubility of BTBPE and the 96h-LC50 values reported (in the range of 1410-1531 mg/L) are well above the water solubility. Therefore, the studies are not considered valid for the assessment. However, it is noted that no fish died during the lowest exposure scenario with 464 mg/L BTBPE, which indicates no acute toxicity of BTBPE at the limit of its water solubility. There is also a preliminary experiment with *Oryzias latipes* to determine the concentration of test material used in a bioaccumulation study *(*CITI, 1976 from GLCC 2002) where a 48h-LC50 value of 230 mg/L, well above the water solubility of the substance, is reported.

5.1.1.2 Long-term toxicity to fish

Studies for chronic aquatic toxicity via aqueous exposure are not available for BTBPE.

Tomy *et al.* (2007) studied the effects of BTBPE in rainbow trout (*Oncorhynchus mykiss*) via dietary exposure. They exposed the fish to an environmentally relevant dose of BTBPE via diet (46±2 ng/g lipid) for 49 days, followed by 154 days of untreated food. They then examined liver extracts from day 0 (as control) and day 49 of the uptake phase and four sampling points of the clearance phase. Debrominated and hydroxylated metabolites were not detected in liver extracts and suggest that either biotransformation or storage of BTBPE metabolites in the hepatic system of fish was minor or that the exposure time frame was too short. The thyroid glandular structure appeared unaffected in fish exposed to the BTBPE concentrations in this study, and therefore, Tomy *et al.* (2007) concluded that BTBPE is not a potent thyroid-disrupting BFR.

Giraudo *et al.* (2017) evaluated the effects of BTBPE in juvenile rainbow trout (*Oncorhynchus mykiss*) that were exposed for 28 days to BTBPE via diet (605±167 µg/g lipid). BTBPE was detected in fish carcasses at 76% of the daily dosage of BTBPE, indicating accumulation of BTBPE. Liver gene transcription analysis using RNA-sequencing indicated that the chronic 28 day dietary exposure of trout to BTBPE impacted the transcription of 33 genes, including genes involved in the immune response, reproduction, and oxidative stress. Additional analysis using qRT-PCR after 48 h and 28 d of exposure confirmed the impact of BTBPE on immune related genes in the liver (apolipoprotein A-I, lysozyme) and the head-kidney (complement c3-4). However, the activity of lysozymes measured at the protein level did not reflect transcriptomic results. One reason for this could be that the exposure duration was too short to reveal the induction of the protein activity after transcriptional over-expression of the gene. Giraudo et al. (2017) emphasised therefore the need for a study with longer exposure duration to identify the impact of BTBPE on lysozyme activity and transcription.

De Jourdan *et al.* (2014) found only limited apparent physiological effects of BTBPE in their aquatic mesocosms experiment. Condition factor, oxidative stress, liver somatic index and gonadal somatic index were unaltered between BTBPE exposed fathead minnow (concentrations between 15 and 37000 ng/g lipid) and the control group. Moreover, no

correlation was found between sex steroid concentration and gonad size. However, de Jourdan *et al.* (2014) stated that the small sample size in this study limited the ability to detect significant trends in hormone production. Male and female fish, exposed to BTBPE, showed elevated concentration of vitellogenin, however, the concentrations differences were not statistically significant.

5.1.2 Aquatic invertebrates

5.1.2.1 Short-term toxicity to aquatic invertebrates

No data available.

5.1.2.2 Long-term toxicity to aquatic invertebrates

No data available.

5.1.3 Algae and aquatic plants

No data available.

5.1.4 Sediment organisms

No data available.

5.1.5 Other aquatic organisms

No data available.

5.2 Terrestrial compartment

5.2.1 Toxicity to soil macro-organisms

No data available.

5.2.2 Toxicity to terrestrial plants

No data available.

5.2.3 Toxicity to soil micro-organisms

No data available.

5.2.4 Toxicity to other terrestrial organisms

No data available.

5.3 Atmospheric compartment

5.4 Microbiological activity in sewage treatment systems

No data available.

5.5 Toxicity to birds

No data available.

5.6 Mammalian wildlife

No data available

5.7 Endocrine disruption (Environment)

Ezechiáš *et al.* (2012) used two yeast reporter-gene assays to determine the potential of several BFRs, including BTBPE to interfere with estrogenic and androgenic pathways. The estrogen-like activity of the tested chemicals was measured using a recombinant strain of *Saccharomyces cerevisiae*, producing β-galactosidase in response to estrogen exposure. The estrogenic and androgenic activity of the chemicals was tested using the bioluminescent yeast strains *S. cerevisiae* BMAEREluc/ERα and *S. cerevisiae* BMAEREluc/AR. BTBPE did not show estrogenic or androgenic activity in both tests. However, 14.5 µM (9.97 mg/L) of BTBPE was able to lower the β-galactosidase production by about 12.2%. BTBPE at a concentration of 12.1 µM (8.3 mg/L) also inhibited the yeast luminescence by 31%. This shows that BTBPE has anti-estrogenic activity. Unfortunately, nominal chemical concentrations at which 50% of the test response inhibition is reached, could not be calculated for BTBPE, because BTBPE was not sufficiently soluble in the tests to explore the concentration dependence.

As indicated in section 4.10 of Annex I, Smythe *et al*. (2017) found no inhibitory effects of BTBPE on thyroid hormone deiodinase (DIO) and sulfotransferase (SULT) activity by incubating active human liver subcellular fractions with thyroid hormones. In the epidemiologic study by Johnson *et al.* (2013) a positive correlation between the level of total 3,3’,5-triiodothyronine (T3) in serum of adult men and the concentration of BTBPE in house dust was found suggesting that high levels of BTBPE may cause thyroid hormone disruption.

As mentioned in section 4.9 of Annex I, Egloff *et al.,* (2011) investigated the concentration-dependent effects of BTBPE in chicken embryonic hepatocytes (CEH) and the dose-dependent effects of BTBPE in chicken embryos following injection into the air cell of eggs prior to incubation. Genes responsive to BTBPE exposure in vitro did elicit similar patterns of expression in the hepatic tissue of embryos exposed to BTBPE. BTBPE significantly induced the expression of CYP1A4/5 genes and suppressed the expression of DIO3 in both hepatocytes and embryonic livers, which identified the AhR pathway and the TH hormone pathway as targets of BTBPE exposure (Egloff *et al*., 2011).

Eng *et al.* (2019) assessed the effects of BTBPE on early developmental exposure of an avian predator, the American kestrel *(Falco Sparverius).* They collected 83 fertile eggs in 2015 and injected 0, 10, 50, or 100 ng/g ww BTBPE into the eggs. A subset of the kestrel eggs from the control and high BTBPE dose groups were sampled on embryonic day (ED) 12 (n=4 control, 3 high), ED18 (n=2 control, 5 high), ED21 (n=3 control, 3 high), and ED25 (n=3 control, 4 high) to measure BTBPE concentrations over the incubation period. On ED24, viable eggs were transferred into individual plastic mesh hatching cells and incubated without rotation at 37 °C and 70% RH until hatching. From ED27 to ED29, eggs were monitored for pipping and hatching. Pipped eggs were left to hatch up to 24 hours, at which point they were considered

failed to hatch. The results showed that BTBPE had no effects on hatching or pipping success. The body mass was also not affected by BTBPE There was also no effect of BTBPE on body condition, and there was also no sex effect or sex treatment interactions (Eng *et al.*, 2019). However, there was an effect on the hepatic deiodinase activity. While there was no overall effect of treatment on D2 activity when sexes were combined, there was a significant interaction between treatment and sex, and a significant effect of sex on D2 activity. Overall, males had higher D2 activity than females (male 44.8 ± 3.7, female 29.7 ± 2.8 pg T3/mg protein/min). Male D2 activity did not significantly change across dose groups, but there was a non-significant tendency for seemingly greater activity at higher dosages. In contrast, female D2 activity declined in a dose dependent manner, and females in the 100 ng/g dose group (D2 range: 14.8–30.3 pg T3/mg protein/min) had significantly lower D2 activity than control females (D2 range: 32.0–61.3 pg T3/mg protein/min), and significantly lower activity than males in all three dose groups.

Thus, Eng *et al.* (2019) found evidence that the exposure to BTBPE disrupted one indicator of thyroid function in females. However, no other significant effects were detected for either compound despite measuring multiple endpoints, which suggests that these BFRs may not be very toxic at these concentrations or they may not have reached the developing kestrel embryos in toxic amounts from the air cell. Furthermore, the authors stated also that the detected effects should be treated with caution due to the large number of physiological variables tested and the possibility of type I errors. Moreover, vertebrates have three types of deiodinases (D1, D2, D3), of which D2 is the most important enzyme in the activation of thyroid hormones, catalyzing the conversion of T4 to the more biologically active T3 via outer ring deiodination. In the female kestrels studied by Eng *et al.* (2019), the reduced D2 activity may have been a compensatory response to maintain circulating thyroid hormones by reducing the conversion of T4 to T3.

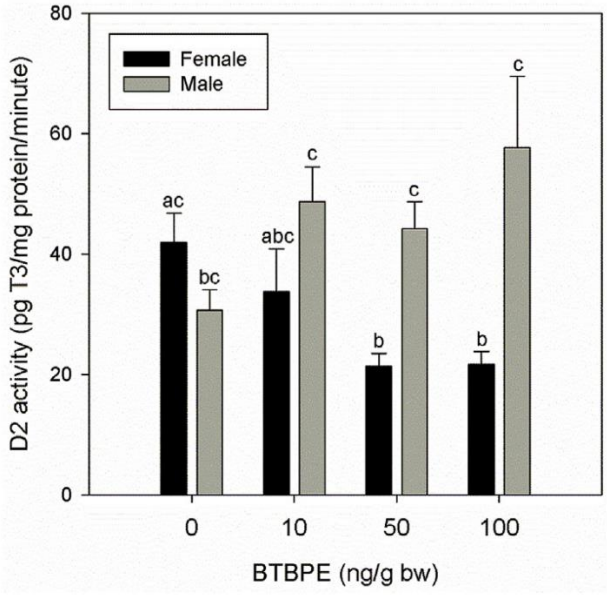

Figure 20 Effect of *in ovo* BTBPE exposure on hepatic deiodinase activity for the D2 isoform in American kestrel hatchlings. Adapted from Eng *et al.* (2019).

Regarding the metabolite/degradation product 2,4,6-TBP, the Norwegian Competent Authority (NO CA) conducted Substance Evaluation (SEv) for the substance in 2012 and concluded that the available *in silico*, *in vitro* and *in vivo* studies suggest that 2,4,6-TBP may interact with the endocrine system through multiple modes of action (MoA). According to the Substance Evaluation Conclusion Document (Norwegian Environmental Agency, 2016)

2,4,6-TBP seems to produce adverse effects such as reduction of oocyte development,

reduction of fertilization success and fecundity, and shift in male ratios of zebrafish being suggestive of an ED MoA. Uncertainty in the complete MoA of 2,4,6-TBP limit the ability to clearly state that 2,4,6-TBP can be confirmed as an ED, and with the current level of knowledge may be appropriately classified as a potential ED. […]

2,4,6-TBP has also been reported to interact /interfere with the transport of TH thyroid hormones and interfere with TH regulation at low concentrations in vitro, albeit adverse effect in vivo are largely unknown.

The NO CA concluded that further information on the *in vivo* adverse effects is needed, in order to firmly conclude on the ED properties. However, as the registrant inactivated its registration shortly after the SEv , the evaluation was terminated with several open concerns.

A recent study investigated the adverse effects of 2,4,6-TBP (Stinckens *et al*., 2018). The authors linked the adverse effect "posterior swim bladder inflation in zebrafish embryo" to the molecular initiating event DIO1 and DIO2 inhibition. The two pathways were described before as AOP 157 (DIO1) and AOP 155 (DIO2), but Stinckens *et al*. (2018) were able to proof these AOPs experimentally. They used an *in chemico* enzyme inhibition assay to measure the molecular initiating events for an array of 51 chemicals, including 2,4,6-TBP. Zebrafish embryos were then exposed to 14 compounds (including 2,4,6-TBP) with different measured inhibition potentials. Six out of seven strong DIO1 inhibitors and all strong DIO2 inhibitors affected posterior chamber inflation and/or surface area. All tested compounds with a low or no DIO2 inhibition capacity caused no effects, with the exception of the estrogenic xenobiotic chemical bisphenol A and the surfactant perfluorooctanesulfonic acid. 2,4,6-TBP was identified as strong DIO1 and DIO2 inhibitor and caused posterior chamber inflation at an EC50 of 0.42 mg/L. Mortality of 50% of the embryos occurred at 0.84 mg/L. As the EC_{50} is very close to the LC_{50} it is difficult to reach definite conclusions about ED mediation of the observed effects in the swim bladder.

In conclusion, BTBPE showed anti-estrogenic activity, significantly induced the expression of CYP1A4/5 genes and suppressed the expression of DIO3 *in vitro* test. No studies exists so far that tested these endocrine disrupting effects *in vivo*, and hence it is not possible to conclude on the ED properties. The structurally very similar PBDEs have been shown to affect thyroid and reproduction systems in captive and wild fish (Noyes and Stapleton, 2014; Yu, Han and Liu, 2015). It is therefore possible that BTBPE can also act as an endocrine disrupting substance.

Furthermore, the metabolite 2,4,6-TBP is likely an endocrine disrupting chemical. However, further *in vivo* tests are needed to firmly conclude.

5.8 Summary and discussion of the environmental hazard assessment

Very limited data on environmental hazards is available for BTBPE. No reliable standard acute or chronic aquatic toxicity tests are available. Therefore, it is not possible to conclude on the aquatic toxicity of BTBPE.

There are indications from *in vitro* tests that BTBPE may have endocrine disrupting potential. Also, the metabolite 2,4,6-TBP is likely to be an endocrine disrupter based on the available information. However, further *in vivo* tests are needed to firmly conclude on these properties.

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Annex III - Particle-bound fraction

99% of BTBPE is particle-bound at 25 °C. This fraction, φ, was calculated as indicated by Glüge *et al*. (2015):

$$\varphi = \varphi_{\mathrm{pf}} + \varphi_{\mathrm{pc}}, \quad (4)$$

$$\varphi_{\mathrm{pf}} = \frac{C_{\mathrm{pf}}V_{\mathrm{pf}}}{C_{\mathrm{pf}}V_{\mathrm{pf}} + C_{\mathrm{pc}}V_{\mathrm{pc}} + c_{\mathrm{a}}V_{\mathrm{a}}} = \frac{1}{1 + \frac{v_{\mathrm{pc}}K_{\mathrm{pcpf}}}{v_{\mathrm{pf}}} + \frac{1}{v_{\mathrm{pf}}K_{\mathrm{pfa}}}}, \quad (5)$$

$$\varphi_{\mathrm{pc}} = \frac{C_{\mathrm{pc}}V_{\mathrm{pc}}}{C_{\mathrm{pf}}V_{\mathrm{pf}} + C_{\mathrm{pc}}V_{\mathrm{pc}} + c_{\mathrm{a}}V_{\mathrm{a}}} = \frac{1}{1 + \frac{v_{\mathrm{pf}}}{v_{\mathrm{pc}}K_{\mathrm{pcpf}}} + \frac{1}{v_{\mathrm{pc}}K_{\mathrm{pca}}}}, \quad (6)$$

where φ_{pf} is the fraction bound to fine particles (or aerosols), and φ_{pc} the fraction bound to coarse particles (or aerosols). These two fractions represent in a simplified way the size distribution of particles in the atmosphere. Here, coarse and fine particles are defined as particulate matter with a diameter of 2.5 to 10 µm and <2.5 µm, respectively. The partition coefficients K_{pca}, K_{pfa}, and K_{pcpf} were calculated as indicated by Glüge *et al*. (2015):

$$K_{\mathrm{pca}} = 1.22 \cdot K_{oa} \cdot f_{\mathrm{ompc}} \cdot \rho_{\mathrm{pc}}/1000, \quad (7)$$

$$K_{\mathrm{pfa}} = 1.22 \cdot K_{oa} \cdot f_{\mathrm{ompf}} \cdot \rho_{\mathrm{pf}}/1000, \quad (8)$$

$$K_{\mathrm{pcpf}} = K_{\mathrm{pca}}/K_{\mathrm{pfa}}, \quad (9)$$

where f_{ompc} and f_{ompf} are the fractions of organic matter, and ρ_{pc} and ρ_{pf} are the densities of the coarse and fine particles, respectively. K_{oa} is the logarithmic octanol–air partition coefficient. The fractions of organic matter were set to 0.08 and 0.22 (Putaud *et al.*, 2004), the densities to 1930 kg/m^3 and 1620 kg/m^3, respectively (Hu *et al.*, 2012). The volume fractions of coarse and fine particles in air (v_{pc}, v_{pf}) were set to $3 \cdot 10^{-12}$ and $9 \cdot 10^{-12}$ respectively, which are representative values for natural background in Europe (Putaud *et al.*, 2004).

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