THE HANDBOOK OF ENVIRONMENTAL CHEMISTRY

16

Volume Editors Ethel Eljarrat · Damià Barceló

Brominated Flame Retardants

Springer

The Handbook of Environmental Chemistry

Founded by Otto Hutzinger

Volume 16

The Handbook of Environmental Chemistry

Recently Published and Forthcoming Volumes

Brominated Flame Retardants
Volume Editors: E. Eljarrat and D. Barceló
Vol. 16, 2011

Effect-Directed Analysis of Complex Environmental Contamination
Volume Editor: W. Brack
Vol. 15, 2011

Waste Water Treatment and Reuse in the Mediterranean Region
Volume Editors: D. Barceló and M. Petrovic
Vol. 14, 2011

The Ebro River Basin
Volume Editors: D. Barceló and M. Petrovic
Vol. 13, 2011

Polymers – Opportunities and Risks II: Sustainability, Product Design and Processing
Volume Editors: P. Eyerer, M. Weller, and C. Hübner
Vol. 12, 2010

Polymers – Opportunities and Risks I: General and Environmental Aspects
Volume Editor: P. Eyerer
Vol. 11, 2010

Chlorinated Paraffins
Volume Editor: J. de Boer
Vol. 10, 2010

Biodegradation of Azo Dyes
Volume Editor: H. Atacag Erkurt
Vol. 9, 2010

Water Scarcity in the Mediterranean: Perspectives Under Global Change
Volume Editors: S. Sabater and D. Barceló
Vol. 8, 2010

The Aral Sea Environment
Volume Editors: A.G. Kostianoy and A.N. Kosarev
Vol. 7, 2010

Alpine Waters
Volume Editor: U. Bundi
Vol. 6, 2010

Transformation Products of Synthetic Chemicals in the Environment
Volume Editor: A.B.A. Boxall
Vol. 2/P, 2009

Contaminated Sediments
Volume Editors: T.A. Kassim and D. Barceló
Vol. 5/T, 2009

Biosensors for the Environmental Monitoring of Aquatic Systems
Bioanalytical and Chemical Methods for Endocrine Disruptors
Volume Editors: D. Barceló and P.-D. Hansen
Vol. 5/J, 2009

Environmental Consequences of War and Aftermath
Volume Editors: T.A. Kassim and D. Barceló
Vol. 3/U, 2009

The Black Sea Environment
Volume Editors: A. Kostianoy and A. Kosarev
Vol. 5/Q, 2008

Emerging Contaminants from Industrial and Municipal Waste
Removal Technologies
Volume Editors: D. Barceló and M. Petrovic
Vol. 5/S/2, 2008

Fuel Oxygenates
Volume Editor: D. Barceló
Vol. 5/R, 2007

Brominated Flame Retardants

Volume Editors: Ethel Eljarrat · Damià Barceló

With contributions by

M. Alaee · D. Barceló · L. Birnbaum · J. de Boer · A. Covaci · A.C. Dirtu · A.A. Domínguez · E. Eljarrat · M.L. Feo · P. Guerra · L. Hearn · D. Herzke · A. Kierkegaard · R.J. Law · P. Lepom · J.F. Mueller · N. Ricklund · L. Roosens · U. Sellström · A. Sjödin · L.-M.L. Toms · S. Voorspoels · D.S. Wikoff · C.A. de Wit

Springer

Editors
Dr. Ethel Eljarrat
Department of Environmental Chemistry
IDAEA-CSIC
c/Jordi Girona 18–26
08034 Barcelona, Spain
eeeqam@cid.csic.es

Prof. Dr. Damià Barceló
Department of Environmental Chemistry
IDAEA-CSIC
c/Jordi Girona 18–26
08034 Barcelona, Spain
and
Catalan Institute for Water Research (ICRA)
H20 Building
Scientific and Technological Park of the
University of Girona
Emili Grahit, 101
17003 Girona, Spain
dbcqam@cid.csic.es

The Handbook of Environmental Chemistry
ISSN 1867-979X e-ISSN 1616-864X
ISBN 978-3-642-19268-5 e-ISBN 978-3-642-19269-2
DOI 10.1007/978-3-642-19269-2
Springer Heidelberg Dordrecht London New York

Library of Congress Control Number: 2011926526

Cover design: SPi Publisher Services

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

The Handbook of Environmental Chemistry Also Available Electronically

The Handbook of Environmental Chemistry is included in Springer's eBook package *Earth and Environmental Science*. If a library does not opt for the whole package, the book series may be bought on a subscription basis.

For all customers who have a standing order to the print version of *The Handbook of Environmental Chemistry,* we offer free access to the electronic volumes of the Series published in the current year via SpringerLink. If you do not have access, you can still view the table of contents of each volume and the abstract of each article on SpringerLink (www.springerlink.com/content/110354/).

You will find information about the

– Editorial Board
– Aims and Scope
– Instructions for Authors
– Sample Contribution

at springer.com (www.springer.com/series/698).

All figures submitted in color are published in full color in the electronic version on SpringerLink.

Aims and Scope

Since 1980, *The Handbook of Environmental Chemistry* has provided sound and solid knowledge about environmental topics from a chemical perspective. Presenting a wide spectrum of viewpoints and approaches, the series now covers topics such as local and global changes of natural environment and climate; anthropogenic impact on the environment; water, air and soil pollution; remediation and waste characterization; environmental contaminants; biogeochemistry; geoecology; chemical reactions and processes; chemical and biological transformations as well as physical transport of chemicals in the environment; or environmental modeling. A particular focus of the series lies on methodological advances in environmental analytical chemistry.

Series Preface

With remarkable vision, Prof. Otto Hutzinger initiated *The Handbook of Environmental Chemistry* in 1980 and became the founding Editor-in-Chief. At that time, environmental chemistry was an emerging field, aiming at a complete description of the Earth's environment, encompassing the physical, chemical, biological, and geological transformations of chemical substances occurring on a local as well as a global scale. Environmental chemistry was intended to provide an account of the impact of man's activities on the natural environment by describing observed changes.

While a considerable amount of knowledge has been accumulated over the last three decades, as reflected in the more than 70 volumes of *The Handbook of Environmental Chemistry,* there are still many scientific and policy challenges ahead due to the complexity and interdisciplinary nature of the field. The series will therefore continue to provide compilations of current knowledge. Contributions are written by leading experts with practical experience in their fields. *The Handbook of Environmental Chemistry* grows with the increases in our scientific understanding, and provides a valuable source not only for scientists but also for environmental managers and decision-makers. Today, the series covers a broad range of environmental topics from a chemical perspective, including methodological advances in environmental analytical chemistry.

In recent years, there has been a growing tendency to include subject matter of societal relevance in the broad view of environmental chemistry. Topics include life cycle analysis, environmental management, sustainable development, and socio-economic, legal and even political problems, among others. While these topics are of great importance for the development and acceptance of *The Handbook of Environmental Chemistry,* the publisher and Editors-in-Chief have decided to keep the handbook essentially a source of information on "hard sciences" with a particular emphasis on chemistry, but also covering biology, geology, hydrology and engineering as applied to environmental sciences.

The volumes of the series are written at an advanced level, addressing the needs of both researchers and graduate students, as well as of people outside the field of "pure" chemistry, including those in industry, business, government, research establishments, and public interest groups. It would be very satisfying to see these volumes used as a basis for graduate courses in environmental chemistry. With its high standards of scientific quality and clarity, *The Handbook of*

Environmental Chemistry provides a solid basis from which scientists can share their knowledge on the different aspects of environmental problems, presenting a wide spectrum of viewpoints and approaches.

The Handbook of Environmental Chemistry is available both in print and online via www.springerlink.com/content/110354/. Articles are published online as soon as they have been approved for publication. Authors, Volume Editors and Editors-in-Chief are rewarded by the broad acceptance of *The Handbook of Environmental Chemistry* by the scientific community, from whom suggestions for new topics to the Editors-in-Chief are always very welcome.

Damià Barceló
Andrey G. Kostianoy
Editors-in-Chief

Volume Preface

The book on *Brominated Flame Retardants* (BFRs) is based on the scientific developments and results achieved along more than 40 years of research. The interest on BFRs started in 1970s as a result of Michigan incident with polybrominated biphenyls (PBBs). At the same time, and after the discovery by Anderson and Blomqvist of high levels of polybrominated diphenyl ethers (PBDEs) in biota from a Swedish river, a great number of scientists started their work on PBDEs. This research reached its peak when Norén and Meironyté reported that PBDE levels doubled every five years in human breast milk. After that, in the middle of 2000s, it became evident that the knowledge on BFRs had moved beyond PBDEs. Thus, other BFRs such as hexabromocyclododecane (HBCD), tetrabromobisphenol A (TBBPA), and decabromodiphenyl ethane also became the subject of scientists' interest. And today, a large number of emerging BFRs are included in different scientific works.

This book aims to review and compile the main developments and knowledge acquired over many years of study. The book is structured into nine different chapters, covering the physicochemical properties and uses of the different commercial BFRs, the advanced chemical analytical methods, the occurrence in environment and biota, the degradation studies, the toxicological effects, and the human exposure. Finally, the last chapter concerns the development of knowledge of the different emerging BFRs, being the starting point to be taken in mind for the future studies in the field of BFRs.

We hope this book will be of interest to a broad audience of scientific researchers such as analytical and environmental chemists, and specially those who are already working in or planning to enter the field of BFRs. Moreover, we hope that the information included in this book can also be useful to expand the initial list of 12 persistent organic pollutants (POPs) accorded during the Stockholm Convention. In fact, some of the BFR families are part of the list of potential candidates.

Finally, we would like to thank all the contributing authors of this book for their time and effort in preparing this comprehensive compilation of research papers.

Barcelona, December 2010

E. Eljarrat
D. Barceló

Contents

Introduction to Brominated Flame Retardants: Commercially Products, Applications, and Physicochemical Properties

P. Guerra, M. Alaee, E. Eljarrat, and D. Barceló

Abstract In order to meet fire safety regulations, flame retardants (FRs) are applied to combustible materials such as polymers, plastics, wood, paper, and textiles. Approximately, 25% of all FRs contain bromine as the active ingredient. More than 80 different aliphatic, cyclo-aliphatic, aromatic, and polymeric compounds are used as brominated flame retardants (BFRs). BFRs, such as polibrominated biphenyls (PBBs), polybrominated diphenyl ethers (PBDEs), hexabromocyclododecane (HBCD), and tetrabromobisphenol A (TBBPA), have been used in different consumer products in large quantities and consequently they were detected in the environment. In this chapter, an overview of the production, application, and properties of most commonly used BFRs is presented.

Keywords Brominated flame retardants, Hexabromocyclododecane, Polybrominated biphenyls, Polybrominated diphenyl ethers, Production, Tetrabromobisphenol A

P. Guerra and E. Eljarrat (✉)
Department of Environmental Chemistry, IDAEA, CSIC, Jordi Girona 18-26, Barcelona 08034, Spain
e-mail: eeeqam@cid.csic.es

M. Alaee
Aquatic Ecosystem Protection Research Division, Water Science and Technology Directorate, Science and Technology Branch, Environment Canada, 867 Lakeshore Road, P.O. Box 5050, Burlington, ON, Canada L7R 4A6

D. Barceló
Department of Environmental Chemistry, IDAEA, CSIC, Jordi Girona 18-26, Barcelona 08034, Spain
and
Catalan Institute for Water Research (ICRA), Parc Científic i Tecnològic de la Universitat de Girona, Pic de Peguera 15, 17003 Girona, Spain

E. Eljarrat and D. Barceló (eds.), *Brominated Flame Retardants*,
Hdb Env Chem (2011) 16: 1–18, DOI 10.1007/698_2010_93,

Contents

Abbreviations and Symbols

ABS	Acrylonitryle butadiene styrene
ATE	2,4,6-Tribromophenyl allyl ether
BEP	Brominated epoxy oligomers
BFR	Brominated flame retardant
BPS	Brominated polystyrene
BSEF	Bromine Science and Environmental Forum
BTBPE	1,2-Bis(2,4,6-tribromophenoxy)ethane
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act
DBDPE	Decabromodiphenyl ethane
DPTE	2,3-Dibromopropyl-2,4,6-tribromophenyl ether
EBFRIP	European BFR Industry Panel
EPA	Environmental Protection Agency
EPCRA	Emergency Planning and Community Right-to-Know
EPS	Polystyrene foams
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FR	Flame retardant
HBBz	Hexabromobenzene
HBCD	Hexabromocyclododecane
HIPS	High impact polystyrene
K_{OW}	Octanol–water partition coefficient
OSHA	Occupational Safety and Health Administration
PBB	Polybrominated biphenyl
PBDE	Polybrominated diphenyl ether
PBEB	Pentabromoethylbenzene
PBT	Pentabromotuelene
POP	Persistent organic pollutant
PVC	Polyvinyl chloride
REACH	Registration, Evaluation, Authorization and Registration of Chemicals

TBBPA	Tetrabromobisphenol-A
TBBPA-DAE	TBBPA diallylether
TBECH	1,2-Dibromo-4-(1,2-dibromoethyl)cyclohexane
TBP	2,4,6-Tribromophenol
TBPA	Tetrabromophthalic anhydride
USA	United States of America
XPS	Extructed polystyrene foams

1 Introduction

Fire is a major source of damage to properties, loss of life, and public expenses. For example, in the United States, in 2007 over 1.5 million fires are reported, which result in 17,675 injuries, 3,430 deaths, and direct losses of over $14 billion [1]. The need to protect materials against fire has been a scientific undertaking for a very long time. In fact, Egyptians used alum to reduce the flammability of wood (450 BC), and about 200 BC Romans used a mixture of alum and vinegar to reduce the combustibility of wood [2]. Today in order to meet fire safety regulations such as California TB 116 and 117, flame retardants (FRs) are applied to combustible materials such as plastics, woods, paper, and textiles. FRs are chemicals that are added to or reacted with combustible materials to increase their fire resistance [3]. Recent advances in technology have resulted in an increase in use of synthetic polymers in household and office products such as computers and electronic equipment, which has drastically contributed to potential fire hazard in our commercial and residential buildings; consequently, over the past decades, the use of FRs has drastically increased. To protect ourselves from fire damage, various types of FRs have been developed based on diverse inorganic compounds such as aluminum and magnesium hydroxides and organic derivatives of nitrogen, phosphorous, chlorine, and bromine as active ingredients.

It should be noted that flame or fire retardant is not the same as flame or fire proof; in the first case, the starting material is flammable, and the application of FR will slowdown the burning process, hence increasing the possibility of escaping from a burning room/house. However, flame or fire proof material does not catch fire at all [4]. Currently, the market demand for FRs is estimated to be valued about US$2.3 billion, corresponding to be in excess of 1,200,000 metric tons of which about 36% of the value is based on brominated flame retardants (BFRs) [5]. To understand the mode of actions of FRs, it is essential to become familiar with the combustion process. Combustion is a gas phase reaction involving a fuel source and oxygen. There are four steps involved in the combustion process, which are preheating, volatilization/decomposition, combustion, and propagation (Fig. 1) [6]. Thus, a FR should inhibit or suppress the combustion in a particular stage of this process [7]. Depending on their mode of action, FRs can act chemically and/or physically in the

solid, liquid, or gas phase. It is important to note that the flammability of a material is not an intrinsic property but depends on the fire conditions. Thus, changing the material composition, for example with the addition of a FR, will also change its reaction to fire behavior [4].

For example, free radicals (highly oxidizing agents) are produced during the combustion process; these are essential elements for the flame to propagate. Halogens are very effective in trapping free radicals, hence removing the capability of the flame to propagate. All four halogens are very effective in trapping free radicals, with trapping efficiency of I > Br > Cl > F [4]. Organohalogen compounds are good materials for storage and delivery of halogens in the polymers. However, not all of the organohalogen compounds are suitable FRs. Fluorinated compounds are very stable and decomposed at much higher temperature than the polymers burn. On the other hand, iodinated compounds are not very stable and decompose at slightly elevated temperatures. Consequently, only organochlorine and organobromine compounds are suitable as FRs. With higher trapping efficiency and lower decomposing temperature, organobromine compounds have became more popular FR than their organochlorine counterparts [5].

2 Bromine Industry and Applications

Bromine is a major ingredient in the production of BFRs. Therefore, it is important to dedicate a few lines to the industrial production and applications of bromine. Bromine is used in the production of BFRs, clear brines for the oil drilling industry,

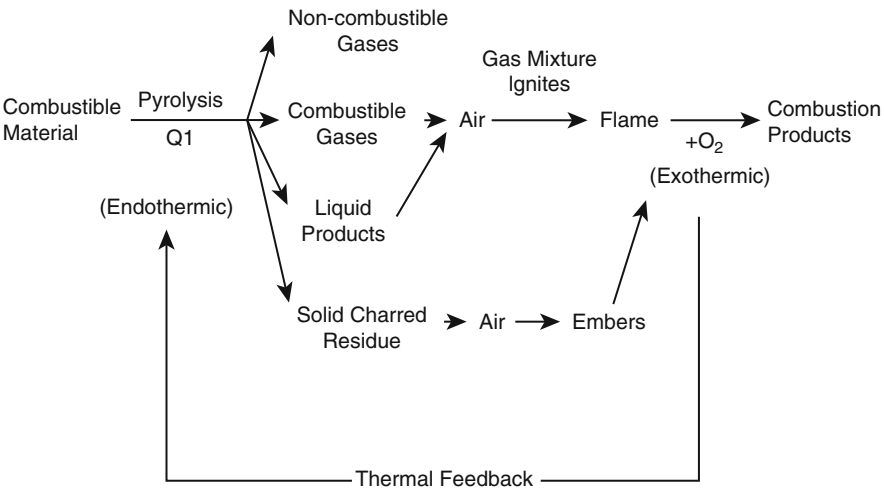


Fig. 1 Combustion process steps. Reproduced from [6]

soil and space fumigation products, and bromine-based biocides for water treatment. However, the main use of bromine is in the manufacturing of BFRs. For example, in the United States, between 40% and 50% of demand for bromine is for BFRs [8].

Bromine is a reactive element, consequently it is mostly found in the form of inorganic salts of the alkalis and alkaline earth metals mainly in seawater, saline lakes, brine, and earth crust. Currently, there are a limited number of brines around the world with high enough concentrations of bromine to make this process commercially viable. Arkansas brine wells with 2–5 g/L bromide are the main source of bromine in the United States [8]. Dead Sea with a concentration up to 12 g/L is the world's largest source of bromine [5].

The production of bromine begins with the oxidation of bromide with chlorine followed by an absorption and purification process. The global production of bromine in 2007 was 556,000 metric tons [8]. As shown in Fig. 2, United States was the largest producer of bromine followed by Israel. The global production of bromine has been fairly stable over the past decade. The emergence of Jordan as the third largest bromine producer is interesting; however, it was not unexpected based on the vast amounts of bromide present in the Dead Sea. China also has rich bromide sources, particularly in Laizhou Bay located in Shangong province [9]. In 2008, there was an increase in the price of bromine and brominated compounds, reflecting the expanding markets for bromine and major increases in energy costs, raw materials, regulatory compliance, and transportation [10]. In Table 1, the estimated world refinery production between 1997 and 2007 was summarized. Growth was expected to increase in demand for BFRs as the result of the Consumer Product Safety Commission approves fire safety standards for upholstered furniture in the United States and if more stringent flammability standards are voluntarily adopted for televisions in Europe. An increase in the global demand for bromine is expected as the use of BFRs in developing countries begin to use more modern materials and develop more stringent flammability standards [8].

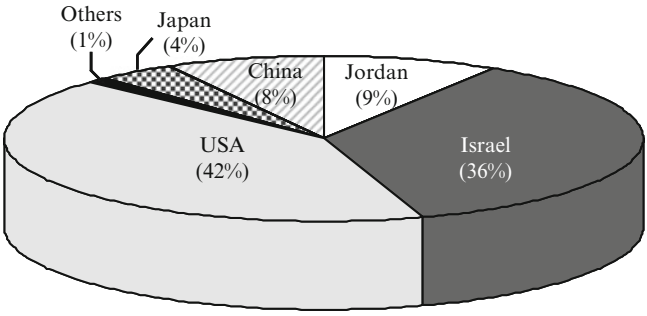


Fig. 2 Global production of bromine. Adapted from [8]

Table 1 Estimated world refinery production of bromine (metric tons). Data from [8, 10]

Country	1997	1999	2001	2003	2005	2007
Azerbaijan	2,000	2,000	2,000	2,000	2,000	2,000
China	50,100	42,000	40,000	75,000	105,000	130,000
France	1,974	1,950	2,000	100	na	na
Germany	700	500	500	388	274	1,612
India	1,500	1,500	1,500	1,500	1,500	1,500
Israel	180,000	181,000	206,000	176,000	207,048	159,400
Italy	300	300	300	na	na	na
Japan	20,000	20,000	20,000	20,000	20,000	20,000
Jordan	na	na	na	na	66,000	69,000
Spain	100	100	100	100	100	100
Turkmenistan	130	150	150	150	150	150
Ukraine	3,000	3,000	3,000	3,000	3,000	3,000
United Kingdom	35,600	55,000	50,000	na	na	na
United States	247,000	239,000	212,000	216,000	226,000	na

na not available

Due to its reactivity and toxicity, transport of bromine is subject to the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) regulating the transport of hazardous goods. Hence the manufacturing of organobromine compounds usually takes place in the vicinity of production sites. As a result, there are limited sites available for manufacturing of organobromine compounds in general and in particular for BFRs. In the Unites States, bromine is a Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) registered pesticide, and the Environmental Protection Agency (EPA) requires labels indicating toxicity to fish and aquatic organisms. The Occupational Safety and Health Administration (OSHA) lists bromine as an air contaminant, and the Department of Transportation identifies bromine as an inhalation hazard. Use of bromine is regulated under portions of the USA Clean Air act governing toxic substances. The Federal Emergency Planning and Community Right-to-Know Act (EPCRA) of 1986 includes bromine under its Toxics Release Inventory, which requires certain manufacturing companies to report environmental releases and transfers [11]. Bromine Science and Environmental Forum (BSEF), a manufacturer based advocacy group based in Brussels, lists four main manufactures, Albemarle Corporation, Chemtura, ICL Industrial Products, and Tosoh Corporation as the main global producers of BFRs. Even though their headquarters are located in United States, the first two manufacture BFRs in Israel and Japan, respectively, and their operations extend over several countries in North America, Europe, and Asia. Since there is limited number of manufactures producing the majority of BFRs, information of the production quantities is not openly accessible. Only on limited occasions, BSEF published estimated market demand on tetrabromobisphenol A (TBBPA), polibrominated diphenyl ethers (PBDE), and hexabromocyclododecane (HBCD), which was produced by all of their members.

3 Brominated Flame Retardants

Approximately, 25% of all FRs (volume basis) contain bromine [12]. Since bromine is the main ingredient of BFRs, there is no particular restriction on the structure of the backbone. Consequently, more than 80 different aliphatic, cyclo-aliphatic, aromatic, and polymeric compounds have been registered as brominated FRs [2]. However, for any organobromine compound to be used as BFR, it should be compatible with the polymer that they are incorporated into including not to alter their appearance and physical properties and to be stable during the life cycle of the product [4]. These two requirements are of major concern in opposite to environmental concerns [3, 13–15]. Polymers in general are petroleum-derived material that they are hydrophobic, and hence they are only compatible with hydrophobic compounds. Hydrophobic compounds have a tendency to bioaccumulate in biota and biomagnify in the food web [14, 15]. Similarly, for an organobromine compound to be used as a BFR, it should be stable for many years. Unfortunately, this property results in compounds that persist in the environment many more years during and after the use of products [3, 15–18].

BFRs are divided into three subgroups: additive, reactive, and polymeric depending on their mode of incorporation into the polymers [5]. Additive BFRs, such as PBDEs and HBCD, are just mixed together with the other components of the polymers. Additive BFRs can easily leach out of the polymers and released into the environment [2, 15, 19, 20]. On the other hand, reactive BFRs are a group of compounds, such as TBBPA, that are chemically bonded to the plastics. Reactive BFRs are more stable and are not easily released into the environment [21]. Finally, in polymeric BFRs such as brominated polystyrene (BPS), bromine atoms are incorporated in the backbone of the polymer resulting into a more stable chemical structure with very high molecular weight resulting in less bioavailability.

The additive BFRs have been detected most frequently in environmental matrices due to their potential to leak from treated consumer products. Reactive BFRs form covalent bonds with the polymer. Provided they are properly bonded, should only be a risk during production and transport. However, reactive BFRs should not be neglected, and in fact, TBBPA has been identified in various compartments [21] at significantly lower concentrations than additive BFRs such as PBDEs.

3.1 Additive BFRs

A revision of information for several additive BFRs is presented in this section. It is important to note that some of them are now in use, banned, or under assessment. The most investigated additive BFRs are polybrominated biphenyls (PBBs), PBDEs, and HBCD (Fig. 3). The main physicochemical properties of these compounds are summarized in Table 2. However, additional additive BFRs are available in the market such as bis(2-ethylhexyl)tetrabromophthalate, tris(tribromophenyl)

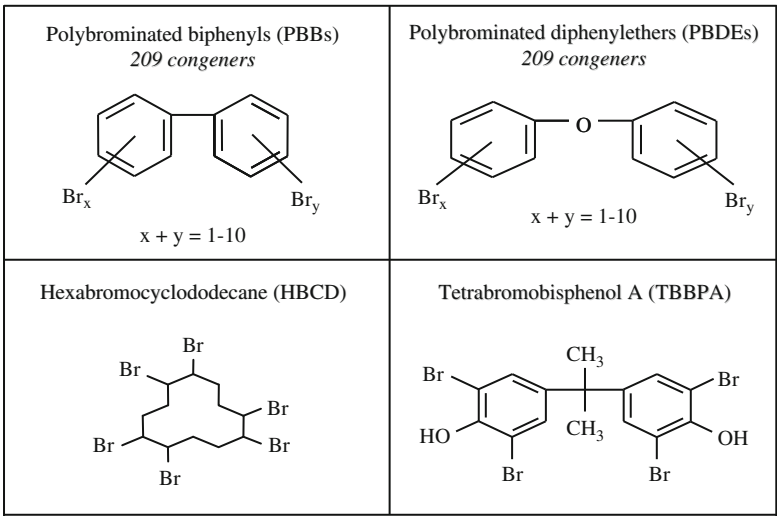


Fig. 3 Chemical structures of the main BFRs

Table 2 Physicochemical properties of PBBs, PBDEs, and HBCD

Chemical	Acronym	Formula	Molecular mass	Melting point (°C)	Decomposition point (°C)	Solubility H_2O (μg/L; 25°C)	Log K_{ow}	References
PBBs	hexa-BB	$C_{12}H_4Br$	627.4	124–248	300–400	11	7.20	[17, 22]
	octa-BB	$C_{12}H_2Br_8$	785.2	200–250	435	30–40	5.53	
	nona-BB	$C_{12}HBr_9$	864.1	220–290	435	Insoluble		
	deca-BB	$C_{12}Br_{10}$	943.0	380–386	395 > 400	<30	8.58	
PBDEs	tetra-BDE	$C_{12}H_6Br_4O$	485.8	82.3	–	14.7	5.87–6.16	[16, 17]
	penta-BDE	$C_{12}H_5Br_5O$	564.7	81.0	>200	4.4	6.64–6.97	
	octa-BDE	$C_{12}H_2Br_8O$	801.5	200	–	–	8.35–8.90	
	deca-BDE	$C_{12}Br_{10}O$	959.2	290–306	>320	20–30	9.97	
HBCD	α-HBCD	$C_{12}H_{18}Br_6$	641.7	179–181	>190	48.8	5.07	[23, 24]
	β-HBCD			170–172		14.7	5.12	
	γ-HBCD			207–209		2.1	5.47	
	Industrial mixture			175–195		6.56	5.63	

triazine, tetrabromocyclooctane, and tetradecabromodiphenoxybenzene (Table 3). Some of these compounds are presented in more detail in Chapter 9 [25].

3.1.1 Polybrominated Biphenyls

The industrial production of PBBs is based on a Fridel–Craft reaction where biphenyl is reacted with bromine in presence of an organic solvent, with aluminum chloride,

Table 3 Chemicals used as additive BFRs

Chemical	CAS number	Br (%)	MP (°C)	Use
Bis(2-ethylhexyl)tetrabromophthalate	26040-51-7	45	Liquid	PVC, neoprene, plasticizer
Tris-dibromopropylisocyanurate	52431-90-9	65.8	–	Polylefin, PVC, polyurethane, ABS, synthetic rubber and fiber
Tris(tribromophenyl)triazine	25713-60-4	67	–	ABS, HIPS
Tetrabromobisphenol-A, bis(2,3-dibromopropylether)	21850-44-2	68	95	Polyolefin, styrene
1,2-Bis(2,4,6-tribromophenoxy)ethane	37853-59-1	68	224	HIPS, ABS, textiles
Ethylenebistetrabromophthalimide	32588-76-4	68	445	HIPS, polyethylene terephthalate
Tetrabromobisphenol S-bis (2,3-dibromo-propylether)	42757-55-1	70.8	52-55	Polypropylene fiber
Octabromo-1-phenyl1, 3,3-trimethylindan	155613-93-7	73	240-255	Most plastics, thermoplastics
Tetrabromocyclooctane	3194-57-8 31454-48-5	74.7	73	EPS, XPS
Dibromoethyldibromocyclohexane	3322-93-8	74.7	72	Polystyrene, polyurethane
Tetradecabromodiphenoxybenzene	58965-66-5	82	370	Polyamides, polyester, wire and cable
Ethane-1,2-bis(pentabromophenyl)	84852-53-9	82.3	350	Styrene

ABS acrylonitrile butadiene styrene; *EPS* expanded polystyrene; *HIPS* high impact polystyrene; *PVC* polyvinyl chloride; *XPS* extructed polystyrene foam

aluminum bromide, or iron as a catalyst [22]. PBBs are formed by substitution of hydrogen with bromine in biphenyl molecule, and thus, PBBs have a large number of possible congeners, depending on the number and position of the bromine atoms on the two phenyl rings. Theoretically, 209 congeners are possible [17].

PBBs were manufactured in the early 1970s for commercial use and consist mainly of hexa-, octa-, nona-, and decabromobiphenyl congeners [22]. PBBs are solids with a low vapor pressure and its volatility has a wide range. PBBs are almost insoluble in water, and the solubility decreases with increasing bromination. Most PBBs have a log $K_{ow} > 7$ and are therefore regarded as lipophilic compounds.

PBBs came to public attention in 1974, when it was discovered that about 1,000 pounds was accidentally substituted by magnesium oxide, a additive in cattle feed, in Michigan in 1973 [26]. After this, the sole USA manufacturer of hexabromobiphenyl ceased production in 1974. Two other companies continued their production of octa- and deca-BB until 1977 [22]. In Europe, PBBs are restricted by the fourth amendment to the marketing and use Directive 76/769/EEC adopted in 1984, and they cannot be used in textiles, intended to come into contact with the skin. Finally, the industry voluntarily ceased production of PBBs in 2000 [27].

3.1.2 Polybrominated Diphenyl Ethers

Diphenyl ether contains ten hydrogen atoms, any of which can be exchanged with bromine, resulting in 209 possible BDE congeners. The hydrogen positions of

Table 4 Total global market demand (values in metric tons) for PBDE mixtures flame retardants. Data from [29]

	1999	2001	2002	2003
Penta-PBDE	8,500	7,500	–	–
Octa-PBDE	3,825	3,790	–	–
Deca-PBDE	54,800	56,150	65,677	56,418

PBDEs are similar to that of PCBs and PBBs; hence the nomenclature proposed by Ballschmiter et al. [28] for PCBs is also used for identification of BDE congeners. Technical PBDEs are commercially produced by brominating diphenyl ether under catalytic conditions resulting in mixtures of PBDEs with varying degrees of bromination [5]. The reaction conditions for the bromination of diphenyl ether by various manufacturers are not disclosed. The three main commercial products were Penta-BDE, Octa-BDE, and Deca-BDE formulations. A typical Penta-BDE formulation is composed of 24–37% tetra-BDEs, 50–60% penta-BDE, and 4–8% hexa-BDE. In general, Octa-BDE formulation consists in a mix of 10–12% hexa-BDE, 44% hepta-BDE, 31–35% octa-BDE, 10–11%, nona-BDE, and <1% deca-BDE; and a characteristic deca-PBDE formulation is >97% deca-BDE (BDE-209) with the rest mainly nona-BDE with a very small amount of octa-BDE [3]. The global market demand for these three PBDE commercial products is summarized in Table 4.

Recently, PBDEs have been studied extensively. Even though the occurrence of these compounds was reported extensively in late 1970s (put references here), they were not noted extensively by the scientific community until 1998 when Noren et al. [30, 31] astound the scientific community by showing that PBDEs were on the rise in human breast milk, while the levels of other persistent organic pollutants (POPs) were dropping in the same samples.

In 2001, EU announces a ban on Penta- and Octa-PBDE formulations by 2003. In 2002, the industry voluntarily banned the production of Penta and Octa formulations as of 2004. Additionally, since July 1, 2006, Penta and Octa-BDE are banned in electrical and electronic applications according to the 2002/95/EC directive. However, the use and environmental effects of Deca-formulation are heavily contested, including a recent judgment by the European Court of Justice, which overturned the exemption of Deca-BDE granted by the European Commission [32]. In the United States, Penta- and Octa-BDE production has been phased out [33], and BSEF member companies have decided to voluntarily phase out of Deca-PBDE formulation by the end of 2013 [34].

3.1.3 Hexabromocyclododecane

HBCD is the most widely used aliphatic cyclic additive BFR with a total global market value between 15,900 and 21,951 metric tons in 1999 and 2003, respectively [29]. HBCD is mainly used in expanded polystyrene (EPS) and extructed polystyrene (XPS), which are commonly used as construction materials, such as

thermal insulation or molded foam packing, and textiles, such as household furniture and appliances [35]. The European market demand for HBCD in 2001 was 9,500 metric tons, which accounts for 57% of the global market demand [29]. In 1999 and 2001, the market demand for HBCD in Europe exceeded the market demand of PBDEs, making HBCD the second largest BFR used in Europe.

Technical 1, 2, 5, 6, 9, 10-HBCD is produced by addition of bromine to *cis–trans–trans*-1,5,9-cyclododecatriene. This process leads theoretically to a mixture of 16 stereoisomers (six pairs of enantiomers and four mesoforms), but commercial products are usually a mixture of three diastereoisomers α-, β-, and γ-isomer [23]. Normally, the γ-isomer is the most dominant in the commercial mixtures (ranging between 75% and 89%), followed by α- and then β-isomer (10–13% and 1–12%, respectively). The physical–chemical properties of HBCD are similar to some PBDEs and other POPs. HBCDs are not covalently bonded to polymers leading to the risk of migration out of the product during use and disposal [23]. Consequently, there is a high potential for this material to absorb to soil and sediments.

The dissimilarities in the structure of α-, β-, and γ-isomer raise differences in polarity, dipole moment, and solubility in water. For example, the solubility of α-, β-, and γ-HBCD in water was 48.8, 14.7, and 2.1 μg/L, respectively. Therefore, these different properties may explain the differences observed in their environmental behavior [36]. Covaci et al. [37] and Morris et al. [38] found that in sediments, the distribution of HBCD isomers was the same of commercial mixture: γ-HBCD is the most abundant isomer. However, in biota α-isomer predominates over the γ-isomer and little or no presence of β-isomer.

α-, β-, and γ-HBCD diastereoisomers are chiral; thus HBCD have three pairs of enantiomers (+) α, (−) α, (+) β, (−) β, (+) γ, and (−) γ. The enantiomers have identical physicochemical properties and abiotic degradation rates but may have different biological and toxicological properties and different biotransformation rates. These transformations may result in nonracemic mixtures of the enantiomers that were industrially synthesized as racemates [36, 39, 40]. The rates of metabolization process of the enantiomers of chiral environmental pollutants may be significantly different.

Few initiatives are underway to assess the need to regulate the use of HBCD [27]. In the USA, EPA is running a review of HBCD that should be ready by the end of 2012. The Environment Canada has launched a risk assessment that should be finalized in 2010 [41]. HBCD is considered as a high volume substance under an EU regulation framework for Registration, Evaluation, Authorization and Registration of Chemicals (REACH) [27].

3.2 Reactive BFRs

Reactive FRs are incorporated into the polymer by either becoming a part or by grafting onto the polymer backbone [5]. It is important to note that the use of

reactive FR is complex due to the enormous effect can exert on the final properties of the polymer, and not all polymers contain reactive sites.

3.2.1 Tetrabromobisphenol A

Tetrabromobisphenol A ($C_{15}H_{12}Br_4O_2$) (Fig. 3) is a reactive BFR with a global market demand from 120,000 to 151,000 tons between 1999 and 2003, which makes it the highest volume BFR on the market. More recently, the European BFR Industry Panel (EBFRIP) reported the size of the global TBBPA market to be 170,000 tons in 2004 [42]. They also stated that the market is increasing and that a shift in consumption volume can be observed in Asia. TBBPA is currently produced in USA, Israel, and Japan [21]. However, it could be imported into any country as a primary product, partially finished products (i.e., polymers and epoxy resins) or in finished (i.e., electronic equipments).

The industrial production process involves the bromination of bisphenol-A with bromine in presence of a solvent, such as methanol or a halocarbon, 50% hydrobromic acid or aqueous alkyl monoethers. Due to the nature of the process and the by-products (hydrobromic acid and methyl bromide) that can be formed, the production process is largely conducted in closed systems. TBBPA is mainly used in epoxy resins and acrylonitrile butadiene styrene (ABS) polymers commonly used in electronic and entertainment appliances and equipments such as laminated printed circuit boards, TV, computers, and office automation equipments [44]. TBBPA is employed both as a chemical bound FR (~90%) in the manufacturing of epoxy, phenolic, and polycarbonate resins and as an additive FR [43]. Since the use of Octa-BDE mixture in ABS application is not longer allowed in the EU, alternative additive FRs are being search. As additive FR, TBBPA does not react chemically with the other components of the polymer and therefore may leach out of the polymer matrix after incorporation, with important implications for human exposure.

Due to its low solubility in water (0.72 mg/L) and high log K_{ow} (4.5) [44], TBBPA is likely to be associated with suspended solids once released in the water column and ultimately buried in sediment [45, 46]. Although TBBPA has been found in abiotic matrices as air, soil, sediment, and sewage sludge [45, 47–50], it is not frequently analyzed in environmental laboratories. This may be due to its lower bioaccumulation potential, resulting in concentrations lower than PBDEs and HBCD in the environment.

Although TBBPA is produced in much higher volumes than other BFRs, reported concentrations for TBBPA in environmental matrices are much lower than other BFRs such as PBDEs and HBCDs. This is reflected in much less stringent regulations for this BFR. However, there is some concern in finalized draft Environment Risk assessment Report for TBBPA for water and terrestrial compartments [27]. Currently, there is no legislation that restricts the use of TBBPA in North America; how about Europe and Japan, is there any regulation?

Some other reactive BFRs are listed together with their physicochemical properties in Table 5. Besides, 2,4,6-tribromophenol and tetrabromophthalic anhydride are presented in more detail in [25].

3.3 Polymeric BFRs

Different polymeric BFRs are in use today, and their high molecular weight gives advantages such as low volatility, low bioavailability, low toxicity, easy handling, and resistance to bloom and plate-out. Table 6 showed the main polymeric BFR. BPS (Fig. 4) is an example of polymeric BFR and is prepared by the bromination of polystyrene. BPS has a degree of polymerization close to 1,800 and is mainly used in glass filled engineering thermoplastics like polyamides and thermoplastic polyesters. Its higher molecular weight affords both good comparative tracking index (CTI) performance and good thermal aging properties. On the other hand, as BPS is a polymer with no vapor pressure, it is nonblooming [51]. In Europe and North America, BPS has been used in the replace of Deca-BDE, in order to address environmental issues [4]. This compound is less expensive than the other polymeric FR and has good thermal stability. However, it has lower efficacy as an FR.

Other examples of polymeric BFR are the brominated epoxy oligomers (BEP) (Fig. 4) that are prepared in several ways, in general by the reaction between TBBPA epichlorohydrin, obtaining materials with molecular weights from 1,600 to 60,000 Da with bromine contents ranging from 52% to 54%. The lower

Table 5 Chemicals used as reactive BFRs

Chemical	CAS number	Br (%)	MP (°C)	Use
Diester/ether diol of tetrabromophthalicanhydride	77098-07-8	46	Liquid	Polyurethane foam
Tetrabromobisphenol-A-bis (allyl ether)	25327-89-3	51	119	EPS, polystyrene foam
Dibromostyrene	31780-26-4	59	Liquid	Styrene polymers, engineering plastics
Dibromoneopentylglycol	3296-90-0	61	109	Polyurethane foam
Tribromophenyl allyl ether	26762-91-4 3278-895	64	74–76	EPS, polystyrene foam
Tetrabromophthalic anhydride	632-79-1	68	270	Unsatured polyesters, styrene-butadiene copolymer, textile
Pentabromobenzylacrylate	59447-55-1	71	117	Polycarbonate, thermoplastics, polybutylene terephthalate
2,4,6-Tribromophenol	75-80-9 118-79-6	72	95.5	Phenolics, epoxy
Tribromoneopentyl alcohol	1522-92-5	74	62–67	Polyurethane

EPS expanded polystyrene

Table 6 Other polymeric BFRs information

Chemical	CAS number	Br (%)	MP (°C)	Use
Tetrabromobisphenol-A carbonate oligomer, phenoxy end capped	94334-64-2 28906-13-0	52	210–230	Thermoplastics
Tetrabromobisphenol-A carbonate oligomer, tribromophenoxy end capped	71342-77-3	58	230–260	Thermoplastics
Epoxy oligomers of TBBPA	68928-70-1	52–54	–	ABS, HIPS
Epoxy oligomers of TBBPA end capped with tribromophenol or phenol	139638-58-7 135229-48-0	55–58	–	Polybulylene terephthalate, styrenic copolymers
Poly(dibromostyrene)	148993-99-1	59	140	Polyamides, thermoplastics polyesters
Poly(dibromo/tribromostyrene)	148993-1	64	137–156	Thermoplastics
Brominated anionic polystyrene	88497-56-7	68	162	Polyesters, polyamides
Poly(2,6-dibromophenylene oxide)	69882-11-7	64	225	Thermoplastics
Poly(2,3,4,5,6-pentabromobenzylacrylate)	59447-57-3	71	190–220	Polycarbonate, thermoplastics, polybutylene terephthalate

ABS acrylonitrile butadiene styrene; *HIPS* high impact polystyrene

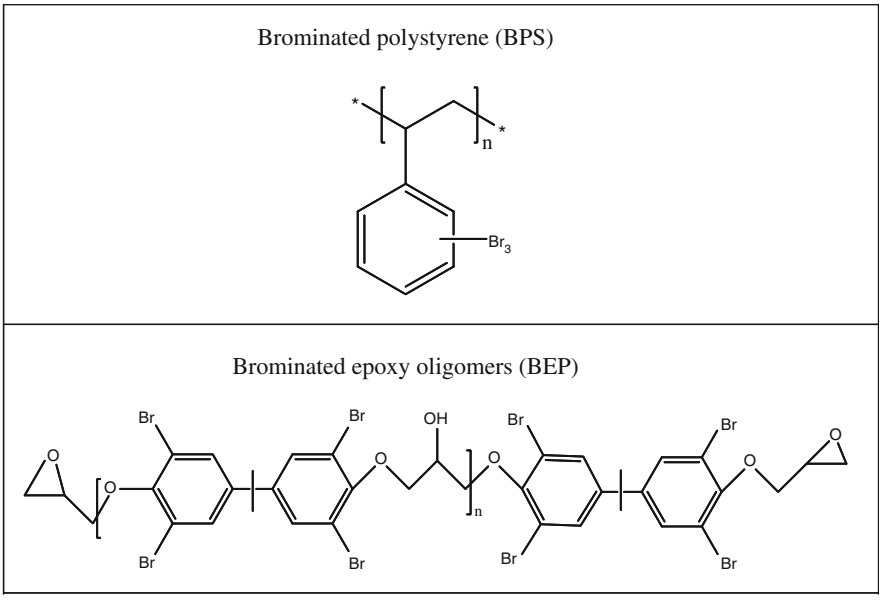


Fig. 4 Chemical structures of some polymeric BFRs

molecular weight products are used primarily in styrenic resins, while the higher molecular weight products are used in engineering thermoplastics [5]. The main properties of these compounds are its high mechanical stability, impact resistance, high thermal stability, and excellent chemical resistance. BEP are widely used in printed circuit boards in order to meet fire safety regulations.

4 Conclusions

It is evident that FRs plays an important role in our daily lives. Unfortunately, some of these compounds have caused adverse effects in the environment. Currently, some BFRs have been banned, others have been voluntarily withdrawn by the manufacturers, and several of them are under review. Over the years, the production of bromine has remained almost constant. The cessation of production of some BFRs results in having to find alternative applications to use the bromine produced. In fact, emerging BFRs has been developed to replace them. Some new additive BFRs are 1,2-Bis(2,4,6-tribromophenoxy)ethane (BTBPE), decabromodiphenyl ethane (DBDPE), hexabromobenzene (HBBz), pentabromoethylbenzene (PBEB), pentabromotoluene (PBT), and 1,2-dibromo-4-(1,2-dibromoethyl)cyclohexane (TBECH). Regarding new reactive BFR, some of them are TBBPA diallylether (TBBPA-DAE), 2,4,6-Tribromophenol (TBP), 2,4,6-Tribromophenyl allyl ether (ATE), 2,3-dibromopropyl-2,4,6-tribromophenyl ether (DPTE), and tetrabromophthalic anhydride (TBPA). Therefore, it is imperative to dedicate adequate resources to the development of effective FRs that do not have any harmful effect to the environment. The BFR industry continues with their innovations introducing new BFRs that are more efficient and environmentally sound. Therefore, it is necessary that the environmental scientists work together with the scientists involved in development of new BFRs ensuring that the new products introduced in the market will provide the required fire protection and to be safe to the environment.

Acknowledgments This research work was founded by the Spanish Ministry of Science and Innovation through the projects CEMAGUA (CGL2007-64551/HID) and Consolider-Ingenio 2010 (CSD2009-00065), by the CSIC through the project Intramural (ref. 200880I096) and by the Fundación BBVA under the BROMACUA project (Evaluación del impacto ambiental de los retardantes de llama bromados en ecosistemas acuáticos de América Latina). Paula Guerra acknowledges her grant from Department d'Innovació, Universitats i Empresa (2008FI_B 00755).

References

1. Karter MJ Jr (2008) Fire loss in the United States 2007. National Fire Protection Association, USA
2. Alaee M, Arias P, Sjodin A, Bergman Ã (2003) Environ Int 29:683

3. WHO (1997) Environmental health criteria 192. Flame retardants: a general introduction. World Health Organization, Geneva
4. Wilkie CA, Morgan AB (2010) Fire retardancy of polymeric materials. CRC, Boca Raton
5. Kirk RE, Othmer DF (2007) Kirk-Othmer encyclopedia of chemical technology. Wiley, New York
6. Troitzsch J (ed) (1990) International plastics flammability handbook: principles, regulations, testings and approval. Hanser, Munich
7. Royal Society of Chemistry (2009) Polymers and fire. Royal Society of Chemistry, London
8. U. S. Geological Survey (2007) Minerals yearbook. Bromine [Advance Release] (2008). US Geological Survey, CA, USA
9. Shandong Haihua Group Bromine Factory (2002) Market survey on bromine and bromides industry in China. CCM International, Dublin
10. U. S. Geological Survey (2009) [Mineral commodity; Bromine]. US Geological Survey, CA, USA
11. Albemarle Corporation. Bromine: Product Stewarship Summary, http://albemarlecorp.org/About_Albemarle/Sustainability/Product_stewardship_and_advocacy/Product_Summaries/Bromine.pdf. Accessed 25 July 2010
12. Andersson PL, Oberg K, Orrn U (2006) Environ Toxicol Chem 25:1275
13. National Research Council (2000) Toxicological risks of selected flame-retardant chemicals. National Academies Press, Washington DC
14. Alaee M, Wenning RJ (2002) Chemosphere 46:579
15. Darnerud PO (2003) Environ Int 29:841
16. WHO (1994) Environmental health criteria 152. Polybrominated biphenyls. World Health Organization, Geneva
17. de Boer J, de Boer K, Boon JP (2000) Polybrominated biphenyls and diphenylethers. Springer, Berlin
18. Watanabe I, Sakai SI (2003) Environ Int 29:665
19. Covaci A, Voorspoels S, Ramos L, Neels H, Blust R (2007) J Chromatogr A 1153:145
20. Law RJ, Herzke D, Harrad S, Morris S, Bersuder P, Allchin CR (2008) Chemosphere 73:223
21. Covaci A, Voorspoels S, Abdallah MAE, Geens T, Harrad S, Law RJ (2009) J Chromatogr A 1216:346
22. WHO (1994) Environmental health criteria 162. Brominated diphenyl ethers. World Health Organization, Geneva
23. Tomy GT, Halldorson T, Danell R, Law K, Arsenault G, Alaee M, MacInnis G, Marvin CH (2005) Rapid Commun Mass Spectrom 19:2819
24. Nordic Cooperation (2008) Hexabromocyclododecane as a possible global POP. Nordic council of Ministers, Copenhagen
25. de Wit CA, Kierkegaard A, Ricklund N, Sellström U (2010) Emerging brominated flame retardants (BFRs) in the environment. In: The handbook of environmental chemistry. Springer, Heidelberg. doi: 10.1007/698_2010_73
26. Kay K (1977) Environ Res 13:74
27. Kemmlein S, Herzke D, Law RJ (2009) J Chromatogr A 1216:320
28. Ballschmiter K, Zell M (1980) Fresenius' Zeitschrift für Analytische Chemie 302:20
29. Bromine Science and Environmental Forum (BSEF) (2003) Major brominated flame retardants volume estimates: total market demand by region in 2001. BSEF, Belgium
30. Meironyté D, Norén K, Bergman Ã (1999) J Toxicol Environ Health A 58:329
31. Norén K, Meironyté D (2000) Chemosphere 40:1111
32. European Environmental Bureau DECA Press Release. http://www.eeb.org/documents/010408-DECA-PRESS-RELEASE-FINAL.pdf. Accessed 20 July 2010
33. Schecter A, Haffner D, Colacino J, Patel K, Papke O, Opel M, Birnbaum L (2010) Environ Health Perspect 118:357
34. Hess G (2009) Industry to phase out decaBDE. Chem Eng News 87(50):1
35. Marvin CH, Tomy GT, Alaee M, MacInnis G (2006) Chemosphere 64:268

36. Janàk K, Covaci A, Voorspoels S, Becher G (2005) Environ Sci Technol 39:1987
37. Covaci A, Gerecke AC, Law RJ, Voorspoels S, Kohler M, Heeb NV, Leslie H, Allchin CR, De Boer J (2006) Environ Sci Technol 40:3679
38. Morris S, Allchin CR, Zegers BN, Haftka JJH, Boon JP, Belpaire C, Leonards PEG, Van Leeuwen SPJ, De Boer J (2004) Environ Sci Technol 38:5497
39. Huhnerfuss H (2000) Chemosphere 40:913
40. Marvin CH, MacInnis G, Alaee M, Arsenault G, Tomy GT (2007) Rapid Commun Mass Spectrom 21:1925
41. (BSEF) Bsaef (2009) Regulation
42. George KW, Hoggblom MM (2008) Environ Sci Technol 42:5555
43. Nakajima A, Saigusa D, Tetsu N, Yamakuni T, Tomioka Y, Hishinuma T (2009) Toxicol Lett 189:78
44. WHO (1995) Environmental health criteria 172. Tetrabromobisphenol A and derivatives. World Health Organization, Geneva
45. Chu S, Haffner GD, Letcher RJ (2005) J Chromatogr A 1097:25
46. Saint-Louis R, Pelletier E (2004) Analyst 129:724
47. Sellstrom U, Jansson B (1995) Chemosphere 31:3085
48. Tollback J, Crescenzi C, Dyremark E (2006) J Chromatogr A 1104:106
49. Zhang XL, Luo XJ, Chen SJ, Wu JP, Mai BX (2009) Environ Pollut 157:1917
50. Guerra P, De La Torre A, Martinez MA, Eljarrat E, Barcelo D (2008) Rapid Commun Mass Spectrom 22:916
51. Weil ED, Levchik SV (2009) Flame retardants for plastics and textiles. Carl Hauser, Munchen, Wien

Human Health Effects of Brominated Flame Retardants

Daniele Staskal Wikoff and Linda Birnbaum

Abstract In this chapter, we review human health effects associated with the brominated flame retardants (BFRs) that have constituted the overwhelming majority of BFR production and subsequent exposure in humans. These include tetrabromobisphenol A (TBBPA), hexabromocyclododecane (HBCD), and three commercial mixtures of polybrominated diphenyl ethers (PBDEs), or biphenyl oxides, which are known as decabromodiphenyl ether (DecaBDE), octabromodiphenyl ether (OctaBDE), and pentabromodiphenyl ether (PentaBDE). The primary endpoint of concern appears to be endocrine disruption. Other potential effects include hepatotoxicity and neurotoxicity, the later particularly during development. While the toxicological database for these chemicals is growing, further research is needed to understand potential health effects associated with less-studied PBDE congeners, examine the potential carcinogenicity of HBCD and TBBPA, and investigate the overall toxicity of a number of developing alternative BFRs. The increasing contamination of the environment and people by BFRs coupled with clear evidence of adverse health effects resulting from their exposure highlights the importance of identifying emerging issues and data gaps to fully understand the human health risks.

Keywords Endocrine disruption, Hexabromocyclododecane, Polybrominated diphenyl ether, Tetrabromobisphenol A, Thyroid hormones

Contents

D.S. Wikoff (✉)
ToxStrategies, 3420 Executive Center Drive, Suite 114, Austin, TX 78731, USA
e-mail: dstaskal@toxstrategies.com

L. Birnbaum
National Institute of Environmental Health Sciences, Durham, NC, USA

E. Eljarrat and D. Barceló (eds.), *Brominated Flame Retardants*,
Hdb Env Chem (2011) 16: 19–53, DOI 10.1007/698_2010_97,

1 Introduction

In this chapter, we review the human health effects associated with five BFRs that have constituted the overwhelming majority of BFR production and subsequent exposure in humans. These include tetrabromobisphenol A (TBBPA), hexabromocyclododecane (HBCD), and three commercial mixtures of polybrominated diphenyl ethers (PBDEs), or biphenyl oxides, which are known as decabromodiphenyl ether (DecaBDE), octabromodiphenyl ether (OctaBDE), and pentabromodiphenyl ether (PentaBDE). The majority of data characterizing toxicity in humans are associated with exposures to PBDEs, though limited data are available for both TBBPA and HBCD. For the later compounds, a more comprehensive overview of the data reported in animal studies is provided. For PBDEs, the primary focus is on information reported in humans, though a discussion on the relationship of human to animal data is also included.

2 Polybrominated Diphenyl Ethers

The majority of laboratory studies on PBDEs published to date have focused on the commercial mixture, PentaBDE, or the individual congeners contained in PentaBDE (primarily BDEs 47 and 99); however, a number of studies are available reporting on exposures to other commercial mixtures, OctaBDE and DecaBDE, or their primary congeners. Similarly, epidemiological studies have also focused on effects associated with exposure to BDEs 47 and 99, as they are the most commonly measured PBDE congeners in humans and tend to be associated with greater toxicity in animal studies relative to other congeners. However, an increasing number of studies have reported on BDEs 100, 153, 154, and 183; very little is still known about the human toxicity of the fully brominated congener, BDE 209. In this section, an overview of the published data in animal

studies is provided, followed by a detailed discussion of the health effects observed in humans.

2.1 Health Effects in Laboratory Studies

Although most of the studies on PentaBDE are based on the oral route of exposure, a limited number of studies have demonstrated toxicity following high-dose inhalation exposures and a general lack of toxicity following dermal exposures [1, 2]. Studies in rats and mice consistently indicate that the liver is a target organ following exposure to PentaBDE or OctaBDE congeners. Effects include increased enzymatic activity, increased liver weight, histopathological changes, and disruptions to normal function [3]. Changes in thyroid hormone levels (also a common finding) have been linked to changes in metabolic function of the liver. Although there is a great deal of controversy, a series of studies have demonstrated neurobehavioral effects in mice following exposure to several PentaBDE congeners [4]. Studies in bacteria indicate that PentaBDE is not mutagenic; these data are supported by studies in mammalian cells. A number of in vitro and in vivo studies have also suggested reproductive toxicity and developmental neurotoxicity following exposure to a number of lower brominated BDE congeners.

The most comprehensive study on any PBDE compound was recently completed by the National Toxicology Program [5]. DE-71 was tested using a 2-year bioassay that included carcinogenicity, acute and chronic toxicity, genetic toxicity, and toxicogenomics. Presently, only the subchronic data are available for 13-week exposures. Results indicate adverse toxicity in the liver (the primary target) in both rats and mice as demonstrated by increases in a number of phase I and II enzymes, pathological changes, and increases in liver weight.

The toxicity of OctaBDE compounds has been evaluated in laboratory animals primarily via oral exposure, though toxicity following inhalation has also been assessed. These compounds are generally of low acute toxicity [4]. Toxicities following repeated exposures tend to be in the liver and include induction of hepatic enzymes, increased liver weight, hyperplastic nodules, and enlargement of the liver. Other effects include increases in thyroid weight and altered levels of thyroid hormones. OctaBDE (the commercial mixture itself) does not cause skin or eye irritation, or sensitization in animal studies, nor is it classified as a mutagenic compound based on Salmonella tests. Developmental studies have demonstrated mixed findings, although they suggest the potential for effects related to changes in thyroid hormones. Data have also been published providing suggestive evidence for developmental neurotoxicity [6, 7] associated with a hexa-substituted congener found in OctaBDE (BDE 153). Research studies are not available to characterize chronic exposures, carcinogenicity, or reproductive effects.

DecaBDE, or BDE 209, has been evaluated less often than the other compounds, even though it is the most widespread BDE congener in use. Bacterial tests indicate that BDE 209 is not mutagenic. Additionally, studies in mice suggest evidence for

thyroid hormone disruption and delayed developmental neurotoxicity [8]. Neonatal exposure to DecaBDE in mice resulted in a dose-related reduction of serum thyroxine levels in males and delayed development of the palpebral reflex in infants [9], and disruption of normal sex- and age- specific characteristics of spontaneous locomotion in adults. Additionally, impairment in performing behavioral tasks was observed in aging mice following neonatal exposure to DecaBDE, while minimal impairment was observed during young adulthood [10]. Disruption of normal spontaneous behavior has also been reported in other studies on mice and rats following neonatal exposure [7, 11]. In a recent study, Xing et al. [12] showed that exposure to BDE 209 during five different developmental periods could lead to impaired synaptic plasticity in adults, and exposure during lactation was the most sensitive scenario. Chronic, oral exposure studies have demonstrated that very high doses of BDE 209 result in hepatic carcinogenicity in rodents [8, 13]. Additionally, follicular cell hyperplasia incidence increased significantly in male mice, and the incidence of thyroid gland follicular adenomas/carcinomas was slightly increased in treated mice of both sexes.

2.2 Effects in Humans

Studies characterizing potential effects in humans have been relatively limited until recently. As public health interest increases, additional epidemiological investigations are being conducted and published. These studies generally focus on three main outcomes: endocrine disruption, neurotoxicity, and reproductive toxicity (and are discussed as such in this section). The latter two outcomes could both be related to endocrine disrupting effects, lending mechanistic support to the overall findings. The available epidemiological studies tend to be based on key toxicological findings in laboratory studies as well as knowledge about compounds with similar structure, such as the polychlorinated biphenyls (PCBs). It is important to note that none of the available studies evaluated BDE 209, the most highly substituted congener, and thus this congener is excluded from the generalizations and trends discussed in this section.

2.2.1 Thyroid Hormone Disruption

The majority of studies in human populations have evaluated disruption of the endocrine system, and most of the focus has been on disruption of thyroid hormones. This is due mainly to the similarity in structure between PBDEs and thyroid hormones triidothyronine (T3) and thyroxin (T4), and thus the potential for PBDEs to mimic and disrupt homeostatic conditions. Furthermore, data in laboratory studies demonstrate altered levels of thyroid hormones following exposures to PBDEs in rodents. Some studies have also reported hyperplastic changes in the

thyroid [14]. Studies in animals have indicated the potential for hydroxylated PBDEs to also interfere with thyroid hormones.

One of the first studies evaluating the potential association between PBDEs and levels of hormones was published by Hagmar et al. in 2001 [15]. These authors assessed associations (after correcting for age) between levels of several persistent organohalogens and a variety of hormones in men who consumed fatty fish from the Baltic Sea. Only two associations were found, one with pentachlorophenol, and a negative association between thyroid-stimulating hormone (TSH) and BDE 47. It is important to note that although the authors noted a relationship, they also stated that given the number of evaluations conducted, there could be some significant correlations that resulted from pure chance. Furthermore, the TSH levels measured in the population were all within normal reference ranges. The author's ultimate conclusion was that the results suggest that it was very unlikely that even a high consumption of such fish polluted with organohalogens would cause disturbances of circulating hormone levels.

Shortly after this investigation, Mazdai et al. [16] published findings of a small ($n = 12$), but important study. In a dataset consisting of paired maternal and cord blood samples, the authors reported that fetal concentrations of PBDEs were very similar to that measured in the mother. Thus, the findings demonstrated that for BDEs 47, 99, 100, 153, 154, and 183, maternal serum concentrations are good predictors of fetal exposures. These data are particularly important, given the role of thyroid hormones during development (including in utero). These authors also evaluated thyroid hormones (T3 and T4; total and free) in the paired maternal and fetal samples, though no correlations were found between concentrations of PBDEs and hormone levels. Furthermore, there were no associations between PBDE concentrations or clinical parameters, including infant birth weight.

Another small-scale study in Sweden evaluated thyroid hormones with few significant findings [17]. This group of investigators assessed the concentration of PBDEs in serum and thyroid status in a small group of workers from an electronic recycling facility. Samples were collected from 11 workers before beginning work at the facility, and thereafter at defined intervals, including measurements following vacation periods. Only seven BDE congeners were measured; levels of BDE 47 were highest, followed by 153 and 99. The authors did not find a consistent increase in concentration with increasing length of exposure (employment). Despite a number of approaches for evaluating thyroid hormones, no significant findings were noted when all data were considered; specifically, no correlations were found between PBDE concentrations and T3, T4, or TSH. Limited correlations were observed on an individual level for three workers. However, the authors noted that all of the levels were within the laboratory reference range and also within the normal physiological range. These findings led to the conclusion that no relevant changes were present in relation to PBDE exposures in the study.

Since 2008, there have been an increasing number of well-conducted studies focused on the association between PBDEs and thyroid homeostasis, all of which examined much larger populations. In an interesting study of Chinese workers from an e-waste dismantling site, Yuan et al. [18] evaluated serum concentrations of

PBDEs, TSH levels, the frequency of micronucleated binucleated cells, and biomarkers of oxidative stress in blood and urine. The objective was to explore factors that may influence selected biomarkers for exposure to e-wastes. Although the PBDE congeners measured were not stated (results only provided as sums), the authors reported that the median serum concentration was 382 ng/g lipid in the e-waste workers and 158 ng/g lipid in the control group (a group located ~50 km from the e-waste facility). The median serum TSH level was significantly higher in the workers as compared to the control group. The frequency of micronucleated cells was 5% in the exposed group and 0% in the control group, thus suggesting an association between exposures to e-waste and DNA damage. However, no differences were observed for other markers of DNA damage (8-hydroxy-2′-deoxyguanosine levels in urine, or SOD, MDA, and GSH levels). Using logistical regression, the authors reported that working with e-wastes was the only significant predictor of the increased micronucleated cell frequency, and no factors were associated with increased serum TSH levels. The authors concluded that exposures to other compounds (such as PAHs or metals) may have been responsible for the observed genotoxic effects; however, PBDEs were associated with altered levels of TSH, suggesting potential adverse effects to the thyroid hormone system in these workers. More recently, Wang et al. [19] reported that people working in e-waste recycling had significantly lower TSH compared with control groups. Additionally, these authors noted a positive association between BDEs 205 and 126 with levels of T4.

Turyk et al. [20] reported on hormone disruption in adult male sport fish consumers. This group of researchers invited participants from a previously studied cohort of frequent and infrequent consumers of Great Lakes fish to participate in a follow-up study on PBDE exposures. Approximately 300 men provided information on fish consumption, medical diseases, use of medications and supplements, as well as blood and urine samples for the study. All samples were analyzed for thyroid and steroid hormone levels as well as concentrations of PBDEs in an effort to determine whether PBDE body burdens were related to hormone levels. Associations between hormones and ∑PBDE levels (∑PBDE = BDE congeners 28, 47, 49, 85, 99, 100, 138, and 153), as well as BDE 47 alone, were modeled using linear regression with consideration for a number of confounding variables (e.g., body mass index, age, serum lipids, smoking, fish meals, etc.). Dose–response relationships were evaluated for ∑PBDE levels by quartile and for individual BDE congeners 47, 99, 100, and 153 by tertile.

The median ∑PBDE concentration was 38 ng/g lipid (range of 16–1,360 ng/g lipid). ∑PBDE concentrations were positively related to measures of T4 (total T4, free T4, and urinary T4), rT3, and the percentage of T4 bound to albumin. In contrast, ∑PBDE concentrations were inversely related to total T3, TSH, and the percentage of T4 bound to thyroid-binding globulin (TBG). Associations were less apparent and generally inconsistent when evaluated with BDE 47 alone. For both sets of evaluations, statistical significance was often dependent on adjustment for other hormone levels and/or other DDE; thus the associations were difficult to interpret. Dose–response evaluations with ∑PBDE concentrations were also difficult

to interpret given the large variability between quartiles; however, the authors reported positive relationships for urinary T4. Only the highest quartile was elevated for free T4, rT3, and T4 binding to serum proteins. Total T3 was negatively associated by quartile. No dose–response relationship was observed for total T4 and TSH. When evaluated by individual congener, urinary T4 was the only parameter that exhibited a positive dose–response relationship with all congeners evaluated. Trends were not apparent or inconsistent for other congeners or parameters.

Importantly, these findings suggest independent pathways for the various BDE congeners evaluated with respect to several effects on thyroid hormones. The authors speculated that some of the observed associations suggested a role of thyroid hormone deiodinases, given their key role in maintaining thyroid homeostasis, and specifically an effect between PBDE exposure and deiodinase activity. The overall conclusion by the authors was that PBDE exposure at levels consistent with those observed in the general US population was associated with increased thyroglobulin antibodies and increased T4 in adult males. However, the authors did not compare the reported hormone or steroid levels to those measured in the general population, and thus the clinical significance of the findings is unclear, particularly considering that none of the cohort participants had diabetes, thyroid disease, or other conditions that could correlate PBDE levels to disease. Their results were initially a surprise, given the lack of consistency with the effects observed in animal studies.

In another study published the same year, Herbstman et al. [21] reported on the relationship(s) between cord serum concentrations of PBDEs and thyroid hormones from cord blood serum and neonatal blood spots in an effort to understand if PBDEs alter umbilical cord levels of thyroid hormones. Furthermore, the authors wanted to understand if the birth delivery mode modified any such associations, given that intrapartum stress could substantially change thyroid hormone levels (and thus potentially mask effects of xenobiotic exposures). Using linear regression, crude and adjusted relationships between log PBDE concentrations (based on individual BDE congeners) and total T4 (TT4), free T4 (FT4), thyrotropin, and TSH were evaluated. Although BDE 100 and 153 were weakly associated with average lower TT4 in cord blood, no significant relationships were observed. When considerations for delivery type (i.e., spontaneous unassisted vaginal delivery [SUVD] vs. all other types) were included in the model, higher levels of three congeners (BDEs 47, 100 and 153) were associated with lower TSH, though the associations were not statistically significant. However, higher concentrations of BDE 100 were significantly associated with lower TT4 in babies born via SUVD. The authors concluded that umbilical cord levels of PBDEs were not associated with higher TSH or FT4. It is of interest to note that this study also evaluated a number of PCB congeners; associations between effects on thyroid hormones and PCBs were much stronger than with PBDEs.

A separate group of researchers also evaluated both PCBs and PBDE exposures with respect to adverse effects on thyroid hormones. Chevrier et al. [22] first evaluated associations between PCB exposures and thyroid hormones in population of pregnant low-income Latina women in California; in a separate study, they

evaluated relationships between PBDE concentrations and thyroid function. Based on the data collected in 1999/2000, multiple linear regression models were used to evaluate the relationship between maternal PBDE concentrations and thyroid hormones (and also included analyses based on clinical definitions of maternal hyperthyroidism). Concentrations of PBDEs were lower than those observed in the general US population and were dominated by BDEs 47, 99, 100, and 153 (BDEs 17, 66, 85, 154, and 183 were detected in fewer than 50% of the samples and thus were not considered in the health-based analyses). Associations between PBDEs and free and total T4 were not statistically significant, though both individual congeners and sum PBDEs were inversely associated with TSH levels. Associations were not linear, though when evaluated by quartile, data demonstrated suggestive evidence of a non-monotonic exposure–response relationship (based on increased odds of subclinical hyperthyroidism in the fourth quartile relative to the first). The authors concluded that the data suggest PBDE exposures are associated with lower TSH during pregnancy, and altered thyroid homeostasis has been shown to be particularly harmful to the developing fetus.

A group of researchers in the USA evaluated associations between the concentrations of PBDEs in house dust and hormone levels in a small group of men ($n = 24$) recruited from an infertility clinic [23]. BDE 47 and 99 were detected in all house dust samples; BDE 100 was detected in 67% of samples. The authors showed that PBDE concentrations in house dust were positively associated with free T4. Because the authors did not evaluate levels of PBDEs in serum, it is very difficult to interpret these findings without direct correlations between dust exposure and serum concentrations in this population, although such a correlation has been seen in other populations. The authors also point out that their results are preliminary and could be due to chance.

When the thyroid hormone disruption data are considered collectively, it is difficult to generate a conclusion given the lack of consistency between studies. Many different populations have been studied worldwide, including both occupationally exposed cohorts and sensitive cohorts (e.g., pregnant women and infants). The difficulties in finding consistencies may be due to the fact that many of the studies did not evaluate the same congeners, nor did they conduct congener-specific analyses, but rather depended on analyses based on the sum of PBDEs measured (which was also not consistent among studies). Furthermore, measurement of thyroid hormones is often subject to a large amount of analytical sensitivity and variability. Importantly, though several of the studies available looked at key parameters, very few evaluated enough parameters (or accessory information) to fully interpret changes in thyroid hormone status. Despite these limitations, the evidence suggests that serum concentrations of PBDEs, and some congeners in particular, are associated with altered levels of thyroid hormones. The data supporting an inverse association with TSH were the strongest, though not all studies consistently reported such. Most studies reported a lack of correlation with T4. Most authors did not evaluate the clinical relevance of changes in thyroid hormone levels – this type of information is a key to determining the impact on human health. Thus, in summary, additional studies are needed to clarify the findings published to

date and to further characterize the relationship between PBDE exposure and changes to the endocrine system in humans.

2.2.2 Diabetes

Lim et al. [24] conducted a cross-sectional evaluation of the National Health and Nutrition Examination Survey (NHANES) data in an effort to identify potential associations between BFRs and diabetes and/or metabolic syndrome in the US population. The NHANES dataset is a part of a large-scale biomonitoring effort led by the Centers for Disease Control and Prevention, designed to characterize the health and nutritional status of the general US population. It is often used as the primary source for establishing "reference ranges" of exposure to various environmental compounds; however, the usefulness for evaluating health status is highly dependent on the outcome of interest. In this study, the authors relied on self-reported data regarding medications for treatment of diabetes or measurements of plasma glucose (not all of which were fasting). Similarly, diagnosis of metabolic syndrome was based on meeting various criteria (e.g., fasting glucose, waist circumference). These outcomes were evaluated relative to serum concentrations of BDE congeners that were above the analytical limit of detection in at least 60% of the study population; thus analyses were limited to BDEs 28, 47, 99, 100, and 153. Participants with serum concentrations less than the limit of detection were used as the reference group; the remaining participants were evaluated by quartiles using logistic regression models.

After adjusting for several confounding variables, there was a nonlinear association with diabetes for BDE 153. Statistically significant associations were not observed for the other congeners. A similar finding was noted by the authors for metabolic syndrome: only BDE 153 showed a weak association, though it was a U-shaped curve when evaluated by quartile. The authors state that the findings should be interpreted with caution due to the cross-sectional nature of the study and because of multiple comparison intrinsic to the dataset (e.g., complex weighting, many compounds evaluated, etc).

2.2.3 Neurotoxicity

A handful of studies have been published recently addressing neurotoxicity outcomes in human populations and potential associations with PBDE exposures. These types of studies are a result of laboratory studies in rodents indicating the potential for neurotoxicity following developmental exposure to several BDE congeners (reviewed by [25]), and also because of structural similarity to known neurotoxic substances, particularly PCBs. The first study was published in 2009 by Roze et al. [26] and was based on findings from a prospective cohort study evaluating neuropsychological function in 62 children in the Netherlands. Blood levels of ten organohalogen compounds including BDEs 47, 99, 100, 153, and 154,

as well as HBCD were measured in mothers during the 35th week of pregnancy. Thyroid hormones were also measured in umbilical cord blood samples. At ages 5–6, children were then evaluated for motor performance (coordination, fine motor skills), cognition (intelligence, visual perception, visuomotor integration, inhibitory control, verbal memory, and attention), and behavior. Correlations were evaluated between the concentrations of the organohalogen compounds in the mothers before birth and the functional analyses in children, both with and without correction for socioeconomic status, sex, and home observation for measurement (HOME, which the authors indicated may exert an influence on the cognition and behavior of the children).

The authors reported that brominated flame retardants (BFRs) were correlated with worse fine manipulative abilities, worse attention, better coordination, better visual perception, and better behavior. The congener-specific data without corrections showed that BDE 47 was negatively associated (described as a worse outcome) with sustained attention, but positively associated (described as a better outcome) with internalizing behavior, total behavior outcome, and coordination. BDE 99 was positively correlated with internalizing behavior and total behavioral outcome. BDE 100 was positively associated with coordination, internalizing behavior, externalizing behavior, and total behavioral outcome. BDE 153 was positively correlated with visual perception. BDE 154 was negatively correlated with fine manipulative abilities, and HBCD was positively associated with coordination. Thus, the majority of outcomes with significant correlations were positive (11 of 13); only BDE 47 and BDE 154 exhibited negative correlations. When the data were corrected for SES, sex, and HOME, 16 correlations were noted for the BFRs in this study. All significant correlations with HBCD were positive (coordination, total intelligence, and verbal intelligence). BDE 153 was negatively associated with verbal memory. BDEs 47, 99, and 100 were negatively associated with sustained attention. BDE 47 was positively associated with selective attention and internalizing behavior. BDEs 99 and 100 were positively associated with total behavior outcome and internalizing behavior.

Regarding the conflicting (positive and negative) correlations between BFRs and outcome, the authors stated “it is difficult to determine implications of these results for functioning later in life.” The authors also noted that it was difficult to determine which effects could reliably be assigned to the specific contaminants, particularly considering colinearity issues. Furthermore, many other contaminants, such as methyl mercury (a known developmental toxicant), may also have played a role (but were not measured in the current study). Thus, given the conflicting nature of the results and limitations in the study design, the findings are difficult to interpret with respect to evaluating human health risk.

In an effort to follow-up on animal studies suggesting neurodevelopmental effects following exposures to PBDEs, Herbstman et al. [27] conducted a prospective cohort study to evaluate the potential associations between prenatal exposure to PBDEs and neurodevelopment. The authors relied on a cohort initiated after 11 September 2001, of women and their children from New York (USA). In total, 210 cord blood samples were collected and analyzed for PBDEs. Approximately

half this number participated in subsequent neurodevelopmental testing in children between 12–48 and 72 months of age (note: a different number of children were tested at each age). Median cord plasma concentrations of BDE 47, 99, and 100 were 12.1, 3.5, and approximately 1.5 ng/g lipid, respectively. PBDE concentrations were evaluated in a cross-sectional analysis using multivariate linear regression to determine associations with Psychomotor Development Index (PDI), Mental Development Index (MDI), full IQ scores, verbal IQ scores, and performance IQ scores. MDI and PDI were evaluated at 12, 24, and 36 months of age, whereas IQ tests were performed at 48 and 72 months of age.

A number of negative associations were found for BDEs 47, 99, 100, and 153; however, only a few were statistically significant. For BDE 47, these included the 12-month PDI (not a strong association), 24-month MDI, and 48-month full and verbal IQ scores. For BDE 99, the 24-month MDI was the only neurodevelopmental endpoint significantly impacted. BDE 100 concentrations were negatively associated with 24-month MDI, 48-month full, verbal and performance IQ scores, as well as 72-month performance IQ scores. And for BDE 153, negative associations were detected for the 48-month and 72-month full and performance IQ scores. The authors reported that for every ln-unit change in BDE 47, 100, or 153, IQs were several points lower. The authors also compared the mean scores from children in the upper 20% of the prenatal exposure distribution to those in the lower 80% and found that generally children with higher PBDE concentrations scored lower than the rest of the population in the neurodevelopmental tests.

The findings reported by Herbstman et al. [27] are consistent with toxicological data published in animal studies, thus lending confidence to these findings with the support of biological plausibility. However, not all trends observed in animal studies were observed by Herbstman et al. [27], suggesting differential mechanisms and/or effects between species. These data are important and demonstrate that additional research is required to understand potential associations, particularly considering a number of the confounders that limit the interpretation of the current dataset (e.g., the authors noted that the associations were impacted by maternal education, breastfeeding, etc). However, when considered collectively, these two studies suggest the potential for neurodevelopmental effects associated with exposures to PBDEs, though the type and severity of effects warrant further assessment.

Using these data, along with data from animal studies, Messer [28] proposed that PBDEs could play a role as risk factors for autism or other disorders of brain development and briefly overviews some of the data to support this hypothesis. The premise of the mini-review leans on data demonstrating endocrine disruption in both animals and humans as a possible mechanistic link between observed neurobehavioral effects observed in rodents. The author also describes further testing paradigms that would be useful for better understanding the potential adverse effects of PBDE exposure, particularly as they relate to characterizing health risk in humans. Such studies would include more thorough pharmacokinetic investigations, evaluations of genetic alterations, and chronic toxicity studies in animal models. The author also suggested additional in vitro assays to characterize binding to key receptors in an effort to further understand the mechanistic processes.

Collectively, these data are required to understand if PBDE exposure is a risk factor for autism.

2.2.4 Reproductive Toxicity

Several studies have evaluated the downstream impact of endocrine disruption, genetic disturbance, and other potential adverse effects on reproductive toxicity. Main et al. [29] assessed the potential association between concentrations of PBDEs and cryptorchidism in newborn boys; Akutsu et al. [30] reported on findings from a pilot study evaluating PBDE concentrations and potential associations with sperm quality in ten Japanese study participants. A third study has found that maternal PBDE serum concentrations were associated with decreases in fecundability [31]. Furthermore, one study examined house dust PBDE levels and reproductive hormone analyses on men at an infertility clinic [23], though this study did not quantify serum PBDE concentrations.

The authors of the study on cryptorchidism [29] pursued the investigation because of the increasing prevalence of undescended testicles in some areas of the world, and the suspected role of environmental factors – particularly those that interfere with hormonal function. Both breast milk ($n = 130$) and placenta samples ($n = 280$) were analyzed as part of a longitudinal cohort study conducted between 1997 and 2001 in Finland and Denmark. In addition to measuring the levels of 14 BDE congeners (28, 47, 66, 71, 75, 77, 85, 99, 100, 119, 138, 153, 154, and 183), in both biological media, levels of gonadotropin, sex hormone-binding globulin (SHBG), testosterone, and inhibin B were also measured. All newborns in the study were evaluated clinically, with specific focus on the position and function of the testes. Serum samples were also drawn from infants at 3 months of age and analyzed for follicle-stimulating hormone (FSH), luteinizing hormone (LH), and SHBG.

Only seven of the fourteen BDE congeners were detected in breast milk samples. Median concentrations of BDE congeners 47, 100, 28, 66, and 154 in breast milk were higher in Danish newborns with cryptorchidism relative to controls, though this trend was not observed in Finnish newborns (who have higher incidences of cryptorchidism). When evaluated together (newborns from both countries), the sum of the seven detected congeners was higher in all newborns with cryptorchidism relative to controls. Serum levels of LH were also correlated with the sum of the seven detected congeners as well as with BDEs 47, 100, and 154; when evaluated by country, this trend was only observed in Finnish newborns. No other endpoints evaluated were significantly associated and correlated with PBDEs.

Very different results were obtained when placental tissue was assessed. Only five BDE congeners were detectable (thus analyses were based on a sum of five vs. seven with breast milk). However, no significant differences in the placenta concentrations of BDES and cryptorchidism were observed. There were also no correlations between placental PBDEs and serum reproductive hormones in the infants. The authors specifically noted that it was not clear why the findings were

not in agreement. It is of interest to note that placental lipid content was not correlated with the sum of PBDEs, and that there were positive correlations between measurements in placenta and breast milk, but absolute concentrations in the placenta were approximately three times lower. Clearly, additional analyses are needed to clarify the findings in this study and to further characterize potential effects of PBDE exposures in early life stages.

Findings reported by Akutsu et al. [30] were generally in line with those reported by Main et al. [29]. In this pilot study of sperm quality in ten Japanese participants, only 4 of 29 BDE congeners were consistently detected (47, 99, 100, and 153). The sum concentration of these four congeners was less than 5 ng/g lipid in all participants except one (8.6 ng/g lipid), demonstrating generally very low levels. Individual congeners were evaluated for trends with sperm concentrations and testis size. No significant trends were observed for BDEs 47, 99, and 100. However, the authors reported a significant inverse relationship between both endpoints for BDE 153 (the data was not shown for testis size). These limited data may suggest BDE congeners 47, 99, 100, and 153 act via different mechanisms and/or demonstrate differential potencies with respect to various endpoints. The trend between BDE 153 concentrations and decreased sperm concentrations warrants further investigation.

In a study mentioned earlier in relation to changes in free T4, a group of researchers evaluated PBDEs in house dust and hormone levels in a small group of men ($n = 24$) recruited from an infertility clinic [23]. With adjusted, multivariable regression models, the authors observed inverse relationships between dust PBDE concentrations and free androgen index, luteinizing hormone and FSH, as well as positive relationships between PBDE concentrations in house dust and levels of inhibin B and SHBG. Again, because the authors did not evaluate levels of PBDEs in serum, it is difficult to interpret these findings.

Harley et al. [31] designed a study aimed at determining potential associations between maternal PBDE serum concentrations during pregnancy and time to pregnancy as well as various menstrual cycle characteristics. The authors focused on BDE congeners 47, 99, 100, 153, and total PBDEs in approximately 200 women from California, USA. Fecundability odds ratios were reduced for BDE 100, 153, and the sum of PBDEs; no effects were noted for the other congeners. No effects were noted for any congeners, or sum congeners, when various parameters associated with the menstrual cycle were examined.

2.2.5 Sensitization

Data characterizing sensitization to PBDEs is limited to two studies with the most fully brominated congener, though details on these studies are limited. One study reported that skin irritation was noted in 9 of 50 human subjects who were exposed to a repeated application of 5% Deca in petrolatum, though the applications did not result in sensitization [32]. Similar findings were reported in a separate study involving repeated Deca exposures to the skin of 200 volunteers;

irritation was noted in some participants but no evidence of skin sensitization was observed [32].

2.2.6 Interpretation of Studies in Humans

Data characterizing potential effects association with exposures to PBDEs in humans are becoming increasingly available as initial studies indicate several potential causes for concern. The variability in findings inhibits the ability to make a definitive conclusion; however, when the data are considered collectively, it appears that human populations may be at risk of health effects, primarily endocrine disrupting effects that may manifest as neurotoxic or reproductive outcomes. However, additional research is clearly needed to more fully understand the mechanistic aspects of toxicity following exposures, as well as to more fully understand the quantitative dose–response relationships between exposure and response. A key component to further assessments may also include discussion of both clinical and public health relevance. Furthermore, these data collectively suggest that some BDE congeners are more potent or operate via different mechanisms than others. Investigators should be urged to analyze and publish data on both a congener-specific basis (including BDE209 and other highly brominated congeners) in addition to the sum PBDEs such that the public health arena can better understand and protect humans from adverse effects resulting from PBDE exposure.

2.3 Mechanistic Studies In Vitro Using Human Cell Lines

Many mechanistic studies have been published in the last decade describing responses in human cells or human cell lines following exposures to PBDEs. These can generally be divided into those that characterize toxicity and those that characterize metabolism in vitro. The studies that evaluated toxicity generally focused on key events associated with genotoxicity, endocrine disruption, neurotoxicity, and changes in development, though the majority of such are aimed at determining key events associated with neurotoxicity. These studies have been conducted in a number of cell lines and evaluate a variety of different endpoints, and also evaluate a number of different individual BDE congeners as well as commercial mixtures. Collectively, these studies provide data that aid in understanding the mechanism(s) of action (MOA) associated with the toxicities of PBDEs.

2.3.1 Toxicity

In an effort to understand potential MOA(s) associated with potential neurotoxic effects in vivo and apoptosis in vitro (based on previous studies), Yu et al. [33]

evaluated the action of DE-71 on a human neuroblastoma cell line. Dose-dependent effects in cell viability were noted (based on an increase in lactate dehydrogenase leakage and 3-4,5,-dimethylthia-zol-2-yl-2,5-diphenyl-tetrazolium bromide reduction). Using morphological examination and flow cytometry, the authors also reported treatment-related apoptosis and DNA degradation in the cell cycle. Further evaluation suggested that apoptosis was caused by a caspase-dependent pathway (but was not related to oxidative stress). The authors also evaluated intracellular calcium, noting a time-dependent increase in intracellular levels – an effect also noted in many rodent cell culture studies. Additional assessments on cellular mechanisms indicated that DE-71 increased the level of Bax translocation to the mitochondria and stimulated the release of cytochrome *c*. Although it is difficult to directly translate the findings of this in vitro study in a human cell line to human health risk, the results provide important information regarding potential mechanisms of toxicity following exposure in humans.

Using a somewhat similar approach, He et al. [34] also conducted a mechanistic study in a cell line derived from a human neuroblastoma (SH-SY5Y cells) to evaluate apoptosis in association with exposures to BDE 47 both in the presence and absence of PCB 153. The authors reported that BDE 47 induced apoptosis via multiple pathways. Furthermore, co-exposure to PCB 153 enhanced the effects. The authors suggested that these findings contribute further to understanding potential neurotoxicity associated with PBDE exposures. The effects of BDE 47 were also assessed by Tagliaferri et al. [35], who used two mathematical models to evaluate the interaction between BDE 47 and BDE 99 on viability of neuronal cells. The model suggested synergistic effects below the threshold concentrations of both compounds.

Schreiber et al. [36] used primary fetal human neural progenitor cells (hNPCs) as an in vitro model of neural development to evaluate the potential toxicity of BDEs 47 and 99. The behavior of the selected cell line mimics proliferation, migration, and differentiation, basic processes in brain development. Using micromolar concentrations, the authors reported that these congeners did not alter proliferation, but did cause treatment-related effects on ion migration and differentiation, specifically differentiation into neurons and oligodendrocytes. Because numerous previous studies in rodents have suggested that thyroid hormones play a role in PBDE-induced toxicity, the authors simultaneously exposed the cells to a thyroid hormone receptor agonist and showed that negative effects on migration and differentiation were eliminated. However, addition of an antagonist did not exert an additive or synergistic effect; thus the role of thyroid hormones in this system was unclear. These findings demonstrate that the primary BDE congeners measured in humans have the potential to cause toxicity via this mechanism, though additional research is needed to link the findings from this in vitro study to exposures in the human population.

In an effort to more fully understand PBDE-induced endocrine disruption, developmental neurotoxicity, and changes in fetal development observed in rodent studies, Song et al. [37] evaluated the potential toxicity of two hydroxylated PBDEs in a human adrenocortical carcinoma cell line (H295R). Cells were exposed to

2-OH-BDE47 or 2-OH-BDE85 and evaluated for cell viability/proliferation, DNA damage, cell cycle distribution, and gene expression profiling. Both of the compounds demonstrated dose-dependent cytotoxic effects, though the hydroxylated BDE 85 was more potent. At the micromolar concentrations tested, no DNA damage was observed, thus suggesting a non-genotoxic mechanism of toxicity for these compounds.

Several studies have directly evaluated genotoxic effects in human cell lines. One of the first studies was reported by Reistad and Mariussen [38], in which the authors assessed the formation of reactive oxygen species (ROS) and calcium levels in human neutrophils following exposure to DE-71, OctaBDE, or BDE 47 in vitro. Both DE-71 and BDE 47 induced a dose-dependent production of ROS, whereas no ROS were observed following OctaBDE exposure. Additional investigations of cell signaling indicated a calcium-dependent activation of PKC. Based on the collective findings, the authors postulated that ROS formation was generated via an initial tyrosine kinase-mediated activation of P13K and enhanced activation of calcium-dependent PKC by enhanced PLC activity, which results in a release of intracellular calcium and ROS formation in neutrophils. This information is particularly useful, given the absence of findings with commercial OctaBDE, and positive findings with DE-71 and BDE 47, further supporting the need for congener-based assessment.

A series of similar studies were published by He and colleagues in 2007 and 2008. Hu et al. [43] reported on the antiproliferative, apoptotic properties of BDE 209 in the human hepatoma Hep G2 cell line. Following 72 h of exposure, BDE 209 inhibited cell viability, increased the release of lactate dehydrogenase, and generated ROS, in a concentration-dependent manner (10–100 μM). Morphological changes, cell cycle alterations, and apoptosis supported antiproliferative effects. These findings are in contrast to the trend observed by Reistad and Mariussen [38] in which the higher brominated compounds did not induce ROS in a dose-dependent manner. He et al. [39] also evaluated cytotoxicity and genotoxicity of BDE 47 in human neuroblastoma cells (SH-SY5Y cells) in vitro. Cells were exposed for 24 h to BDE 47 concentrations ranging from 1 to 8 μg/ml, and then evaluated for cell viability, proliferation, lactate dehydrogenase leakage, ROS formation, cell apoptosis, DNA breakage, and cytogenic damage. Under the conditions of this assay, BDE 47 inhibited cell viability, increased LDH leakage, and induced cell apoptosis at concentrations $\geq$4 μg/ml. Concentration-dependent increases in ROS and DNA damage were observed. Based on these findings, the authors concluded that BDE 47 was cytotoxic and genotoxic in SH-SY5Y cells in vitro.

In a separate study, He et al. [39] reported on the findings of a bridging the gap between genetic and functional changes following exposures to PBDEs. The authors evaluated gene expression and enzymatic and hormone levels in a human adrenocortical carcinoma cell line (H295R) following exposure to 1 of 20 PBDE metabolites (hydroxylated, methoxylated, and/or chlorinated derivatives). Most compounds tested altered the expression of CYP11B2, which is involved in the synthesis of aldosterone. Expression of CYP19 (aromatase) was also altered,

though it was much less sensitive to exposure to the PBDE metabolites. Treatment-related effects on aromatase activity and 17β-estradiol activity were observed, though a consistent or dose-dependent relationship was unclear. The authors concluded that several metabolites adversely impacted steroidogenesis in vitro in this cell line.

Another group of researchers had previously reported on aromatase activity (and other endpoints) following exposures to PBDEs and other BFRs in vitro [40] using the same human adrenocortical carcinoma cells (H295R cell line). Micromolar concentrations of 19 PBDE congeners, 5 hydroxylated PBDEs, 1 methoxylated PBDE, TBBPA, TBBPA-DBPE, 2,4,6-tribromophenol (TBP), 4-bromophenol (4BP), and 2,4,6-tribromoanisole (TBA) were evaluated for inhibitory effects on aromatase activity. 6-OH-BDE47 and 6-OH-BDE99 demonstrated concentration-dependent inhibition of activity (though the authors note that some of this inhibition may have been due to cytotoxicity). TBP and the methoxy-PBDE also caused treatment-related inhibition of aromatase activity. The authors noted that chemical structure influenced toxicity, demonstrating the importance of structure–activity relationships for these compounds. This study provides useful information concerning the synthesis of estrogens resulting from exposure to BFRs.

This same group of researchers [41] published additional findings on a potential mechanism of action associated with CYP17 enzymatic activities following exposures to various PBDE congeners and their hydroxylated derivatives in the same cell line (H295R cells). CYP17 is involved in sex hormone steroidogenesis and is required for the biosynthesis of DHEA and androstenedione. Using an in vitro system designed by the authors, various endpoints were evaluated, each aimed at understanding key events in CYP17 activity following exposures. Results indicated that some hydroxylated PBDEs had the potential to disrupt CYP17 activity in the in vitro system. Effects were clearly congener specific and did not demonstrate a clear structure–activity relationship. The authors further noted that the relevance of these events in vivo has not been adequately determined, and thus additional research is required to further understand the impact of this propose mechanism of action in humans.

A fourth study reported on changes to aromatase activity, though the findings reported by these authors [42] were not as consistent as those reported by Hu and colleagues [43]. In this study, 15 PBDE metabolites, 2 commercial PBDE mixtures (DE-71 and DE-79), and TBBPA were evaluated for the potential to induce changes in gene expression, aromatase activity, and levels of testosterone and 17β-estradiol in the H295R human adrenocortical carcinoma cell line. Of all the compounds evaluated, only selected hydroxylated PBDE metabolites induced changes in expression of steroidogenic genes. Similarly, only selected PBDE metabolites induced changes in aromatase activity. None of the compounds impacted sex hormone production at the concentrations tested. Thus, the important finding of this study demonstrated that the observed changes in gene expression did not result in functional changes in enzyme activity.

In an effort to more fully understand toxicity during fetal development, Shao et al. [44] evaluated the mechanisms associated with BDE-47-mediated injury in

primary human fetal liver hematopoeitic stem cells. Exposure to BDE 47 at concentrations in the low micromolar range led to a loss of mitochondrial membrane potential and apoptosis. At a high concentration (50 μM), a loss of viability and generation of ROS were observed. While the authors noted that the findings supported the role for oxidative stress in the cytotoxicity of BDE 47, they also noted that the findings should be interpreted with caution, given the in vitro model and relevance of high concentrations.

2.3.2 Metabolism

Two important studies have been published characterizing the metabolism of selected PBDE congeners. One of the most important scientific data gaps in the health assessment of these compounds revolves around understanding the kinetics of the various BDE congeners in humans, given the widespread, ongoing use of commercial Deca relative to the discontinued production of the lower brominated commercial mixtures, Penta and Octa. BDE 47 remains the most commonly measured congener in human biomonitoring exercises, followed by other lower brominated congeners. Thus, characterizing the scientific rationale for its dominance (despite the low international usage) is very important, particularly considering that the lower brominated congeners may have greater toxicity.

A key study characterized the capacity of human liver cells to metabolize BDE congeners 99 and 209 [45], the primary congeners found in the PentaBDE and DecaBDE commercial mixtures. Specifically, the objective was to determine whether reductively debrominated and/or hydroxylated metabolites occurred. The study authors also reported changes in gene expression in an effort to identify and/or examine genes coding for enzymes involved in PBDE metabolism via oxidative and reductive pathways. Hepatocytes from three human donors (two cryopreserved and one fresh) were exposed to BDE 99 or 209 for up to 72 h at a concentration of ~10 μM. The majority of BDE 209 was recovered, suggesting little metabolism or perhaps little uptake into the cell, whereas much less BDE 99 was recovered, suggesting metabolism of the parent compound. No reductively debrominated metabolites were identified with exposures to either BDE compound. The authors noted that these findings were in contrast to in vitro studies in fish. Several oxidative metabolites were identified following exposures to BDE 99, but not 209.

Results of the gene expression component of this study demonstrated upregulation of mRNA expression of CYP1A2, CYP3A4, deiodinase type 1 (DI1), and glutathione S-transferase M1 (GSTM1) by both BDE congeners. The authors suggested that the measurement of oxidative metabolites of BDE 99 and upregulation of CYP enzymes support a role for CYP-mediated metabolism. The upregulation of deiodinase enzymes is also of interest, given their role in thyroid homeostasis. These data also further demonstrate the need for congener-specific assessment in humans, given that the metabolism of BDE 99 and 209 is clearly different.

Lupton et al. [46] reported similar findings: the more fully brominated congener BDE 153 was not metabolized by human liver microsomes, yet BDE 47 and 99 were. In this study, exposures were limited to 120 min. Multiple metabolites were identified for both BDEs 47 and 99. Importantly, the authors also reported large interindividual differences.

2.3.3 Interpretation of Mechanistic Studies in Human Cells

With respect to neurotoxicity, the studies generally demonstrate treatment-related effects on toxicity, including apoptosis, decreased cell viability, and altered differentiation in human neuroblastoma and primary fetal hNPCs following exposures to the lower brominated congeners typically found in the environment (i.e., BDEs 47 and 99). Several other congeners, including hydroxylated congeners, were investigated in studies assessing cell viability, proliferation, DNA damage (often assessed by measuring ROS), cell signaling, and gene expression. Similar to the neurotoxicity studies, BDE 47 and the commercial mixture DE-71 appeared to be the most potent in these assays, though one study found that BDE 209 inhibited cell viability and generated ROS. Because of the inconsistencies among the studies, it is difficult to determine with confidence whether PBDEs are directly genotoxic, though generally data lean toward non-genotoxic mechanisms. Several BDE congeners were also associated with alterations in steroidogenic genes.

One of the primary uncertainties associated with interpreting data derived from in vitro systems involves extrapolation of the doses used in the studies to environmental exposures. This is of particular importance when the findings of Mundy et al. [47] are considered. This group of authors evaluated the concentration and time-dependent accumulation of BDE 47 in primary cultures of rat cortical neurons in an effort to more fully understand the findings from studies published using in vitro cell culture models. The authors reported that approximately 15% of the BDE 47 was associated with the cells, 55% was in the medium, and 30% was in the culture dish. Addition of serum proteins decreased accumulation, and the total volume of exposure also influenced accumulation. Thus, these factors can greatly influence the accumulation of BDE 47 in cells. The authors estimated that the use of the concentration in the medium underestimates tissue concentrations in the cells by up to two orders of magnitude.

Despite the shortcomings associated with the in vitro data, the mechanistic information provided is very useful, particularly considering that the studies were conducted in human-based cell lines or in primary cells. The data generally indicate that some PBDE congeners have the potential to cause toxic effects in vitro. These may translate into downstream effects associated with endocrine disruption, neurotoxicity, and developmental toxicity – findings that are consistent with the data in human studies. And, importantly, these mechanistic studies indicate that BDE congeners induce differential effects, may act through different mechanisms, and clearly have different relative potencies.

3 Tetrabromobisphenol A

In this section, an overview of the data published in animal studies is provided, followed by a detailed discussion of the health effects observed in humans, primarily in human cell lines. Despite the widespread, high volume use of this compound, there are relatively few studies available examining toxicity.

3.1 Studies in Laboratory Animals

Data are available to characterize a number of endpoints following exposures to TBBPA in laboratory animals, including acute toxicity, skin sensitization, neurotoxicity, reproductive toxicity, genotoxicity, and endocrine disruption. This research has been conducted in a number of species, including rats, mice, and rabbits, and ranges from very short exposures to chronic 90-day exposures. Many of the studies have used rather high doses, and toxicity has been seen mainly following oral exposures. TBBPA is generally considered to act via different mechanisms/elicit differential toxicity as compared to other commonly studied BFRs, given its structure and kinetic properties.

TBBPA demonstrates low acute toxicity by all routes of exposure in all species evaluated. Studies in rats provide LC50 and oral LD50 values of >1.3 mg/l (1 h) and >50 g/kg, respectively, and studies on mice resulted in a similarly high LD50 of >10 g/kg [48–52]. LD50 values from dermal exposure to rabbits were >10 g/kg [49, 53]. No significant toxic effects were noted after administration of TBBPA via any route of exposure in these studies. Furthermore, TBBPA is not considered to be irritating to the eye, skin, or respiratory tract, and is not a corrosive agent [48].

Dietary levels of 0.05–100 mg TBBPA/kg body weight/day in 30- and 90-day rodent studies did not produce any effects on behavior, appearance, food consumption, body weight gain, or mortality [54], and more recent 90-day repeated-dose studies showed that oral exposures did not cause adverse effects at doses up to 1,000 mg/kg [55–57]. No adverse effect on fertility, reproductive performance, development, or neurobehavioral effects were noted in rats in a two-generational study [48, 58, 59]. However, more recent studies have also shown that prenatal and postnatal exposure can result in lipid metabolic disorders and hepatic or kidney lesions [60, 61], as well as changes in behavior, locomotion, and hearing [62, 63]. However, Williams and DeSesso [64] found no adverse developmental neurotoxic effects associated with exposure to TBBPA. Further research is clearly warranted in this area.

TBBPA has produced negative results in several in vitro mutagenicity assays [65, 66], a chromosomal aberration study [67], and an intragenic recombination assay [68] using bacterial strains, yeast, and mammalian cells, and is therefore not considered genotoxic. No studies have yet addressed the carcinogenic potential of TBBPA.

In vitro, TBBPA is toxic to cerebellar granule cells, induces calcium influx, inhibits dopamine, generates free radicals, and induces cell death (LC50 = 7 μM) [69–71]. In isolated liver cells, exposure also results in membrane dysfunction and inhibits the activity of a key mixed-function oxidase, cytochrome P450 2C9 (CYP2C9) [72], although no effects on rat hepatic CYP levels were seen in vivo [73]. TBBPA is also highly immunotoxic in culture, which is demonstrated by its ability to specifically inhibit the expression of CD25 at concentrations as low as 3 μM [129].

Some concerns regarding the potential for adverse effects from TBBPA focus on the possibility that TBBPA may act as an endocrine disruptor by two mechanisms: competitively binding to estrogen receptors, which was postulated due to the structural similarities of TBBPA to a known weak estrogen, bisphenol A; and disruption of thyroid homeostasis. Some in vitro estrogen assays showed that TBBPA does not display estrogenic activity [74, 75]; however, TBBPA exhibited estrogenic effects in a mouse uterotropic assay [76]. TBBPA was a potent inhibitor of E2 sulfation in an E2SULT in vitro assay with an IC50 of 0.016 μM, making it almost 13 times more potent than PCP [77]. Very recently, Li et al. [78] showed that TBBPA is an estrogen receptor (ERα) agonist and progesterone receptor (PR) antagonist in yeast.

The central mechanism of TBBPA toxicity is thought to be through disruption of thyroid homeostasis [3]. This is of primary importance during development when small thyroidal changes in the mother can result in cognitive defects in the children [79]. TBBPA inhibited T3 and thyroid hormone receptor binding, enhanced proliferation of rat pituitary GH3 cells stimulating their production of growth hormone, and enhanced the proliferation of MtT/E-2 cells, whose growth is estrogen dependent [80]. A recent in vitro assay suggested that TBBPA can evoke a receptor-mediated thyroidal response based on evidence that TBBPA acts as a weak agonist up to 1 μM, but exhibits an antagonistic effect on the thyroid hormone receptor above 5 μM [81]. TBBPA shows considerable binding ability to TTR, a key T4 transport protein in the blood, with an affinity up to ten times greater than that of T4 [74, 77]. An in vivo study showed no effect of TBBPA on maternal or fetal T3, T4, or TTR levels; however, TSH levels in fetal plasma were increased, indicating a distinct mechanism of thyroid homeostasis disruption in vivo [82]. In addition, a 14-week reproduction study in mice showed an increase in T3 and decrease in circulating T4 [83]. This study also observed brainstem auditory evoked potentials (BAEP) and saw responses indicative of changes in hearing latency and hearing threshold [62].

3.2 Studies in Humans

Human studies of TBBPA are generally limited to in vitro assays evaluating mechanisms associated with toxicities observed in laboratory species. However, TBBPA was evaluated in a multiple insult sensitization test conducted on 54 human

subjects and was not found to be a skin sensitizer [48]. In vitro studies have demonstrated that TBBPA induces a dose-dependent formation of ROS and calcium levels in human neutrophils [84] and anti-estrogenic activity against 17β-estradiol in a human breast cancer cell line [85]. TBBPA was also shown to compete for binding to the estrogen receptor and to induce proliferation in human breast cell lines [86]. Other data based on assessments in human cell lines, discussed below, demonstrate important kinetic parameters and immunotoxicity associated with exposures to TBBPA.

Schauer et al. [87] characterized metabolic capacities across species. Both humans and rats were exposed to TBBPA via oral administration, and similar metabolite profiles were reported in both species. However, the presence of TBBPA-sulfate was not measured, whereas TBBPA-glucuronide was detected in the blood of all human subjects. Additional metabolites were measured in rats, but this may have been associated with the differential dose levels (0.1 mg/kg in humans and 300 mg/kg in rats). Based on time course analysis, TBBPA was absorbed and rapidly conjugated, suggesting that TBBPA has low systemic bioavailability in both humans and rats. Zalko et al. [88] also reported important toxicokinetic findings related to TBBPA metabolism in both rats and humans using an in vitro approach. No major qualitative differences in in vitro metabolism using human and rat subcellular fractions (microsomes and S9) were observed following exposure to 20–200 μM TBBPA. Two primary metabolites were noted in both species: a hepta-brominated dimer-like compound and a hexa-brominated compound with three aromatic rings. These data are useful in evaluating human health risk, particularly when the majority of data are in animal models.

Data reported by Kibakaya et al. [89] suggest the potential for TBBPA to induce the immunosuppressive effects in human natural killer cells. Cells were exposed to TBBPA at varying concentrations for up to 6 days and then evaluated for lytic function, tumor-target-binding function, and ATP levels. TBBPA exposures resulted in dose-dependent decreases in all parameters evaluated; however, at concentrations $\leq$2.5 μM, ATP concentration was not impacted. Additional assays in which cells were only exposed to TBBPA for 1 h and then left in TBBPA-free media for up to 6 days resulted in decreased lytic function, but did not impact binding or ATP levels. These data are important as interference with natural killer cell function could increase the risk of viral infection or other adverse effects (e.g., tumor promotion).

4 Hexabromocyclododecane

In this section, an overview of the data published in animal studies is provided, followed by a discussion of the health effects observed in humans (primarily human cell lines). Despite the widespread, high volume use of this compound, there are relatively few studies available characterizing toxicity. Even fewer studies fully

characterized the compound with respect to stereoisomer composition, which may be of particular importance with respect to both exposure and toxicity.

4.1 Studies in Laboratory Animals

Data are available to characterize a number of endpoints following exposure to HBCD in laboratory animals, including acute toxicity, skin irritation/sensitization, hepatic and thyroid toxicity, neurotoxicity, reproductive toxicity, and genotoxicity. This research has been conducted in a number of species, including rats, mice, and rabbits, and ranges from very short exposures to chronic 90-day exposures. Many of the studies have used rather high oral doses.

HBCD has very low acute toxicity following oral, inhalation, or dermal exposures. Two early studies addressing dermal toxicity of HBCD on white New Zealand rabbits documented no effects after occluded patch exposure at the highest dose of 20 g/kg [90, 91]. When mice and rats were administered doses of 20–40 g/kg of HBCD by gavage, no deaths were observed though some studies noted animals with slight diarrhea, transitory hypoactivity, trembling, and body weight reduction [91–95]. In acute inhalation studies in rats, no deaths were observed following exposure to 202 mg/l for 4 h, or 200 mg/l for 1 h [90, 91].

Several guideline-based studies have been conducted evaluating the irritation and sensitization potential of HBCD. Results generally indicate that although some mild irritation occurred, effects were not significant enough for HBCDD to be classified as an irritant or corrosive [96]. HBCD is also not considered a skin sensitizer based on output from both the Magnusson–Kligmann test and Local Lymph Node (LLN) assay [97, 98].

Repeated-dose oral toxicity studies collectively point to the liver and thyroid as target organs for HBCD toxicity; these data are generally supported by in vitro assays. Early 28- and 90-day feeding studies in rats showed significant, dose-related, increased relative liver weights [99, 100]. In the 28-day study only, both sexes exhibited thyroid hyperplasia at the lowest administered dose (940 mg/kg-day). Increased liver weight was also observed by Chengelis [101] following a 28-day exposure in rats. Additionally, thyroid weight was increased in females (300 mg/kg-day), and changes in serum T4 and TSH were apparent in all rats administered 100 mg/kg-day or higher. A similar 28-day study found that female rats exhibited significant increased absolute liver and thyroid weight and decreased serum T4 levels, with effect-specific NOAELs of 23, 2, and 55 mg/kg-day, respectively [102]. The most recent 28-day study focused on changes in hepatic gene expression, identifying lipid metabolism, cholesterol biosynthesis, and phase I and II metabolism as affected pathways [103].

Several studies have shown that HBCD does not have substantial mutagenic or cytotoxic potential [104–109]. Additionally, an in vivo micronucleus test in mice showed no clastogenic activity [110]. Additionally, a chronic feeding study on mice evaluated the effects of up to 1,300 mg/kg-day HBCD after 18 months [96].

While various types of tumors were observed in several organs, incidences were sporadic and the authors determined them not to be substance related. Collectively, these data indicate that HBCD lacks significant genotoxic potential in vitro as well as in vivo.

A two-generation, reproductive toxicity study on rats suggested a NOAEL of 10 mg/kg-day based on decreased fertility index and number of primordial follicles [111]. Although this study demonstrated increased pup mortality during lactation, there was no evidence of fetotoxicity, teratogenicity, or adverse effects on postpartum development; this is confirmed in two other studies [112, 113]. A recent study identified several adverse effects in F1 offspring, including decreased bone density, testis weight, and fraction of nuclear granulocytes [114]. Neonatal HBCD exposure has been shown to have adverse effects on neurodevelopment [69, 111, 115, 116, 130]. HBCD has also been shown to block dopamine uptake in rat brain synaptosomes in vitro [69] and inhibit neurotransmitter release [117].

4.2 Studies in Humans

A handful of in vitro studies in human cell lines have reported on the cytotoxicity, receptor binding, and changes in gene expression associated with HBCD exposures. These studies underscore the importance of evaluating specific stereoisomers as there are clearly differences in toxicokinetic profiles [118] and toxicity. For example, using a cell line derived from human liver tissue, Zhang et al. [119] evaluated the cytotoxicity of the six α-, β-, and γ-HBCD (+/−) enantiomers. Various release assays were used to evaluate cytotoxicity following exposures to HBCD in Hep G2 cells, resulting in a potency of $\gamma > \beta > \alpha$. The authors further noted that Hep G2 cells exposed to (+) enantiomers expressed significantly lower cell viability than those exposed to (−) enantiomers. Additional assays revealed a positive correlation between LDH release and ROS formation, leading the authors to posit that HBCD toxicity may be mediated via oxidative damage.

Changes in gene expression and DNA methylation were also evaluated in HepG2 cells as well as in primary human hepatocytes [120]. At the concentrations tested, HBCD exposures did not impact DNA methylation globally, though it did cause a lack of promoter demethylation in specific regions in primary hepatocytes. Expression of mRNA from specific genes associated with key events in the cell cycle was also evaluated for potential correlations with DNA methylation status. In primary hepatocytes, N-cym was upregulated by HBCD, whereas p16, RB1, ERα, ERβ, and N-cym were downregulated in HepG2 cells. Given these findings, the authors concluded that there was no correlation between proliferation and DNA methylation. The findings of this study also provide important information regarding the differential responses between a human-derived tumor cell line and primary human cells.

Hinkson and Whalen [121] evaluated the immunotoxicity of HBCD in human natural killer cells in vitro; the authors noted that adverse effects in these cells could

be associated with an increased risk of tumor development and/or viral infections. Cells were exposed for various lengths of time to concentrations of HBCD, resulting in decreased lytic function and decreases in ATP. The lack of a consistent relationship between the two, or a relationship with time or dose, makes the findings only qualitatively useful with respect to potential impacts on the human immune system. These researchers posited that these findings were due to decreased binding and cell-surface marker expression [122] in human NK cells. Using the same cell line, HBCD exposures caused a significant decrease in NK cell binding and expression of multiple cell-surface proteins; these effects appeared to have a strong relationship with dose and time.

Using an in vitro system based on transfected human liver cells (HeLaTR), Yamada-Okabe et al. [123] assessed activation of the thyroid receptor by HBCD (and other compounds). Results indicated that the receptor was activated in the presence of T3, though at a relatively low level compared to other activators. This study also included an assessment of cytotoxicity; authors reported that HBCD did not cause toxicity or proliferation in this cell line at the doses tested.

The only human study evaluating the toxicity of HBCD was performed in 1972 and evaluated skin sensitization [96, 124]. Patches of fabric soaked in 10% HBCD were worn for 6 days, removed for 2 weeks, and reapplied for 48 h. No skin reactions were reported in any subjects at any evaluation.

5 Assessment of Human Health Risk by Regulatory Agencies

In an effort to put into perspective the health effects observed in laboratory studies and in humans following exposures to PBDEs, HBCD, and TBBPA, we have provided a short discussion on the health assessments conducted by regulatory bodies for these compounds. Information is provided regarding assessments issued in the USA and Europe. Although these regulatory bodies take different approaches when evaluating risk, both consider the weight of the evidence available, focus on a critical effect, and then quantitatively evaluate safe levels of exposure.

5.1 The United States

In the USA, the Environmental Protection Agency (USEPA) developed various toxicological benchmarks for several PBDE congeners, but not HBCD or TBBPA, as part of the Integrated Risk Information System [1, 2, 6, 8]. This human health assessment program evaluated quantitative and qualitative risk information on effects that may result from exposure to a specific chemical in the environment. When supported by available data, information to characterize hazard and dose–response relationships is used to develop cancer and noncancer toxicological

benchmarks (e.g., oral reference dose for noncancer and an oral slope factor for cancer). These toxicological benchmarks are then used to quantify health risk. For BDEs 47, 99, 153, and 209, oral reference doses (RfDs) were developed. RfDs are defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime (expressed as milligram of substance/kilogram body weight-day) [125]. For BDE 209, the USEPA also derived an oral cancer slope factor (note: it was the only congener with data for carcinogenic assessment). A slope factor is defined as an upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime exposure to an agent by ingestion (expressed as units of proportion affected per milligram of substance/kilogram body weight-day) [125].

Because no human studies were available when the assessment was conducted, all toxicological benchmarks derived by the USEPA were based on animal studies. For each congener, a critical study was first selected and then a principal effect for the point of departure (e.g., no observed adverse effect level) was identified. Standard mathematical equations were then used to derive the benchmarks; for the noncancer assessment, uncertainty factors (UFs) were included in the calculation. The approach and resulting toxicological benchmark values are described below:

- *BDE 47: RfD* = 0.0001 mg/kg-day based on decreased habituation in mice in a neurobehavioral study reported by Eriksson et al. [126]. Benchmark dose modeling was applied to this dataset to develop a POD (0.35 mg/kg). An UF of 3,000 was then applied to develop the RfD [intraspecies variability (10), interhuman variability (10), extrapolation from subchronic to chronic (3), and database deficiencies (10)].
- *BDE 99: RfD* = 0.0001 mg/kg-day based on rearing habituation in a neurobehavioral study in mice reported by Viberg et al. [127]. Benchmark dose modeling was applied to this dataset to develop a POD (0.29 mg/kg). An UF of 3000 was then applied (based on the UFs described for BDE 47) to develop the RfD.
- *BDE 153: RfD* = 0.0002 mg/kg-day based on spontaneous motor behavior and learning ability in mice as reported by Viberg et al. [7]. USEPA concluded that this was the only available study appropriate for dose–response. As such, the USEPA relied on the NOAEL of 0.45 mg/kg as the POD. As for BDEs 47 and 99, an UF of 3,000 was then applied to develop the RfD.
- *BDE 209: RfD* = 0.007 mg/kg-day based neurobehavioral changes in mice as reported by Viberg et al. [7]. USEPA relied on NOAEL of 2.22 mg/kg-day as the POD and applied UFs for interhuman variability (10), interspecies variability (10), and extrapolation from subchronic to chronic exposures (3). The oral *CSF* of 7×10^{-4}/mg/kg-day was based on neoplastic nodules or carcinomas (combined) in the liver of male rats in a 2-year bioassay conducted by the National Toxicology Program [13].

5.2 Europe

The European Union (EU) has issued Risk Assessment Reports (RARs) for the PentaBDE, OctaBDE, and DecaBDE commercial mixtures. Based on an overall evaluation of the data, selection of critical endpoints and studies, and assessment of the margin of safety (MOS) between exposures and effects, conclusions regarding human health effects are assigned. In the final RAR for Deca [32], the EU determined that with respect to human health, there is at present no need for further information and/or testing and no need for risk reduction measures beyond those that were already being applied. For octabromo derivatives, the EU reported that there was a need for further information and/or testing, and that there was a need for limiting the risk in workers and in humans exposed via the environment [128]. This conclusion was based on the data demonstrating potential endocrine disruption (primarily thyroid hormones) with specific considerations regarding exposures during sensitive life stages such as breast feeding.

In the RAR for pentabromodiphenyl ethercongeners, it was determined that there was a need for further information and/or testing for occupationally exposed humans [14]. This was based on hepatic effects observed in laboratory studies with considerations related to the bioaccumulative potential of these compounds in combination with exposure levels. The lack of data characterizing toxicity following dermal exposures was also considered a significant gap when determining risk. Because of these same uncertainties, the EU assigned two conclusions regarding human exposed indirectly via the environment: (a) there is a need for further information and/or testing and (b) there is at present no need for further information and/or testing for risk reduction measures beyond those which are being applied already, as the synthesis and use of this compound were banned in the EU in 2004, and production voluntarily ceased in the USA that same year. The EU suggested the need for data on potential effects associated with lifelong exposures as well as the need to characterize exposure data from local sources. Furthermore, when considering combined exposures, the EU concluded that there was a clear need for further information and/or testing due to the MOS (described as unacceptably low) associated with both liver effects and behavioral effects. When evaluating exposures to infants via breast milk, the EU identified many data gaps that resulted in a need for further information or testing. The data needs included data on pharmacokinetics, more data on developmental effects, and more data on repeated-dose exposures (note: many of these data gaps were related to extrapolating observed effects in laboratory studies to potential effects in humans).

5.3 Stockholm Convention

Over the past several years, many of the PBDEs have been added to the United Nations Stockholm Convention on POPs. Commercial PentaBDE was the first

to be added in 2005, followed by HexaBDE and HeptaBDE (identified as the main components of the commercial octabromodiphenyl ether mixture). The later compounds are listed under Annex A with a specific exemption for use in articles containing these chemicals for recycling. TetraBDE and PentaBDE (identified as commercial pentabromodiphenyl ether mixture compounds) are also listed under Annex A with an exemption for use as articles containing these chemicals for recycling. More recently, HBCD was nominated for inclusion as a POP under the Stockholm Convention. The review committee determined that because of its persistence, adverse effects, bioaccumulative properties, and long range transport, further evaluations would be conducted with the intention of future inclusion.

6 Conclusions

The widespread production and use of BFRs, and strong evidence of increasing contamination of the environment and people by these chemicals heighten the importance of identifying emerging issues and data gaps, and of generating a future research agenda. Available data clearly indicate that exposures to PBDEs, TBBPA, and HBCD can result in adverse effects. Although the effects are compound- and dose-dependent, the primary endpoint of concern appears to be disruption of the endocrine system. The mechanism(s) are not well delineated but may include estrogenic activity, androgenic activity, variations in receptor binding (CAR and PXR), and, most likely, disruptions to thyroid hormones. Other effects of concern include hepatotoxicity and neurotoxicity, the later particularly during development. However, more studies are needed to elucidate the dose–response relationship for these effects in humans. For example, it has been stated that due to species differences in thyroid metabolism, it is unlikely that effects on the thyroid status via an induction of phase II hepatic enzymes would occur in humans. However, mechanisms other than hepatic metabolism cannot be disregarded, particularly in light of findings reported in several epidemiological studies on PBDEs. Further research is also needed to understand potential health effects associated with PBDE congeners not typically studied, and in particular, higher brominated congeners that may be associated with the breakdown of BDE 209. More toxicity studies are also needed on HBCD and TBBPA – particularly carcinogenicity studies and studies including in utero exposures, as well as a number of alternative BFRs that are replacing these compounds in commerce.

Disclaimer This chapter does not reflect the opinions or policies of the National Institutes of Health. The use of trade, firm, or corporation names in this publication is for the information and convenience of the reader. Such use does not constitute an official endorsement or approval by the NIH.

References

1. USEPA (2008) IRIS Health Assessment of 2,2',4,4'-Tetrabromodiphenyl Ether (BDE-47) CASRN 5436-43-12. U.S. Environmental Protection Agency, Washington, DC, 2008. EPA/635/R-07/005F
2. USEPA (2008) IRIS Health Assessment of 2',4,4',5-Pentabromodiphenyl Ether (BDE-99) CASRN 60348-60-92. U.S. Environmental Protection Agency, Washington, DC, 2008. EPA/635/R-07/006F
3. Birnbaum LS, Staskal DF (2004) Brominated flame retardants: cause for concern? Environ Health Perspect 112:9–17
4. Birnbaum LS, Hubal EAC (2006) Polybrominated diphenyl ethers: a case study for using biomonitoring data to address risk assessment questions. Environ Health Perspect 114:1770–1775
5. Dunnick JK, Nyska A (2009) Characterization of liver toxicity in F344/N rats and B6C3F1 mice after exposure to a flame retardant containing lower molecular weight polybrominated diphenyl ethers. Exp Toxicol Pathol 61(1):1–12
6. USEPA (2008) IRIS Health Assessment of 2',4,4',5,5'-Hexabromodiphenyl Ether (BDE-153) CASRN 68631-49-22. U.S. Environmental Protection Agency, Washington, DC, 2008. EPA/635/R-07/007F
7. Viberg H, Fredriksson A, Jakobsson E, Orn U, Eriksson P (2003) Neurobehavioral derangements in adult mice receiving decabrominated diphenyl ether (PBDE 209) during a defined period of neonatal brain development. Toxicol Sci 76:112–120
8. USEPA (2008) IRIS Health Assessment of 2',3,3',4,4',5,5',6,6'-Decabromodiphenyl Ether (BDE-209) CASRN 1163-19-5. U.S. Environmental Protection Agency, Washington, DC, 2008. EPA/635/R-07/008F
9. Rice DC, Reeve EA, Herlihy A, Zoeller RT, Thompson WD, Markovich VP (2007) Developmental delays and locomotor activity in the C57BL6/J mouse following neonatal exposure to the fully-brominated PBDE, decabromodiphenyl ether. Neurotoxicol Teratol 29(4):511–520
10. Rice DC, Thompson WD, Reeve EA, Onos KD, Assadollahzadeh M, Markovich VP (2009) Behavioral changes in aging but not young mice after neonatal exposure to the polybrominated flame retardant decaBDE. Eviron Health Perspect 117(12):1903–1911
11. Viberg H, Fredriksson A, Eriksson P (2007) Changes in spontaneous behaviour and altered response to nicotine in the adult rat, after neonatal exposure to the brominated flame retardant, decabrominated diphenyl ether (PBDE 209). Neurotoxicology 28(1):136–142
12. Xing T, Chen L, Tao Y, Wang M, Chen J, Ruan DY (2010) Effects of decabrominated diphenyl ether (PBDE 209) exposure at different developmental periods on synaptic plasticity in the dentate gyrus of adult rats In vivo. Toxicol Sci 110(2):401–410
13. NTP (National Toxicology Program) (1986) Toxicology and carcinogenesis studies of decabromodiphenyl oxide (CAS No 1163-19-5) in F344/N rats and B6C3F mice (feed studies). NTP TR 309
14. EU (2001) European Union Risk Assessment Report (RAR): Diphenyl ether, pentabromo derivative (pentabromodiphenyl ether). EUR 19730 EN
15. Hagmar L, Bjork J, Sjodin A, Bergman A, Erfurth EM (2001) Plasma levels of persistent organohalogens and hormone levels in adult male humans. Arch Environ Health 56(2): 138–143
16. Mazdai A, Dodder NG, Abernathy MP, Hites RA, Bigsby RM (2003) Polybrominated diphenyl ethers in maternal and fetal blood samples. Environ Health Perspect 111(9): 1249–1252
17. Julander A, Karlsson M, Hagstrom K, Ohlson CG, Engwall M, Bryngelsson IL, Westberg H, van Bavel B (2005) Polybrominated diphenyl ethers-plasma levels and thyroid status of workers at an electronic recycling facility. Int Arch Occup Environ Health 78:584–592

18. Yuan J, Chen L, Chen D, Guo H, Bi X, Ju Y, Jiang P, Shi J, Li L, Jiang Q, Sheng G, Fu J, Wu T, Chen X (2008) Elevated serum polybrominated diphenyl ethers and thyroid-stimulating hormone associated with lymphocytic micronuclei in Chinese workers from an E-waste dismantling site. Environ Sci Technol 42:2195–2200
19. Wang H, Zhang Y, Liu Q, Wang F, Nie J, Qian Y (2010) Examining the relationship between brominated flame retardants (BFR) exposure and changes of thyroid hormone levels around e-waste dismantling sites. Int J Hyg Environ Health 231(5):369–380
20. Turyk ME, Persky VW, Imm P, Knobeloch L, Chatterton R, Anderson HA (2008) Hormone disruption by PBDEs in adult male sport fish consumers. Environ Health Perspect 116: 1635–1641
21. Herbstman JB, Sjodin A, Apelberg BJ, Witter FR, Halden RU, Patterson DG, Panny SR, Needham LL, Goldman LR (2008) Birth delivery mode modifies the associations between prenatal polychlorinated biphenyl (PCB) and polychlorinated diphenyl ether (PBDE) and neonatal thyroid hormone levels. Environ Health Perspect 116(19):1376–1382
22. Chevrier J, Harley KG, Bradman A, Gharbi M, Sjodin A, Eskanzi B (2010) Polybrominated diphenylether (PBDE) flame retardants and thyroid hormone during pregnancy. Environ Health Perspect 118:1444–1449
23. Meeker JD, Johnson PI, Camann D, Hauser R (2009) Polybrominated diphenyl ether (PBDE) concentrations in house dust are related to hormone levels in men. Sci Total Environ 407(10):3425–3429
24. Lim JS, Lee DK, Jacobs DRJ (2008) Association of brominated flame retardants with diabetes and metabolic syndrome on the U.S. population, 2003–2004. Diabetes Care 31(9):1802–1807
25. Costa LG, Giordano G (2007) Developmental neurotoxicity of polybrominated diphenyl ether (PBDE) flame retardants. Neurotox 28(6):1047–1067
26. Roze E, Meijer L, Bakker A, Van Braeckel KN, Sauer PJ, Bos AF (2009) Prenatal exposure to organohalogens, including brominated flame retardants, influences motor, cognitive, and behavioral performance at school age. Environ Health Perspect 117:1953–1958
27. Herbstman JB, Sjodin A, Kurzon M, Lederman SA, Jones RS, Rauh V, Needham LL, Tang D, Niedzwiecki M, Wang RY, Perera F (2010) Prenatal exposure to PBDEs and neurodevelopment. Environ Health Perspect 118(5):712–719
28. Messer A (2010) Mini-review: polybrominated diphenyl ether (PBDE) flame retardants as potential autism risk factors. Physiol Behav 100:245–249
29. Main KM, Kiviranta H, Virtanen HE, Sundqvist E, Tuomisto JT, Tuomisto J, Vartiainen T, Skakkebaek NE, Toppari J (2007) Flame retardants in placenta and breast milk and cryptorchidism in newborn boys. Environ Health Perspect 115:1519–1526
30. Akutsu K, Takatori S, Noxawa S, Toshiike M, Nakazawa H, Hayakawa K, Makino T, Iwamoto T (2008) Polybrominated diphenyl ethers in human serum and sperm quality. Bull Environ Contam Toxicol 80:345–350
31. Harley K, Marks AR, Chevrier J, Bradman A, Sjodin A, Eskenazi B (2010) PBDE concentrations in women's serum and fecundability. Environ Health Perspect 118(5):699–704
32. EU (2002) European Union Risk Assessment Report (RAR): bis(pentabromophenyl) ether. EUR 20402 EN
33. Yu K, He Y, Yeung LW, Lam PK, Wu RS, Zhou B (2008) DE-71-induced apoptosis involving intracellular calcium and the Bax-mitochondria-caspase protease pathway in human neuroblastoma cells *in vitro*. Toxicol Sci 104:341–351
34. He P, Wang AG, Xia T, Gao P, Niu Q, Guo LJ, Xu BY, Chen XM (2009) Mechanism of the neurotoxic effect of PBDE-47 and interaction of PBDE-47 and PCB153 in enhancing toxicity in SH-SY5Y cells. Neurotoxicology 30:10–15
35. Tagliaferri S, Caglieri A, Goldoni M, Pinelli S, Alinovi R, Poli D, Pellacani C, Giordano G, Mutti A, Costa LG (2010) Low concentrations of the brominated flame retardants BDE-47 and BDE-99 induce synergistic oxidative stress-mediated neurotoxicity in human neuroblastoma cells. Toxicol In Vitro 24:116–122

36. Schreiber T, Gassmann K, Gotz C, Hubenthal U, Moors M, Krause G, Merk HF, Nguyen NH, Scanlan TS, Abel J, Rose CR, Fritsche E (2010) Polybrominated diphenyl ethers induce developmental neurotoxicity in a human *in vitro* model: evidence for endocrine disruption. Environ Health Perspect 118:572–578
37. Song R, Duarte TL, Almeida GM, Farmer PB, Cooke MS, Zhang W, Sheng G, Fu J, Jones GD (2009) Cytotoxicity and gene expression profiling of two hydroxylated polybrominated diphenyl ethers in human H295R adrenocortical carcinoma cells. Toxicol Lett 185:23–31
38. Reistad T, Mariussen E (2005) A commercial mixture of the brominated flame retardant pentabrominated diphenyl ether (DE-71) induces respiratory burst in human neutrophil granulocytes *in vitro*. Toxicol Sci 87:57–65
39. He W, He P, Wang A, Xia T, Xu B, Chen X (2008) Effects of PBDE-47 on cytotoxicity and genotoxicity in human neuroblastoma cells *in vitro*. Mutat Res 649:62–70
40. Canton RF, Sanderson JT, Letcher RJ, Bergman A, van den Berg M (2005) Inhibition and induction of aromatase (CYP19) activity by brominated flame retardants in H295R human adrenocortical carcinoma cells. Toxicol Sci 88:447–455
41. Canton RF, Sanderson JT, Nijmeijer S, Bergman A, Letcher RJ, van den Berg M (2006) *In vitro* effects of brominated flame retardants and metabolites on CYP17 catalytic activity: a novel mechanism of action? Toxicol Appl Pharmacol 216:274–281
42. Song R, He Y, Murphy MB, Yeung LW, Yu RM, Lam MH, Lam PK, Hecker M, Giesy JP, Wu RS, Zhang W, Sheng G, Fu J (2008) Effects of fifteen PBDE metabolites, DE71, DE79 and TBBPA on steroidogenesis in the H295R cell line. Chemosphere 71:1888–1894
43. Hu XZ, Xu Y, Hu DC, Hui Y, Yang FX (2007) Apoptosis induction on human hepatoma cells Hep G2 of decabrominated diphenyl ether (PBDE-209). Toxicol Lett Jun 15;171(1-2):19–28. Epub 2007 Apr 10
44. Shao J, White CC, Dabrowski MJ, Kavanagh TJ, Eckert ML, Gallagher EP (2008) The role of mitochondrial and oxidative injury in BDE 47 toxicity to human fetal liver hematopoietic stem cells. Toxicol Sci 101:81–90
45. Stapleton HM, Kelly SM, Pei R, Letcher RJ, Gunsch C (2009) Metabolism of polybrominated diphenyl ethers (PBDEs) by human hepatocytes *in vitro*. Environ Health Perspect 117:197–202
46. Lupton SJ, McGarrigle BP, Olson JR, Wood TD, Aga DS (2009) Human liver microsome-mediated metabolism of brominated diphenyl ethers 47, 99, and 153 and identification of their major metabolites. Chem Res Toxicol 22:1802–1809
47. Mundy WR, Freudenrich TM, Crofton KM et al (2004) Accumulation of PBDE-47 in primary cultures of rat neocortical cells. Toxicol Sci 82:164–169
48. EU (2006) European Union Risk Assessment Report (RAR): 2,2',6,6'-tetrabromo-4.4'iso-propylinenediphenol (tetrabromobisphenol-A or TBBP-A) Part II – Health Assessment. EUR 22161 EN
49. Hill Top Research, Inc (1966) Acute toxicity and irritation studies in Tetrabromobisphenol A (unpublished)
50. International Research and Development Corporation (1978) Acute oral toxicity (LD50) study in mice (unpublished)
51. Leberco Laboratories (1958) Acute oral toxicity test (unpublished)
52. Pharmakon Laboratories (1981) Acute oral toxicity study in rats (14 day) (unpublished report no. PH 402-ET-001-81)
53. Pharmakon Laboratories (1981) Acute dermal toxicity study in rabbits (unpublished report no. PH 422-ET-001-81)
54. WHO (1995) Tetrabromobisphenol A and derivatives. Environmental Health Criteria 172. World Health Organization, Geneva
55. MPI Research (2002) A 90-day oral toxicity study of tetrabromobisphenol-A in rats with a recovery group (unpublished)
56. Noda T, Morita S, Ohgaki S, Shimizu M (1985) Safety evaluation of chemicals for use in household products (VII) teratological studies on tetrabromobisphenol-A in rats. Annual report of the Osaka Institute of Public Health and Environmental Sciences 48:106–112

57. MPI Research (2001) Final report – an oral prenatal developmental toxicity study with tetrabromobisphenol-A in rats (unpublished)
58. MPI Research (2002) An oral two generation reproductive, fertility and developmental neurobehavioural study of tetrabromobisphenol-A in rats (unpublished)
59. MPI Research (2003) Amendment to the final report. An oral two generation reproductive, fertility and developmental neurobehavioural study of tetrabromobisphenol-A in rats (Unpublished report)
60. Fukuda N, Ito Y, Yamaguchi M, Mitumori K, Koizumi M, Hasegawa R, Kamata E, Ema M (2004) Unexpected nephotoxicity induced by tetrabromobisphenol A in newborn rats. Toxicol Lett 150:145–155
61. Tada Y, Fujitani T, Yano N, Takahashi H, Yuzawa K, Ando H, Kubo Y, Nagasawa A, Ogata A, Kaminmura H (2006) Effects of tetrabromobisphenol A, brominated flame retardant, in ICR mice after prenatal and postnatal exposure. Food Chem Toxicol 44(8):1408–1413
62. Lilienthal H, Verwer CM, van der Ven LT, Piersma AH, Vos JG (2008) Exposure to tetrabromobisphenol A (TBBPA) in Wistar rats: neurobehavioral effects in offspring from a one-generation reproduction study. Toxicology 246:45–54
63. Nakajima A, Saigusa D, Tetsu N, Yamakuni T, Tomioka Y, Hishinuma T (2009) Neurobehavioral effects of tetrabromobisphenol A, a brominated flame retardant, in mice. Toxicol Lett 189(1):78–83
64. Williams AL, DeSesso JM (2010) The potential of selected brominated flame retardants to affect neurological development. J Toxicol Environ Health B Crit Rev 13(5):441–448
65. Ethyl Corporation (1981) Salmonella/microsomal assay-tetrabromobisphenol A EPA/OTS Doc Number 878216192
66. Mortelmans K, Haworth S, Lawlor T, Speck W, Tainer B, Zeigler E (1986) Salmonella mutagenicity test: II. Results from the testing of 270 Chemicals. Environ Mutagen 8(7): 1–119
67. BioReliance (2001) An *in vitro* mammalian chromosome aberration test with tetrabromobisphenol-A (unpublished)
68. Helleday T, Tuominen K, Bergman A, Jenseen D (1999) Brominated flame retardants induce intragenic recombination in mammalian cells. Mutat Res 439:137–147
69. Mariussen E, Fonnum F (2002) The effect of pentabromodiphenyl ether, hexabromocyclododecane and tetrabromobisphenol- A on dopamine uptake into rat brain synaptosomes. Organohalogen Compounds 57:395–399
70. Reistad T, Mariussen E, Fonnum F (2002) The effect of brominated flame retardants on cell death and free radical formation in cerebellar granule cells. Organohalogen Compounds 57:391–394
71. Reistad T, Mariussen E, Ring A, Fonnum F (2007) *In vitro* toxicity of tetrabromobisphenol-A on cerebellar granule cells: cell death, free radical formation, calcium influx and extracellular glutamate. Toxicol Sci 96:268–278
72. Boecker RH, Schwind B, Kraus V, Pullen S, Tiegs G (2001). Cellular disturbances by various brominated flame retardants [Abstract]. Presented at the Second International Workshop on Brominated Flame Retardants, 14–16 May 2001, Stockholm, Sweden
73. Germer S, Piersma AH, van der Ven L, Kamyschnikov A, Fery Y, Schmitz H-J, Schrenk D (2006) Subacute effects of the brominated flame retardants hexabromocyclododecane and tetrabisphenol A on hepatic cytochrome P450 levels in rats. Toxicology 218:229–236
74. Meerts IATM, Letcher RL, Hoving S, Bergman A, Lemmen JG, van der Burg B, Brouwer A (2001) *In vitro* estrogenicity of polybrominated diphenyl ethers, hydroxylated PBDEs and polybrominated bisphenol A compounds. Environ Health Perspect 109(4):399–407
75. Miller D, Wheals BB, Beresford N, Sumpter JP (2001) Estrogenic activity of phenolic additives determined by an *in vitro* yeast bioassay. Environ Health Perspect 109(2): 133–138
76. Kitamura S, Kato T, Iida M, Jinno N, Suzuki T, Ohta S, Fujimoto N, Hanada H, Kashiwaga K, Kashiwaga A (2005) Anti-thyroid hormonal activity of tetrabromobisphenol A, a flame retardant, and related compounds: affinity to the mammalian thyroid hormone receptor, and effect on tadpole metamorphosis. Life Sci 76:1589–1601

77. Hamers T, Kamstra JH, Sonneveld E, Murk AJ, Kester MHA, Andersson P, Legler J, Brouwer A (2006) *In vitro* profiling of the endocrine disrupting potency of brominated flame retardants. Toxicol Sci 92(1):157–173
78. Li J, Ma M, Wang Z (2010) *In vitro* profiling of endocrine disrupting effects of phenols. Toxicol In Vitro 24(1):201–207
79. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J et al (1999) Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 341:549–555
80. Kitamura S, Jinno N, Ohta S, Kuroki H, Fujimoto N (2002) Thyroid hormonal activity of the flame retardants tetrabromobisphenol A and tetrachlorobisphenol A. Biochem Biophys Res Commun 293:554–559
81. Freitas J, Cano P, Craig-Veit C, Goodson ML, Furlow JD, Murk AJ (2011) Detection of thyroid hormone receptor disruptors by a novel stable *in vitro* reporter gene assay. Toxicol In Vitro 25:257–266
82. Meerts IATM, Assink Y, Cenijin PH, Weijers BM, van den Berg HHJ (1999) Distribution of the flame retardant tetrabromobisphenol A in pregnant and fetal rats and effect on thyroid hormone homeostasis. Brominated Flame Retardants P068/. Organohalogen Compounds 40:375–378
83. Van der Ven LT, Ven de Kuil T, Verhoef A, Verwer CM, Lilienthal H, Leonards PE et al (2008) Endocrine effects of tetrabromobisphenol- A (TBBPA) in Wistar rats as tested in a one-generation reproduction study and a subacute toxicity study. Toxicology 260(1–3): 150–152
84. Reistad T, Mariussen E, Fonnum F (2005) The effect of a brominated flame retardant, tetrabromobisphenol-A, on free radical formation in human neutrophil granulocytes: the involvement of the MAP kinase pathway and protein kinase C. Toxicol Sci 83:89–100
85. Kitamura S, Suzuki T, Sanoh S, Kohta R, Jinno N, Sugihara K, Yoshihara S, Fujimoto N, Watanabe H, Ohta S (2005) Comparative study of the endocrine-disrupting activity of bisphenol A and 19 related compounds. Toxicol Sci 84:249–259
86. Samuelsen M, Olsen C, Holme JA, Meussen-Elhoom E, Bergmann A, Hongslo JK (2001) Estrogen-like properties of brominated analogs of bisphenol A in the MCF-7 human breast cancer cell line. Cell Biol Toxicol 14:139–151
87. Schauer UM, Volkel W, Dekant W (2006) Toxicokinetics of tetrabromobisphenol a in humans and rats after oral administration. Toxicol Sci 91:49–58
88. Zalko D, Prouillac C, Riu A, Perdu E, Dolo L, Jouanin I, Canlet C, Debrauwer L, Cravedi JP (2006) Biotransformation of the flame retardant tetrabromo-bisphenol A by human and rat sub-cellular liver fractions. Chemosphere 64:318–327
89. Kibakaya EC, Stephen K, Whalen MM (2009) Tetrabromobisphenol A has immunosuppressive effects on human natural killer cells. J Immunotoxicol 6:285–292
90. Lewis AC, Palanker AL (1978) A dermal LD_{50} study in albino rabbits and an inhalation LC_{50} study in albino rats. Test material GLS-S6-41A. Client: Saytech Inc. (not published). 78385-2, Consumer product testing
91. Wilson PD, Leong BKJ (1977) Acute toxicity studies in rabbits and rats. Test material Firemaster 100 Lot 53 77.902. Sponsored by: Velsicol Chemical Corporation (not published). pp 163–499, International Research and Development Corporation
92. Lewis AC and Palanker AL (1978) A primary dermal irritation study, a dermal corrosion study, and an ocular irritation study in albino rabbits and an oral LD_{50} study in albino rats. Test material GLS-S6-41A. Client: Saytech Inc. (not published). 78385-1, Concumer Product Testing
93. Ogaswara S, Fukushi A, Midorikawa Y (1983) Report on acute toxicity test of pyroguard SR-103 in rats (not published)
94. Tobe et al (1984) Acute toxicity test of hexabromocyclododecane (not published). Research Center for Biological Safety National Public Health Research Institute

95. USEPA (1990) Report on the study of the acute oral toxicity of hexabromocyclododecane in the mouse. Letter from BASF. 86-900000383, EPT/OTS Doc
96. EU (2008) European Union Risk Assessment Report (RAR): Hexabromocyclododecane
97. Wenk ML (1996) Maximization test in guinea pigs. Test article: Hexabromocyclododecane; p 43. Microbiologial Associates, Inc., Rockvill, MD, USA
98. Wolhiser MR, Anderson PK (2003) Hexabromocyclododecane: contact sensitization potential via the local lymph node assay (including a primary irritancy screen) using CBA/J mice. Study ID 031013, p 24. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan, USA
99. Zeller H, Kirsch P (1969) Hexabromocyclododecane: 28-day feeding trials with rats. BASF (not published)
100. Zeller H, Kirsch P (1970) Hexabromocyclododecane: 90-day feeding trials with rats. BASF (not published)
101. Chengelis CP (2001). A 90-day oral (gavage) toxicity study of HBCD in rats. WIL-186012, p 1527. Wil Research Laboratories, Inc., Ashland, Ohio, USA
102. Van der Ven LTM, Verhoef A, van de Kuil T, Slob W, Leonards PEG, Visser TJ, Hamers T, Håkansson H, Olausson H, Piersma AH, Vos JG (2006) A 28-day oral dose toxicity study of hexabromocyclododecane (HBCD) in Wistar rats. Toxicol Sci 94:281–292
103. Canton RF, Peijnenburg AA, Hoogenboom RL, Piersma AH, van der Ven LT, van den Berg M, Heneweer M (2008) Subacute effects of hexabromocyclododecane (HBCD) on hepatic gene expression profiles in rats. Toxicol Appl Pharmacol 231(2):267–272
104. Baskin AD, Phillips BM (1977) Mutagenicity of two lots of FM-100, Lot 53 and residue of lot 3322 in the absence and presence of metabolic activation. Sponsored by: Velsicol Chemical Corporation (not published). Industrial BIO TEST Laboratories, Inc
105. GSRI (1979) Mutagenicity test of GLS-S6-41A (not published). Gulf South Research Institute
106. Hossack DJN, Richold M, Jones E, Bellamy RP (1978) Ames metabolic activation test to assess the potential mutagenic effect of compound no. 49. pp 1–2. Huntingdon Research Centre
107. Simmon VF, Poole DC, Newell GW, Skinner WA (1976) *In vitro* microbiological mutagenicity studies of four CIBA-GEIGY corporation compounds. Prepared for CIBAGeigy Corporation (not published). 5702, SRI Project LSC
108. USEPA (1990) Ames test with hexabromides. Letter from BASF. 86-900000379, EPA/OTS Doc
109. Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K, Speck W (1987) Salmonella mutagenicity tests: III. Results from the testing of 255 chemicals. Environ Mutagen 9(Suppl 9):1–110
110. Engelhardt and Hoffman (2000) Cytogenetic study *in vivo* with of hexabromocyclododecane in the mouse micronucleus test after two intraperitoneal administrations. BASF, Ludwigshafen, Germany
111. Ema M, Fujii S, Hirata-Koizumi M, Matsumoto M (2008) Two-generation reproductive toxicity study of the flame retardant hexabromocyclododecane in rats. Reprod Toxicol 25(3): 335–351
112. Murai T, Kawasaki H, Kanoh S (1985) Studies on the toxicity of insecticides and food additives in pregnant rats (7). Fetal toxicity of hexabromocyclododekane. Oyo Yakuri 29:981–986
113. Stump DG (1999) Prenatal developmental toxicity study of hexabromocyclododecane (HBCD) in rats. WIL Research Laboratories, Inc, Ashland, Ohio, USA, p 410
114. Van der Ven LT, van de Kuil T, Leonards PEG, Slob W, Lilienthal H, Litens S, Herlin M, Hakansson H et al (2009) Endocrine effects of hexabromocyclododecane (HBCD) in a one-generation reporoduction study in Wistar rats. Toxicol Lett 185:51–62
115. Lilienthal H, van der Ven L, Roth-Haerer A, Hack A, Piersma A, Vos J (2006) Neurobehavioral toxicity of brominated flame retardants: differential effects of PBDE-99, TBBPA and

HBCD and endocrine relation. Dioxin Conference 2006 Oslo. Organohalogen Compounds 68: 3 pages
116. Lilienthal H, van der Ven LT, Piersma AH, Vos JG (2009) Effects of the brominated flame retardant hexabromocylcododecane (HBCD) on dopamine-dependent behavior and brainstem auditory evoked potentials in a one-generation reproduction study in Wistar rats. Toxicol Lett 185(1):63–72
117. Dingemans MML, Heusinkveld HJ, de Groot A, Bergman A, van de Berg M, Westerink RHS (2009) Hexabromocylcododecane inhibits depolarization-induced increase in intracellular calcium levels and neurotransmitter release in PC12 cells. Toxicol Sci 107(2):490–497
118. Szabo DT, Diliberto JJ, Hakk H, Huwe JK, Birnbaum LS (2010) Toxicokinetics of the flame retardant hexabromocyclododecane gamma: effect of dose, timing, route, repeated exposure, and metabolism. Toxicol Sci 117(2):282–293
119. Zhang X, Yang F, Xu C, Liu W, Wen S, Xu Y (2008) Cytotoxicity evaluation of three pairs of hexabromocyclododecane (HBCD) enantiomers on Hep G2 cell. Toxicol In Vitro 22:1520–1527
120. Aniagu SO, Williams TD, Chipman JK (2009) Changes in gene expression and assessment of DNA methylation in primary human hepatocytes and HepG2 cells exposed to the environmental contaminants-Hexabromocyclododecane and 17-beta oestradiol. Toxicology 256:143–151
121. Hinkson NC, Whalen MM (2009) Hexabromocyclododecane decreases the lytic function and ATP levels of human natural killer cells. J Appl Toxicol 29:656–661
122. Hinkson NC, Whalen MM (2010) Hexabromocyclododecane decreases tumor-cell-binding capacity and cell-surface protein expression of human natural killer cells. J Appl Toxicol 30:302–309
123. Yamada-Okabe T, Sakai H, Kashima Y, Yamada-Okabe H (2005) Modulation at a cellular level of the thyroid hormone receptor-mediated gene expression by 1, 2, 5, 6, 9, 10-hexabromocyclododecane (HBCD), 4, 4´-diiodobiphenyl (DIB), and nitrofen (NIP). Toxicol Lett 155:127–133
124. McDonnell (1972) Human Patch Test, Haskell Laboratory Report. p. 185-72, Haskell Laboratory for toxicology and Industrial Medicine, E.I. du Pont de Nemours and Company
125. USEPA (2010) IRIS glossary/Acronyms and Abbreviations. Available: http://www.epa.gov/ncea/iris/help_gloss.htm. Accessed 29 Nov 2010
126. Eriksson P, Jakobsson E, Fredriksson A (2001) Brominated flame retardants: a novel class of developmental neurotoxicants in our environment? Environ Health Perspect 109:903–908
127. Viberg H, Fredriksson A, Eriksson P (2004) Investigations of strain and/or gender differences in developmental neurotoxic effects of polybrominated diphenyl ethers in mice. Toxicol Sci 81:344–353
128. EU (2003) European Union Risk Assessment Report (RAR): Diphenyl ether, octabromo derivative. EUR 20403 EN
129. Pullen S, Boecker R, Tiegs G (2003) The flame retardants tetrabromobisphenol A and tetrabromobisphenol A-bisallylether suppress the induction of interleukin-2 receptor alpha chain (CD25) in murine splenocytes. Toxicology Feb 14;184(1):11–22
130. Eriksson P, Fischer C, Fredriksson A (2006) Polybrominated diphenyl ethers, a group of brominated flame retardants, can interact with polychlorinated biphenyls in enhancing developmental neurobehavioral defects. Toxicol Sci Dec;94(2):302–9. Epub 2006 Sep 15

Sample Preparation and Chromatographic Methods Applied to Congener-Specific Analysis of Polybrominated Diphenyl Ethers

Adrian Covaci, Alin C. Dirtu, Stefan Voorspoels, Laurence Roosens, and Peter Lepom

Abstract This chapter reviews the recent literature and highlights the technical and methodological improvements in the analysis of polybrominated diphenyl ethers (PBDEs). Sample preparation, extraction of the analytes and clean-up are discussed with emphasis on recent developments. Gas chromatography coupled with mass spectrometry (GC-MS) is discussed for the instrumental analysis of PBDEs. The most important parameters that may affect accurate measurements of PBDEs are also included. Information related to quality assurance/quality control (QA/QC) procedures used in the analysis of PBDEs, including method validation parameters and possible sources for biased results, is given in detail. An overview of recent

A. Covaci (✉)
Toxicological Center, Department of Pharmaceutical Sciences, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium

Laboratory for Ecophysiology, Biochemistry and Toxicology, Department of Biology, University of Antwerp, Groenenborgerlaan 171, 2020 Antwerp, Belgium
e-mail: adrian.covaci@ua.ac.be

A.C. Dirtu
Toxicological Center, Department of Pharmaceutical Sciences, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium

Department of Chemistry, "Al. I. Cuza" University of Iasi, Carol I Bvd. No 11, 700506 Iasi, Romania

S. Voorspoels
European Commission, Joint Research Centre, Institute for Reference Materials and Measurements (IRMM), Retieseweg 111, 2440 Geel, Belgium

Flemish Institute for Technological Research (VITO), Boeretang 200, 2400 Mol, Belgium

L. Roosens
Toxicological Center, Department of Pharmaceutical Sciences, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium

P. Lepom
Umweltbundesamt, PO Box 33 00 22 14191 Berlin, Germany

Vietnam Environment Administration Centre for Environmental Monitoring (CEM), 556 Nguyen Van Cu, Long Bien, Hanoi, Vietnam

E. Eljarrat and D. Barceló (eds.), *Brominated Flame Retardants*,
Hdb Env Chem (2011) 16: 55–94, DOI 10.1007/698_2010_81,

inter-laboratory studies on PBDEs and a discussion of the scores and outcomes conclude the chapter.

Keywords Analytical methods, Gas chromatography, Mass spectrometry, Mass spectrometryPBDEs, Polybrominated diphenyl ethers, Quality assurance, Recent developments, Review

Contents

1 Introduction

Due to their widespread environmental occurrence and their possible adverse effects in organisms, brominated flame retardants (BFRs), such as polybrominated diphenyl ethers (PBDEs), hexabromocyclododecane (HBCD) and tetrabromobisphenol-A (TBBP-A), are being determined in a growing number of laboratories. Analytical methods for BFRs have shown a rapid development and they were in many cases based on protocols previously established for other persistent organic pollutants (POPs), such as organochlorine pesticides (OCPs), polychlorinated biphenyls (PCBs) or polychlorinated dioxins and furans (PCDD/Fs). Although different properties of BFRs (e.g. polarity or vapour pressure) suggest that different procedures should be applied for their analysis, some common approaches can be found depending on the analyte, and the type of sample or detection method [1–4]. Some compounds, such as individual HBCD isomers and TBBP-A, may require specific analytical approaches due to their particular properties [126]. The methods described in the literature for the analysis of PBDEs have been reviewed in the past years [2–5]. This chapter focuses on recent literature until 2010 and highlights the technical and methodological improvements in the analysis of PBDEs. It also gives detailed information on quality assurance issues including results of recent inter-laboratory studies

2 Sample Preparation

Although sampling is a crucial step in the complete analytical process, it is not considered in this chapter since the approach needed for BFRs is not different than for other POPs. The sample preparation will therefore be covered from sample collection onwards. Since the use and production of PBDEs have been restricted and concentrations of some congeners are declining in many regions, scientists were encouraged to search for more sensitive and selective analytical techniques to monitor current environmental levels. This has resulted in a growing number of analytical papers exploring alternate sample preparation methodologies (Table 1) for the analysis of PBDEs in abiotic and biotic matrices. In order of execution, sample preparation usually consists of sample pre-treatment, extraction of the analytes and clean-up of the crude extract.

2.1 Sample Pre-Treatment

If non-polar solvents are used during sample preparation, the matrix has to be water-free to enable extraction of the analytes. Biological samples, such as food and tissue samples, are often subjected to water depletion by mixing the sample with sodium sulphate or by freeze drying. Subsequent thorough mixing ensures a homogeneous and water-free matrix. Soil, sediment, sludge and dust samples should be dried before extraction. In addition, they may be sieved to ensure particle size homogeneity and to facilitate further manipulations of the samples, but this is not imperative for a successful extraction or clean-up procedure.

Analysis of hair requires a different sample pre-treatment [32]. This matrix received increasing attention in medical settings where hair analyses are indicative of pharmaceutical and illicit drug use. The hair has to be washed to eliminate external contamination, dried and cut. Subsequent destruction of the hair matrix is necessary to enable the extraction of the analytes. Destruction can consist of an acid digestion with HCl or a basic digestion with NaOH followed by an overnight incubation at 40–50°C. Tadeo et al. [32] have investigated different sample pre-treatment techniques to analyse the PBDE content of hair. Acidic digestion provided cleaner hair extracts with less interfering compounds than those obtained with alkaline digestion. Moreover, alkaline digestion may degrade some halogenated compounds (such as some OCPs), although this effect was not observed for PBDEs.

2.2 Extraction

There are some particularities in the sample extraction for PBDE analysis that requires additional attention. First, the wide range in molecular weights of the PBDE congeners (between 250 and 960 u) yields different physical behaviours, indicating that extraction techniques may not work equally well for all PBDE

Table 1 Overview of typical analytical procedures used for the determination of PBDEs in selected matrices

BFRs (# cong.)	Sample type (g, mL)	Pre-treatment	Extraction procedure[a]	Clean-up	Instrumental analysis	Recovery (%)	RSD (%)	LOD	References
Water									
Di-deca-BDEs (8)	Waste water (5)	Add NaCl	ORMOSIL-SPME	/	GC-ECNI-MS GC-ECD	/	<20	0.2–3.6 pg/mL	[6]
Tetra-hexa-BDEs (4)	Water (10)	/	Cloud point extraction (NaCl, surfactant and buffer)	Ultrasound-assisted back-extraction (isooctane)	GC-MS	96–106	<8.5	1–2 pg/mL	[7]
Tri-deca-BDEs (8)	River water	Filtration	SPE	-Anhydrous Na_2SO_4 -Fractionation on Florisil® -Acid silica, activated silica, neutral alumina	GC-ECNI-MS	57–101	<16	3–150 pg/L	[8]
Tri-deca-BDEs (8)	River water (particulate phase)	Filtration centrifugation	Ultrasound-assisted extraction	Anhydrous Na_2SO_4 Fractionation on Florisil® Acid silica, activated silica, neutral alumina	GC-ECNI-MS	/	/	4–95 pg/L	[8]
Air and dust									
Tri-deca-BDEs (16)	Indoor air and dust	PUF filtration	Soxhlet extraction (24 h, toluene)	Mixed silica (33% 1 M NaOH and 44% H_2SO_4) (170 mL, heptane) alumina (50 mL, hexane/DCM, 1:1)	GC-MS		7	0.04–0.18 pg/m^3 (air) 0.007–0.13 ng/g (dust)	[9]
Tri-deca BDEs (11)	Outdoor air	PUF filtration	Soxhlet extracted (72 h, Acet: hexane, 1:1)	Acid/basic silica column (70 mL DCM:*n*-hexane, 1:1)	GC-ECNI-MS	/	/	0.15–15.9 pg/m^3	[10]
Tri-deca (8)	Indoor air and dust	PUF filtration	Soxhlet extraction (>16 h, toluene)	Mixed silica (10% $AgNO_3$, 22% H_2SO_4, 44% H_2SO_4, 2% KOH) (*n*-hexane: DCM, 80:20) activated carbon silica (*n*-hexane:DCM, 75:25, toluene)	GC-EI-MS	57	/	/	[11]

Mono-deca BDEs (56)	Combustion gas	Filtration	Soxhlet extraction (3.5 h, DCM, 16 h, toluene)	Mixed silica (acid, basic, neutral) basic alumina (DCM)	GC-HRMS	10.1–87.9			[12]
Tri-deca BDEs (12)	Clothes dryer lint (0.2-1)		Soxhlet (24 h, toluene)	Silica/acidified silica/ alumina	GC-HRMS	70	/	/	[13]
Sediment and sewage									
Tri-deca BDEs (13)	Sediment (7)		PLE (DCM)	Activ. Cu Silica–alumina LC fractionation	GC-ECNI-MS	/	/	/	[14]
Tri-deca BDEs (10)	Sediment	Freeze drying Grounding Homogenisation	PLE (Acet:*n*-hexane, 1:1)	Activ. Cu Silica/alumina (*n*-hexane/DCM, 6:4) Alumina/neutr. silica / H_2SO_4 silica (*n*-hexane)	GC-ECD GC-ECNI-MS	72–115	/	/	[15]
Tri-deca BDE (11)	Sediment	/	Soxhlet (72 h Acet/*n*-hexane, 1:1) + activated Cu	Mixed silica (acid/basic) column (70 mL DCM:*n*-hexane)	GC-ECNI-MS	73.5–86.7	<10	/	[16]
Tri-deca BDE (14)	Sewage sludge	Freeze drying Homogenisation Cu powder	MSPD (alumina and Na_2SO_4) assisted by sonication	Silica (AcN) Filtration	GC-EI-MS	91–104		0.05–5.6 ng/g	[17]
Tri-deca BDEs (17)	Soil (10)	Freeze drying Homogenisation Sieving	PLE (DCM:*n*-hexane, 1:1)	Silica gel, basic silica, silica, acid silica, silica (100 mL *n*-hexane)	GC-HRMS	70–143	/	0.34 ng/g	[18]
Tetra-hexa-BDEs (6)	Sediment	$KMnO_4$ H_2SO_4 Water	SPME (using polyacrylate fibre – headspace mode)	/	GC-MS/MS	76–111	<14	<0.15 ng/g	[19]

(*continued*)

Table 1 (continued)

BFRs (# cong.)	Sample type (g, mL)	Pre-treatment	Extraction procedure[a]	Clean-up	Instrumental analysis	Recovery (%)	RSD (%)	LOD	References
Tri-deca BDEs (8)	Sediment (2)	Anhydrous Na_2SO_4	UAE	Anhydrous Na_2SO_4 Fractionation on Florisil® Acid silica, activated silica, neutral alumina	GC-ECNI-MS	76–100	/	5–145 pg/g	[8]
Abiotic samples									
Tri-deca BDEs (14)	E-waste and autoshredder waste	Sieving (2 mm)	MAE (DCM: Acet)	- Silica and alumina	GC-ECD	49–150	10	/	[20]
Deca BDE	Polyethylene + polystyrene	/	MAE (toluene: MeOH)	/	HPLC-UV	85	/	/	[21]
Deca BDE	E-waste (0.5)		MAE i-PrOH: MeOH (1:1) and i-PrOH:hexane (1:1)	Filtered (0.45 mm pore HPLC Teflon filter)	HPLC-UV	30	<12		[22]
Biological samples									
Tri-deca-BDEs (13)	Polar bear adipose and liver tissue (0.5)	Homogenisation Anhydrous Na_2SO_4	Column extraction (DCM: hexane, 1:1, 200 mL)	LLE (H_2SO_4) Deact. Florisil® (1.2% H_2O)	GC-MS	79(adip) 77(liver)	30(adip) 37(liver)	0.1 ng/g ww	[23]
Tri-deca-BDEs (13)	Polar bear brain tissue (2)	Homogenisation Na_2SO_4	Soxhlet extracted (4 h Acet: hexane, 1:1, 150 mL)	LLE (H_2SO_4) Deact. Florisil® (1.2% H_2O)	GC-MS	51	64	0.1 ng/g ww	[23]
Tri-deca-BDEs (13)	Polar bear whole blood (2)	Add 1 mL 6 M HCl Add 3 mL 2-propanol	LLE (MTBE: hexane, 1:1)	LLE (H_2SO_4) Deact. Florisil® (1.2% H_2O)	GC-MS	74	33	0.1 ng/mL ww	[23]
Tri-deca BDEs (13)	Freeze-dried mussels (5)	Homogenisation Freeze drying	PLE (DCM)	GPC silica-alumina (*n*-hexane) LC fractionation	GC-ECNI-MS	/	4–31	/	[14]

Tri-hepta-BDEs (14)	Sea mammal blubber (1)	/	3 × SLE (25 mL DCM, 100°C, 15 min, microwave)	GPC (bio-beads, DCM/hexane, 1:1)	GC-MS	93–105	8.8–11	/	[24]
Tri-deca BDEs (8)	Human serum and breast milk (5)	Add HCl Add isopropanol	2 × LLE (*n*-hexane/MTBE, 1:1) Wash NaCl/H_2O	2 × LLE H_2SO_4 (2 mL) Silica/H_2SO_4 column (2:1, 1 g, *n*-hexane)	GC-ECNI-MS	/	/	/	[25]
Tri-deca BDEs (11)	Bird liver and brain tissue	/	Extracted twice with cyclohexane and Acet (3:2)	LLE (H_2SO_4)	GC-MS	87	6	0.03–0.3 ng/g ww	[26]
Tri-hepta-BDEs (16)	Food (30) Blood (30)	Centrifugation (blood) Homogenisation Na_2SO_4	SLE (pentane/Acet, 1:1)	LLE H_2SO_4 (60°C, 1 h) Activ. Alumina (*n*-hexane:DCM) silica (hexane)	GC-MS				[9]
Tri-hepta-BDEs (10)	Fish muscle tissue (3–6)	Freeze drying Homogenisation	Hot Soxhlet (acet/hexane, 1:3)	Acidified silica (8 g) Florisil® (1 g)	GC-ECNI-MS	70–100	<10	0.2–0.3 ng/g lw	[27]
Tri-hexa-BDEs (6)	Human milk (10)	Add 5 mL 2% calcium oxalate 10 mL EtOH-diethylether (1:1, v/v)	2 × 15 mL hexane wash with H_2O dry over Na_2SO_4	GPC Silica (*n*-hexane:DCM, 88:12, 15 mL)	GC-MS	/	5.5–9.2	0.1–2.5 ng/g lw	[28]
Tri-deca BDEs (12)	Placental tissue (22)	Homogenisation Drying with diatomaceous earth	Soxhlet extraction (7 h, 500 mL, *n*-hexane:Acet, 4:1)	Deact. alumina (10% H_2O) /activ. silica/acid silica (40%) (250 mL *n*-hexane)	GC-ECNI-MS	80–120	/	/	[29]
Mono-deca BDEs (42)	Tree leaves (2)	Rinsing and drying Na_2SO_4 and ground	LLE (30 mL, *n*-hexane:DCM, 1:1) Centrifugation	Activ. silica/basic silica/activ silica/acid silica (44% H_2SO_4)/acid silica (22% H_2SO_4)/activ. silica (100 mL *n*-hexane)	GC-ECNI-MS	75–115	/	0.001–0.05 ng/g dw	[30]

(*continued*)

Table 1 (continued)

BFRs (# cong.)	Sample type (g, mL)	Pre-treatment	Extraction procedure[a]	Clean-up	Instrumental analysis	Recovery (%)	RSD (%)	LOD	References
Tri-hexa-BDEs (9)	Muscle tissue bluefin tuna (3)	-Na_2SO_4 and ground	Hot Soxhlet extraction (2 h, 100 mL, *n*-hexane: Acet, 3:1)	Acid silica (8 g) (20 mL *n*-hexane and 15 mL DCM)	GC-EI-MS	96–120	<10	0.1–0.25 ng/g lw	[31]
Tri-deca (14)	Hair (2)	Wash, dry, cut, mix 3 N HCl (24 h, 40°C) 2.5 N NaOH (24 h, 40°C)	Extract 4 × 2 mL hexane	Florisil®/Na_2SO_4 column (hexane: EtOAc, 80:20)	GC-EI-MS	>90	<14	0.08–0.9 ng/g	[32]
Mono-hepta-BDEs (40)	Freeze-dried milk (1)	Freeze drying	PLE	Alumina SPE (5 g, 40 mL *n*-hexane, 40 mL *n*-hexane:DCM, 1:2)	GC-ECNI-MS	70–131	<18	0.01–0.05 ng/g	[33]
Mono-deca BDEs (43)	Placental tissue (4)	Homogenisation Freeze drying	MSPD (Florisil®, *n*-hexane: DCM, 8:2)	GPC (*n*-hexane:DCM, 1:1) neutral, basic, acid, neutral silica (*n*-hexane)	GC-ECNI-MS	91–114			[34]
Tri-hepta-BDEs (9)	Human serum (4)	MeOH vortexing	LLE (3 × 2 mL DEE: *n*-hexane, 1:1)	Florisil®	GC-ECNI-MS	75–130	/	/	[35]
Tri-hepta-BDEs (9)	Human serum (1); sheep serum (1)	1 mL of 5% AcN in conc. formic acid	RP-SPDE	Activated silicagel Acid silica	GC-ECNI-MS	>50	/	0.5 ng/g	[35]
Tri-hepta-BDEs (9)	Human serum (0.1–1); sheep serum (0.1–1)	0.5 mL DDW 0.5 mL formic acid 1 mL of DDW Stirring 2 h, 500 rpm	Thermal desorption cryotrapping	/	GC-ECNI-MS	39–91	19–25	0.007–0.17 ng/g	[36]

Acet acetone, *AcN* acetonitrile, *DCM* dichloromethane, *EtOAc* ethyl acetate, *EtOH* ethanol, *MTBE* methyl-tert-butyl ether, *DEE* diethyl ether, *DDW* distilled deionised water, *PUF* polyurethane foam. Other acronyms, as identified in the body text

[a]Solvent mixtures ratios are expressed on volume basis (v:v)

congeners alike [37]. Second, the increasing environmental awareness and the need for lower detection limits require adaptations of the existing extraction and clean-up procedures. PBDEs can be successfully extracted by Soxhlet or liquid–liquid extraction (LLE), but this requires lengthy extraction times and high solvent volumes. Advanced extraction techniques, such as pressurised liquid extraction (PLE), ultrasonic-assisted extraction (UAE), microwave-assisted extraction (MAE) and supercritical-fluid extraction (SFE), have recently been introduced to reduce extraction time and solvent consumption, as well as to improve extraction efficiency.

PLE is widely used for the extraction of PBDEs from solid matrices, such as fish and sediment. It provides high extraction yields due to the combination of high temperatures and pressures. The main advantages of this technique are the reduced extraction time and low solvent consumption, compared to Soxhlet or UAE, and the possibility to conduct a large number of unsupervised extractions, providing increased efficiency and better reproducibility. However, solvent type and system-specific parameters, such as pressure, temperature, heating time, static time, flush volume, purge time and static cycles, need to be thoroughly optimised for optimal analyte recoveries. For the analysis of milk samples, an additional advantage of PLE is its capability to disrupt fat globules and release contaminants from milk resulting in improved extraction yields [33]. PLE has been successfully used to extract PBDEs from human and environmental samples, such as milk [33, 38], sediment and fish [38]. Although PLE has many advantages over other extraction techniques, an extensive clean-up of PLE extracts is often required due to the large amounts of co-extracted compounds (Table 1).

MAE is based on the application of microwave energy to heat the extraction solvent, while controlling temperature, pressure and microwave energy. The main advantage of MAE is a significantly reduced solvent consumption, as low as 20 mL of solvent per sample [21]. Temperature and pressure control allow the heating of the solvent system under pressure above its boiling point. Due to the combination of high pressure and high temperature, the solvent remains liquid, promoting analyte diffusion. The extraction time is shortened compared to Soxhlet extraction. However, optimisation of influential factors, such as extraction temperature, particle size, hold-up time and the employed solvent system, is necessary. The addition of polar compounds, such as methanol, is required for microwave absorption and therefore for heating of the extraction solvent. Mixtures of polar with non-polar solvents are commonly used in MAE (e.g. acetone:*n*-hexane, isopropanol:cyclohexane, xylene:dichloromethane or methanol:toluene). The extraction of BDE-209 from e-waste resulted in low extraction yields due to its high molecular weight and its non-polar nature [22]. Therefore, the extraction of BDE-209 might require additional adaptations, such as higher temperature and longer extraction time.

Matrix solid-phase dispersion (MSPD) is increasingly used for extracting contaminants from a variety of solid and semi-solid matrices. The basic procedure comprises three major steps: (1) sample grinding in the presence of an excess amount of sorbent (e.g. alumina), (2) loading of the ground mixture onto an empty SPE cartridge, and (3) elution with a suitable solvent. Prior to elution, extraction can be facilitated by placing the cartridges in an ultrasonic water bath [17].

The efficiency of the MSPD depends on multiple factors, particularly the sorbent type and the eluting solvent. A careful selection according to the sample matrix and the substance/substance group to be analysed and the sample matrix is therefore critical. The advantages of MSPD are its simplicity, efficiency, low cost, and its speed due to simultaneous extraction and clean-up. MSPD extraction has also been proven useful in the analysis of placental tissue [34], which requires an extraction technique that is vigorous enough to surface the analytes buried in the tissue. The optimised MSPD method performed similarly to the Soxhlet extraction [34].

Solid-phase microextraction (SPME) is increasingly being used for the determination of PBDEs in various samples, such as water, sediment, biota tissue and in manufactured products. In SPME, the analytes are absorbed on a silica fibre coated with a thin layer of polymers. After insertion of the loaded SPME fibre in the gas chromatographic (GC) system, the analytes are readily desorbed from the polymeric fibre, thus eliminating the need for additional sample clean-up. Headspace SPME has been used to determine PBDEs levels in water, soil, sediment and sewage sludge [6]. However, due to the broad range in molecular weight and volatility of PBDEs, relatively high extraction temperatures were required. Room temperature extraction of a broader spectrum of PBDE congeners from natural waters by SPME can be obtained by using the organically modified silicate (Ormosil), an SPME phase that possesses specific selectivity for PBDEs [19]. From sediments, a significantly lower extraction yield of PBDEs compared to that from water has been observed. However, mixing of the sediment with potassium permanganate, sulphuric acid and water had an important positive effect on the extraction yield of SPME for tetra to hexa-BDEs [19].

The applicability of SPME to PBDEs analysis in wastewater influents has recently been questioned, since most PBDE congeners are absorbed to the biosolids during the treatment process, causing a drastic reduction (>95%) of the PBDE levels in the effluent [39]. Hence, if particle adsorption was predominant in aqueous media, it might be the best to collect particles and analyse them separately.

Other extraction techniques. A novel technique referred to as *cloud point extraction-ultrasound-assisted back-extraction* was recently applied to extract and pre-concentrate PBDEs from water and soil [7]. This technique is based on the induction of a micellar-organised medium by using a non-ionic surfactant to extract PBDEs. To couple this efficient extraction technique with GC analysis, ultrasound-assisted back-extraction (UABE) into an organic solvent was required. The cloud point of a non-ionic surfactants aqueous solution is defined as the temperature at which the solution becomes turbid. The cloud point phenomenon occurs in a narrow temperature range and depends on the nature of the amphiphile and its concentration. The analytes are extracted in the surfactant-rich (coacervate) phase, which is small in volume, and decanted into the bottom of a centrifuge tube. To enable subsequent GC analysis, a simple back-extraction of the coacervate phase with isooctane is sufficient. Main advantages include low organic solvent consumption, low cost, simple set-up, environmental friendliness and no need for sample clean-up. One should mention that the efficiency of the extraction procedure varies with sample pH, concentration of surfactant, equilibration time and temperature, matrix

modifiers and ionic strength. Therefore, to achieve a high extraction efficiency of PBDEs from the aqueous bulk, these variables were optimised to establish the optimal working conditions.

2.3 Clean-Up and Fractionation

Clean-up techniques for PBDEs are often based on multiple silica layer columns containing varying amounts of neutral, acid and basic silica, with different degrees of acid or base impregnation. Anhydrous sodium sulphate is often added to ensure a water-free extract after elution with the most suitable organic solvents. Alumina and Florisil® columns are also used and can be eluted with similar solvents. Importantly, the use of pre-packed columns minimises the risk of contamination of the adsorbent by particles from laboratory air, which might contain PBDEs. Both the minimised exposure of the sample to dust and the use of relatively small volumes of solvents in the automated fractionation process should be considered particularly valuable in PBDE analysis since procedural blanks are often a problem (see below). Efficient removal of large amounts of lipid may be necessary when analysing biota or food. This is possible using LLE of the raw extracts with concentrated sulphuric acid [26] or gel permeation chromatography (GPC). A short summary of the existing clean-up procedures and their recent applications is illustrated below and in Table 1.

Food samples often have high lipid contents and extracts therefore require an extensive clean-up, such as sulphuric acid treatment at 60°C for 1 h [9]. Afterwards, the organic phase can be separated, dried, re-dissolved and fractionated into two parts using a small glass column filled with activated alumina. The first fraction was eluted with *n*-hexane and contained the non-polar constituents, while the second fraction was eluted with a mixture of DCM and *n*-hexane (50:50, v/v) and contained the PBDEs. This clean-up procedure combines the advantages of a clean-up with sulphuric acid and SPE fractionation. Such procedure is ideal to obtain clean chromatograms, but requires thorough validation to ensure the stability of the analytes. Extracts from air and dust, with lower lipid content compared to food and serum, were subjected to a clean-up on a mixed acid (44% H_2SO_4, w/w) and basic silica (33% 1 M NaOH, w/w) column [9], followed by subsequent fractionation on alumina. The hexane fraction was discarded and PBDEs were eluted with 50 mL of *n*-hexane/DCM (1:1, v/v).

Removal of lipids from marine mussel extracts was tested using a GPC system filled with Bio-Beads S-X3 and elution with DCM [14]. Subsequent fractionation was done on silica and alumina, extracts were then treated with concentrated sulphuric acid and further fractionated using a two-dimensional LC system with two columns coupled in series. GPC has also been used to clean-up soil samples to remove humic substances and sulphur [18]. Subsequently, the collected fractions were eluted with *n*-hexane through a multilayer silica column. A similar technique was applied to clean-up soil samples, with acetonitrile as the eluting solvent [17]. Afterwards, the extract was filtered before injection.

Lacorte et al. [38] developed a comprehensive, highly sensitive and robust ultra-trace analytical method for the quantification of OH-PBDEs, MeO-PBDEs and their parent PBDE congeners in relevant environmental matrices (sediment, fish and milk), by means of PLE, followed by GPC and Florisil® clean-up. In contrast to previous studies [40, 41] where PBDEs, OH- and MeO-PBDEs were collected in separate fractions, all target compounds were eluted in a single fraction, which was further analysed by GC-HRMS [38].

Another approach modified a clean-up and fractionation technique for PCDD/F purification from environmental matrices (Table 1) [12]. Adaptations include changes in the solvent composition and volume and the elimination of the carbon fractionation step for brominated compounds, which significantly increased the recovery of PBDEs. In another study, a carbon-dispersed column was used in the analytical procedure for brominated compounds in air and dust samples [11]. After clean-up on a mixed silica gel column and elution of the PBDE fraction with hexane:DCM, the eluate was additionally purified on a carbon-dispersed silica column and analytes were further eluted with hexane:DCM and toluene. Using this technique, recoveries for PBDEs and PCBs were 57 and 54%, respectively, while recoveries of HBCDs and PBDD/DFs ranged between 74 and 126%.

Simultaneous analysis of PBDEs and their HO- and MeO-metabolites in the same sample requires extensive clean-up and fractionation procedures, owing to the different nature of the metabolites. Lipids from polar bear tissue extracts were removed with concentrated H_2SO_4 and protonated $MeSO_2$-PCBs (remaining in the acid phase) were separated from all other contaminants, which migrated to the organic phase [23]. Neutral contaminants (PCBs, PBDEs and MeO-PBDEs) were separated from halogenated phenolic contaminants (HPCs) by aqueous KOH partitioning. The organic phase containing the neutral contaminants was further cleaned on a deactivated Florisil® column (8 g, 1.2% H_2O, w/w). The KOH fraction, which contains the HPCs, was then acidified with concentrated H_2SO_4 and the reprotonated HPCs were extracted with MTBE:*n*-hexane and derivatised to their MeO-analogues using diazomethane. The MeO-HPCs were purified on a silica column (3g, 22% H_2SO_4, w/w) and eluted with 15% DCM in *n*-hexane (v/v). The final extract contained OH-PCBs, OH-PBDEs and other HPCs.

3 State-of-the-Art of GC-MS Analysis

GC has become a routine technique for the analysis of PBDEs. Yet, due to their physico-chemical properties (e.g. vapour pressure or polarity) and to their thermal instability, specific PBDE congeners need special precautions during GC analysis. It was shown that thermal degradation may occur during GC analysis of higher brominated PBDE congeners (especially BDE-209) [42, 43]. Therefore, before selecting an analysis methodology for PBDEs, the characteristics of the GC system should carefully be optimised in agreement with the properties of the analytes. These characteristics include column brand, stationary phase, as well as column

length, internal diameter and injection technique may have a very strong influence on the accuracy of PBDE analysis [3, 44]. Finally, the detection technique completes the set of parameters that have to be optimised for an accurate determination of PBDEs.

3.1 GC Separation of PBDEs

Sample injection. Although various injection methods can be used for the analysis of PBDEs, the most common injectors are splitless, on-column and programmable temperature vaporisation (PTV) injection systems. Their advantages and disadvantages derive primarily from their availability, price, detection limits, extract constitution and discrimination of PBDE congeners on the basis of molecular weight.

Due to the relatively low levels of PBDEs in environmental samples, splitless injection is the preferred technique, but special precautions should be taken to minimise thermal degradation and discrimination of higher molecular weight PBDEs. Therefore, the optimal injector temperature and splitless time should be kept as high as possible (e.g. 325°C and 4 min, respectively) to obtain an increased response factor especially for fully brominated PBDE (e.g. BDE-209) [44]. An attractive way to reduce thermal degradation of PBDEs in injection system is to apply on-column injection. Its main advantage is that it shortcuts the injector-interface between extract and column by delivering the extract directly to the capillary column. As a result, a higher precision for the analysis of BDE-209 was observed when such injection was applied [44]. One of the main disadvantages is the need for very clean sample extracts so that potential matrix residues do not reach the capillary column, giving rise to increased noise, peak tailing, retention time shifts, more frequent column trimming and reduced column lifetime. Both splitless and on-column injection methods are limited to volumes from 1 to 3 μL. In comparison, PTV injection may accommodate up to 125 μL after thorough optimisation [45–47]. Although splitless is the most common injection technique, injections in a properly used PTV system may have some advantages, such as minimal degradation of labile PBDEs [3, 42, 46]. Recently, it was shown that especially for the analysis of BDE-209, the use of PTV injector in solvent vent mode may not only positively influence the response factor of BDE-209, but may also reduce the formation of its main thermal degradation product, BDE-207 [42].

Capillary column selection. In general, capillary GC columns offer adequate resolution to determine individual PBDE congeners. To achieve adequate separation of all PBDE congeners present in the sample and possible interferences, there is a need for sufficiently long columns (30–50 m) with small internal diameters ($\leq$0.25 mm). In case of clean extracts, the use of short narrow-bore capillary columns (internal diameter $\leq$ 0.1 mm) may also provide satisfactory resolution [45]. To facilitate the selection of the most suitable GC columns for developing a congener-specific analysis, the elution order of 126 PBDEs was tested on seven different GC stationary phases [48]. First, less co-elutions for PBDE congeners with

different bromine numbers were observed compared to PCBs. Second, a stationary phase-dependent degradation was seen, indicating that column equivalency is not always a suitable criterion for column selection [46, 48]. The most efficient column for PBDE congener-specific separation was found to be a DB-XLB (J&W Scientific) column with a DB-1 (J&W Scientific) column as first runner-up. However, the latter is preferred for routine analysis due to reduced degradation of hepta and higher brominated PBDE congeners.

Even on the most efficient stationary phases, single dimension GC cannot separate all PBDE congeners. Of the 126 PBDE congeners that were tested by Korytár et al., 55 congeners were involved in 22 co-elutions for DB-XLB, which is the most efficient stationary phase [48]. As a consequence, six column combinations were evaluated for GC × GC separation of PBDEs coupled to μ-ECD or time of flight-mass spectrometry (TOF-MS) detectors [49]. It was concluded that a DB-1 × 007-65HT (Quadrex) combination was the most suitable due to (1) the highest number of PBDE congeners separated, (2) less decomposition of higher brominated congeners, and (3) most suitable maximum operating temperature. With this set-up, there were only 17 co-eluting pairs involving 35 congeners.

Special precautions are needed for BDE-209 analysis due to its thermal sensitivity and thus its higher susceptibility for degradation in the GC system. Therefore, the GC column should be relatively short (10–15 m) to reduce the residence time in the system [1]. Based on the ability of the low pressure-GC (LP-GC) technique to elute compounds at lower temperatures compared to conventional GC techniques [50], BDE-209 was analysed at temperatures below the degradability limit. It was shown that the low elution temperature of BDE-209 (<295°C), combined with its short residence time in GC lead to minimal thermal degradation [42]. Besides minimal thermal degradation, the analysis of BDE-209 using LP-GC system resulted in an analysis time of merely 6.5 min. Baseline separation of 22 PBDE congeners (major components of PBDE technical mixtures) was possible in less than 12 min using this LP-GC system (Fig. 1).

Interferences might not only be due to co-eluting congeners, but can also be caused by other brominated compounds, such as MeO-PBDEs or polybrominated biphenyls (PBBs). Two MeO-PBDEs, namely 5-MeO-BDE-47 and 5-Cl-6-MeO-BDE-47, were found to co-elute with BDE-100 and BDE-99, respectively, using a DB-5 column [40], while BDE-154 and BB-153 were also co-eluting on the same type of column [2]. Therefore, alternative stationary phases have been suggested [2, 40].

3.2 Mass Spectrometric Detection for BFRs

The most widely used detectors for PBDE determination are mass spectrometers, classified into low-resolution (LR) or high-resolution (HR) mass spectrometric (MS) instruments. The LR-MS instruments are operated either in EI or in ECNI mode.

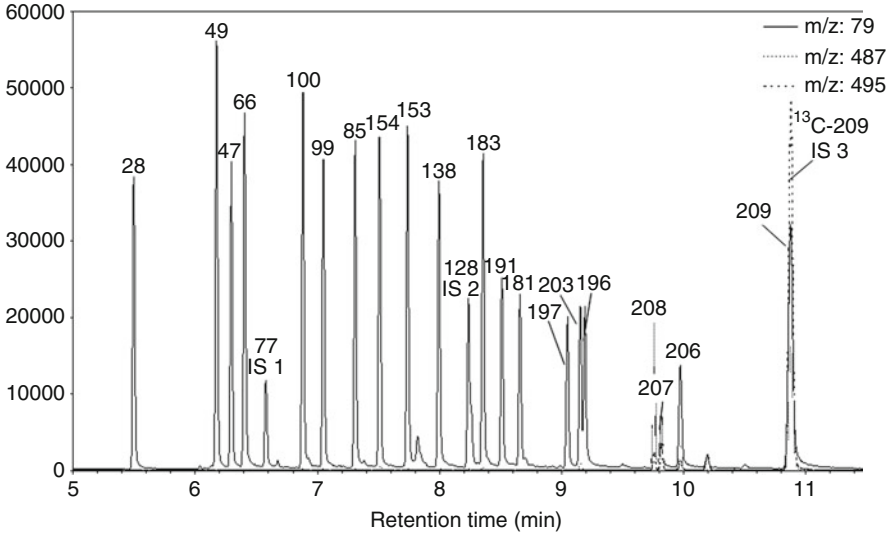


Fig. 1 Mass chromatogram (m/z = 79, 487 and 495) of a standard mixture of 22 PBDE congeners (major components of penta, octa and deca-BDE technical mixtures) injected in the LP-GC-ECNI-MS system (analytical column: 10 m × 0.53 mm ID, df = 0.15 µm AT-5). Peak numbers correspond to PBDE congener nomenclature (modified from [42])

Using EI-MS for PBDE analysis, the major ions formed are $[M^{\cdot}]^{+}$ and $[M\text{-}2Br]^{\cdot+}$, which can be used for their identification and quantification [51]. The main potential interferences that may influence the accuracy originate from chlorinated compounds, such as PCBs. For example, the nominal masses corresponding to ions monitored for di-BDEs and penta-CBs (m/z = 326), and also for tetra-BDEs and hepta-CBs (m/z = 396) are the same and therefore a resolution power of 24,000 is needed to separate them, if they co-elute on the GC column [3]. However, this is not recommended due to the significant loss of sensitivity at this elevated resolution [52].

LR-EI-MS provides a higher selectivity compared to LR-ECNI-MS, since for the latter only the bromine trace can be monitored (m/z 79 and 81). However, LR-EI-MS (with quadrupole as mass analyser) is not routinely used for PBDE analysis due to its relatively low sensitivity, especially when measuring PBDE congeners with more than six bromine atoms. Recently, GC-EI-MS operated in SIM mode was used to analyse PBDEs in human hair samples with limit of quantification (LOQ) as low as 0.3–0.6 ng/g of sample for tri to hepta-BDEs and 3 ng/g of sample for BDE-209 [32]. Determination of mono to deca-PBDE congeners together with PBBs in electrical and electronic equipments was also achieved by GC-EI-MS [53]. Method limits of detection (LOD) ranged between 0.2 and 8 ng/g for mono to hepta-BDE, and 70 ng/g for BDE-209, respectively.

In contrast to EI, the low-energy electrons (thermal electrons) generated in ECNI by interactions between a high-energy electron beam and a moderating gas (e.g. methane), react with the analytes to form negative ions. The electron energy

should be low to facilitate electron capture and the specific energy required for electron capture depends on the molecular structure of the analyte. PBDEs do normally not form molecular ions or other diagnostic ions under ECNI conditions (except BDE-209), thus only bromide ions (*m*/z 79 and 81) may be monitored.

Compared to EI-MS, ECNI-MS is less selective because non-specific bromide ions $[Br]^-$ at *m*/*z* 79 and 81 are used for the quantification of all homologue groups, except BDE-209, which gives rise to specific fragments ($[C_6Br_5O]^-$; *m*/*z* 486.7). However, ECNI-MS is a very sensitive method with LODs that are one order of magnitude lower than those for LR-EI-MS. Therefore, this technique proves to be suitable for the analysis of low contaminated samples, such as human serum and milk. Reliable results have also been obtained for the quantification of selected PBDEs in river water and sediment samples. Detection limits ranged from 3 to 160 pg/L and 5 to 145 pg/g for river water and sediment, respectively [8]. The use of GC-ECNI-MS in combination with stir-bar sorptive extraction and automated thermal desorption/cryotrapping was applied for the simultaneous determination of PBDEs and PBBs in sheep and human serum samples [36].

Selectivity of LR-ECNI-MS can be improved under optimised conditions. By optimising the electron energy, emission current, source temperature and system pressure, the relative abundances of the larger molecular fragments $[M - xH - yBr]^-$ increases and therefore the technique can be used for the monitoring of each homologue group instead of the non-specific bromide ions [54]. Monitoring high mass fragments under optimised ion source conditions was successfully applied for the determination PBDEs in environmental and biological samples at concentration levels <0.01 pg in one single instrumental run was recently described [55]. Good repeatabilities (1.7–9.1%) and reproducibilities (4.1–20%), and low LODs (e pg/mL) were obtained, allowing PBDEs quantification in snow and human serum samples.

Besides MS operated in either EI or ECNI modes, other MS type detectors were used to analyse PBDEs. PCBs and PBDEs were simultaneously determined in soil by GC-TOF-MS. Method detection limits ranged between 0.1 and 0.4 mg/kg for PCBs and 0.1 and 0.6 mg/kg for PBDEs with RSD < 7.3% for PCBs and <6.3% for PBDEs [56]. Another multi-residue method for the quantification of 30 organohalogenated compounds in human breast tissue using GC-triple quadrupole MS has recently been developed. Analyses were performed in both EI and ECNI modes and the acquisition of two transitions (in EI) or two ions (in ECNI) per analyte were acquired. This approach allowed confirmation through matching of ion ratios between the quantification and the confirmation transitions (EI) or ions (ECNI) [57]. To analyse tri to hexa-BDEs in sediments, GC combined with an ion trap mass analyser operated in EI mode was applied [19]. All PBDEs showed a common MS/MS transition consisting in the elimination of two Br atoms. Instrumental LOQs ranged from 0.05 pg/μL (BDE-47) to 0.5 pg/μL (BDE-154) for an injection volume of 2 μL.

4 Analysis of PBDEs in Polymers

The European Commission Directive 2002/95/EC on the "restriction of the use of certain hazardous substances in electrical and electronic equipment" (RoHS) prohibits the usage of several BFRs in electric and electronic devices. As of 1 July 2006, The Commission Decision 2005/681/EC specifies a limit of 1 g/kg for the sum of PBDEs and PBBs in plastics. Proper enforcement of this regulation requires reliable testing of products for their content of BFRs.

PBDEs were analysed in matrix polymers by Raman spectroscopy without any sample pre-treatment [58]. The LOD was approximately 100 μg/g and the analysis took only 1 min. Deca-BDE could be identified based on distinctive bands. Energy dispersive X-ray fluorescence (ED-XRF) analysis, GC-MS and infrared spectroscopy techniques have also been evaluated for the analysis of polymers after various extraction procedures [59]. A portable XRF analyser was successfully used for non-destructive semi-quantitative determination and screening purposes for the presence of BFRs in consumer products [60]. During validation, XRF-measured bromine was highly correlated with the GC-MS-measured bromine for furniture foam and plastics of electronic consumer products. In the field study phase, the XRF-measured bromine in room furniture was highly correlated with the penta-BDE concentrations in room dust. This technique has shown great potential as a fast field-applicable screening tool.

Although having low recoveries for styrenic polymers, UAE can be an easy, fast and robust analytical tool for the determination of BFRs in polypropylene (PP) and polyethylene (PE) [61]. The characterisation of the two certified reference materials (CRMs; ERM-590 and ERM-591) for BFRs in polymer materials indicates that several laboratories successfully applied UAE during the characterisation measurements [62, 63]. Apart from UAE, other extraction techniques were used, such as Soxhlet extraction, PLE, static extraction and even complete dissolution of the polymer. Details of all analytical protocols used in this certification study are given in Table 2.

In another study, a flow-injection (FI) system was coupled to inductively coupled plasma-mass spectrometry (ICP-MS) and used for the detection of bromine traces in polymers, plastic paints and enamels containing BFRs [64]. Using this approach, individual PBDEs cannot be unambiguously identified, but materials can be rapidly screened for bromine-containing compounds. Sample preparation is based on MAE and after appropriate optimisation of the digestion procedure and the ICP-MS detection, a detection limit of 4.2 mg/kg was obtained for synthesised polyurethane standards containing known amounts of bromine. The precision of the proposed method, evaluated as the RSD of signals obtained from three replicate analyses of polymeric standard BFRs at the normative EU level, was as low as 3.6%. The proposed system provides rapid binary (yes/no) overall responses, being appropriate for the screening of bromine above a pre-set threshold. The unreliability region (UR), given by the probability of false positives and false negatives (set at 5% in both cases), was in the range of 442 and 678 mg/kg of

Table 2 Different analytical techniques used for the certification measurements of the first certified reference materials for BFRs in polymers, modified from [63]

Grinding	Sample taken as is and various grinding techniques (scissors, laboratory mill, cryo-grinding). Particle sizes from 0.25 to 2 mm
Sample intake	20–1,000 mg
Extraction	Soxhlet extraction with toluene or dichloromethane
	UAE with toluene or isooctane
	PLE with toluene or isooctane
	Static extraction with toluene
	Complete dissolution in xylene/dimethyl glutarate
Internal standards	One or multiple PCBs
	Fluorinated PBDEs
	Unlabelled PBDEs
	^{13}C-labelled PBDEs
GC injectors	Cool-on-column
	Split/splitless
	PTV
GC columns	One column: DB-HT, DB-5MS, ZB-5HT, Rtx5-Sil-MS, Rtx CLP, Rtx-5MS, ZB-5HT Inferno
	Two columns: DB-5MS/CP-Sil8; DB-5/Rtx-5MS
Ionisation technique	Electron ionisation
	Electron capture negative ionisation
MS systems	Quadrupole MS
	Sector-field MS with resolution >5,000

bromine (at a cut-off level of 0.1% in BFRs by weight of homogeneous material fixed by the EU normative). Finally, the applicability of the proposed screening system was tested for the reliable control of bromine in different commercial samples including flame-retarded paints and enamels.

5 Quality Assurance Parameters: How to Tweak the Quality of Your Analytical Results

Every step in the analysis of BFRs has critical parameters that need optimisation to minimise the uncertainty of the final result and thus improve the quality of the data. The ISO/IEC 17025 standard, which describes general requirements for the competence of calibration and testing laboratories, requires that accredited laboratories use validated methods, demonstrate traceability of calibrations and apply an appropriate quality control programme. Over the years, intensive effort was put in mapping possible and specific pitfalls in PBDE analysis, which improved the quality of the released data over time.

Reference materials and method validation. The access to analytical standards of sufficient purity (i.e. reference materials), both "external" calibrants and (mass-labelled) internal standards, is a key aspect for reliable quantification of PBDEs. In the last 10 years, almost all individual or mixtures of native and

numerous $^{13}C_{12}$-labelled PBDE congeners became available as standard solutions or as neat crystals. These commonly used standards are often not very well characterised and a large uncertainty is associated with the PBDE concentration of solutions (up to 5%) and with the purity of the solid substance (in some cases exceeding 5%). A recently organised CCQM study pointed at the necessity to verify and correct if necessary the purity of the calibrants indicated by the suppliers or to incorporate this uncertainty into the uncertainty budget of the measurements [65].

Extensive sample preparation is often needed in PBDE analysis and demands for internal standards (IS) and syringe standards (SS) to compensate for losses of target analytes during sample preparation and for inter-injection fluctuations. Several PBDE congeners (such as BDE 77, 116 and 126, but also others) are most likely to combine all the above-mentioned characteristics and are therefore suited as IS [66]. Preferably, the selected IS should be a $^{13}C_{12}$-labelled analogue, but this limits the choice of detection to EI-MS (except for BDE-209, see below). The use of BDE-138 should be discouraged, since it has been reported in the technical mixture Bromkal 70-5 DE [67]. Alternatively, PBBs not present in the Firemaster® mixtures can be used. BB-103 and BB-155 were also used as IS for different levels of bromination of PBDE homologues [68]. BB-209 has been proposed as IS for the determination of BDE-209 in sediments. Although BB-209 was produced commercially until 2000 in small amounts in France [69], it could not be identified in a large number of sediment and biota samples from the Netherlands [70]. Alternatively, the use of $^{13}C_{12}$-BDE-209 as IS for BDE-209 analysis by ECNI-MS is possible when *m*/z 484.7/486.7 and 494.7/496.7 are monitored for BDE-209 and $^{13}C_{12}$-BDE-209, respectively.

Recently, fluorinated derivatives (F-PBDEs) became available and it was proven that they are suitable IS or SS for the analysis of PBDEs [71]. Although the use of mass-labelled IS should be encouraged, a recent publication has shown that results obtained by using isotopically labelled internal standards do not render superior results per se compared to those obtained with other carefully selected suitable internal standards (such as, e.g. PCB-209, other PBDE congeners, polychlorinated diphenyl ethers (PCDEs) or F-PBDEs) [65]. Despite the limited amount of data sets for either approach, it could be seen that (1) the within-laboratory intermediate precision data were well comparable for all analytes and were about the same using either isotope dilution MS (IDMS) or other methodology, (2) mean results compared well for all analytes except BB-209, and (3) the standard deviation of the mean of means for both data sets and all analytes was comparable. Although these conclusions were based upon data provided by National Metrology Institutes, which spend more time on QA/QC compared to regular analytical laboratories, it shows that the analytical process can be controlled even without mass-labelled IS if proper measures are taken. Additional recommendations regarding internal standards were given in the literature [72].

Monitoring the ion intensity ratios in EI-MS is widely used to verify identification of target analytes. If the isotopic ratio of the quantitation and confirmation ion differ more than 15% [73, 74] or 20% [45], results should be flagged as questionable

and should not be used to check compliance with limit or threshold values. For ECNI-MS, relatively good specificity is obtained by measuring the bromine trace (*m*/*z* 79 and 81) and possible co-elutions are limited to compounds yielding bromine fragments upon ionisation.

The imprecision level of PBDE determination depends on the analyte (between 10 and 20% for tri to hepta-BDEs and around 25% for BDE 209 and HBCD). The first worldwide inter-laboratory studies on BFRs showed that laboratories should improve their method precision [66]. Since then a lot of effort has been invested in pinpointing the pitfalls in BFR analysis [4], which resulted in improved performance of analytical laboratories if proper procedures and protocols are used [65].

Although trueness assessment during validation is preferably done by means of a CRM, this is not always possible for BFRs due to limited availability of adequate reference materials. Standard addition procedures are accepted in this case as a valid approach to evaluate the trueness of the analytical procedure [72]. Recovery measurements of spiked samples (especially solid samples, such as sediments and sewage sludge) may yield higher recoveries of analytes due to a possibly easier extraction from these spiked samples, since they are not naturally incurred in the matrix. When possible, proper incubation and ageing of the spiked samples should be carried out so that the spiked compounds mimic as much as possible the behaviour of the naturally incurred analytes [75]. The best procedure to evaluate the trueness of analytical methods used for PBDE determination is the analysis of CRMs. Stapleton recently reported on the mass fractions of PBDEs on several existing NIST SRMs [76]. Few environmental reference materials certified for PBDE content exist, such as NIST SRM 2585 (indoor dust), NIST SRMs 1957 and 1958 (human serum), NIST SRMs 1953 and 1954 (human milk), NIST SRMs 2257 and 2258 (organic solution), NIST SRM 2977 (mussel tissue) and NIST SRM 1945 (whale blubber). While the number of these materials is currently limited, it is anticipated that with time their number will increase.

The method stability and reliability (maintenance of its performance over time) should be assessed through regular analysis of standard solutions, procedural blanks, duplicate samples, in-house prepared reference materials or CRMs (in order of increasing importance). The use of such materials with each analytical batch is encouraged seeing the numerous possible problems associated with PBDE analysis. Recoveries can be influenced by a variety of parameters, such as adsorption to glass (higher brominated BDEs), UV-degradation (BDE-209) or losses caused by evaporation (BDE-28). In addition to the internal QA/QC measures, laboratories are encouraged to participate in inter-laboratory studies and proficiency tests.

*Integrity of the analytes***.** To eliminate potential sources of error during sample preparation, some treatments should be avoided to preserve the integrity of particular PBDEs. High temperatures and/or extensive saponification times can result in decomposition of higher brominated BDEs [1]. BDE-209 and possibly other higher brominated BDE congeners are photosensitive and thus direct exposure to UV light should be avoided. Wrapping the containers, extraction funnels and solvent receptacles with aluminium foil or using amber glassware are probably the simplest

preventive measures. The use of UV filters on laboratory windows and fluorescent lighting is also highly recommended. Both photolytic and thermal degradation may lead to degradation products formed through debromination. A combination of exposure to daylight and poor solubility may even result in the complete disappearance of BDE-209 from solutions placed on laboratory benches and directly exposed to sunlight [4].

The extended exposure of PBDEs to elevated temperatures can be avoided through various means, such as (1) using short and narrow-bore GC columns with thin films, which reduces the residence time of the compounds in the GC system, (2) using short injector residence times, e.g. by means of *cold* or pressure-pulse injection modes or by using on-column injection, and (3) guaranteeing a clean GC-injector liner free of matrix residues that could retain the analytes and enhance thermal degradation in the injector. Yet, the stability of the GC system deteriorates over time by accumulation of matrix particles in the inlet and column, which requires regular replacement of injector liners and column trimming.

Because BDE-209 is most sensitive to thermal degradation, it can be used as an indicator of the system performance status. Several degradation products, such as BDE-206 and BDE-207 can be used to monitor the stability of the system [42, 65]. Preventing degradation is important because it cannot fully be compensated for by using labelled IS (that undergo a similar degradation). Thermal degradation that occurs during analysis was shown to be also concentration dependent [77].

In contrast to the above-mentioned analyte degradation, signal enhancement has also been reported [17], probably caused by an increased protection of the analytes from adsorption in the injector when matrix residues are present in the extract. Sellström has reported a similar effect for fish tissue for which the recovery of BDE-209 was higher when a matrix was present [51]. If relative recoveries from spiked samples are acceptable and not statistically different from recoveries calculated from standard solutions, calibration curves can be made from standard solvent-based solutions [78]. If matrix effects are pronouncedly present, calibration curves should be established by means of matrix-matched spiked standards.

Complete evaporation of the extracts to dryness should be avoided as PBDEs tend to adsorb to glass even more strongly than PCBs, which may result in incomplete dissolution upon reconstitution. Reconstitution time should therefore be sufficiently long and validated during method optimisation. Extended evaporation of the extracts might also lead the selective loss of certain compounds that are relatively more volatile than others, i.e. BDE-28. For analysis of BDE-209, the use of solvents such as toluene, DCM or acetone:*n*-hexane mixtures is preferred, because of its limited solubility in other organic solvents [2, 79].

Background contamination. An important QC measure to be considered on a routine basis includes the regular analysis of reagent and procedural blanks. Reagent blanks should be run regularly not only to check for possible contamination of solvents but also to check the status of the instrument, which is closely related to the integrity of the analytes as discussed previously. Procedural blanks should be analysed to monitor and compensate for a possible background contamination

(whether it is noticed or not depends mainly on the LOQ of the instrumental method, see below).

Guidelines are available on how to minimise background contamination of PBDEs in the analytical laboratory [2–4, 66]. The use of plastics should be reduced to a minimum. Moreover, significant concentrations of BDE-47 and BDE-99 have been identified in laboratory air [80]. Dust and air-borne particles are a known carrier of high loads of PBDEs, especially of BDE-209 [81]. If possible, a dedicated PBDE sample preparation environment where special measures are implemented should be installed (clean room). Any materials that are not needed in the laboratory should be avoided (e.g. packaging materials, upholstered chairs, etc.) [4]. (Cross-) contamination can be avoided by implementing strict and validated washing and cleaning procedures. It is suggested to wash all glassware in 2.5% RBS 25 foaming cleaner, followed by rinsing with distilled water and subsequently heating at 450°C for 4 h [80, 82]. Glassware that cannot be washed after use, e.g. Soxhlet coolers, should be thoroughly rinsed with one or more organic solvents to prevent cross-contamination.

Due to the specific problems associated with, e.g. BDE-209, procedural blanks should be implemented at a much more regular interval as for any other organic analysis, i.e. for each analytical batch or at least every ten samples [4, 81]. A high background contamination with BDE-209 can compromise more than just the result of BDE-209 itself, since (non-systematic) degradation of BDE-209 can result in formation of other lower brominated BDEs that can compromise the trueness of those results as well. Furthermore, where solution blanks have a shorter residence time at the bench than the sample extracts, BDE-209 may migrate to and be retained on the glass wall of recipients, whereas it will migrate into the extracts where the storage period is longer. This gives rise to unrealistically clean blanks and more contaminated samples [4]. A $^{13}C_{12}$-labelled IS for BDE-209 is therefore highly recommended.

Up-to-date, no uniform approach has been adopted or implemented to deal with laboratory background contamination of PBDEs. While some laboratories consistently measure (low) blank values and correct for them to enhance the trueness of their results [83–85], others report that blanks are below LOD [86–88]. Vonderheide summarised this discrepancy, stating that low sample intake necessitates a very sensitive method to allow accurate determination of blank contamination, while a high sample intake procedure is relatively less sensitive to blank problems [37]. Although less sensitive to blank problems, a high sample intake procedure, however, might suffer from other drawbacks, such as clean-up and chromatographic separation difficulties.

The LOD and the LOQ as defined by IUPAC [89] may be estimated in different ways. Current state-of-the-art equipment is able to accurately measure amounts that are several times lower than what is commonly present in the blanks, which renders instrumental LOQ obsolete. When reporting low mass fractions, it is prerequisite to actually measure the background contamination to assess its potential contribution to the total analyte signal. When this approach is not followed, values just above the LOQ (mainly background contamination) can be reported, which clearly should be

avoided if data of an acceptable quality are desired. One might argue that whenever blanks cannot be measured due to lack of sensitivity of the method used, the uncertainty of the measurements should be adapted accordingly. For the analysis of serum samples, various authors used different blank samples, such as calf serum [90], sterilised water containing 0.9% NaCl [91] or water [92]. It appears necessary to include more information regarding blank composition and preparation in scientific manuscripts because such information may collectively allow researchers to better pinpoint the source of contamination.

Taking into account the above considerations, blank measurements can be subtracted from the measured sample values before final reporting under the conditions the blank is under control, i.e. a stable measurement is obtained over time (e.g. RSD of 10 determination <30%). Finally, the variation of blank values should be incorporated into the LOQ. According to literature, PBDE mass fractions should only be reported when exceeding the levels found in procedural blanks by a minimum factor of two [72]. Alternatively, it was proposed that reported levels of PBDEs should be above a value equal to the procedural blank value plus ten times [93], five times [79] or three times [84, 94] the SD of the procedural blanks. Some authors applied a correction for procedural blanks if the blank value was between 10 and 20% of the measured value in the sample [73]. If the procedural blank value was less than 10%, no corrective action was taken. Data were excluded from further consideration if the blank value exceeded 30% of sample measurements. Some analytical alternatives to reduce blank values have been recommended in the literature [72]. Some authors have set the LOQ at five times the blank level, if blank interference was present [95, 96]. This correction method resulted in many unusable data, since blank interference raised the LOQ to higher levels than those present in most samples. Given the low PBDE levels that often need to be measured in environmental or food samples, the use of a method blank cut-off value equal to three times SD of the blank measurement (after subtraction of the blank value) is a good compromise between detection power and data quality. Table 3 briefly summarises specific PBDE QA/QC measures, their impact and the possibilities to implement them.

6 Recent Inter-Laboratory Studies on BFRs

During the last decade, laboratories have increasingly become involved in the analysis of BFRs in environmental, human and food samples. To assure as well as to improve the quality of BFR analyses, a series of international inter-laboratory exercises has been organised.

The first worldwide inter-laboratory study on PBDE analysis was conducted in 1999/2000 and involved five biological samples, two sediments and two standard solutions sent to 26 participants in nine countries [66]. The results reported for BDE-47 were considered acceptable with a range of RSDs of 17–40%, while results for BDE-99 (25–77%), BDE-100 (19–48%), BDE-153 (30–48%) and BDE-154

Table 3 QC measures for reliable results in PBDE analysis

Implementation	What	Why	How
Lab	Reduce direct exposure to sunlight/UV light	PBDEs are light sensitive and degrade through UV exposure	Use special covers on lamps; use window filters; use amber glassware
	Ensure clean, dust-free working environment	PBDEs adsorb significantly to dust. Free-floating dust is a potential source of contamination (blank problem)	Keep lab dust free
Operator	PBDEs need special care	They do not behave quite similar to the most common halogenated compounds	Training and awareness-raising
	Prevent loss of analytes during sample preparation	Some PBDE congeners are relatively volatile (e.g. BDE 28)	Prevent complete solvent evaporation during extract concentration
	Prevent loss of analytes during sample preparation	Some PBDEs adhere strongly to glass (e.g. higher brominated compounds)	Prevent complete solvent evaporation during extract concentration
	Avoid using plastics whenever possible	PBDEs can be present in these matrices	Find alternative consumables or adapt method protocol
Method	Keep column in good condition	Degradation, loss of sensitivity	Run performance check samples
	Keep injector in good condition	Adsorption, degradation,	Run performance check samples, clean regularly
	Clean detector	Degradation, loss of sensitivity	Run performance check samples, clean regularly
	Adequate selection of internal standards	Compensate for losses	
	QC parameters (degradation monitoring)	Degradation of congeners is compound and amount dependent	
	QC parameters (method blanks)		
	Matrix-dependent validation parameters	Interaction between matrix components and analytes in injector	Matrix dependent validation

(25–43%) showed that further improvement was needed. Analysis of BDE-209 was not under control of the participating laboratories at that time.

Following this first study, three inter-laboratory exercises were organised under the Quality Assurance of Information for Marine Environmental Monitoring in Europe (QUASIMEME) project [4]. These exercises conducted between 2001 and 2004 included eel, mussel, lake trout, salmon, herring, mackerel, cormorant liver, porpoise liver, porpoise blubber, capelin oil, sewage sludge, sediments, sediment extracts, human milk and test solutions of undisclosed concentrations. The targeted congeners were BDEs-28, 47, 99, 100, 153, 154, 183 and 209, but HBCD and TBBP-A were also included. The authors stressed that it was very difficult to establish any kind of quality-related trend in the data set due to the numerous parameters that varied from round to round. But nevertheless, they identified a number of specific problems and drew some clear conclusions [4]. The Horwitz function [97], which states that the analytes' mass fractions are inversely correlated with the associated RSD of the measurements, was also applied to this data set. Tables 4 and 5 summarise the results of the following eight rounds held by QASIMEME between 2005 and 2009 including harbour, coastal and open sea sediments as well as dab, plaice, salmon, shrimp, and mussel tissue [98–105]. Statistical evaluation and laboratory assessment in these inter-laboratory studies were done using the Cofino Model [106, 107] and robust statistics according to the German Standard DIN 38402-45 [108].

Ten inter-comparison studies on PBDEs in sediment were evaluated (Table 4). The number of participants ranged from 9 to 16. There were no significant temporal trends as regards laboratory performance but according to the Horwitz equation there was a negative correlation of RSD and PBDE concentration. The median RSDs over ten rounds conducted from 2005 to 2009 for BDE28, 47, 99, 100, 153, 154, 183 and 209 were 46, 29, 30, 39, 40, 31, 53 and 51%, respectively. The high median RSD seen for BDE28 might be attributed to its very low concentration in most of the inter-comparison samples. However, the median RSD of 51% observed for BDE209 still reflects unsatisfactory performance of the participating laboratories. Results for BDE183 are difficult to assess but low levels present in the inter-comparison samples seem at least partly to explain the high RSD.

Just like for the analysis of PBDEs in sediments ten inter-comparison studies on PBDE in marine biota samples have been evaluated (Table 5). The number of participating laboratories in these exercises ranged from 13 to 18. In the five rounds organised in 2005 and 2006, fish tissue samples including common dab, common plaice, and salmon were distributed to the participants. In the following five inter-comparisons, mussel tissue and one shrimp homogenate had to be analysed. As PBDE levels in fish are distinctly higher than those in mussels the results for fish tissue and mussel/shrimp homogenates were evaluated separately. Median RSDs for six tri to hexa-BDEs in fish ranged from 22% for BDE-47 to 36% for BDE-28 indicating acceptable performance of the participating laboratories. No assigned value could be calculated for BDE-183 and BDE-209 due to the very few numerical results reported. Unlike laboratory performance for PBDE in fish samples, laboratory performance for the analysis of PBDE in mussels was generally disputable

Table 4 QUASIMEME inter-laboratory comparison on PBDEs in marine sediments (2005–2009). Summary statistics for eight BDE congeners [98–105]

Year	Round	Code	Sample	BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154	BDE-183	BDE-209
2005	41	07MS	Coastal sediment	0.50; 14	7.6; 15	11.2; 21	1.49; 45	1.62; 33	0.78; 27	0.95; 39	179; 65
				12; 2	16; 0	16; 0	16; 0	16; 0	16; 0	13; 1	10; 1
		08MS	Harbour sediment	0.9; 10	11.3; 18	31.7; 14	3.06; 26	4.5; 42	2.09; 32	0.23; 41	37.0; 48
				13; 1	16; 0	15; 0	14; 0	15; 0	14; 0	11; 2	9; 2
2006	45	09MS	Harbour sediment	0.84; 16	10.5; 21	29.3; 28	3.25; 21	4.26; 38	2.18; 30	0.20; 51	27.3; 25
				13; 0	13; 0	14; 0	13; 0	13; 0	13; 0	10; 1	10; 0
		10MS	Marine sediment	0.03; 82	0.45; 45	0.58; 68	0.09; 72	0.07; 42	0.05; 29	0.10; 66	8.67; 22
				8; 3	13; 0	12; 1	9; 1	7; 4	7; 5	8; 3	9; 0
2006	46	11MS	Marine sediment	0.04; 282	0.42; 73	0.29; 60	0.05; 58	0.07; 64	0.03; 110	0.04; 64	14.5; 48
				5; 4	9; 1	10; 1	6; 4	5; 5	5; 4	5; 4	6; 1
2007	48	12MS	Harbour sediment	0.75; 18	9.98; 33	27.6; 24	2.88; 42	3.46; 42	1.77; 25	0.16; 64	25.2; 53
				10; 2	13; 0	13; 0	13; 0	11; 1	11; 1	9; 1	7; 1
	50	13MS	Harbour sediment	0.02; 45	0.34; 16	0.53; 32	0.11; 34	0.11; 34	0.09; 60	0.11; 28	5.76; 74
				8; 7	15; 0	15; 0	13; 2	13; 2	12; 3	10; 5	13; 0
2008	52	19MS	Harbour sediment	0.01; 117	0.04; 57	0.05; 50	0.02; 64	0.02; 122	0.02; 162	0.02; 95	0.52; 136
				10; 5	12; 4	11; 5	11; 5	8; 8	8; 7	8; 7	9; 3
	54	21MS	Marine sediment	0.01; 115	0.11; 47	0.10; 39	0.02; 31	0.02; 60	0.02; 46	0.03; 55	5.08; 55
				6; 3	8; 1	7; 1	8; 1	7; 2	6; 2	6; 3	8; 0
2009	56	23MS	Coastal sediment	0.02; 46	0.35; 25	0.56; 25	0.13; 36	0.13; 35	0.11; 30	0.10; 38	4.40; 42
				6; 6	11; 2	11; 1	11; 2	10; 1	9; 2	10; 2	9; 1

Upper line: laboratory mean in ng/g ww, RSD in %. *Lower line*: number of numerical results, number of left-censored values

Table 5 QUASIMEME inter-laboratory comparison on PBDEs in marine biota (2005–2009). Summary statistics for eight BDE congeners [98–105]

Year	Round	Code	Sample	BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154	BDE-183	BDE-209
2005	41	08BT	Common dab	0.03; 30	1.09; 18;	0.02; 89,	0.17; 38;	0.01; 59;	0.03; 49;	–; –	–; –
				13; 3	18; 0	11; 7	17; 1	11; 6	14; 4	11; 4	8; 1
	41	09BT	Common plaice	0.06; 36;	1.42; 22	0.04; 37	0.18; 27	0.03; 30	0.04; 26	–; –	–; –
				12; 3	17; 0	11; 5	16; 0	11; 4	12; 4	11; 3	7; 1
2006	45	10BT	Common dab	0.12; 36	1.76; 30	0.39; 33	0.43; 26	0.06; 34	0.14; 24	–; –	–; –
				12; 3	17; 0	17; 0	16; 0	13; 3	13; 3	12; 1	6; 2
	45	11BT	Salmon	0.12; 36	1.76; 30	0.39; 33	0.43; 26	0.06; 34	0.14; 24	–; –	–; –
				12; 3	17; 0	17; 0	16; 0	13; 3	13; 3	12; 1	6; 2
	46	12BT	Salmon	0.11; 23	1.53; 18	0.3; 15	0.36; 29	0.05; 12	0.12; 28	–; –	0.33; 123
				9; 2	12; 1	13; 1	12; 1	8; 4	9; 2	8; 2	5; 4
2007	48	13BT	Mussel	0.01; 62	0.13; 36	0.04; 43	0.03; 38	0.00; 44	0.01; 87	0.01; 78	0.08; 157
				8; 3	13; 1	12; 2	11; 2	8; 5	9; 3	6; 5	4; 3
	50	14BT	Shrimp	0.006; 73	0.051; 28	0.026; 55	0.014; 48	0.01; 80	0.009; 56	0.012; 100	0.282; 154
				7; 5	11; 2	10; 2	9; 3	9; 4	8; 5	7; 5	5; 3
2008	52	18BT	Mussel	0.01; 70	0.12; 33	0.04; 43	0.03; 57	0.01; 98	0.01; 66	0.04; 107	0.07; 166
				11; 4	15; 1	15; 1	14; 2	11; 5	11; 5	8; 6	6; 5
	54	20BT	Mussel	0.02; 73	0.24; 36	0.09; 48	0.08; 49	0.01; 30	0.02; 49	0.01; 55	0.49; 72
				11; 0	12; 0	12; 0	12; 0	10; 2	7; 3	6; 4	7; 2
2009	56	22BT	Mussel	0.01; 111	0.08; 32	0.02; 68	0.03; 62	0.00; 113	0.01; 74	0.02; 47	0.05; 112
				7; 5	14; 0	13; 0	13; 1	7; 6	6; 6	7; 6	6; 3

Upper line: laboratory mean in ng/g ww, RSD in %. *Lower line*: number of numerical results, number of left-censored values

except for the major congener BDE-47 for which a median RSD of 33% was calculated. Actually, the majority of laboratories were not in a position to produce reliable results for samples containing very low PBDE concentrations.

Takahashi et al. [109] reported the results of an inter-laboratory comparison between six Japanese laboratories on the analysis of PBDEs, polybrominated and monobromo-polychlorinated dibenzodioxins and furans in a test solution of undisclosed concentrations and one air-dried sediment sample. All laboratories used isotopic dilution HRGC-HRMS operated in the EI mode. RSDs for the individual PBDEs in the standard mixture were between 9 and 24%, while those for the sediment samples ranged from 17 to 39%, except for BDE-100, for which an RSD of 74% was reported. Average concentrations for tri to hexa-BDE congeners ranged from 0.029 to 0.38 ng/g dw, whereas those for BDE-183 and BDE-209 were 2 and 170 ng/g dw, respectively. The strong variation in BDE-100 results was due to the poor separation of BDE-100 from interferences when using a DB-17HT capillary column. There were indications that adding copper may lead to formation of lower brominated PBDE congeners and PBDFs due to degradation of BDE-209 during Soxhlet extraction [109].

Since 2000, the Norwegian Institute for Public Health (NIPH) has been organising inter-laboratory studies on the analysis of dioxins and dioxin-like PCBs in frequently consumed foods (chicken meat, trout fillet and palm oil) [110–112]. In the fifth round organised in 2004, the participants were for the first time asked to voluntarily report concentrations of PBDEs and HBCD in food samples. Laboratories were requested to determine BDEs-28, 47, 99, 100, 153, 154, 183 and 209. Analysis was performed using the laboratory's own methods for sample preparation and instrumental analysis, their own reference standards and quantification procedures, and their own method for lipid determination. Since then, PBDEs have been included in this yearly programme for a number of environmentally relevant matrices, in particular fish tissue (trout, halibut, salmon, eel, and herring) and have attracted a large number of laboratories [112–117]. Usually around 40 participants reported results for tri to hepta-BDEs. In the first years, the calculated consensus values for BDE-209 were only indicative as too few laboratories had reported this congener but later the number of reported results increased. To our knowledge, the reports of these inter-comparison studies provide the most comprehensive database on laboratory performance in PBDE analysis in biological matrices available at the moment. It is important to note that the majority of participating laboratories have used isotopic dilution HRGC-HRMS.

Here, we report only on the results of PBDEs in fish tissue from 2004 to 2009 (Table 6) as this is an important matrix for monitoring spatial and temporal trends in the aquatic environment as well as for checking compliance with environmental quality standards, threshold values or background reference concentrations. Other matrices included in these inter-comparisons were chicken, reindeer, deer and beef meat, palm oil, cod liver oil, butter oil, egg yolk, breast milk, butter, and cream. There was a clear tendency towards lower RSDs for the sum of tri to hepta-BDEs over time. While the average RSD in 2004 was 40%, it dropped down to 25% in 2009. This improvement was independent of the PBDE concentration in the

Table 6 Inter-laboratory comparison on dioxins in food (2004–2009). Summary statistics for BDE-209 and tri to hepta-BDE congeners and BDE-209 in fish tissue [111–117]. Concentrations are given in ng/g ww

Year	Sample	Number of results for tri to hepta-BDEs	Consensus median of tri to hepta-BDE	Range (average) of RSD %	Number of results for BDE-209	Number of outliers	Number of NDs[a]	Consensus median of BDE-209 in ng/g ww[b]	RSD %
2004	Trout	19–21	240	35–44 (40)	8	3	1	0.063[b]	50
2005	Herring	36–38	0.64	28–34 (31)	19	6	8	0.015[b]	71
2006	Halibut	38–39	1.40	28–69[c] (38)	27	8	7	0.015[b]	74
2007	Salmon	40–42	0.52	26–43 (33)	28	11	10	0.038	74
2008	Eel	39–40	24	20–30 (23)	28	8	14	0.027	72
2009	Herring	40–41	0.86	20–38 (25)	25	8	7	0.022	75

[a]*ND* not detected

[b]Indicative value due to low number of reported results

[c]The highest RSD of 69% was seen for BDE-183 probably due to its extremely low concentration in the sample. The consensus mean was 0.0009 ng/g ww

sample. These results provide evidence that the performance of governmental, private and research laboratories in conducting PBDE analysis (tri to hepta-BDEs) in fish samples has significantly improved.

Results for BDE-209 are difficult to interpret due to the extremely low concentrations of this congener in the inter-comparison samples and the fairly high number of outliers as well as left-censored values (Table 6). Yet, RSDs of 50–75% still indicate unsatisfactory performance. Hence, when interpreting PBDE levels in fish tissue the high uncertainty associated with results of BDE-209 needs definitely to be considered. There was no trend in the quality of results of the standard solutions (Table 7). RSDs were satisfactory even for BDE-209 and varied between 8 and 18% and were much lower than those reported by de Boer and Wells [4].

To assist environmental monitoring programmes as well as for the purpose of certification of reference materials, the National Institute of Standards and Technology (NIST) regularly conducts inter-laboratory exercises that also comprise PBDEs [118–121]. The materials distributed for the 2007 exercise included SRM 1945 Organics in Whale Blubber, SRM 1958 Human Serum, a homogenised blubber control material "Marine Mammal Quality Assurance Exercise Homogenate VIII" (Homogenate VIII) from a female pilot whale and "Marine Mammal Control Material 1-Serum" (MMCM1-serum) also derived from a female pilot whale [121]. Twelve laboratories reported data for BDEs-47, 99, 100, 153 and 154. Median mass fractions reported for SRM 1945 were within the uncertainties of the certified value for BDE-99, BDE-100 and BDE-154, and slightly below and above for BDE-47 and BDE-153, respectively. These discrepancies were mainly due to the low uncertainties of the certified values of these two congeners. RSDs ranged from 20 to 47% with highest values for BDE-153. RSDs for the blubber homogenate were between 12 and 21%, except for BDE-99 (39%), indicating excellent performance of the participating laboratories [121].

An inter-laboratory study comprising two rounds on the analysis of BDE-209 in environmental samples has been conducted within the European project NORMAN

Table 7 Inter-laboratory comparison on dioxins in food (2004–2009). Summary statistics for tri to hepta-BDE congeners and BDE-209 in test solutions of undisclosed concentrations [112–117]. Concentrations are given in ng/mL

Year	Test solution	Number of results	Number of outliers	Target concentrations	RSD %
2004	Tri to hepta-BDE	19–21	1	25	11–18
	BDE-209	9	4	125	15
2005	Tri to hepta-BDE	31–33	–	25	8–13
	BDE-209	21	3	100	18
2006	Tri to hepta-BDE	40–41	1	25	11–13
	BDE-209	29	5	100	12
2007	Tri to hepta-BDE	39–41	1	25	10–14
	BDE-209	30	1	100	16
2008	Tri to hepta-BDE	36–37	2	25	8–16
	BDE-209	27	–	100	13
2009	Tri to hepta-BDE	40–41	1	25	8–10
	BDE-209	26	1	100	8

(Network of Reference Laboratories and Related Organisations for Monitoring and Biomonitoring of Emerging Environmental Pollutants) [122, 123]. In the first round, six laboratories experienced in PBDE analysis measured BDE-209 in a test solution of undisclosed concentration and a dust sample (NIST SRM 2585). Each laboratory was allowed to use its own analytical methodology. Rigorous implementation of previously agreed recommendations including the obligatory use of $^{13}C_{12}$-labelled BDE-209 as internal standard resulted in relative reproducibility and repeatability standard deviations below 10% for both samples. All reported results for the dust sample were in agreement with the certified value of the NIST SRM 2585 [122].

In a follow-up study, expert and other laboratories were involved (ten participants in total). Prior to the second round, a meeting with the participants was held to discuss analytical difficulties and problems. Experiences from the first round as well as recommendations from the literature were exchanged and solutions discussed. The laboratories were given advice on the use of the preferred conditions for extraction, clean-up and GC. In this exercise, a test solution of undisclosed concentration, a dust sample (NIST SRM 2585) and a low contaminated marine sediment had to be analysed [123]. The reproducibility variation coefficients for the sediment, dust and the test solution were 31, 20 and 13%, respectively. The repeatability variation coefficients were less than 10% for all samples. The performance of the participating laboratories was surprisingly good given the differences in their experience to analyse BDE 209.

The measurement of PBDE in polymers is similar to that in environmental samples, but due to the high concentrations of PBDEs that are present in plastics, sample intake can be significantly reduced compared to the environmental analyses described above and thus little effort has to be made with regard to the clean-up. This can result in simple analytical procedures, and hence, better laboratory performances than for environmental samples might be expected. However, in a recent inter-comparison exercise on analysis of PBDEs in PET spiked with technical mixtures of penta-BDE, octa-BDE, and deca-BDE as well as deca-BB at 0.4–0.8 g/kg, high RSDs for the major constituents BDE-47, 99, 183, 209, and BB-209 of 33, 27, 40, 47 and 44%, respectively, have been observed [124].

The German Federal Environment Agency commissioned the Federal Institute for Materials Research and Testing to develop and validate a method for the analysis of technical mixtures of penta and octa-BDE in polymers. The method was subjected to an inter-laboratory study with 18 participants from seven countries which had to analyse four polymers spiked with technical Penta- or Octa-BDE at 1 g/kg [125]. The relative reproducibility standard deviations for the sum of congeners representing penta-BDEs in the epoxy resin and polyurethane sample were 15% for either type of polymer while for the sum of octa-BDEs in poly (acrylonitrile, butadiene, styrene) (ABS) copolymer and in polystyrene, relative reproducibility standard deviations of 27% and 26%, respectively, were obtained.

A recent certification inter-laboratory study involving 16 selected laboratories demonstrated that BDEs-28, 47, 99, 100, 153, 154, 183, 197 + 204, 209, and BB-209 can be measured in spiked PP and PE samples with high accuracy. After

elimination of technically doubtful results, the RSDs between laboratories ranged from 3% for BDE-209 to 12% for BDE-47 and BB-209 [63]. To the best of our knowledge, these are the best results ever obtained in an inter-laboratory study on the analysis of PBDEs.

In 2009, the Organic Analysis Working Group of CCQM (Consultative Committee for Amount of Substance – Metrology in Chemistry) carried out a laboratory inter-comparison (pilot study P114) for assessing the current state-of-the-art measurement capabilities of National Metrology Institutes (NMIs) to accurately quantify representative PBDE and PBB congeners in a polymer sample [65]. The study involved eight NMIs, which were asked to analyse BDEs-47, 183, 206 and 209 and BB-209 in a commercially prepared PP granulate material and a test solution of undisclosed concentration. The same PP sample as in the certification inter-laboratory study mentioned above was used. Results for the test solution of undisclosed concentration were in good agreement with the certified values. The analytical procedures used to analyse PP in this CCQM study differed substantially. Nevertheless, results were all in agreement, except some technical exceptions. Since the same PP material was used in two independent inter-laboratory exercises, results could be compared. Good agreement between the two data sets (study means versus certified values) has been achieved for all four PBDE congeners and BB-209 [65]. Within-lab repeatability of the NMIs was $\leq$10% for all labs and all congeners. Expanded uncertainties as estimated by the NMIs were in the range of about 5–10% in most cases and significantly lower than those reported by the laboratories that participated in the certification round.

7 Future Perspectives

Due to their recent restriction in usage and bans from EU and other markets (e.g. USA, Canada, Asia), it is expected that PBDEs will be (if not already done) added on priority monitoring lists (e.g. food and environmental control, Water Framework Directive). Therefore, accurate analytical methodologies are necessary to control the effectiveness of the implementation of legal regulations and emission reduction measures, as well as to estimate human exposure to these chemicals. As results of PBDE measurements have to comply with environmental quality standards, limit or threshold values the regulatory requirements as regards the tolerable uncertainty of PBDE data are high. Hence, it is of utmost importance that all steps of the analytical method are carefully addressed following the recommendations given in the QA/QC section and that laboratories involved in PBDE analysis operate comprehensive QA/QC programmes to demonstrate the reliability of the data they produce. A recent trend was seen towards the introduction of new analytical methodologies for the analysis of PBDE and other BFRs based on LC/MS [126]. These new methods may lead to similar low detection limits as the GC-based methods, but mostly include simpler protocols for the sample preparation, making them attractive for routine analysis.

Acknowledgements Dr Alin C. Dirtu acknowledges financial support from the University of Antwerp, Belgium. Dr Adrian Covaci was financially supported by the Research Council of the University of Antwerp and by a postdoctoral fellowship from the Research Scientific Foundation – Flanders (FWO). Prof. Dr Hendrik Emons (IRMM) is acknowledged for the improvement of the metrological aspects.

Disclaimer for the EC. Certain commercial equipment, instruments, and materials are identified in this paper to specify adequately the experimental procedure. In no case does such identification imply recommendation or endorsement by the European Commission, nor does it imply that the material or equipment is necessarily the best available for the purpose.

References

1. de Boer J, Allchin C, Law R, Zegers B, Booij JP (2001) Method for the analysis of polybrominated diphenyl ethers in sediments and biota. Trends Anal Chem 20:591–599
2. Covaci A, Voorspoels S, de Boer J (2003) Determination of brominated flame retardants, with emphasis on polybrominated diphenyl ethers (PBDEs) in environmental and human samples – a review. Environ Int 29:735–756
3. Covaci A, Voorspoels S, Ramos L, Neels H, Blust R (2007) Recent developments in the analysis of brominated flame retardants and brominated natural products. J Chromatogr A 1153:145–171
4. de Boer J, Wells DE (2006) Pitfalls in the analysis of brominated flame retardants in environmental, human and food samples – including results of three international inter-laboratory studies. Trends Anal Chem 25:364–372
5. Stapleton HM (2006) Instrumental methods and challenges in quantifying polybrominated diphenyl ethers in environmental extracts: a review. Anal Bioanal Chem 386:807–817
6. Li MKY, Lei NY, Gong C, Yu Y, Lam KH, Lam MHW, Yu H, Lam PKS (2009) An organically modified silicate molecularly imprinted solid-phase microextraction device for the determination of polybrominated diphenyl ethers. Anal Chim Acta 633:197–203
7. Fontana AR, Silva MR, Martínez LD, Wuilloud RG, Altamirano JC (2009) Determination of polybrominated diphenyl ethers in water and soil samples by cloud point extraction-ultrasound-assisted back-extraction-gas chromatography–mass spectrometry. J Chromatogr A 1216:4339–4346
8. Labadie P, Tlili K, Alliot F, Bourges C, Desportes A, Chevreuil M (2010) Development of analytical procedures for trace-level determination of polybrominated diphenyl ethers and tetrabromobisphenol A in river water and sediment. Anal Bioanal Chem 396:865–875
9. Fromme H, Korner W, Shahin N, Wanner A, Albrecht M, Boehmer S, Parlar H, Mayer R, Liebl B, Bolte G (2009) Human exposure to polybrominated diphenyl ethers (PBDE), as evidenced by data from a duplicate diet study, indoor air, house dust, and biomonitoring in Germany. Environ Int 35:1125–1135
10. Chen D, Bi X, Zhao J, Chen L, Tan J, Mai B, Sheng G, Fu J, Wong M (2009) Pollution characterization and diurnal variation of PBDEs in the atmosphere of an E-waste dismantling region. Environ Pollut 157:1051–1057
11. Takigami H, Suzuki G, Hirai Y, Sakai S (2009) Brominated flame retardants and other polyhalogenated compounds in indoor air and dust from two houses in Japan. Chemosphere 76:270–277
12. Wyrzykowska B, Tabor D, Gullett BK (2009) Same-sample determination of ultratrace levels of polybrominated diphenyl ethers, polybromodibenzo-p-dioxins/furans, and polychlorodibenzo-p-dioxins/furans from combustion flue gas. Anal Chem 81:4334–4342
13. Schecter A, Shah N, Colacino JA, Brummitt SI, Ramakrishnan V, Harris RT, Päpke O (2009) PBDEs in US and German clothes dryer lint: a potential source of indoor contamination and exposure. Chemosphere 75:623–628

14. Hong SH, Munschy C, Kannan N, Tixier C, Tronczynski J, Héas-Moisan K, Shim WJ (2009) PCDD/F, PBDE, and nonylphenol contamination in a semi-enclosed bay (Masan Bay, South Korea) and a Mediterranean lagoon (Thau, France). Chemosphere 77:854–862
15. Liu G, Zhang G, Jin Z, Li J (2009) Sedimentary record of hydrophobic organic compounds in relation to regional economic development: a study of Taihu Lake, East China. Environ Pollut 157:2994–3000
16. Chen L, Huang Y, Peng X, Xu Z, Zhang S, Ren M, Ye Z, Wang X (2009) PBDEs in sediments of the Beijiang River, China: levels, distribution, and influence of total organic carbon. Chemosphere 76:226–231
17. Sanchez-Brunete C, Miguel E, Tadeo JL (2009) Analysis of polybrominated diphenyl ethers in sewage sludge by matrix solid-phase dispersion and isotope dilution GC–MS. J Sep Sci 32:109–117
18. Wang P, Zhang Q, Wang Y, Wang T, Li X, Li Y, Ding L, Jiang G (2009) Altitude dependence of polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) in surface soil from Tibetan Plateau, China. Chemosphere 76:1498–1504
19. Montes R, Rodríguez I, Cela R (2010) Solid-phase microextraction with simultaneous oxidative sample treatment for the sensitive determination of tetra- to hexabrominated diphenyl ethers in sediments. J Chromatogr A 1217:14–21
20. Petreas M, Oros D (2009) Polybrominated diphenyl ethers in California wastestreams. Chemosphere 74:996–1001
21. Ranz A, Maier E, Trampitsch C, Lankmayr E (2008) Microwave-assisted extraction of decabromodiphenylether from polymers. Talanta 76:102–106
22. Vilaplana F, Ribes-Greus A, Karlsson S (2009) Microwave-assisted extraction for qualitative and quantitative determination of brominated flame retardants in styrenic plastic fractions from waste electrical and electronic equipment (WEEE). Talanta 78:33–39
23. Gebbink WA, Sonne C, Dietz R, Kirkegaard M, Riget FF, Born EW, Muir DCG, Letcher RJ (2008) Tissue-specific congener composition of organohalogen and metabolite contaminants in East Greenland polar bears (*Ursus maritimus*). Environ Pollut 152:621–629
24. Meng X, Blasius ME, Gossett RW, Maruya KA (2009) Polybrominated diphenyl ethers in pinnipeds stranded along the southern California coast. Environ Pollut 157:2731–2736
25. Jin J, Wang Y, Yang C, Hu J, Liu W, Cui J, Tang X (2009) Polybrominated diphenyl ethers in the serum and breast milk of the resident population from production area, China. Environ Int 35:1048–1052
26. Sagerup K, Helgason LB, Polder A, Strøm H, Josefsen TD, Skåre JU, Gabrielsen GW (2009) Persistent organic pollutants and mercury in dead and dying glaucous gulls (*Larus hyperboreus*) at Bjørnøya (Svalbard). Sci Total Environ 407:6009–6016
27. Losada S, Roach A, Roosens L, Santos FJ, Galceran MT, Vetter W, Neels H, Covaci A (2009) Biomagnification of anthropogenic and naturally-produced organobrominated compounds in a marine food web from Sydney Harbour, Australia. Environ Int 35:1142–1149
28. Haraguchi K, Koizumi A, Inoue K, Harada KH, Hitomi T, Minata M, Tanabe M, Kato Y, Nishimura E, Yamamoto Y, Watanabe T, Takenaka K, Uehara S, Yang H, Kim M, Moon C, Kim H, Wang P, Liu A, Hung NN (2009) Levels and regional trends of persistent organochlorines and polybrominated diphenyl ethers in Asian breast milk demonstrate POPs signatures unique to individual countries. Environ Int 35:1072–1079
29. Frederiksen M, Thomsen M, Vorkamp K, Knudsen LE (2009) Patterns and concentration levels of polybrominated diphenyl ethers (PBDEs) in placental tissue of women in Denmark. Chemosphere 76:1464–1469
30. Zhao YX, Qin XF, Li Y, Liu PY, Tian M, Yan SS, Qin ZF, Xu XB, Yang YJ (2009) Diffusion of polybrominated diphenyl ether (PBDE) from an e-waste recycling area to the surrounding regions in southeast China. Chemosphere 76:1470–1476
31. Abaurrea MP, Weijs L, Ramos L, Borghesi N, Corsolini S, Neels H, Blust R, Covaci A (2009) Anthropogenic and naturally-produced organobrominated compounds in bluefin tuna from the Mediterranean Sea. Chemosphere 76:1477–1482

32. Tadeo JL, Sánchez-Brunete C, Miguel E (2009) Determination of polybrominated diphenyl ethers in human hair by gas chromatography-mass spectrometry. Talanta 78:138–143
33. Lacorte S, Guillamon M (2008) Validation of a pressurized solvent extraction and GC–NCI–MS method for the low level determination of 40 polybrominated diphenyl ethers in mothers' milk. Chemosphere 73:70–75
34. Priyanthi RMA, Dassanayake S, Wei H, Chen RC, Li A (2009) Optimization of matrix solid phase dispersion extraction procedure for the analysis of polybrominated diphenyl ethers in human placenta. Anal Chem 81:9795–9801
35. Loconto PR, Isenga D, O'Keefe M, Knottnerus M (2008) Isolation and recovery of selected polybrominated diphenyl ethers from human serum and sheep serum: coupling reversed-phase solid-phase disk extraction and liquid-liquid extraction techniques with a capillary gas chromatographic electron capture negative ion mass spectrometric determinative technique. J Chromatogr Sci 46:53–60
36. Loconto PR (2009) Evaluation of automated stir bar sorptive extraction-thermal desorption-gas chromatography electron capture negative ion mass spectrometry for the analysis of PBDEs and PBBs in sheep and human serum. J Chromatogr Sci 47:656–669
37. Vonderheide AP (2009) A review of the challenges in the chemical analysis of the polybrominated diphenyl ethers. Microchem J 92:49–57
38. Lacorte S, Ikonomou MG, Fischer M (2010) A comprehensive gas chromatography coupled to high resolution mass spectrometry based method for the determination of polybrominated diphenyl ethers and their hydroxylated and methoxylated metabolites in environmental samples. J Chromatogr A 1217:337–347
39. Vonderheide AP, Mueller KE, Meija J, Welsh GL (2008) Polybrominated diphenyl ethers: causes for concern and knowledge gaps regarding environmental distribution, fate and toxicity. Sci Total Environ 400:425–436
40. Marsh G, Athanasiadou M, Bergman Å, Asplund L (2004) Identification of hydroxylated and methoxylated polybrominated diphenyl ethers in Baltic Sea salmon (*Salmo salar*) blood. Environ Sci Technol 38:10–18
41. Sinkkonen S, Rantalainen A-L, Paasivirta J, Lahtiperä M (2004) Polybrominated methoxy diphenyl ethers (MeO-PBDEs) in fish and guillemot of Baltic, Atlantic and Arctic environments. Chemosphere 56:767–775
42. Dirtu AC, Ravindra K, Roosens L, van Grieken R, Neels H, Blust R, Covaci A (2008) Fast analysis of decabrominated diphenyl ether using low-pressure gas chromatography – electron-capture negative ionization mass spectrometry. J Chromatogr A 1186:295–301
43. Roosens L, Dirtu AC, Goemans G, Belpaire C, Gheorghe A, Neels H, Blust R, Covaci A (2008) Brominated flame retardants and organochlorine contaminants in fish from the Scheldt River, Belgium. Environ Int 34:976–983
44. Björklund J, Tollbäck P, Hiarne C, Dyremarck E, Östman C (2004) Influence of the injection technique and the column system on gas chromatographic determination of polybrominated diphenyl ethers. J Chromatogr A 1041:201–210
45. Covaci A, de Boer J, Ryan JJ, Voorspoels S, Schepens P (2002) Determination of polybrominated diphenyl ethers and polychlorinated biphenyls in human adipose tissue by large-volume injection – narrow-bore capillary gas chromatography/electron impact low-resolution mass spectrometry. Anal Chem 74:790–798
46. Björklund J, Tollbäck P, Östman C (2003) Large volume injection GC-MS in electron capture negative ion mode utilizing isotopic dilution for the determination of polybrominated diphenyl ethers in air. J Sep Sci 26:1104–1110
47. Tollbäck P, Björklund J, Östman C (2003) Large-volume programmed-temperature vaporiser injection for fast gas chromatography with electron capture and mass spectrometric detection of polybrominated diphenyl ethers. J Chromatogr A 991:241–253
48. Korytár P, Covaci A, de Boer J, Gelbin A, Brinkman UATh (2005) Retention-time database of 126 polybrominated diphenyl ether congeners and two Bromkal technical mixtures on seven capillary gas chromatographic columns. J Chromatogr A 1065:239–251

49. Korytár P, Covaci A, Leonards PEG, de Boer J, Brinkman UATh (2005) Comprehensive two-dimensional gas chromatography of polybrominated diphenyl ethers. J Chromatogr A 1100:20–31
50. Ravindra K, Dirtu AC, Covaci A (2008) Low-pressure gas chromatography: recent trends and developments. Trends Anal Chem 27:291–303
51. Sellström U (1999) Determination of some polybrominated flame retardants in biota, sediment and sewage sludge. PhD Thesis, University of Stockholm, Sweden
52. Eljarrat E, de la Cal A, Barcelo D (2003) Potential chlorinated and brominated interferences on the polybrominated diphenyl ether determinations by gas chromatography-mass spectrometry. J Chromatogr A 1008:181–192
53. Li Y, Wang T, Hashi Y, Li H, Lin J-M (2009) Determination of brominated flame retardants in electrical and electronic equipments with microwave-assisted extraction and gas chromatography-mass spectrometry. Talanta 78:1429–1435
54. Ackerman LK, Wilson GR, Simonich SL (2005) Quantitative analysis of 39 polybrominated diphenyl ethers by isotope dilution GC/low-resolution MS. Anal Chem 77:1979–1987
55. Vizcaino E, Arellano L, Fernandez P, Grimalt JO (2009) Analysis of whole congener mixtures of polybromodiphenyl ethers by gas chromatography-mass spectrometry in both environmental and biological samples at femtogram levels. J Chromatogr A 1216: 5045–5051
56. Park H-M, Hong S-M, Agustin-Camacho MR, Dirwono W, Lee K-B (2009) Pressurized liquid extraction for the simultaneous analysis of polychlorinated biphenyls and polybrominated diphenyl ethers from soil by GC-TOF-MS detection. J Chromatogr Sci 47:681–688
57. Medina CM, Pitarch E, Portolés T, López FJ, Hernández F (2009) GC-MS/MS multi-residue method for the determination of organochlorine pesticides, polychlorinated biphenyls and polybrominated diphenyl ethers in human breast tissues. J Sep Sci 32:2090–2102
58. Kikuchi S, Kawauchi K, Ooki S, Kurosawa M, Honjo H, Yagishita T (2004) Non-destructive rapid analysis of brominated flame retardants in electrical and electronic equipment using Raman spectroscopy. Anal Sci 20:1111–1112
59. Altwaiq AM, Wolf M, van Eldik R (2003) Extraction of brominated flame retardants from polymeric waste material using different solvents and supercritical carbon dioxide. Anal Chim Acta 491:111–123
60. Allen JG, McClean MD, Stapleton HM, Webster TF (2008) Linking PBDEs in house dust to consumer products using X-ray fluorescence. Environ Sci Technol 42:4222–4228
61. Vilaplana F, Karlsson P, Ribes-Greus A, Ivarsson P, Karlsson S (2008) Analysis of brominated flame retardants in styrenic polymers – comparison of the extraction efficiency of ultrasonication, microwave-assisted extraction and pressurised liquid extraction. J Chromatogr A 1196:139–146
62. Linsinger TPJ, Birgersson-Liebich A, Pellizzato F, Venelinov T, Voorspoels S, Lamberty A (2009) EUR 23677 EN, ISBN 978-92-79-11105-1
63. Linsinger TPJ, Birgersson-Liebich A, Lamberty A, Pellizzato F, Venelinov T, Voorspoels S (2009) Development of the first certified reference materials for several brominated flame retardants in polymers. Anal Chem 81:3792–3800
64. Vazquez AS, Costa-Fernandez JM, Encinar JR, Pereiro R, Sanz-Medel A (2008) Bromine determination in polymers by inductively coupled plasma-mass spectrometry and its potential for fast first screening of brominated flame retardants in polymers and paintings. Anal Chimica Acta 623:140–145
65. Zeleny R, Voorspoels S, Ricci M, Becker R, Jung C, Bremser W, Sittidech M, Panyawathanakit N, Wong WF, Choi SM, Lo KC, Yeung WY, Kim DH, Han J, Ryu J, Mingwu S, Chao W, Schantz MM, Lippa KA, Matsuyama S (2008) Evaluation of the state-of-the-art measurement capabilities for selected PBDEs and decaBB in plastic by the international intercomparison CCQM-P114 (2010). Anal Bioanal Chem 396:1501–1511
66. de Boer J, Cofino WP (2002) First world-wide inter-laboratory study on PBDEs. Chemosphere 46:625–633

67. Sjödin A, Jakobsson E, Kierkegaard A, Marsh G, Sellström U (1998) Gas chromatographic identification and quantification of polybrominated diphenyl ethers in a commercial product, Bromkal 70-5DE. J Chromatogr A 822:83–89
68. Voorspoels S, Covaci A, Maervoet J, Schepens P (2004) PBDEs in marine and freshwater sediments from Belgium: levels, profiles and relations with biota. J Environ Monitor 6: 914–918
69. de Boer J, de Boer K, Boon JP (2000) Polybrominated Biphenyls and Diphenylethers. In: Paasivirta J (ed) The Handbook of Environmental Chemistry. New Types of Persistent Halogenated Compounds. Part 3K, Springer-Verlag, Berlin/Heidelberg, pp 61–95. ISBN: 978-3-540-65838-2
70. de Boer J, Wester PG, van der Horst A, Leonards PEG (2003) Polybrominated diphenyl ethers in influents, suspended particulate matter, sediments, sewage treatment plant and effluents and biota from the Netherlands. Environ Pollut 122:63–74
71. Luthe G, Leonards PEG, Rijerink GS, Liu HL, Johansen JE, Robertson LW (2006) Monofluorinated analogues of polybrominated diphenyl ethers as analytical standards: synthesis, NMR, and GC-MS characterization and molecular orbital studies. Environ Sci Technol 40:3023–3029
72. Päpke O, Furst P, Herrmann T (2004) Determination of polybrominated diphenylethers (PBDEs) in biological tissues with special emphasis on QC/QA measures. Talanta 63: 1203–1211
73. Dodder N, Strandberg B, Hites RA (2002) Concentrations and spatial variations of polybrominated diphenyl ethers in fish and air from the North-Eastern United States. Environ Sci Technol 36:146–151
74. Luross JM, Alaee M, Sergeant DB, Cannon CM, Whittle DM, Solomon KR, Muir DCG (2002) Spatial distribution of polybrominated diphenyl ethers and polybrominated biphenyls in lake trout from the Laurentian Great Lakes. Chemosphere 46:665–672
75. Martinez A, Ramil M, Montes R, Hernanz D, Rubi E, Rodriguez I, Cela R (2005) Development of a matrix solid-phase dispersion method for the screening of polybrominated diphenyl ethers and polychlorinated biphenyls in biota samples using gas chromatography with electron-capture detection. J Chromatogr A 1072:83–91
76. Stapleton HM, Keller JM, Schantz MM, Kucklick JR, Leigh SD, Wise SA (2007) Determination of polybrominated diphenyl ethers in environmental standard reference materials. Anal Bioanal Chem 387:2365–2379
77. Voorspoels S (2006) Environmental distribution of brominated flame retardants in Belgium. PhD Dissertation, University of Antwerp, Belgium
78. Thomsen C, Leknes H, Lundanes E, Becher G (2002) A new method for determination of halogenated flame retardants in human milk using solid-phase extraction. J Anal Toxicol 26:129–138
79. Sjödin A (2000) Occupational and dietary exposure to organohalogenated substances with special emphasis on polybrominated flame retardants. PhD Thesis, Stockholm University, Sweden
80. Thomsen C, Leknes H, Lundanes E, Becher G (2001) Brominated flame retardants in laboratory air. J Chromatogr A 923:299–304
81. Wilford BH, Thomas GO, Jones KC, Davidson B, Hurst DK (2008) Decabromodiphenyl ether (deca-BDE) commercial mixture components, and other PBDEs, in airborne particles at a UK site. Environ Int 34:412–419
82. Thomsen C, Lundanes E, Becher G (2001) A simplified method for determination of tetrabromobisphenol A and polybrominated diphenyl ethers in human plasma and serum. J Sep Sci 24:282–290
83. Kuiper RV, Vethaak AD, Cantón RF, Anselmo H, Dubbeldam M, van den Brandhof EJ, Leonards PEG, Wester PW, van den Berg M (2008) Toxicity of analytically cleaned pentabromodiphenylether after prolonged exposure in estuarine European flounder (*Platichthys*

flesus), and partial life-cycle exposure in fresh water zebrafish (*Danio rerio*). Chemosphere 73:195–202
84. Voorspoels S, Covaci A, Lepom P, Escutenaire S, Schepens P (2006) Remarkable findings concerning PBDEs in the terrestrial top-predator red fox (*Vulpes vulpes*). Environ Sci Technol 40:2937–2943
85. Covaci A, Voorspoels S, Roosens L, Jacobs W, Blust R, Neels H (2008) Polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) in human liver and adipose tissue samples from Belgium. Chemosphere 73:170–175
86. Bodin N, Abarnou A, Fraisse D, Defour S, Loizeau V, Guellec AML, Philippon X (2007) PCB, PCDD/F and PBDE levels and profiles in crustaceans from the coastal waters of Brittany and Normandy (France). Mar Pollut Bull 67:657–668
87. Verreault J, Shahmiri S, Gabrielsen GW, Letcher RJ (2007) Organohalogen and metabolically-derived contaminants and associations with whole body constituents in Norwegian Arctic glaucous gulls. Environ Int 33:823–830
88. Raab U, Preiss U, Albrecht M, Shahin N, Parlar H, Fromme H (2008) Concentrations of polybrominated diphenyl ethers, organochlorine compounds and nitro musks in mother's milk from Germany (Bavaria). Chemosphere 72:87–94
89. IUPAC (1976) Nomenclature, symbols, units and their usage in chemical analysis: data interpretation. Anal Chem 48:2294–2296
90. Bloom M, Spliethoff H, Vena J, Shaver S, Addink R, Eadon G (2008) Environmental exposure to PBDEs and thyroid function among New York anglers. Environ Toxicol Pharmacol 25:386–392
91. Thomsen C, Liane VH, Becher G (2007) Automated solid-phase extraction for the determination of polybrominated diphenyl ethers and polychlorinated biphenyls in serum—application on archived Norwegian samples from 1977 to 2003. J Chromatogr B 846:252–263
92. Jaraczewska K, Lulek J, Covaci A, Voorspoels S, Kaluba-Skotarczak A, Drews K, Schepens P (2006) Distribution of polychlorinated biphenyls, organochlorine pesticides and polybrominated diphenyl ethers in human umbilical cord serum, maternal serum and milk from Wielkopolska region, Poland. Sci Total Environ 372:20–31
93. Pirard C, de Pauw E, Focant JF (2006) Suitability of tandem-in-time mass spectrometry for polybrominated diphenylether measurement in fish and shellfish samples: comparison with high resolution mass spectrometry. J Chromatogr A 1115:125–132
94. Stapleton HM, Baker JE (2003) Comparing polybrominated diphenyl ether and polychlorinated biphenyl bioaccumulation in a food web in Grand Traverse Bay, Lake Michigan. Arch Environ Contam Toxicol 45:227–234
95. Sjödin A, Carlsson H, Thuresson K, Sjölin S, Bergman Å (2001) Flame retardants in indoor air at an electronics recycling plant and at other work environments. Environ Sci Technol 35:448–454
96. Jakobsson K, Thuresson K, Rylander L, Sjödin A, Hagmar L, Bergman Å (2002) Exposure to polybrominated diphenyl ethers and tetrabromobisphenol A among computer technicians. Chemosphere 46:709–716
97. Horwitz W, Kamps LR, Boyer KW (1980) Quality assurance in the analysis of foods for trace constituents. J Assoc Off Anal Chem 63:1344–1354
98. QUASIMEME Laboratory Performance Studies, DE-8 Brominated Flame Retardants, Round 41, Exercise 656, 2005, Report, Issue 1: 161205
99. QUASIMEME Laboratory Performance Studies, DE-8 Development Exercise Brominated Flame Retardants in Sediment, Round 45, Exercise 719, 2006, Report, Issue 1: 26090
100. QUASIMEME Laboratory Performance Studies, BS-1 Brominated Flame Retardants, Round 46, Exercise 729, 2006, Report, Issue 1: 050107
101. QUASIMEME Laboratory Performance Studies, BS-1 Brominated Flame Retardants, Round 48, Exercise 748, 2007, Report, Issue 1: 150607
102. QUASIMEME Laboratory Performance Studies, BS-1 Brominated Flame Retardants, Round 50, Exercise 773, 2007, Report, Issue 1: 031207

103. QUASIMEME Laboratory Performance Studies, BS-1 Brominated Flame Retardants, Round 52, Exercise 790, 2008, Report, Issue 1: 170608
104. QUASIMEME Laboratory Performance Studies, BS-1 Brominated Flame Retardants, Round 54, Exercise 818, 2008, Report, Issue 1: 191208
105. QUASIMEME Laboratory Performance Studies, BS-1 Brominated Flame Retardants, Round 56, Exercise 835, 2009, Report, Issue 1: 25052009
106. Cofino WP, van Stokkum IHM, Wells DE, Ariese F, Wegener JWM, Peerboom RAL (2000) A new model for the inference of population characteristics from experimental data using uncertainties. Application to inter-laboratory studies. Chemometr Intell Lab Syst 53: 37–55
107. Cofino WP, van Stokkum IHM, van Steenwijke J, Wells DE (2005) A new model for the inference of population characteristics from experimental data using uncertainties – Part II. Application to censored datasets. Anal Chim Acta 533:31–39
108. DIN 38402-45: German standard methods for the examination of water, waste water and sludge – general information (group A) – Part 45: Inter-laboratory comparisons for proficiency testing of laboratories (A 45), 2003
109. Takahashi S, Sakai S-I, Watanabe I (2006) An intercalibration study on organobromine compounds: results on polybrominated diphenylethers and related dioxin-like compounds. Chemosphere 64:234–244
110. Becher G, Haug LS, Thomsen C (2004) World-wide comparison on the quality of analytical determinations of PCDDs/PCDFs and dioxin-like PCBs in food. Talanta 63:1115–1122
111. Haug L, Thomsen C, Becher G (2005) The quality of PBDE analysis in food – results from an inter-laboratory comparison study. Organohalogen Compd 67:622–625
112. Haug LS, Becher G (2004) Inter-laboratory comparison on dioxins in food 2004 – sixth round of an international study, report 2004:6, ISBN 82-8082-100-7. Norwegian Institute of Public Health, Oslo, Norway
113. Haug LS, Becher G (2005) Inter-laboratory comparison on dioxins in food 2005 – sixth round of an international study, report 2005:7, ISBN 82-8082-145-7. Norwegian Institute of Public Health, Oslo, Norway
114. Haug LS, Becher G (2006) Inter-laboratory comparison on dioxins in food 2006 – seventh round of an international study, report 2006:7, ISBN 82-8082-178-3. Norwegian Institute of Public Health, Oslo, Norway
115. Liane VH, Becher G (2007) Inter-laboratory comparison on dioxins in food 2007 – eight round of an international study, report 2007:7, ISBN 978-82-8082-216-1. Norwegian Institute of Public Health, Oslo, Norway
116. Liane VH, Bjellaas T, Becher G (2008) Inter-laboratory comparison on dioxins in food 2008 – ninth round of an international study, report 2008:13, ISBN 978-82-8082-286-4. Norwegian Institute of Public Health, Oslo, Norway
117. Liane VH, Becher G (2009) Inter-laboratory comparison on dioxins in food 2009 – tenth round of an international study, report 2009:10, ISBN 978-82-8082-367-0. Norwegian Institute of Public Health, Oslo, Norway
118. Stapleton HM, Keller JM, Schantz MM, Kucklick JR, Wise SA (2005) NIST Inter-comparison exercise program for polybrominated diphenyl ethers (PBDES) in marine sediment: description and results of the 2004 intercomparison exercise. National Institute of Standards and Technology, Gaithersburg, MD, NISTIR 7278
119. Kucklick JR, Pugh RS, Becker PR, Schantz MM, Wise SA, Rowles TK (2005) Description and results of the 2003 NIST/NOAA inter-laboratory comparison exercise program for organic contaminants in marine mammal tissues. National Institute of Standards and Technology, Gaithersburg, MD, NISTIR 7269
120. Kucklick JR, Pugh RS, Becker PR, Schantz MM, Poster DL, Wise SA, Rowles TK (2007) Description and results of the 2005 NIST/NOAA inter-laboratory comparison exercise program for organic contaminants in marine mammal tissues, National Institute of Standards and Technology, Gaithersburg, MD, NISTIR 7410

121. Schantz MM, Parris RM, Wise SA (2008) Description and results of the 2007 NIST/NOAA inter-laboratory comparison exercise program for organic contaminants in marine mammal tissues. National Institute of Standards and Technology, Gaithersburg, MD, NISTIR 7501
122. Duffek A, Sawal G, Warmbrunn-Suckrow E, Lepom P (2007) Inter-laboratory study on DecaBDE in dust within the EU-Project NORMAN. Abstracts of the 4th International Workshop on Brominated Flame Retardants BFR 2007, Amsterdam, The Netherlands, April 24–27, http://www.bfr2007.com/abstracts/mainb.html?p=3
123. Duffek A, Leonards P, Lepom P (2008) Inter-laboratory study on Deca-BDE analysis in environmental samples involving routine laboratories. Organohalogen Compd 70:2025–2028
124. Linsinger TPJ, Voorspoels S, Liebich A (2008) Results of an inter-laboratory comparison on the determination of polybrominated flame retardants in poly(ethyleneterephthalate). Anal Bioanal Chem 390:399–409
125. Kemmlein S, Bergmann M, Jann O (2005) Standard measurement method for the determination of polybrominated flame retardants (pentabromodiphenylether, octabromodiphenylether) in products. UBA-Texte 31/05, http://www.umweltdaten.de/publikationen/fpdf-l/2971.pdf
126. Eljarrat E, Covaci A, Guerra P, Barceló D (2010) Recent methodologies for BFR determinations by means of LC-MS. Hdb Env Chem (in this volume)

Recent Methodologies for Brominated Flame Retardant Determinations by Means of Liquid Chromatography–Mass Spectrometry

P. Guerra, A. Covaci, E. Eljarrat, and D. Barceló

Abstract In this chapter, an overview of current analytical methods, including different sample preparation techniques as well as the different instrumental approaches, is presented. The strategy literature search for the preparation of this chapter was based on the recent analytical reviews published on brominated flame retardants (BFRs), with emphasis on hexabromocyclododecane (HBCD) and tetrabromobisphenol-A (TBBPA). Additionally, we have included all new articles published in peer-reviewed scientific journals, conference proceedings, or official reports found on the internet. The analytical procedures based on the use of liquid chromatography, used for the determination of some BFRs such as TBBPA, HBCD, as well as some metabolites and transformation products are presented. Analytical performances of the different approaches (ESI, APCI, and APPI as ionization modes) are reported and compared with those obtained by gas chromatographic techniques. Conclusions and future perspectives are outlined.

Keywords BFR metabolites, Brominated flame retardants, Hexabromocyclododecane, Liquid chromatography, Tandem mass spectrometry, Tetrabromobisphenol A

P. Guerra and E. Eljarrat (✉)
Department of Environmental Chemistry, IDAEA, CSIC, Jordi Girona 18-26, Barcelona 08034, Spain
e-mail: eeeqam@cid.csic.es

A. Covaci
Toxicological Center, University of Antwerp, Universiteitsplein 1, Wilrijk 2610, Belgium

D. Barceló
Department of Environmental Chemistry, IDAEA, CSIC, Jordi Girona 18-26, Barcelona 08034, Spain
and
Catalan Institute for Water Research (ICRA), Parc Científic i Tecnològic de la Universitat de Girona, Pic de Peguera 15, Girona 17003, Spain

E. Eljarrat and D. Barceló (eds.), *Brominated Flame Retardants*,
Hdb Env Chem (2011) 16: 95–122, DOI 10.1007/698_2010_94,

Contents

Abbreviations

APCI	Atmospheric pressure chemical ionization
APPI	Atmospheric pressure photoionization
BEHTBP	Bis(2-ethyl-1hexyl)tetrabromophthalate
BFR	Brominated flame retardant
BPA	Bisphenol A
Br_4Cl_2-DBP	1,1′-dimethyl-3,3′,4,4′-tetrabromo-5,5′-dichloro-2,2′-bipyrrole
BRP	Brominated phenols
Cl_7-MBP	2,3,3′,4,4′,5,5′-heptachloro-1′-methyl-1,2′-bipyrrole
CRM	Certified reference material
DBDPE	Decabromodiphenylethane
DCM	Dichloromethane
DiBBPA	Dibromobisphenol A
ECNI	Electron capture negative ionization
EF	Enantiomeric fraction
EHTeBB	2-ethylhexyl-2,3,4,5-tetrabromobenzoate
EI	Electron ionization
EPI	Enhanced product ion
ESI	Electrospray ionization
GC	Gas chromatography
GPC	Gel permeation chromatography
HBCD	Hexabromocyclododecane
HCH	Hexachlorocyclohexane
HRMS	High resolution mass spectrometry
IDL	Instrumental limit of detection
IS	Internal standard

ISP	Ion spray
K_{OW}	Octanol–water partition coefficient
LC	Liquid chromatography
LLE	Liquid–liquid extraction
LOD	Limit of detection
LOQ	Limit of quantification
LRMS	Low resolution mass spectrometry
MAE	Microwave assisted extraction
MeO	Methoxylated
MonoBBPA	Monobromobisphenol A
MS	Mass spectrometry
MS–MS	Tandem mass spectrometry
NCI	Negative chemical ionization
OH	Hydroxylated
PBB	Polybrominated biphenyls
PBCD	Pentabromocyclododecenes
PBDE	Polybrominated diphenyl ether
PLE	Pressurized liquid extraction
POP	Persistent organic pollutant
ppt	Parts per trillion
QqLIT	Quadrupole linear ion trap
QqQ	Triple quadrupole
QqTOF	Quadrupole time of flight
RF	Response factor
S/N	Signal-to-noise
SD	Standard deviation
SIM	Selected ion monitoring
SPE	Solid-phase extraction
SRM	Selected reaction monitoring
T4	Thyroxin
TBBPA	Tetrabromobisphenol-A
TBCD	Tetrabromocyclododecadienes
TBECH	1,2-dibromo-4-(1,2-dibromoethyl)cyclohexane
TriBBPA	Tribromobisphenol A
UAE	Ultrasonic-assisted extraction
UPLC	Ultra pressure liquid chromatography
USDP	Ultrasonic-supported dissolution and precipitation
WHO	World Health Organization

1 Introduction

Traditionally, the analysis of persistent organic pollutants (POPs) has been based upon gas chromatography (GC) as the principal separation technique due to the volatility of these compounds. The analysis of polybrominated diphenyl ethers (PBDEs), one

of the main brominated flame retardant (BFR) family, has been focused almost exclusively on GC coupled to mass spectrometry (GC–MS). More detailed information of PBDE determinations by means of GC–MS is presented in Chapter 3 [1].

During the last years, scientific interest for other BFRs, such as hexabromocyclododecane (HBCD) and tetrabromobisphenol A (TBBPA), has emerged, and consequently, new analytical methods have been developed. At the beginning, similar GC–MS approaches used for PBDE analysis were used for HBCD and TBBPA. HBCD has been determined using GC–electron capture negative ionization (ECNI)–MS. However, this technique has some limitations: interconversion of HBCD diastereoisomers above 160°C, decomposition of HBCDs at temperatures above 240°C, and partial breakdown in dirty GC systems [2]. On the other hand, acidification and derivatization steps are compulsory in the GC–MS analysis of more polar BFRs such as TBBPA [3].

The difficulties encountered in the GC analysis of HBCD and TBBPA created the need for alternative methods. Despite the relatively limited chromatographic resolving power of liquid chromatography (LC), methods employing LC–MS and LC–MS–MS offer good results for HBCD and TBBPA. LC allows the isomer-specific determination of HBCD, in contrast with the total HBCD analysis obtained by GC–MS. The identification and quantification of the three HBCD isomers is important because the isomeric patterns differ under different production condition and between matrices. Besides, HBCD enantiomers can be separated and determined using chiral LC–MS methods [4]. Since TBBPA is a phenolic compound, its determination by LC is the simplest and the most attractive option [4].

However, it is known that GC–MS has the advantage to have higher sensitivity compared with LC–MS methods [5]. To improve sensitivity and specificity of LC–MS methods in the field of environmental analysis, approaches based on LC–tandem MS (MS–MS) have been developed. First studies were focused on the use of triple quadrupole instruments (QqQ), but more recently, other instrumental configurations were developed and applied to BFR determinations. New works applied LC–hybrid MS techniques such as quadrupole time of flight (QqTOF) and quadrupole linear ion trap (QqLIT) instruments [6]. Different ionization techniques were also tested for LC–MS–MS methodologies, but the most used is electrospray ionization (ESI). It is well known that ESI is subjected to sample matrix effects that can cause enhancement or suppression in the signal of the target analytes [7, 8]. For this reason, the possibility to use isotopic-labeled standards such as ^{13}C- or d_{18}-α, β and γ-HBCD, and ^{13}C-TBBPA is very useful in order to compensate the matrix effects.

It is also important to note that LC methods may be useful in the analysis of BFR metabolites and transformation products. For example, the nonpolar nature of the diphenyl ether structure in PBDEs and the introduction of polar hydroxyl functional groups upon its metabolization provide a new molecule with different properties, such as nonvolatile nature that does not allow the direct analysis of PBDEs metabolites by GC–MS. Recent papers are focused on the development of LC–MS approaches for this purpose [9].

The development of analytical methods for BFRs is difficult due to the complexity of the environmental matrices and the usually low concentrations of target compounds [10]. Sample preparation techniques must also be developed and optimized to obtain sensitive and selective methodologies. In this chapter, extraction methods applied to a wide range of matrices are reviewed as well as the different purification and fractionation strategies.

2 Sample Preparation

For HBCD and TBBPA, sample treatment procedures have typically been based on protocols previously developed and used for the determination of PBDEs. Because of the complexity of environmental matrices and the low levels at which these compounds are present, such sample treatments include a number of steps for exhaustive extraction and preconcentration of the target compounds, followed by purification and fractionation before final chromatographic separation and detection. Below are relevant data on selected analytical procedures used for the determination of HBCD and TBBPA in a wide variety of abiotic and biotic samples. Furthermore, due to particular physicochemical properties, the determination of individual HBCD diastereomers and TBBPA may require specific analytical approaches, including additional fractionation.

2.1 Extraction

For both abiotic and biotic samples, the selection of the extraction technique depends on the nature of the matrix investigated. Different procedures are used for solid and liquid samples. The amount of sample required varies largely depending on the contamination level anticipated in the sample and on the sensitivity provided by the detection technique. Similar to abiotic samples, only drying and homogenization is usually carried out before extraction of biological samples. Except for serum and plasma, (semi) liquid (e.g., eggs) samples are usually freeze-dried and then treated as any other solid biotic sample. In general, similar extraction techniques and solvents are used for BFR analysis in abiotic and fat-containing matrices, and the main differences between both sets of analytical protocols refer only to the subsequent cleanup steps.

2.1.1 Water

Because of their hydrophobic character and thus low concentrations in water, large volumes (up to 1,000 mL) are typically required to ensure detectability. Suzuki et al. [11] reported recoveries above 77% for α-, β-, and γ-HBCD, after two

sequential liquid–liquid extractions (LLE) with dichloromethane (DCM) of a spiked landfill leachate. However, solid-phase extraction (SPE) on Abselut Nexus cartridges was suggested as a faster alternative allowing the simultaneous determination of TBBPA (recovery 103 ± 16%) and a significant reduction in the organic solvent consumption (from 50 mL DCM to 5 mL acetone) that still provided acceptable recoveries (54–85%) of the three HBCD diastereomers. To the best of our knowledge, no other techniques have been described for the measurement of HBCD and TBBPA in water samples.

2.1.2 Air and Dust

For abiotic solid samples, Soxhlet is widely accepted as a robust, efficient, and low cost solid–liquid extraction technique. Soxhlet has been used for the determination of HBCDs in indoor air (after preconcentration on polyurethane foam) [12, 13]. Typical solvents include *n*-hexane, DCM, acetone, and their binary mixtures. The main drawbacks of the Soxhlet extraction, i.e., long extraction times (typically >8 h) and large solvent consumption, can be at least partially avoided by pressurized liquid extraction (PLE). Abdallah et al. [14] included an *in-cell* purification using 1.5 g Florisil and Hydromatrix in the extraction cell under the sample. Even using this approach, the extracts had to be further purified by LLE extraction with concentrated H_2SO_4 followed by column chromatography on Florisil before instrumental analysis.

2.1.3 Soil, Sediment, and Sewage Sludge

Soxhlet extraction is the most used extraction technique for the determination of HBCDs and TBBPA in soils and sediments. In general, mixtures of acetone and *n*-hexane in different proportions (1:1 or 1:3, v/v) have been found to provide the best recoveries for HBCDs and TBBPA [15, 16]. PLE has also been evaluated for the analysis of BFRs in dried soils, sediments, and sewage sludge, and mixtures of DCM and *n*-hexane at 100°C have been used [17]. Recently, ultrasonic-assisted extraction (UAE) has been used for the extraction of HBCD isomers from sewage sludge using a mixture of DCM-acetonitrile (1:1) [18]. Microwave-assisted extraction (MAE) with acetone/*n*-hexane (1/3, v/v) at 90°C for 12 min has been employed for the extraction of HBCD isomers from marine sediments [19].

2.1.4 Biological Tissues

BFRs are usually extracted from serum by successive treatment with solvents of different polarity. In some cases, a treatment with a HCl:2-propanol mixture is carried out for protein denaturation before LLE [20]. However, direct solvent shaking with ethyl acetate and acetonitrile has also been demonstrated to

provide low but reproducible recoveries for γ-HBCD and TBBPA. One of the main limitations of these LLE-based procedures is the long waiting time or centrifugation required for phase separation. Alternatively, an SPE-based method using Abselut Nexus sorbents have been proposed for the determination of TBBPA in serum [21]. After serum or milk denaturation with formic acid and isopropanol, Thomsen et al. [22, 23] have employed SPE on OASIS HLB cartridges to extract HBCD from human serum or milk. Furthermore, the SPE-based methods proved to be less laborious and allowed reduced solvent consumption and processing time, possibility of miniaturization, and parallel sample preparation, which increases throughput.

A comprehensive method for the determination of major BFRs, including HBCD isomers and TBBPA, has been reported in human samples (serum, adipose tissue, and freeze-dried milk) [24]. For serum samples, a first LLE with ethyl acetate was performed. For freeze-dried milk samples, a first SLE with acetone: DCM 1:1 (v/v) was realized. Further, for all samples, an LLE with simultaneous partitioning with acetonitrile and hexane was applied on dried extracts (serum, milk) or directly on liquid fat samples.

For fat and oil samples, the first sample treatment is to dissolve the lipids in an appropriate solvent. Typically, sample intake was between 0.5 and 1 g, and quantitative recoveries >60% have been reported for HBCDs [25]. Column extraction using a multilayer column containing appropriate sorbents for a preliminary purification has been widely used for biological tissues. This technique has a number of advantages, such as minimum sample pretreatment required, simplicity, and high recoveries for HBCDs and TBBPA (>80%) [26].

Alternative enhanced extraction techniques, such as PLE or MAE, have also been used. Eljarrat et al. [27] adapted a selective PLE for the simultaneous analysis of total HBCDs in fish tissue. Ready-to-analyze extracts were obtained also here, but slightly higher recoveries (52–103%) were reported as compared to those found for sediments. A similar method has been used by Eljarrat et al. [28] for the extraction of HBCD isomers from lyophilized human milk. Fredriksen et al. [29] have also used PLE for the extraction of HBCD and TBBPA from marine biological samples.

2.1.5 Consumer Products

BFRs, such as HBCD and TBBPA, have been extracted from various polymers or from consumer products based on these polymers. The extraction efficiency of several methods, such as PLE, MAE, and UAE, were compared for the recovery of HBCD and TBBPA from styrenic polymeric plastics [30]. PLE resulted in complete extraction of TBBPA and HBCD (recovery >95%), while MAE gave comparable performance to PLE for HBCD but lower extraction yields for TBBPA (~80%). UAE, finally, offered relatively low extraction recoveries (10–50%) for both BFRs. In another study, BFRs, including HBCD and TBBPA, were extracted in a short step by ultrasonic-supported dissolution and precipitation (USDP) from styrenic polymers [31]. To analyze HBCD in flame-retarded textiles (e.g., curtains), three

different extraction methods (Soxhlet, UAE, and soaking extractions with toluene and DCM) were compared [32]. During Soxhlet extraction using toluene, the percent contribution of α-HBCD to total HBCDs increased slightly and that of γ-HBCD decreased, indicating that γ-HBCD was isomerized to some extent at the boiling point of toluene (around 120°C). For UAE, the temperature of the water bath can easily increase over time during the extraction, which might lead to undesirable effects. Soaking extraction with DCM was chosen as the most facile procedure to extract HBCD diastereomers from textiles.

2.2 Cleanup and Fractionation

The nonselective nature of the exhaustive extraction procedures and the complexity of the sample matrices result in complex extracts that require further purification. For abiotic samples (sediment, soil, and sewage sludge), the cleanup should ensure sulfur removal, while for biotic samples, lipid elimination should be accomplished before chromatographic analysis. Lipid elimination can be accomplished by destructive or nondestructive methods. Otherwise, similar protocols can be used for purification of the extracts almost irrespective of the matrix nature.

2.2.1 Sulfur Removal

Sediment, soil, and sewage sludge extracts often contain relatively large amounts of elemental sulfur, which may hamper the determination of BFRs even if selective separation and detection techniques are used. Treatments with Cu powder [33] or by gel permeation chromatography (GPC) [16, 32] are efficient approaches for sulfur elimination.

2.2.2 Nondestructive Methods for Lipid Removal

GPC [20] and adsorption chromatography on selected sorbents [17] are nondestructive treatments applied for lipid elimination. Silica gel, alumina, and Florisil with different degrees of activation have been widely used for lipid removal by adsorption chromatography under atmospheric conditions. Because of its limited capacity for retention of lipids, silica has been used in combination with alumina [33]. Alumina and Florisil have been preferred as fat retainers because of their higher lipid-retaining capacity in procedures involving *in-cell* PLE [14]. For obvious reasons, when extraction and cleanup are combined in a single step, the total lipid content determination should be carried out separately.

A cleanup based on dispersive solid phase extraction with primary–secondary amine was used recently for sewage sludge extracts [18]. Yet, it has been shown

that such cleanup is not sufficient for complete matrix removal as matrix effects showed high ion suppression up to 50% for all three HBCD diastereoisomers. Method recoveries ranged between 80 and 113% (standard deviation (SD) <9%).

2.2.3 Destructive Methods for Lipid Removal

Similarly to PBDEs, HBCDs and TBBPA are stable under strong acid conditions [2, 33]. The simplest approach consists of direct addition of the acid (e.g., concentrated sulphuric acid) to the sample extract dissolved in *n*-hexane. However, this treatment requires several sequential LLE and centrifugation steps, which result in a multistep and time-consuming procedure. The dispersion of sulphuric acid onto the surface of activated silica gel results in a sorbent, which can be easily loaded into a column. The use of acidified silica avoids the emulsion problems of the LLE approach, reduces the sample handling and solvent consumption, and increases sample throughput [33]. Although in many applications, the use of acidified silica is enough to yield sufficiently clean extracts, several studies have described the use of acidified silica in combination with silica, Florisil, or alumina in multilayer columns for improved purification [33]. All approaches provide similar satisfactory results concerning recovery and reproducibility. Although not thoroughly investigated, the use of silica gel modified with alcoholic NaOH or KOH may cause losses of bromine atoms from HBCD [33].

2.2.4 Fractionation

For specific applications, isolation of the target analytes from other organohalogenated compounds present in the extract can be mandatory to avoid interferences during final determination. Deactivated silica gel has also been successfully applied for the quantitative isolation of PBDEs from HBCD diasteroisomers and TBBPA. In this case, *iso*-octane was used for the elution of PBDEs, while a more polar solvent, i.e., 15% diethyl ether:*iso*-octane (v/v), was required to elute HBCDs and TBBPA [16, 26]. The use of the semipolar diethyl ether was necessary to recover the late eluting β-HBCD isomer [16].

Florisil (activated at 450°C for 12 h and subsequently deactivated with 0.5% H_2O, w/w) has been successfully used to separate neutral organohalogenated compounds from phenolic analytes, including TBBPA [34]. In this case, neutral compounds (e.g., PBDEs) were firstly eluted with mixtures of DCM and *n*-hexane (1:3, v/v), while polar mixtures of acetone and *n*-hexane (15:85, v/v) and methanol and DCM (12:88, v/v) were needed to elute phenolic analytes.

Polystyrene divinyl benzene-based sorbents, such as Oasis HLB®, are a valuable alternative for the fast separation of HBCD diasteroisomers from TBBPA. Only 7 mL of a mixture DCM:*n*-hexane (1:1, v/v) was required to elute HBCDs from the SPE cartridge, while 8 mL of DCM sufficed for subsequent quantitative elution of TBBPA [24]. The two resulting fractions containing HBCDs and TBBPA,

respectively, were further purified onto a silica cartridge using *n*-hexane–dichloromethane for elution.

The retention behavior of individual HBCD isomers on silica gel and Florisil was investigated using diverse mobile phase solvents and accounting for matrix effects. The β-HBCD diastereomer is substantially retained on both Florisil and silica regardless of the solvent used, and therefore, it undergoes selective loss during cleanup [35]. This sequence is counterintuitive to sequences based on reverse-phase chromatography with a C_{18}-column, in which the α- (and not the β-) isomer is eluted first when using a polar solvent. These results indicate that care should be taken when isolating HBCDs and other molecular diastereomers from environmental and biological samples and that reported concentrations of β-HBCD in the literature may be negatively biased.

3 Shortcomings of Gas Chromatography

Instrumental analysis of HBCDs and TBBPA are generally performed by means of GC−MS and/or LC−MS. The analytical methodology for the determination of HBCDs and TBBPA has been previously reviewed by Covaci et al. [2, 36]. The present section builds on the previous review and highlights advances in their separation and detection post-2007.

3.1 HBCD

Traditionally, HBCD has been analyzed using GC–MS, usually operated in ECNI mode for which the monitoring of the $[Br]^-$ ions allows a higher sensitivity. Detailed information regarding the GC–MS analysis of HBCDs can be found in recent reviews by Covaci et al. [2, 36]. However, the GC technique is more problematic for HBCD than for most PBDEs and has a number of serious limitations:

Technical HBCD consists of three diastereoisomers: α-, β-, and γ-HBCD, the latter being predominant. Interconversion of the HBCD diastereoisomers occurs when technical HBCD is exposed to temperatures above ca. 160°C [37], and therefore, diastereoisomer-specific analysis of HBCDs by GC–MS is not possible.

Close inspection of chromatograms shows that the HBCD peak is always somewhat broader than the near eluting PBDE peaks. Because HBCD elutes from the GC column at temperatures higher than 160°C, and due to thermal isomerization, a broad, unresolved peak is observed [2]. Since the response factors of the three diastereoisomers do not apparently differ very much [38], HBCDs can be quantified as total HBCDs by GC–MS. However, uncertainties are larger compared to those obtained for a number of PBDEs, which is shown by a larger relative SD in quality charts (ca. 25–30%).

At higher temperatures (around 240°C), as well as in dirty injection systems, HBCDs further degrade to lower brominated analogs (Fig. 1) [39]. Also, it has been shown that pure HBCD undergoes decomposition by elimination of HBr at temperatures above 240°C [37]. Not surprisingly, partial breakdown and even complete loss of HBCD have been reported in GC systems. When analyzing HBCDs by GC–MS, the cleanliness of extracts and the liner are essential.

In ECNI–MS, the dominant ions for HBCD are the $[Br]^-$ ions (m/z 79 and 81), while the larger fragment ions have low abundances [39]. In this case, structural confirmation of HBCD, for which the formation of larger fragment ions is necessary, is not possible in ECNI–MS.

Brominated compounds, which have been used as internal standards (e.g., PBDE or polybrominated biphenyls (PBB) congeners), have a better thermal stability and so cannot be used to compensate for the breakdown of HBCD during GC separation. Furthermore, since isotopically labeled HBCD standards cannot be used when monitoring only Br^- ions, the quantification of HBCD by GC–ECNI–MS is problematic.

Due to its lack of stereoisomer specificity, the use of GC in the analysis of HBCDs should be discouraged. If GC is the only alternative, thermal degradation of HBCDs should be minimized through cold on-column injection, short narrow-bore GC columns, thin film stationary phases, and high carrier gas flow rates. Cold on-column injection, short GC columns, thin film stationary phases, and high flow rates are several measures to minimize the risk of thermal degradation and to reduce the elution temperature of HBCD. Such approach has been recently applied for the identification and quantification of BFRs, including HBCD and TBBPA in styrenic polymers. Short run times (<10min) were employed for the separation of all BFRs using 15 m DB-5 type capillary columns (0.32 mm ID) combined with high oven

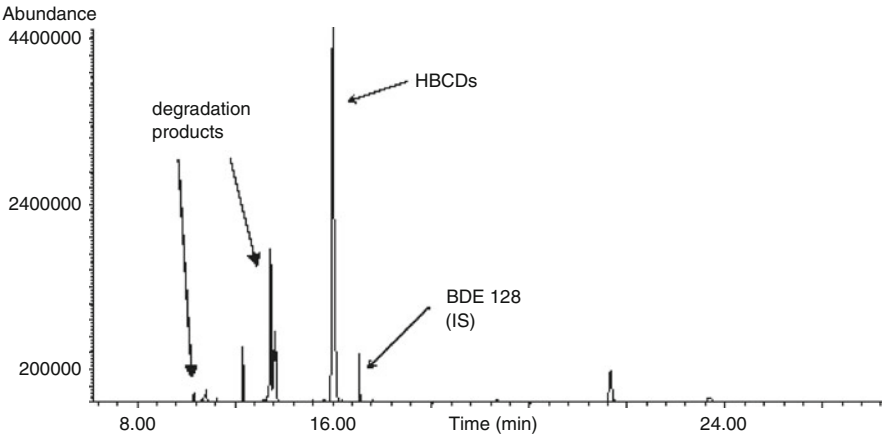


Fig. 1 GC–ECNI–MS chromatogram in selected ion monitoring mode of ions m/z 79 for a dust sample. Degradation products (corresponding to PBCDes and TBCDes) are also indicated. Reproduced from [39]

ramping. Retention time for HBCD was 4 min, and there was minimal degradation seen in the chromatograms [31].

3.2 TBBPA

Although TBBPA is the most widely used BFR, this compound is not frequently measured, probably due to its presence at lower concentrations in biota compared to PBDEs and HBCDs and due to its lower bioaccumulation potential. Among the predominant BFRs, TBBPA is the most polar molecule, which demands therefore more complicated methods for a proper determination. Acidification and derivatization are compulsory before GC analysis, while LC has the advantage that no derivatization step is required [4]. Both the derivatization and acidification step can introduce errors and/or losses [4]. In terms of sensitivity, LC–ESI–MS–MS can be competitive with published GC–EI–MS–MS techniques, with LODs in the ppt-range [21].

A GC–HRMS method requiring derivatization with methyl-chloroformate was developed by Berger et al. [34]. However, this method suffered from a rather restricted linear range and incomplete derivatization, leading to lower recoveries. This might also be explained by the presence of bulky bromine substituents adjacent to the two hydroxyl groups, resulting in an incomplete double derivatization. Derivatization that can lead to insertion of even larger groups on the TBBPA molecule is even more difficult.

4 Analysis by Liquid Chromatography

4.1 TBBPA

Due to polar characteristic of TBBPA molecule, LC–MS method appears to be the method of choice for their analysis because no derivatization of the phenolic group is required [3, 36, 40]. Another advantage of the LC–MS determination of TBBPA is the possibility to use the ^{13}C-labeled TBBPA as surrogate standard. This greatly enhances the quality of the analytical data obtained by compensating for matrix-related effects that can affect analyte ion intensity [3].

Tollbäck et al. [41] reported that the most suitable LC–MS interface for TBBPA analysis is ESI operating in negative ionization mode finding LODs 30–40 times lower compared to atmospheric pressure chemical ionization (APCI). In addition, it permits monitoring of the intact TBBPA molecule through the soft ionization of ESI resulting in improved method selectivity and accuracy. Similar results were found by Morris et al. [26].

The LC behavior of TBBPA depends greatly on the mobile phase. Chu et al. (2005) found that by using methanol as mobile phase, the response of target compounds was about one third greater than when using acetonitrile. The use of methanol as mobile phase resulted in better limit of quantification (LOQ) due to the more stable detector baseline obtained. In general, a more advantageous analysis was obtained using methanol and water as mobile phase [3, 42]. It is important to note that in terms of sensitivity, LC–ESI–MS can be competitive with published GC–EI–MS techniques with LODs in the ppt range [21].

Ion-trap MS was also reported for the determination of TBBPA in sediment and sewage sludge after LC separation [43]. The ion-trap scan range was set from m/z 145–543. On the other hand, Guerra et al. [42] proposed a methodology based in the use of LC–QqLIT–MS in order to analyze TBBPA and related compounds bisphenol A (BPA), monobromobisphenol A (MonoBBPA), dibromobisphenol A (DiBBPA), and tribromobisphenol A (TriBBPA) in sewage sludge and sediment samples. Figure 2 showed the chromatographic separation of TBBPA and related

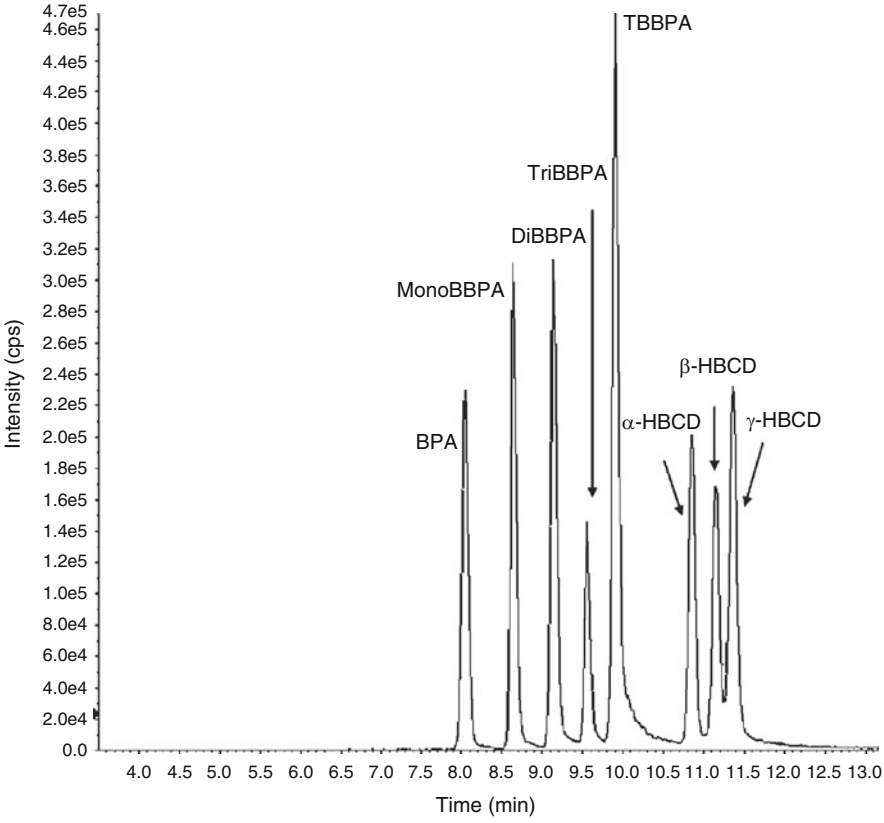


Fig. 2 Total ion chromatogram (TIC) obtained for a standard mixture containing BPA, MonoBBPA, DiBBPA, TriBBPA, TBBPA, α-, β-, and γ-HBCD at 500 pg/μL

compounds together with the diastereoisomeric HBCDs. On the other hand, ultra performance liquid chromatography (UPLC)–ESI–MS–MS was reported to analyze TBBPA in soil and food samples [44, 45]. This technique combines all the advantages of LC–MS–MS in addition to shorter residence time of the analyte on-column. The short analysis time (4 min) can double the efficiency of the analytical method [3].

4.2 HBCD

4.2.1 Diastereoisomer Determination

Regarding detection systems, MS is the preferred analytical technique, in terms of selectivity and sensitivity. Among different MS analysers, the QqQ is the most used [42, 46]. However, the increasing robustness and widespread use of ion trap instruments, due to their high versatility and relatively low cost, led to the development of methodologies based on this technique for HBCD detection and quantification [16, 42, 47–50].

There has been some concern due to the apparent differences in the stability of HBCD diastereoisomers in different solvents. This was explained by the relatively lower solubility of γ-HBCD in acetonitrile compared to methanol. Thus, Tomy et al. [50] suggested the use of methanol for final extracts to inject in LC–MS analysis.

Regarding diastereoisomers separation, any ratio of methanol/acetonitrile as mobile phase allows the separation of all three diastereoisomers. However, an increase in the percentage of acetonitrile in the mobile phase resulted in a slightly better separation of HBCDs, mainly between β- and γ-HBCD [46]. In order to enhance the sensitivity, mobile phase modifiers have been used, commonly ammonium acetate [7, 11, 26, 42, 51] and acetic acid [24]. It is well documented and experimentally confirmed that HBCD tend to associate with several anions forming different adducts that can affect the sensitivity and the accuracy of the determinations [16, 47, 52]. The addition of different ammonium salts to the mobile phase, i.e., ammonium chloride or ammonium acetate, in order to encourage (Cl method) or try to inhibit (Ac method), respectively, the formation of the chlorine adducts of the molecular ion were carried out. The Cl method showed higher sensitivity, and the limits of detection (0.23–0.41 pg on column) and quantification (0.77–1.35 pg on column) were up to 14 times lower than those obtained applying the Ac method.

LC–MS or LC–MS–MS using ESI or APCI are versatile tools for the isomeric-specific determination of HBCDs trace levels. Budakowsky and Tomy [53] have shown that APCI have lower intensities compared with a similar experiment with ESI. Consequently, ESI mode is the preferred one for determining diastereoisomer HBCDs by several studies [7, 42, 48, 53]. However, Suzuki and Hasegawa [11]

reported signal to noise (S/N) ratio values 2–5 times higher compared to ESI when APCI was applied on the HBCD analysis in leachate.

Different methods for the analysis of diastereoisomeric HBCD using LC–ESI–MS–MS and the selective reaction monitoring (SRM) for the transition $[M–H]^-$ (m/z 640.6) → $[Br]^-$ (m/z 79 and 81) have been developed obtaining LODs between 0.5 and 6 pg on-column [46, 53]. Morris et al. observed differences in the sensitivity of different HBCDs between two MS instrument: α-HBCD proved to be the most sensitive of the three stereoisomers with the single quadrupole instrument, while γ-HBCD was the most sensitive on the ion-trap [16].

Matrix-related effects, either signal enhancement or more commonly signal suppression, can have a pronounced effect on quantitative measurements. Based on these observations, the use of isotopic-labeled standards are helpful to achieve accurate analytical measurement data on the diastereoisomers. For this reason, several methodologies include the use of both ^{13}C- and d_{18}-labeled surrogates as recovery and/or instrument standards [7, 42, 46, 53].

It is important to note that some other LC–ESI–MS–MS methods have been developed for the simultaneous analysis of diastereoisomeric HBCDs and TBBPA [11, 42]. Two different LC–QqLIT–MS methods were developed by Guerra et al. comparing an SRM experiment with an enhanced product ion (EPI) experiment to analyze α-, β-, and γ-HBCD together with TBBPA and related compounds (BPA, MonoBBPA, DiBBPA, and TriBBPA). The developed methods display excellent LODs in SRM mode (0.1–1.8 pg), but even better results are obtained in EPI mode (0.01–0.5 pg) [42].

4.2.2 GC Versus LC for HBCD Analysis

A few studies have investigated the comparability of results issued using GC or LC methods. However, the results are not conclusive due to a large variation in the methodologies employed in each studies and the type of samples for which the comparison was achieved. In a study by Van Leeuwen and de Boer [54], total HBCD determined by GC–ECNI–MS was measured in 22 out of the 44 fish samples in concentrations between 0.20 and 230 ng/g wet weight (ww). The sum of the three HBCD diastereomers as obtained by LC–ESI–MS–MS was found to differ from the total HBCD by GC, with the GC–ECNI–MS results being in average 4.4 times higher, according to the regression analysis. The authors concluded that the LC–ESI–MS–MS data are more accurate than those obtained by GC–ECNI–MS.

In a similar study, Abdallah et al. [39] have analyzed HBCDs in indoor dust samples ($n = 37$) using GC–ECNI–MS and LC–ESI–MS–MS. This study has investigated also the suitability of using different internal standards (IS), including ^{13}C-labeled HBCD during the GC analysis and using the response factors (RF) of individual α-HBCD and γ-HBCD isomers to calculate the total HBCD concentrations by GC. Statistical comparison showed that concentrations obtained via GC–ECNI–MS were statistically indistinguishable ($p > 0.05$) from those obtained

using LC–ESI–MS–MS. The closest match between the two techniques was obtained using ^{13}C-α-HBCD as IS and the average RF for α-HBCD and γ-HBCD. Significant correlations (Pearson coefficient values $r > 0.9$, $p < 0.01$) were obtained between the GC–ECNI–MS and LC–ESI–MS–MS results obtained for the investigated dust samples, with slopes ranging from 0.76 to 1.36 for the various IS and RF calculations. Although the conclusion was that LC–ESI–MS–MS results in reliable data and, most important, in individual isomeric concentrations, it was acknowledged that GC–ECNI–MS can give a good estimation of the total HBCDs, if the appropriate ISs and calculation methods are used.

4.2.3 Enantiomeric Determination

Since α-, β- and γ-HBCD are chiral, each diastereoisomer has a pair of enantiomers: (+)α, (−)α, (+)β, (−)β, (+)γ, and (−)γ, respectively [36]. The enantiomers have identical physicochemical properties and abiotic degradation rates but may have different biological and toxicological properties and therefore different biotransformation rates. These transformations may result in nonracemic mixtures of the enantiomers that were industrially synthesized as racemates [8, 49, 53, 55, 56]. The rates of metabolization process of the enantiomers of environmental pollutants may be significantly different. For example, there are some cases where only one enantiomer is being decomposed while the second is being accumulated in the environment, such as for hexachlorohexane (HCH) [15]. Because of that, an understanding of the environmental and biological fate of the HBCD enantiomers is required.

In order to separate the enantiomers of (+/−)α, (+/−)β and (+/−)γ-HBCD, permethylated β-cyclodextrin columns has been successfully used [7, 28, 49]. The separation is achieved in a single analysis with LODs between 10 and 20 injected pg on-column. It is well known that ESI is subject to sample matrix effects that can cause enhancement or suppression of the target analytes signal and can adversely affect their quantification [8, 50]. In order to avoid this effect that can affect enantiomeric fraction (EF) calculations, Marvin et al. [8] introduced the corrected EF values. This correction is based on the use of isotopic-labeled standards (d_{18}-HBCDs) since d_{18}-labeled enantiomeric analogs behave in an identical manner to their native counterparts. Two other factors influencing the obtained EF values were observed by Marvin et al. The first one is the organic solvent content in the mobile phase; an EF decrease with increasing organic fraction content in the mobile phase was observed. The second factor is the column bleed that would compete with the enantiomers during the ion charge process in the ion spray source [8].

Different enantiomeric behavior studies were done by Jànak et al. [46, 56] and Guerra et al. [49, 57]. The first author [46] studied the EF in different fish species from the Western Scheldt Estuary, where a strong enrichment of (+)-α-HBCD was observed for bib and whiting liver. In the case of sole, the EFs were similar for liver and muscle, with a slight enrichment of (−)-α-HBCD. In 2008, the same author

[56] found clear differences between α-HBCD enantiomeric fractions in the different species analyzed, indicating species-specific stereoselective mechanism for uptake and metabolism of α-HBCD enantiomers. In Spanish sediment samples [49], EF obtained suggested a higher presence of (+)-α-HBCD and (+)-γ-HBCD as compared to technical mixtures. Finally, EF values in human breast milk from Spain have been analyzed [57], where an enrichment of (+)-γ-HBCD in the human body have been found. Regarding α-enantiomer, it was possible to determine EF value only in two samples, showing enrichment of (−)-α-HBCD. Figure 3 shows the chromatogram obtained for a standard solution and for two human breast milk samples.

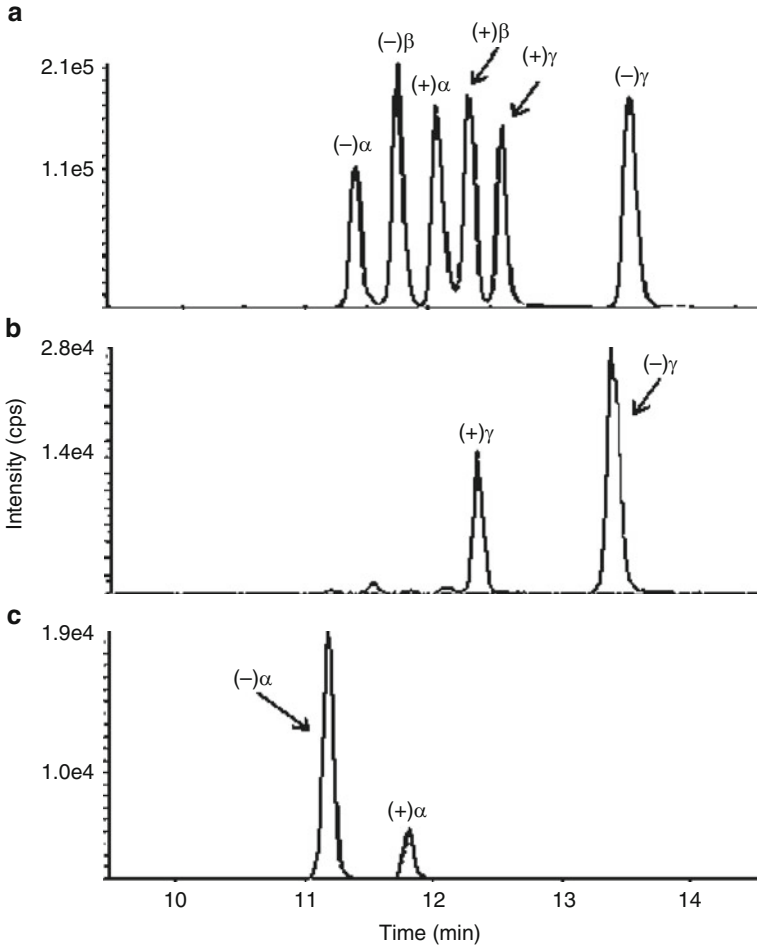


Fig. 3 Enantiomeric HBCD analysis by LC–ESI–MS–MS for (**a**) standard solution at 1,000 pg/μL, and (**b**, **c**) human breast milk samples from Spain

4.3 Other BFRs

ESI, APCI, and atmospheric pressure photoionization (APPI) are the ionization techniques commonly used in LC–MS analyses. These techniques are suitable for the ionization of polar, less polar, and slightly polar to nonpolar compounds, respectively. Although ESI efficiently ionizes HBCD isomers and TBBPA [42, 43, 50, 51, 53], the use of this ionization mode for other emerging BFRs have failed. APCI ionization has been also applied only for the analysis of TBBPA and HBCDs [11]. APPI is the most used ionization mode for the analysis of PBDEs, but the limited availability of APPI in most analytical laboratories has made this mode of ionization less appealing [58]. Abdallah et al. [59] performed a ^{13}C-labeled isotope

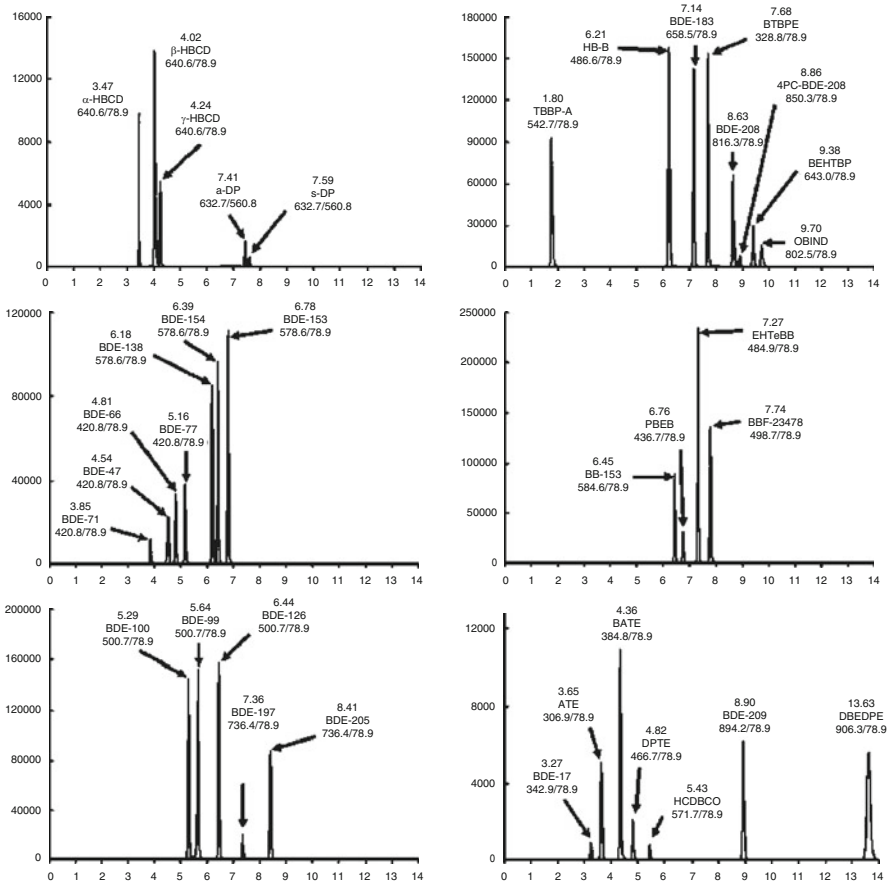


Fig. 4 Reconstructed MRM chromatograms obtained from 400 pg on-column injection of various BFRs with the peak intensity (cps) of *y*-axis and retention time (min) of *x*-axis by LC–APPI–MS–MS. Reproduced from [58]

dilution LC–APPI–MS–MS method to analyze 14 different PBDEs, between tetra- to deca-BDE congeners in house hold dust.

Another method was developed to analyze 36 halogenated flame retardants (HFR) in fish by LC–APPI–MS–MS. Some of the quantified compounds were 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (EHTeBB), bis(2-ethyl-1hexyl)tetrabromophthalate (BEHTBP), HBCD isomers, and BDE-47, -66, -71, -77, -100, -99, -126, -138, -154, -153, -183, -197, -206, and -209. Moreover, LC–APCI–MS–MS was performed for the analysis of 38 HFRs in wastewater, finding EHTeBB, decabromodiphenylethane (DBDPE), BEHTBP, and TBBPA at pg/mL levels (Fig. 4) [58]. Different LC columns were evaluated, and a C18 column was selected due to the adequate selectivity for the 38 compounds, using a mixture of water and methanol as the optimal mobile phase. The average of on-column instrumental limit of detection (IDLs) was 6.1 pg, showing better sensitivity compared with some literature values [58].

A new emerging BFR recently included in some environmental studies is the 1,2-dibromo-4-(1,2-dibromoethyl)cyclohexane (TBECH). This compound can exist as four diastereoisomers are thermally sensitive, and they can interconvert at temperatures of 123°C or higher. That is because the development of a LC–MS method may be useful in order to obtain the separation of the four isomers. Arsenault et al. [60] developed a LC–ESI–MS method for the four TBECH isomers. They could not detect the molecular ion; however, analytes were detected monitoring the bromide ion (Br^-) using SIM mode. They also observed that, using APCI conditions, a very weak molecular ion was detected.

4.4 BFR Metabolites and Transformation Products

When organic compounds are into the environment, they could be widely distributed and subjected to different processes that contribute to their elimination and/or transformation [61]. Depending on the compartment in which the transformation occurs, the products could be a metabolite, when the organism metabolism is involved or, a transformation product if it reacts in the environment. Therefore, in exposed organism, metabolism is an important factor in determining the bioaccumulation, fate, pharmacokinetics (or toxicokinetics), and toxicity of contaminants.

In order to analyze metabolites and transformation products of BFRs, LC–MS is a useful technique due to the higher polarity of these compounds compared with the parent compounds.

4.4.1 HBCD Metabolites and Transformation Products

Abdallah et al. [39] found HBCD transformation/degradation products in dust samples via LC–MS–MS using a C18 analytical column and water/methanol as mobile phase in presence of ammonium acetate. These products were identified as

four pentabromocyclododecene (PBCDe) isomers. Moreover, two additional peaks were observed in chromatograms and corresponded to two congeners of tetrabromocyclododecadienes (TBCDe). The monitoring of m/z 560.8→79.0 and 480.4→79.0 was done for PBCDs and TBCDs, respectively. The elution of all compounds is obtained in less than 15 min. Different results were observed by Davis et al. [62] when analyzed in waste water sludge and freshwater sediments by LC–APPI–MS. In this study, only one TBCD isomer as a degradation product of HBCD was detected. It was proposed that TBCD is the result of a dihaloelimination reaction of HBCD resulting in the loss of two bromines from vicinal carbons with the further formation of a double bond between the adjacent carbon atoms.

A small number of studies have been carried out in order to determine HBCD metabolism. In a study with dolphins, three HBCD metabolites were detected using an LC–ESI–MS instrument [63]. Two metabolites were identified as monohydroxy-HBCD and the third metabolite could not be identified. Hydroxylated metabolites of β- and γ-HBCD were found; however, no significant decrease in α-HBCD concentration was observed during the incubation with rat and harbor seal microsomes. However, in vitro experiments with microsomes of dab and flounder showed that α-HBCD was also biotransformed resulting in two monohydroxy-HBCD metabolites. Huhtala et al. [64] confirmed this result by finding a monohydroxy-HBCD after an in vitro study in rainbow trout liver microsomes.

Brandsma et al. [65] studied the presence of hydroxylated metabolites of HBCD in three wildlife species (tern egg, seal, and flounder) as well as Wistar rats exposed to HBCD for 28 days. A total of four different types of metabolites were found using LC–MS–MS: the monohydroxy metabolites of TBCDe, PBCDe, and HBCD, and a dihydroxy-HBCD (Fig. 5). Another metabolic pathway in the rat is debromination of HBCD to PBCDe and TBCDe. In this study, all the hydroxylated metabolites found with LC–MS–MS were confirmed by GC–MS, but an additional metabolite was found with GC–MS, the dihydroxy-PBCDe [65].

4.4.2 PBDE Metabolites

The nonpolar nature of de diphenyl ether structure in PBDEs and the introduction of polar hydroxyl functional groups in the molecule upon its metabolism provide a special challenge in the analysis of PBDEs metabolites. Due to the structural similarity of some hydroxylated (OH)-PBDE compounds to thyroid hormones such as thyroxin (T4), these metabolites are suspected to mimic hormones in the body, making them more deleterious than the parent compounds [9].

Direct analysis of OH-PBDEs by GC–MS is not amenable due to their nonvolatile nature. All analytical methods applying GC–MS for the analysis of OH-PBDE metabolites must include a derivatization step. Usually, diazomethane was used as derivatizing agent. This compound needs to be handled with extreme care due to its explosive characteristics. On the other hand, the efficiency of the derivatization varies from sample to sample since the reaction may give less than 100% yield.

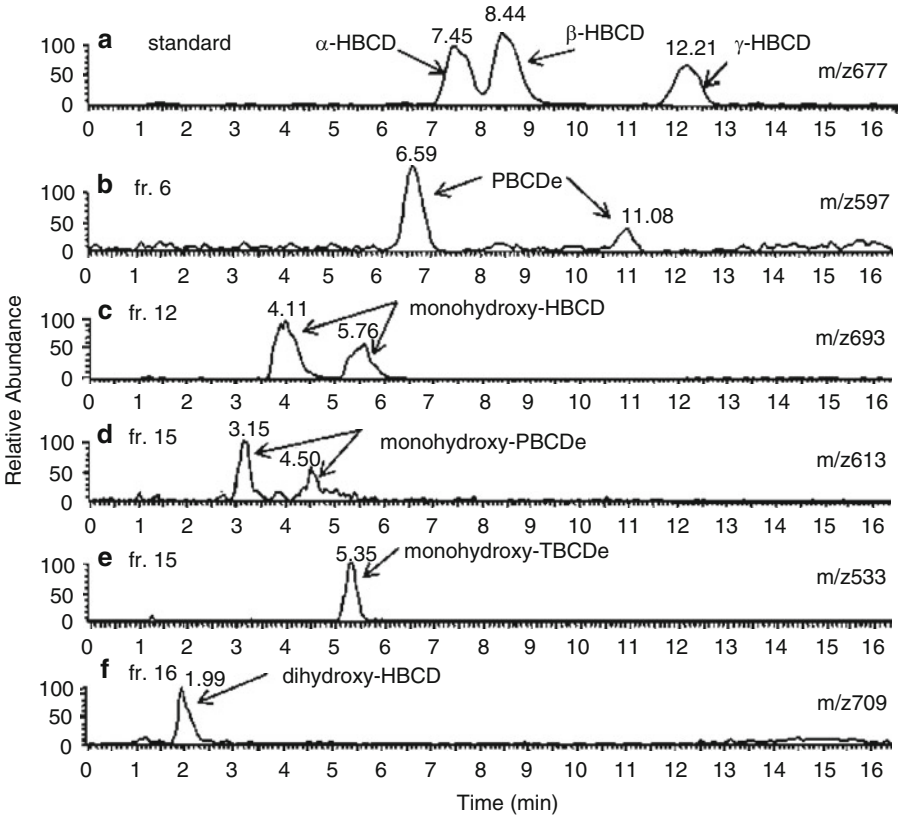


Fig. 5 (**a**) Selected ion LC–MS chromatogram of α-, β-, and γ-HBCD standard extract. Selected ion LC–MS chromatograms in adipose tissue of a male rat sample: (**b**) PBCDe in fraction 6, monohydroxy-HBCD in fraction 12, (**c**) monohydroxy-HBCD in fraction 12, (**d**) monohydroxy-PBCDe in fraction 15, (**e**) monohydroxy-TBCDe fraction 15, (**f**) dihydroxy-HBCD in fraction 16. Reproduced from [65]

Finally, additional sample preparation/cleanup steps could introduce errors and long analysis time. For all these reasons, the analysis of OH-PBDE metabolites by LC–MS seams interesting. However, these metabolites are poorly ionized by LC–ESI–MS and consequently are not easily detected at low levels [9, 66].

In 2007, Mas et al. [66] proposed the analysis of eight underivatized OH-di to OH-tetraBDEs by negative ion spray ionization (ISP) tandem mass spectrometry (LC–ISP–MS–MS) in soil fish, sludge, and particular matter. This method was shown to be efficient, robust, sensitive, and selective with LOQ at the high pg/g dry weight level. Another LC–APCI–MS–MS method was developed for the separation and detection of nine OH-PBDEs, ranging from tri- to hexa-brominated, as well as MS–MS fragmentation information [9]. As mobile phase, water and acetonitrile were used and the reversed-phased separation was completed on a C18 analytical

column, resulting in a 35 min separation of the nine congeners followed by a 10 min reequilibration.

Methoxylated (MeO)-PBDEs have been reported in a few studies and the current knowledge indicates that the MeO-PBDEs found in wildlife are mostly a consequence of accumulation via natural sources in marine environments such as in sponges and green algae [67]. Kato et al. [68] have analyzed OH- and MeO-tetraBDEs and hydroxylated and methoxylated analogs of tetrabromobiphenyl (diOH-tetraBB and diMeO-tetraBB) using LC–APCI–MS–MS in marine biota. A good advantage of the proposed APCI method is that the simultaneous determination of OH- and MeO-brominated analogs could be completed within 22 min after a single cleanup GPC procedure.

A selective and sensitive method using negative LC–APCI–MS–MS [69] was also developed to enable analysis of selected natural persistent organohalogens accumulated in marine biota. Selected analytes were three MeO-tetraBDEs, a diMeO-tetraBDE and two halogenated methyl bipyrroles (Cl_7-MBP and Br_4Cl_2-DBP). The method only required 10 min to allow the separation of selected analytes. In this method, the fragmentation pathways of MeO-BDEs produced characteristic SRM transitions needed to resolve isomeric compounds, $[M–Br+O]^-$ and Br^- ions, for MeO–BDE analogs and $[M–Cl+O]^-$ and Br^- or degradation product ions for 1,1′-dimethyl-3,3′,4,4′-tetrabromo-5,5′-dichloro-2,2′-bipyrrole (Br_4Cl_2-DBP) and 2,3,3′,4,4′,5,5′-heptachloro-1′-methyl-1,2′-bipyrrole (Cl_7-MBP), respectively.

Finally, a LC–ESI–MS–MS method with greater sensitivity and better separation efficiency [70] was established for the simultaneous analysis of four estrogens, BPA, 10 OH-PBDEs, and 15 brominated phenols (BRPs) in blood plasma sample, using dansyl chloride as derivatization agent that reacts, which provides a new method to derivatize phenolic compounds prior to LC–MS analysis. The ionization and fragmentation of the isolated dansyl derivatives ESI–MS–MS resulted in protonated molecular ions $[MH]^+$ or $[MH]^+$-2 of their dansyl derivatives, producing the same major product ions at m/z 171 and 156. Thus, 30 analytes belonging to four classes of phenolic compounds could be analyzed within 22 min after sample treatment (Fig. 6). However, the sample preparation is longer due to the use of dansyl chloride.

5 Interlaboratory Studies

An important gap is the lack of harmonized methods for the determination of HBCDs and TBBPA in environmental matrices. Regular intercalibration studies and participation in laboratory proficiency studies (when available) are important so as to maintain high quality of analytical data. Up to now, only a limited number of intercalibration studies have been performed with a rather limited number of participating laboratories. Moreover, these interlaboratory studies referred to HBCDs, but none of them reported intercomparison for TBBPA determination.

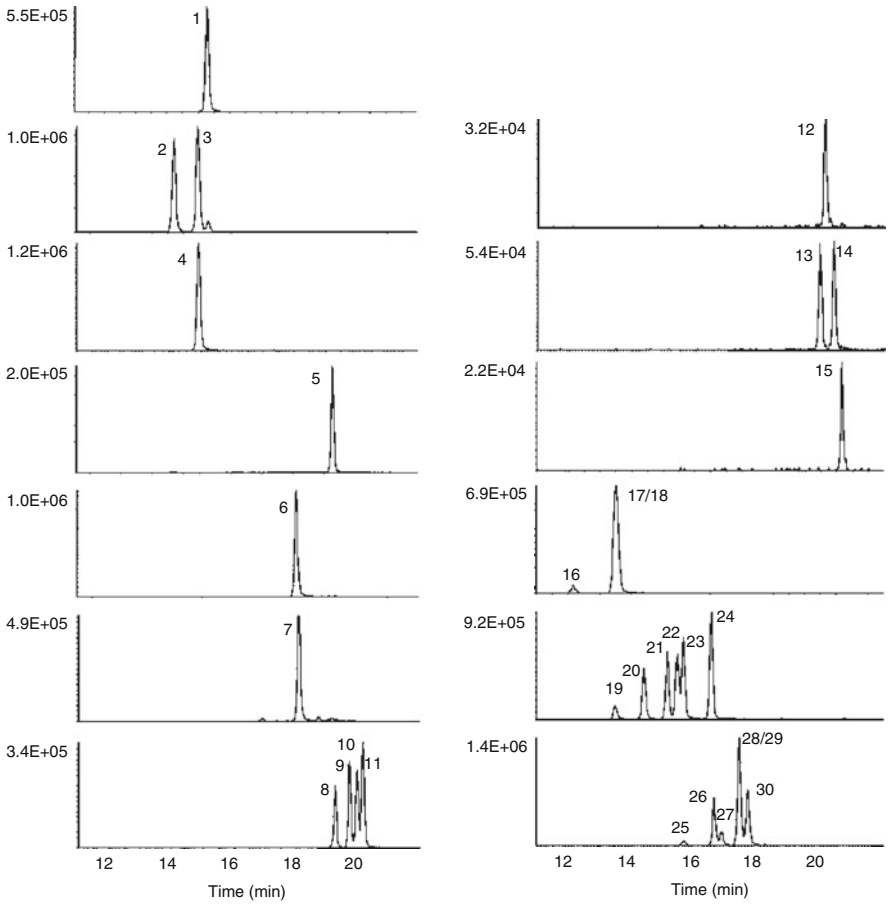


Fig. 6 LC–MS–MS MRM chromatographic profiles of 30 analytes in a standard mixture of 10 ng/mL: E1 (1), βE2 (2), αE2 (3), EE (4), BPA (5), 2′-OH-6′-Cl-BDE-7 (6), 6′-OH-BDE-17 (7), 3-OH-BDE-47 (8), 5-OH-BDE-47 (9), 6-OH-BDE-47 (10), 4′-OH-BDE-49 (11), 2′-OH-6′-Cl-BDE-68 (12), 6-OH-BDE-90 (13), 2-OH-BDE-123 (14), 6-OH-BDE-137 (15), 3-BRP (16), 2/4-BRP (17/18), 2,6-diBRP (19), 2,3-diBRP (20), 2,5-diBRP (21), 2,4-diBRP (22), 3,4-diBRP (23), 3,5-diBRP (24), 2,3,6-triBRP (25), 2,3,4-triBRP (26), 2,4,6-triBRP (27), 2,3,5/2,4,5-triBRP (28/29), 3,4,5-triBRP (30), analyzed on a 100 × 2.1 mm^2, i.d.; Waters XBridge column. E1: estrone; βE2: 17β-estradiol; αE2: 17α-estradiol; EE2: Ethinyl estradiol. Reproduced from [70]

In order to assess the quality of HBCD determinations, the Norwegian Institute of Public Health organized interlaboratory comparison studies in 2005 and 2007. The purposes of these studies were (a) to assess the comparability of results obtained using different analytical techniques, (b) to provide a quality assurance instrument for the participating laboratories, and (c) to assess the readiness of expert laboratories to determine HBCD in biological samples [71]. Up to 13 laboratories determined either the total HBCD concentration, or concentrations of individual HBCD isomers, or both in cod liver oil, herring filet, salmon filet, butter,

and chicken meat. The laboratories were able to determine total HBCD concentrations in the marine samples with satisfying quality (RSD <35%). However, the analysis of samples with low HBCD contamination (<about 2 ng/g lipid weight) should be improved. No statistically significant differences were found between total HBCD concentrations obtained by LC–MS and GC–MS.

An additional factor is that there are currently no certified reference materials (CRMs) for HBCDs that can be used for method validation. Up to now, indicative values for HBCDs have been issued for several reference materials (e.g., lake trout from Cambridge Isotope Laboratories or indoor dust from the US National Institute for Standards and Technology), but the certification of HBCDs and TBBPA in a wider range of environmentally relevant materials is needed.

6 Conclusions and Perspectives

PBDEs have typically been analyzed using GC–MS, but the high injection port temperatures required to transfer these analytes to the GC column can result in degradation of the desired compounds. These could occur in the case of highly PBDEs and other BFRs such as HBCDs. In the case of TBBPA or metabolites (OH-PBDES), a derivatization step is needed, given more possibilities for errors because it is not always reproducible and quantitative.

The LC–MS and LC–MS–MS methods appear to be methodologies of choice to analyze TBBPA, HBCD-isomers, and HBCD-enantiomers because no derivatization is needed, and the isomeric separation is obtained. The ESI, APCI, and APPI are the atmospheric pressure ionization modes commonly used in LC–MS analyses. On the other hand, the use of ^{13}C-TBBPA and ^{13}C- and d_{18}-HBCD-isomer-labeled standards as internal standards enhances the quality of the analytical data through compensation for matrix-related effects that can affect analyte ion intensity, reproducibility, and trueness.

Also important is the recent development of methods for the identification of metabolites of PBDEs and HBCD by LC–MS–MS, thereby avoiding the problems of derivatization. The future challenge is to adapt these LC–MS techniques for the analysis of emerging flame retardants in different sample matrices as well as their potential metabolites and transformation products.

On the other hand, in order to improve the quality of these methodologies, interlaboratories comparison studies should be done, especially in the case of HBCDs and TBPPA where more experience and interest have been obtained in the last years. Finally, another relevant point is the lack of CRMs. While effective analytical quality control requires the availability of CRMs, there is a need to certify HBCD and TBBPA in various appropriate CRMs.

Acknowledgments This research work was founded by the Spanish Ministry of Science and Innovation through the projects CEMAGUA (CGL2007-64551/HID) and Consolider-Ingenio 2010 (CSD2009-00065), by the CSIC through the project Intramural (ref. 200880I096) and by the

Fundación BBVA under the BROMACUA project (Evaluación del impacto ambiental de los retardantes de llama bromados en ecosistemas acuáticos de América Latina). Paula Guerra acknowledges her grant from the Department d'Innovació, Universitats i Empresa (2008FI_B 00755). Adrian Covaci was financially supported by the Research Council of the University of Antwerp and by a postdoctoral fellowship from the Research Scientific Foundation – Flanders (FWO).

References

1. Covaci A, Dirtu AC, Voorspoels S, Roosens L, Lepom P (2010) Sample preparation and chromatographic methods applied to congener specific analysis of polybrominated diphenyl ethers. In: The handbook of environmental chemistry. Springer, Heidelberg. doi:10.1007/698_2010_81
2. Covaci A, Voorspoels S, Ramos L, Neels H, Blust R (2007) J Chromatogr A 1153:145
3. Covaci A, Voorspoels S, Abdallah MAE, Geens T, Harrad S, Law RJ (2009) J Chromatogr A 1216:346
4. De Boer J, Wells DE (2006) Trends Anal Chem 25:364
5. Petersen M, Hamm S, Schäfer A, Esser U (2004) Organohalogen Compd 66:226
6. Petrovic M, Barcelo D (2006) Anal Bioanal Chem 385:422
7. Dodder NG, Peck AM, Kucklick JR, Sander LC (2006) J Chromatogr A 1135:36
8. Marvin CH, MacInnis G, Alaee M, Arsenault G, Tomy GT (2007) Rapid Commun Mass Spectrom 21:1925
9. Lupton SJ, McGarrigle BP, Olson JR, Wood TD, Aga DS (2010) Rapid Commun Mass Spectrom 24:2227
10. Díaz-Cruz MS, García-Galán MJ, Guerra P, Jelic A, Postigo C, Eljarrat E, Farré M, Alda MJLd, Petrovic M, Barceló D (2009) Trends Anal Chem 28:12
11. Suzuki S, Hasegawa A (2006) Anal Sci 22:469
12. Birnbaum LS, Staskal DF (2004) Environ Health Perspect 112:9
13. Ronen Z, Abeliovich A (2000) Appl Environ Microbiol 66:2372
14. Abdallah MAE, Harrad S, Covaci A (2008) Environ Sci Technol 42:6855
15. Jin J, Yang CQ, Wang Y, Liu AM (2009) Fenxi Huaxue/Chin J Anal Chem 37:585
16. Morris S, Bersuder P, Allchin CR, Zegers B, Boon JP, Leonards PEG, De Boer J (2006) Trends Anal Chem 25:343
17. Samara F, Tsai CW, Aga DS (2006) Environ Pollut 139:489
18. Garcia-Valcarcel AI, Tadeo JL (2009) J Sep Sci 32:3890
19. Wu HH, Chen HC, Ding WH (2009) J Chromatogr A 1216:7755
20. Stapleton HM, Brazil B, Holbrook RD, Mitchelmore CL, Benedict R, Konstantinov A, Potter D (2006) Environ Sci Technol 40:4653
21. Hayama T, Yoshida H, Onimaru S, Yonekura S, Kuroki H, Todoroki K, Nohta H, Yamaguchi M (2004) J Chromatogr B Anal Technol Biomed Life Sci 809:131
22. Thomsen C, Knutsen HK, Liane VH, Froshaug M, Kvalem HE, Haugen M, Meltzer HM, Alexander J, Becher G (2008) Mol Nutr Food Res 52:228
23. Thomsen C, Molander P, Daae HL, Janàk K, Froshaug M, Liane VH, Thorud S, Becher G, Dybing E (2007) Environ Sci Technol 41:5210
24. Cariou R, Antignac JP, Marchand P, Berrebi A, Zalko D, Andre F, Le Bizec B (2005) J Chromatogr A 1100:144
25. Kakimoto K, Akutsu K, Konishi Y, Tanaka Y (2008) Food Chem 107:1724
26. Morris S, Allchin CR, Zegers BN, Haftka JJH, Boon JP, Belpaire C, Leonards PEG, Van Leeuwen SPJ, De Boer J (2004) Environ Sci Technol 38:5497
27. Eljarrat E, de la Cal A, Raldua D, Duran C, Barcelo D (2004) Environ Sci Technol 38:2603
28. Eljarrat E, Guerra P, Martínez E, Farré M, Alvarez JG, López-Teijón M, Barcelo D (2009) Environ Sci Technol 43:1940

29. Frederiksen M, Vorkamp K, Bossi R, Riget F, Dam M, Svensmark B (2007) Int J Environ Anal Chem 87:1095
30. Vilaplana F, Karlsson P, Ribes-Greus A, Ivarsson P, Karlsson S (2008) J Chromatogr A 1196–1197:139
31. Pohlein M, Bertran RU, Wolf M, van Eldik R (2008) J Chromatogr A 1203:217
32. Kajiwara N, Sueoka M, Ohiwa T, Takigami H (2009) Chemosphere 74:1485
33. De Boer J, Allchin C, Law R, Zegers B, Boon JP (2001) Trends Anal Chem 20:591
34. Berger U, Herzke D, Sandanger TM (2004) Anal Chem 76:441
35. Mariussen E, Haukas M, Arp HPH, Goss KU, Borgen A, Sandanger TM (2010) J Chromatogr A 1217:1441
36. Covaci A, Gerecke AC, Law RJ, Voorspoels S, Kohler M, Heeb NV, Leslie H, Allchin CR, De Boer J (2006) Environ Sci Technol 40:3679
37. Barontini F, Cozzani V, Petarca L (2001) Ind Eng Chem Res 40:3270
38. Vetter W, von der Recke R, Herzke D, Nygard T (2007) Environ Int 33:17
39. Abdallah MAE, Ibarra C, Neels H, Harrad S, Covaci A (2008) J Chromatogr A 1190:333
40. Chu S, Haffner GD, Letcher RJ (2005) J Chromatogr A 1097:25
41. Tollback J, Crescenzi C, Dyremark E (2006) J Chromatogr A 1104:106
42. Guerra P, De La Torre A, Martínez MA, Eljarrat E, Barceló D (2008) Rapid Commun Mass Spectrom 22:916
43. Saint-Louis R, Pelletier E (2004) Analyst 129:724
44. Jin J, Peng H, Wang Y, Yang R, Cui J (2006) Organohalogen Compd 68
45. Worrall K, Hancock P, Fernandes A, Driffield M (2007) Organohalogen Compd 69
46. Janàk K, Covaci A, Voorspoels S, Becher G (2005) Environ Sci Technol 39:1987
47. Gómara B, Lebrón-Aguilar R, Quintanilla-López JE, González MJ (2007) Anal Chim Acta 605:53
48. Guerra P, Eljarrat E, Barcelo D (2010) Anal Bioanal Chem 397:2817
49. Guerra P, Eljarrat E, Barceló D (2008) J Chromatogr A 1203:81
50. Tomy GT, Halldorson T, Danell R, Law K, Arsenault G, Alaee M, MacInnis G, Marvin CH (2005) Rapid Commun Mass Spectrom 19:2819
51. Tomy GT, Budakowski W, Halldorson T, Whittle DM, Keir MJ, Marvin C, Macinnis G, Alaee M (2004) Environ Sci Technol 38:2298
52. Galindo-Iranzo P, Quintanilla-López JE, Lebrón-Aguilar R, Gómara B (2009) J Chromatogr A 1216:3919
53. Budakowski W, Tomy G (2003) Rapid Commun Mass Spectrom 17:1399
54. Van Leeuwen SPJ, De Boer J (2008) Mol Nutr Food Res 52:194
55. Huhnerfuss H (2000) Chemosphere 40:913
56. Janàk K, Sellstrom U, Johansson AK, Becher G, de Wit CA, Lindberg P, Helander B (2008) Chemosphere 73
57. Eljarrat E, Guerra P, Barcelo D (2008) Trends Anal Chem 27:847
58. Zhou SN, Reiner EJ, Marvin C, Kolic T, Riddell N, Helm P, Dorman F, Misselwitz M, Brindle ID (2010) J Chromatogr A 1217:633
59. Abdallah MAE, Harrad S, Covaci A (2009) Anal Chem 81:7460
60. Arsenault G, Lough A, Marvin C, McAlees A, McCrindle R, MacInnes G, Pleskach K, Potter D, Riddell N, Sverko E et al (2008) Chemosphere 72:1163
61. Perez S, Petrovic M, Barcelo D (2009) Analyzing transformation products of synthetic chemicals. In: Boxall BA (ed) Handbook of environmental chemistry, vol 2: Reactions and processes. Springer, Heidelberg, p 43
62. Davis JW, Gonsior SJ, Markham DA, Friederich U, Hunziker RW, Ariano JM (2006) Environ Sci Technol 40:5395
63. Zegers BN, Mets A, Van Bommel R, Minkenberg C, Hamers T, Kamstra JH, Pierce GJ, Boon JP (2005) Environ Sci Technol 39:2095
64. Huhtala S, Schultz E, Nakari T, MacInnes G, Marvin C, Alaee M (2006) Organohalogen Compd 68:1987–1990

65. Brandsma SH, Van Der Ven LTM, De Boer J, Leonards PEG (2009) Environ Sci Technol 43:6058
66. Mas S, Jauregui O, Rubio F, De Juan A, Tauler R, Lacorte S (2007) J Mass Spectrom 42:890
67. Verreault J, Gabrielsen GW, Chu S, Muir DCG, Andersen M, Hamaed A, Letcher RJ (2005) Environ Sci Technol 39:6021
68. Kato Y, Okada S, Atobe K, Endo T, Matsubara F, Oguma T, Haraguchi K (2009) Anal Chem 81:5942
69. Haraguchi K, Kato Y, Atobe K, Okada S, Endo T, Matsubara F, Oguma T (2008) Anal Chem 80:9748
70. Chang H, Wan Y, Naile J, Zhang X, Wiseman S, Hecker M, Lam MHW, Giesy JP, Jones PD (2010) J Chromatogr A 1217:506
71. Haug LS, Thomsen C, Liane VH, Becher G (2008) Chemosphere 71:1087

Current Levels and Trends of Brominated Flame Retardants in the Environment

Robin J. Law and Dorte Herzke

Abstract Intensive study of the environmental occurrence and impacts of brominated flame retardants (BFRs) began during the 1990s, while the number of investigations reported has increased year-on-year. In this chapter, we review recent literature concerning levels and trends of BFRs in environmental samples, mainly published between 2008 and early 2010. In many areas of the world, controls have been put in place regarding the use of polybrominated diphenyl ethers (PBDEs), and environmental concentrations are beginning to fall as a result. Investigations into the potential impacts of TBBP-A in Asia, around sites of manufacture and first use, are still required in order to assess the risks of continued production and use. The use of "novel" BFRs is being studied in order to assess their significance and potential impacts, as their environmental presence has been noted recently in a number of studies. New sources have emerged, such as e-waste recycling operations. In addition, secondary sources, such as glacier ice and permafrost soils, might become increasingly important in the future as a result of climate change. There is still concern that BDE209 (from the deca-mix PBDE technical product) may be debrominated in the environment to yield lower brominated BDE congeners, particularly as a large reservoir of BDE209 is accumulating in sediments. Even today, many ecosystems and regions are not studied well enough for us to be able to establish a global overview concerning BFR concentrations and their toxic effects.

Keywords Environmental samples, E-waste recycling, Hexabromocyclododecane, Polybrominated diphenyl ethers, Tetrabromobisphenol-A

R.J. Law (✉)
The Centre for Environment, Fisheries and Aquaculture Science, Cefas Lowestoft Laboratory, Pakefield Road, Lowestoft, Suffolk NR33 0HT, UK
e-mail: robin.law@cefas.co.uk

D. Herzke
Norwegian Institute for Air Research, The Polar Environmental Centre, 9296 Tromsø, Norway

E. Eljarrat and D. Barceló (eds.), *Brominated Flame Retardants*,
Hdb Env Chem (2011) 16: 123–140, DOI 10.1007/698_2010_82,

Contents

1 Introduction

Although brominated flame retardants (BFRs) were first identified as environmental contaminants in the 1980s, intensive studies of their occurrence and impacts began only during the 1990s. Since then, the number of investigations reported in the scientific literature has increased year-on-year. In the month in which this chapter was begun (December 2009), a single influential journal, *Environmental Health Perspectives*, the journal of the US National Institute of Health, featured two articles on BFRs and human health and two more on related animal studies [1–4]. Children's health is of particular concern as, unusually for industrial chemicals, the major exposure is in the home, and toddlers are particularly exposed via dust. They also carry the highest body burdens [5]. These topics are considered elsewhere in this volume, but those concerns reflect those relating to exposures in the wider environment, the main subject of this chapter. We have included references to papers published or available on journal websites between 2008 and up until the end of January 2010, covering outdoor and indoor air, dust, water, and sediments and soils, as well as "hot-spots" such as e-waste recycling operations.

A number of recent reviews have summarised the current situation regarding BFRs in the environment [6–8]. The last of these indicated that, although the USA has historically led the world production of polybrominated diphenyl ethers (PBDEs), scientific studies addressing the sources, behaviour and fate of PBDEs in the environment of the USA were limited when compared to those in Europe. Concern regarding BFRs began in Sweden, where PBDEs were first detected in environmental samples [9] and this concern has continued to develop as additional compounds have been detected. The manufacturers of BFRs have at least 75 products on the shelf and available for use [10], although the major use to date has been of the PBDE formulations (the penta-, octa- and deca-mix PBDE products), hexabromocyclododecane (HBCD) and tetrabromobisphenol-A (TBBP-A).

Most attention on the environmental aspects of BFRs has, therefore, been focussed on these compounds. The environmental occurrence of "novel" BFRs (mainly those which have been begun to be used as alternatives or additions to the major products, or which have, historically, been used in small volumes) has also been reviewed recently [11–14]. This review of the current situation regarding environmental levels and trends of the major BFRs in the environment is primarily based on the scientific literature published between 2008 and 2010, so as to best reflect the current situation.

Muir and de Wit [15] have reviewed the recent literature on the presence of BFRs in Arctic media, important as an indicator of long-range atmospheric transport. PBDEs have been reported in air and biota samples since the early to mid-2000s. Most surprising, which the authors noted, was the predominance of BDE209 in Arctic air samples, transported on airborne particulates rather than in the vapour phase. Another study [16] noted that atmospheric concentrations of BDE209 were increasing at Alert station in northern Canada to 2005 with a doubling time of 3.5 years. The presence of HBCD in Arctic biota is another recent observation. The γ-HBCD isomer predominates in air samples (as in the commercial product), [15], while α-HBCD predominates in biota and all three major isomers (α-, β- and γ-) occur in marine sediments. Spatial trends in seabirds and marine mammals are similar to those seen earlier for PCBs and PBDEs, presumably reflecting similar transport pathways. Western Europe and eastern North America are important sources to the most contaminated areas, East Greenland and Svalbard. Five "novel" BFRs were also detected in Arctic locations, again indicating long-range atmospheric transport.

2 Outdoor Air and Precipitation

In the Great Lakes area of North America, concentrations and atmospheric deposition of BDEs were studied during 2005–2006 [17, 18]. The highest mean concentrations of ΣBDEs (the sum of the congeners determined) were found at urban sites in Chicago and Cleveland (65 ± 4 and 87 ± 8 pg m^{-3}, respectively), and the lowest at the remote site at Eagle Harbour (5.8 ± 0.4 pg m^{-3}). With the exception of Chicago, the atmospheric concentrations of BDE47 and BDE99 in the particle and gas phases were decreasing rapidly, with half-lives of ca. 2 years. Concentrations of BDE209 were not decreasing at any of the five sites studied. Volume weighted mean concentrations of ΣBDEs in precipitation ranged from 94 ± 19 ng L^{-1} in urban Chicago to 0.65 ± 0.14 ng L^{-1} at the rural Sturgeon Point site. The highest mass transfer rates for ΣBDEs and BDE209 were 310 ± 79 kgpa in Lake Michigan and 79 ± 56 kgpa in Lake Erie, respectively. At Point Petre, another rural site in the Great Lakes area sampled in 2002–2004, average ΣBDE concentrations were 7.0 ± 13 pg m^{-3} (excluding BDE209) and 1.8 ± 1.5 pg m^{-3} for that congener [19].

Noël et al. [20] studied BDEs in air from two sites in western Canada, a remote site on western Vancouver Island and a near-urban site in the Strait of Georgia. Mean concentrations of ΣBDEs in air and rain were 12.2 pg m^{-3} and 14.8 ng L^{-1}, respectively, in the Strait of Georgia and 13.7 pg m^{-3} and 0.1 ng L^{-1}, respectively, on Vancouver Island. Investigation of back trajectories suggested that the rapid movement of westerly air masses across the Pacific Ocean provided a mechanism for the ready delivery of BDEs to North America from sources in Asia. It was also noted that such sources were likely to increase as a result of both production of electronic products and the recycling of electronic waste.

At a background location in the Eastern Mediterranean, the average ΣBDE concentration in air was 3.9 ± 2.1 pg m^{-3}. BDE profiles did not show any day/night shifts that could be attributed to hydroxyl radical reactions or photolysis, in contrast to CBs [21].

During 2006–2007, outdoor air and precipitation samples were collected in the Pearl River Delta area of South China [22]. Σ15BDE concentrations ranged from 77 to 372 pg m^{-3} in air (particulate + vapour) and 2.0 to 16 ng L^{-1} in rain from Guangzhou. BDE209 was the predominant congener. The estimated annual dry and wet depositional rates were 6.7 and 2.5 tonnes per annum for BDE209, and 7.3 and 2.9 tonnes per annum for Σ15BDE, indicating a dominant pathway for PBDE input to the soil and aquatic environments in the PRD region.

Doubling times of BDEs in Arctic air at Alert, Canada, ranged from 3.5 years for BDE209 (as above) to 28 years for BDE153, with doubling times for BDE17 to BDE100 ranging from 6.4 to 17 years. This reflects the phasing out of the penta-mix PBDE product in Europe and North America in recent years [16].

The Tibetan plateau is considered to be a potential cold trap for POPs and may play an important role in the global long-range atmospheric transport of these compounds and others with similar properties [23]. The mean Σ12BDE concentration in butter from Tibet (chosen as a typical local food which also acts as an integrated surrogate for ambient air concentrations) was 0.13 μg kg^{-1}. The samples with the highest and lowest concentrations (0.96 and 0.018 μg kg^{-1}, respectively) were from the S and SE of the plateau, as a result of atmospheric deposition, the BDE deposition being mainly influenced by the tropical monsoon arriving from south Asia.

3 Indoor Air and Dust

As well as homes and offices, exposure to BFRs in cars, buses, trains and aircraft need to be considered, although the time spent in these is less. Mandalakis et al. [24] investigated PBDEs in air samples taken from car interiors (n = 33) in Heraklion, Greece, during 2006–2007. Σ19BDE concentrations varied widely, from 0.4 to 2,640 pg m^{-3}, with BDE209 generally averaging 40% or more of the total. Concentrations decreased over time (i.e. with the age of the vehicle) and increased with rising temperature. The daily inhalation rate of PBDEs during commuting was

estimated to be 29% of the daily total (18% excluding BDE209), compared with 22% in the home. Congeners from both the penta- and deca-mix PBDE formulations were observed, and the authors ascribed increases in the BDE47/BDE99 ratio over time to progressive debromination of more highly brominated BDE congeners, including BDE209. Lagalante et al. [25] determined BDEs in 60 dust samples taken in 2007–2008 from second-hand vehicles for sale in the eastern USA. The dominant congener was BDE209, comprising 95% of the total and with a median concentration of 48 mg kg^{-1}.

Harrad et al. [26] studied PBDEs in dust from 30 homes, 18 offices and 20 cars from the UK in 2006–2007. Average concentrations of Σ13BDEs were 260, 31 and 340 mg kg^{-1}, respectively. Average concentrations of two "novel" BFRs were lower: 1,2-*bis*(2,4,6-tribromophenoxy)ethane (BTBPE) 120, 7.2 and 7.7 μg kg^{-1} and decabromodiphenylethane (DBDPE) 270, 170 and 400 μg kg^{-1}, respectively. Concentrations of BDE209 in three samples were the highest recorded at that time: 2,600 (car), 2,200 (home) and 1,400 (office) mg kg^{-1}. Estimated intake by UK toddlers was 180 ng of tri- to hexa-BDEs and 310 μg of BDE209 per day. In south-central China in 2008, Huang et al. [27] collected dust samples from 76 homes and 12 offices. Mean concentrations of Σ9BDE and BDE209 were 64 and 2,600 μg kg^{-1}, respectively, in houses, and 31 and 3,150 μg kg^{-1} in offices. Forty-three samples of outdoor dust were also collected from the vicinity of the homes sampled during the study. Mean concentrations of Σ9BDE and BDE209 in these samples were 20 and 1,080 μg kg^{-1}. In Queensland, Australia, Toms et al. [28] studied PBDEs in homes and offices sampled in 2005. In indoor air, ΣBDE concentrations ranged from 0.5 to 179 and 15 to 487 pg m^{-3} in homes and offices, respectively. In dust, ΣBDE concentrations were 87–733 and 583–3,070 μg kg^{-1} in homes and offices, respectively. Congener profiles for both air and dust were dominated by BDE209. In a similar study undertaken in two houses in Japan in 2006, Takigami et al. [29] reported ΣBDE concentrations of 33 and 39 pg m^{-3} in indoor air and 240 and 730 μg kg^{-1} indoor dust. In outdoor air from the same locations, ΣBDE concentrations were 19 and 25 pg m^{-3}. In comparison, Takigami et al. [30] reported concentrations of BDEs and HBCD in indoor dust from a hotel in Japan sampled in 2006. Σ27BDE concentrations in dust were 9.8–1,700 μg kg^{-1} and total HBCD concentrations were 72–1,300 μg kg^{-1}. Toms et al. [31] reported concentrations of BDEs in indoor air and dust from Brisbane, Australia in 2007–2008. Σ6BDE concentrations ranged from <1.3 to 341 pg m^{-3} and 219 to 3,060 μg kg^{-1}, respectively. Σ16BDE concentrations in indoor air and dust from homes in Bavaria, Germany, in 2005 ranged from 8.2 to 477 pg m^{-3} and 37 to 1,580 μg kg^{-1}, respectively [32]. The average daily intake of tri- to hepta-BDEs was estimated to be 1.2 ng kg^{-1} body weight, and the results of a parallel duplicate diet study suggested that dietary exposure was the dominant intake pathway for this adult population, responsible for ca. 95% of the total. In both air and dust, BDE209 was the dominant congener. Figure 1 indicates the spread of concentrations observed in five countries, with the highest values observed in China.

Personal exposure to HBCD and its degradation products via ingestion of indoor dust was assessed by Abdallah and Harrad [33]. Under an average dust ingestion

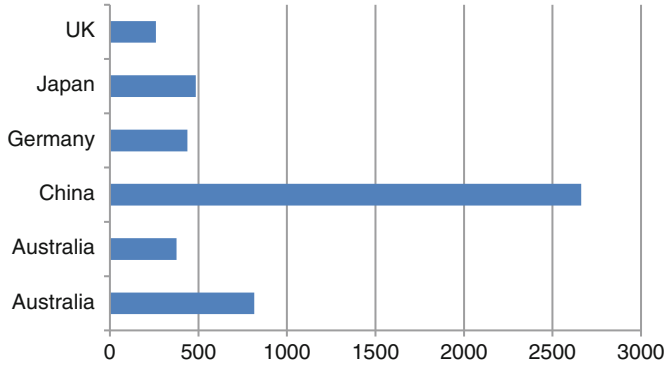


Fig. 1 Mean concentrations of ΣBDE (including BDE209) in indoor house dust (μg kg^{-1}) reported between 2008 and early 2010 (UK: [26]; Germany: [32]; China: [27]; Japan: [29]; Australia: [28, 31])

scenario, personal exposures to ΣHBCDs ranged from 4.5 to 1,850 ng day^{-1}; under a high dust ingestion scenario this was 11–4,630 ng day^{-1}. On average, ingestion from house dust dominated due to the large time fraction spent in houses.

4 Water

Harrad et al. [34] determined HBCD and TBBP-A in water from nine English lakes in 2008–2009. Concentrations ranged from 80 to 270 pg L^{-1} and 140 to 3,200 pg L^{-1}, respectively. Aqueous concentrations were significantly, positively, correlated, indicating a common source. Average dissolved phase concentrations were 4.7% (HBCD) and 61% (TBBP-A).

5 Sediments and Soils

In sediments around a former sewage sludge disposal site in the outer Firth of Clyde at Garroch Head, Webster et al. [35] reported Σ17BDE concentrations up to 23 μg kg^{-1} dry weight. BDE209 was found at very high concentrations in sediment cores from this area, up to 98,100 μg kg^{-1} dry weight. The highest concentrations were found in the top 4 cm of all of the cores, reflecting recent use.

Zhang et al. [36] studied BFRs (BDEs, TBBP-A and DBDPE) in river sediments and cores from a heavily industrialised region of South China. TBBP-A and DBDPE were detected at concentrations ranging from 3.8 to 230 μg kg^{-1} dry weight and 23 to 430 μg kg^{-1} dry weight, respectively. Σtri- to hepta-BDEs and Σnona- to deca-BDEs

ranged from 0.7 to 7.6 μg kg^{-1} dry weight and 30 to 5,700 μg kg^{-1} dry weight, respectively. The former group showed an increasing trend, whereas the latter group showed a decreasing trend, possibly due to the substitution of DBDPE in some applications. The rapid increasing trend of TBBP-A and DBDPE in recent sediment layers reflected increasing usage. Sun et al. [37] studied soils irrigated by sewage or wastewater in China. Σ40BDE concentrations in soils ranged from 0.5 to 3.3 μg kg^{-1} dry weight and BDE209 predominated (93% of the total BDE concentration).

Luo et al. [38] determined the free and bound fractions of BDEs and TBBP-A in freshwater sediments from the lower reaches of the Dongjiang River in the Pearl River Delta, China. The river runs through a large electronics manufacturing region. Free residues were obtained by Soxhlet extraction with 1:1 hexane:acetone, after which bound residues were recovered by alkaline saponification followed by solvent extraction. Concentrations of free and bound tri-hepta congeners (Σ8BDEs) ranged from 0.7 to 7.6 μg kg^{-1} dry weight and 0.013 to 0.14 μg kg^{-1} dry weight, respectively. Concentrations of free and bound nona–deca congeners (Σ4BDE) ranged from 30 to 2,300 μg kg^{-1} dry weight and not detected, respectively. Concentrations of free and bound TBBP-A ranged from 3.8 to 230 μg kg^{-1} dry weight and 1.2 to 20 μg kg^{-1} dry weight, respectively. In two sediment cores, a decreasing trend was observed in the concentrations of nona–deca-BDEs in the upper sections of the cores, which was ascribed to the increasing use of DBDPE as an alternative to the deca-mix PBDE product [36].

In sediment samples from a contaminated Norwegian fjord, Haukås et al. [39] determined HBCD concentrations in sediments along a transect away from a known point source. Mean ΣHBCD concentrations declined with distance at the four downstream sampling sites: 9,000 ± 2,700 μg kg^{-1} organic carbon; 900 ± 240 μg kg^{-1} organic carbon; 700 ± 130 μg kg^{-1} organic carbon; 35 ± 6.1 μg kg^{-1} organic carbon.

Hong et al. [40] determined BDEs in sediments from two locations in France and South Korea. Mean Σ13BDE concentrations were 11 μg kg^{-1} dry weight in Masan Bay, South Korea, but were not detectable in Thau lagoon, France.

Johannessen et al. [41] studied BDEs in seven sediment cores collected in the Strait of Georgia, western USA, in 2003–2004. Surface Σ40BDE concentrations ranged from 0.27 to 12.6 μg kg^{-1} dry weight. BDE concentrations were strongly influenced by proximity to sources. BDEs were dominated by BDE209; the authors noted that their accumulation into domestic dust through the use of treated fabric (and other consumer products) supports the efficient transport of these compounds to the coastal ocean via municipal wastewater systems.

In dated sediment cores from Tokyo Bay, over the period from the 1960s to near present, both BDEs and HBCD increased from the 1960s and 1970s, respectively. The doubling time was shortest for BDE209 (4.6–7.9 years); for ΣBDEs and HBCD these were 6.1–12 and 7.1–12 years, respectively. These appeared to peak in the 1990s following controls in Japan [42].

Harrad et al. [34] determined HBCD and TBBP-A in sediments from nine English lakes collected in 2008–2009. Concentrations ranged from 0.88 to 4.8 μg kg^{-1} dry weight and 0.33 to 3.8 μg kg^{-1} dry weight, respectively.

Tetrabromocyclododecadienes were detected in all sediments, and pentabromocyclododecenes in some. This suggests that HBCD degrades via sequential loss of HBr.

In a sediment core from Greifensee collected in 2003, a small eutrophic lake 10 km east of Zurich, Kohler et al. [43] studied BDEs (with particular attention to possible BDE209 debromination products) and HBCD. PBDEs first appeared in the core in the mid-1970s. Total tri- to hepta-BDE concentrations (BDE28, BDE47, BDE99, BDE100, BDE153, BDE154 and BDE183) levelled off in the mid-1990s at about 1.6 μg kg^{-1} dry weight. BDE209 levels increased to 7.4 μg kg^{-1} dry weight in 2001 with a doubling time of 9 years. HBCD first appeared in the mid-1980s, and increased continuously to 2.5 μg kg^{-1} dry weight in 2001. Next to BDE209, all three nona-BDE congeners (BDE206, BDE207 and BDE208) and at least 7 of the 12 possible octa-BDE congeners (BDE194, BDE196/200, BDE201, BDE202, BDE198/203, BDE197/204 and BDE205) were detected in the sediments of the Greifensee Lake. Highest concentrations were found in the surface sediments.

Jin et al. [44] determined BDEs in a river sediment core sampled in 2006 from Laizhou Bay, China. Σ11BDE concentrations (including BDE209) in sediments ranged from 1.3 to 1,800 μg kg^{-1} dry weight, with the highest concentration in the slice taken at 4–6 cm depth. BDE209 predominated at all depths in the core, consistent with the major use of the deca-mix PBDE product in China.

In soils collected in 2006 from 17 locations in Harbin, China, a major city of three million inhabitants, Wang et al. [45] determined BDEs, HBCD, pentabromoethylbenzene (PBEB) and BTBPE. Of the 17 samples, nine were from urban sites, four from suburban sites, three from rural sites and one background sample (remote from the city). Σ9BDE concentrations ranged from 0.002 to 0.056 μg kg^{-1} dry weight, with a mean of 0.026 μg kg^{-1} dry weight. Concentrations of BDE209 (not included in Σ9BDE) ranged from not detected to 1.75 μg kg^{-1} dry weight, with a mean of 0.52 μg kg^{-1} dry weight. Levels of Σ9BDE were significantly lower than those observed in Europe and the USA, while those of BDE209 were similar to those values. This suggests a major use of the deca-mix PBDE product in the area of Harbin, with little use of the penta- and octa-mix PBDE products locally. HBCD concentrations ranged from not detected to 7.7 μg kg^{-1} dry weight (mean 1.8 μg kg^{-1} dry weight), those of PBEB from not detected to 0.002 μg kg^{-1} dry weight and of BTBPE from not detected to 0.034 μg kg^{-1} dry weight. In summary, BDE209 and HBCD were the dominant BFR compounds, consistent with their high production volume in China. Domestic production of BFRs was estimated to be 10,000 tonnes per annum in 2000, with an estimated additional import of 35,000 tonnes per annum in e-waste [46].

Vane et al. [47] determined Σ16BDE concentrations in six short sediment cores from the Clyde estuary in Scotland. These ranged from 1 to 2,650 μg kg^{-1} dry weight, with a mean value of 287 μg kg^{-1} dry weight. BDE209 was the dominant congener and its concentration ranged from 1 to 2,340 μg kg^{-1} dry weight. Elevated total BDE concentrations were observed in the uppermost 10 cm of four of the six cores. The proportion of nona-BDE congeners was higher than that reported for commercial deca-mix PBDE products, possibly arising from the octa-mix product.

Surface sediments and porewaters from 12 sites in Xiamen offshore areas were sampled and Σ8BDE concentrations determined [48]. Concentrations of Σ8BDE and BDE209 ranged from 0.3 to 76.5 μg kg^{-1} dry weight and 0.1 to 70.1 μg kg^{-1} dry weight, respectively. Σ8BDE concentrations in porewater ranged from ranged from 2.5 to 34.1 ng L^{-1}.

6 Sewage Sludge

Petreas and Oros [49] determined PBDEs in wastestreams (e-wastes, autoshredder waste and sewage sludge). E-wastes represented the predominant wastestream (1,200 Mt $year^{-1}$), followed by autoshredder waste (31 Mt $year^{-1}$) and sewage sludge (2.3 Mt $year^{-1}$). Ricklund et al. [50] reported data for DBDPE and BDE209 in sewage sludge from 42 wastewater treatment plants in 12 countries. DBDPE was present in sewage sludge from all countries and may therefore represent a worldwide concern. The flux via wastewater treatment plants within the EU was 1.7 ± 0.34 mg per person per year for DBDPE; cf. 41 ± 22 mg per person per year for BDE209. In Australia, Clarke et al. [51] studied 16 wastewater treatment plants. The mean ΣBDE concentration was 1,140 μg kg^{-1} dry weight. Urban and rural sludges showed similar mean concentrations (1,310 and 911 μg kg^{-1} dry weight) and these were similar to those seen in Europe. Low levels of BB153 were seen in all samples (mean 0.6 μg kg^{-1} dry weight).

Peng et al. [52] found Σ17BDE concentrations from 13 to 2,500 ng L^{-1} in raw wastewater from two sewage treatment plants in the Pearl River Delta, South China. These concentrations declined to 0.9–4.4 ng L^{-1} in the treated effluent and were closely associated with the SPM content. BDE209 was the dominant congener in both wastewater and sewage sludge. Σ17BDE concentrations in sewage sludge ranged from 158 to 23,800 μg kg^{-1} dry weight, with BDE209 representing >90% of the total.

A major concern regarding BFR concentrations in sewage sludge has related to their transfer to soils and crops following application of sewage sludge as a fertiliser on agricultural land [53]. Gottschall et al. [54] showed that land applications of liquid effluents can also be a source of PBDEs to drainage systems, adjacent surface waters and groundwater. In another study, Xia et al. [55] studied PBDEs in biosolids and land to which biosolids had been applied for 33 years. Σ5BDEs were present in most biosolids at mean concentrations from 240 to 630 μg kg^{-1} dry weight. In treated land, most of the BDEs were retained within the upper 120 cm of the soil, indicating very limited leaching and implying slow degradation rates for these compounds.

Release of PBDEs to the environment in sewage sludge and effluent from a conventional sewage treatment plant in Australia was studied by Clarke et al. [56]. Over 99% of the PBDEs (determined as Σ34BDE) entering the plant was removed, principally by sedimentation. The mean concentration of the sewage sludge was 300 μg kg^{-1} dry weight. The main congeners detected were BDE47, BDE99 and BDE209, representing the penta-mix and deca-mix PBDE products. The BDEs

were thought to arise from domestic sources as domestic wastewater represented ~95% of the inflow. The flux of PBDEs to the environment in sewage sludge was estimated to be only 2.3 ± 0.3 kgpa.

7 Wastewater Discharges

Guan et al. [57] studied 96 riverine runoff samples from eight major outlets in the PRD during 2005–2006. Annual outflows of Σ10BDE and BDE209 were estimated at 126 and 940 kgpa, respectively. The majority of both discharged into the Pearl River Estuary was transported to the coastal ocean (i.e. transferred to the marine environment).

Oram et al. [58] established a mass budget of PBDEs in San Francisco Bay as a step towards understanding local sources and transport processes controlling their fate in a highly urbanised estuary. The Bay inventories of BDE47 and BDE209 were estimated to be 33 ± 3 and 153 ± 45 kg, respectively. Estimated annual inputs ranged from 11 to 28 kg $year^{-1}$ and 22 to 24 kg $year^{-1}$, respectively. BDE47 loads were dominated by wastewater, while runoff from local tributaries represented the largest contributor to BDE209 loads.

8 Sites of BFR Manufacture and Use

Xu et al. [59] determined BDEs in muscle, liver and eggs of freshwater fish and surface sediments from the Nongkang River in Jinhu, China, close to a PBDE-manufacturing plant. Maximum Σ13BDE concentrations in muscle, liver and eggs of fishes were 130, 252 and 33 μg kg^{-1} lipid weight, respectively. In surface sediments close to a sewage outfall, upstream and downstream of the factory were 52, 9.2 and 7.1 μg kg^{-1} organic carbon, respectively. Compared to these seen elsewhere (e.g. in the UK: [60]) these concentrations are modest. A relatively high proportion of BDE183 was found, consistent with the production of the octa-mix PBDE formulation at the site.

9 E-Waste Recycling Operations

One topic which has come to the fore recently is that of e-waste recycling operations. These can be very rudimentary set-ups, involving open burning and manual handling, and are prevalent in parts of China. Concerns relate to the release of flame retardants from the units being recycled and to the generation of polybrominated dibenzo-*p*-dioxins and dibenzofurans [61]. Human exposure is via the ingestion and dermal absorption of dust (e.g. electronic shredder waste) and soils. For adults, the estimated average daily intake of PBDD/PBDFs via dermal exposure (0.63 pg

TEQ per kilogram body weight per day) was greater than that from soil/dust ingestion (0.37 pg TEQ per kilogram body weight per day). For children, this was reversed (0.41 vs 0.11 pg TEQ per kilogram body weight per day for soil/dust ingestion and dermal exposure, respectively). E-waste recycling in China is a significant source of both PBDD/PBDF and PBDE to both workers and the environment, but the likely effects are unknown. Studying BDE concentrations in vegetation around a recycling centre in southeast China, Zhao et al. [62] concluded that diffusion of PBDEs resulted in a halo of contamination at least 74 km in radius, which may also lead to their accumulation in other wildlife species. Zhang et al. [63] also demonstrated the accumulation of HBCD from sediments close to an e-waste recycling site in fish and winkles. γ-HBCD dominated in sediments, but α-HBCD in the aquatic organisms, as is found generally.

Luo et al. [64] determined BDEs, DBDPE and BB153 in muscle of five waterbird species collected from an extensive e-waste recycling area in the PRD, China. Median Σ13BDE concentrations were 37–2,200 μg kg^{-1} lipid weight; those of DBDPE and BB153 10–176 μg kg^{-1} and 3–140 μg kg^{-1} lipid weight, respectively. Concentrations of BDEs in Chinese pond heron were higher than those from earlier studies with birds from similar trophic levels.

Levels of BDEs in free-range domestic fowl (chickens and ducks) close to an e-waste recycling centre were determined [65]. The site houses more than 1,300 workshop, is about 3.3 km^2 in area and employs more than 80,000 workers in dismantling and recycling 1.7 million tonnes of e-waste annually. In chickens, Σ16BDE concentrations in muscle and liver ranged from 5.7 to 4,380 μg kg^{-1} and 1.5 to 7,900 μg kg^{-1} lipid weight, respectively. In ducks, Σ16BDE concentrations in muscle and liver ranged from 2.4 to 51 μg kg^{-1} and 1.9 to 134 μg kg^{-1} lipid weight, respectively. The intake of BDEs from consumption of poultry was estimated to be between 7.8 and 3,580 ng day^{-1} (median value 68 ng day^{-1}), comparable to the intake from all foodstuffs in other studies. The authors suggested that the total dietary intake of BDEs by local residents might be considerably enhanced due to the e-waste recycling activities. The PBDE concentrations in muscle were significantly higher than those in liver for chicken. For duck samples, the PBDE concentrations in muscle and liver were not statistically different. BDE209 was the most abundant congener followed by nona-BDEs (BDE207, BDE206 and BDE208). Their sum collectively accounted for 78–82% and 70–81% of the total PBDE concentrations in chicken and duck, respectively. BDE47and BDE99, two major congeners of penta-BDE technical mixtures, contributed between 5.1 and 6.8% and between 6.2 and 15% to the total PBDEs in chicken and duck, respectively. BDE183, the major congener of octa-BDE technical mixtures, represented between 2.7 and 3.7% and between 3.6 and 5.5% of the total PBDEs in chicken and duck, respectively. These patterns suggest the deca-mix PBDE technical product as the major source of PBDEs in this region.

Wu et al. [66] sampled Chinese mystery snail, prawn, fish and water snake from a reservoir surrounded by several e-waste recycling workshops in South China. Σ18BDE concentrations ranging from 53 to 1,700 μg kg^{-1} wet weight were observed in this area relative to those at a reference location, 13–21 μg kg^{-1} wet

weight. The highest concentrations were found in water snake. In a single study, Wu et al. [67] determined BDEs in frogs from a contaminated site in South China. Σ18BDE concentrations were 0.6–12 μg kg^{-1}, 4.6–56 μg kg^{-1} and 11–125 μg kg^{-1} wet weight, in muscle, liver and eggs, respectively. The congener profiles were intermediate between those commonly seen in terrestrial and aquatic species. The ratio of levels in eggs/female liver, indicating transfer capacity mother–offspring, increased with increasing bromine number to hepta-BDEs, then declined.

Qin et al. [68] conducted a semi-field experiment using Chinese loach, with larval fish kept in net-cages for 3 months in an e-waste recycling site and at a reference site in SE China. There was a significant difference in survival rate at the two sites: 27% at the recycling site and 70% at the reference site. Histopathological responses were found in the livers of all the fish from the recycling site. Low concentrations of BDE209 (1.4 μg kg^{-1} lipid weight; less than 0.01% of Σ33BDEs, 17,000 μg kg^{-1} lipid weight) and high concentrations of BDE47 (6,670 μg kg^{-1} lipid weight) in loach from the recycling site were observed. The Σ33BDE concentration in loach from the reference site was, in contrast, only 343 μg kg^{-1} lipid weight. In sediment samples from the two sites, Σ33BDE and BDE209 concentrations were 10,500 and 3,000 μg kg^{-1} dry weight, respectively, at the recycling site, and 5.9 and 0.08 μg kg^{-1}, respectively, at the reference site.

Robinson [69] assessed the scale and impacts of e-waste recycling operations. He estimated the global production of e-waste to be 20–25 million tonnes per year, with most being produced in Europe, the USA and Australasia. China, Eastern Europe and Latin America are expected to become major e-waste producers within the next decade. Although illegal under the Basel Convention, rich countries export an unknown quantity of e-waste to poor countries, where recycling is often crude and poorly controlled. Such reprocessing initially results in extreme local contamination followed by migration of contaminants into surface waters and food chains. E-waste workers suffer negative health effects through skin contact and inhalation, while the wider community are exposed to the contaminants via smoke, dust, drinking water and food. There is also evidence that e-waste-associated contaminants may be present in some agricultural products going for export. Frazzoli et al. [70] undertook a diagnostic health risk assessment of the general populations in developing countries in relation to e-waste recycling operations. This indicated that exposure to contaminants from e-waste recycling poses an actual public health emergency, as it may entail significant health risks for generations to come as well as to the currently exposed populations. Data gaps were also identified in relation to some of the areas of the developing world in which e-waste recycling is being undertaken, particularly in Africa.

Σ13BDE concentrations near to an e-waste recycling area in Taizhou, China, were 506 pg m^{-3} in summer and 1,660 pg m^{-3} in winter [71]. The winter concentration was about seven times higher than that obtained at an urban reference site, but much lower than that seen in Guiyu, another major e-waste recycling site in China. BDE209 was the major congener and occurred mainly in coarse particles. Also in the Taizhou region, Tang et al. [72] studied contaminants resulting from e-waste recycling in soils from Wenling, an emerging centre in the Taizhou area.

They highlighted elevated concentrations of heavy metals, PAHs and PCBs (although they did not determine BFRs), demonstrating that a holistic assessment of these recycling practices is needed in order to fully assess the risks. Further to this, Zhao et al. [73] studied the body burdens of two pollutants from two sites in Taizhou resulting from e-waste recycling operations (PCBs and PBDEs) with the intention of studying the combined health risks to the local population. Mean blood concentrations of Σ5CBs and Σ8BDE were 204 and 118 μg kg^{-1} lipid weight, respectively, in Luqiao (where PCB-containing wastes are recycled) and 84 and 357 μg kg^{-1} lipid weight, respectively, in Wenling (where PBDE-containing wastes are recycled). The authors suggested that these dual pollutant body burdens may pose health risks for local residents unconnected with the recycling operations.

10 Municipal Solid Waste Incinerators

Many products containing PBDEs will be disposed of in waste incinerators, particularly as many are now being built for power generation. Wang et al. [74] sampled the stack flue gases and ashes in two municipal solid waste incinerators in southern Taiwan in 2008. Bottom ashes showed higher ΣBDE concentrations (di – deca-BDEs) (20–186 μg kg^{-1}) than fly ashes (0.3–26 μg kg^{-1}), suggesting incomplete destruction of the PBDEs in wastes. High concentrations were also observed in stack flue gases (26–109 ng Nm^{-3}), indicating that neither stack flue gases nor reuse of bottom ash should be neglected when considering PBDE inventories.

11 Other Industries

Hitherto, there has been no focus on metallurgical processes (including electric arc furnaces and sinter plants) as significant emission sources for BDEs. Wang et al. [75] have recently reported PBDE emission rates of 4.5–27 mg h^{-1} from such plants, with BDE209 the dominant congener. No raw materials containing PBDEs were fed into the sinter plants studied, and brominated dioxins and furans were also formed and emitted from the metallurgical facilities.

12 Conclusions

BFRs continue to be an intensive area of study. Due to bans for some BFRs and the introduction of “novel” non-PBDE BFRs, long established sources still need to be studied. New sources have emerged, such as e-waste recycling operations. In addition, secondary sources, such as glacier ice and permafrost soils, might become increasingly important in the future as a result of climate change. The maintenance

of time trend studies covering long periods will become even more important so that we can assess the success of governmental regulation of current-use BFRs (PBDEs) and the importance of emerging BFRs. Even today, many ecosystems and regions are not studied well enough for us to be able to establish a global overview concerning BFR concentrations and their toxic effects.

In many areas of the world, controls have been put in place regarding the use of PBDEs, and environmental concentrations are beginning to fall as a result. Investigations into the potential impacts of TBBP-A in Asia, around sites of manufacture and first use, are still required in order to assess the risks of continued production and use [76]. The use of "novel" BFRs is being studied in order to assess their significance and potential impacts, as their environmental presence has been noted recently in a number of studies.

There is still concern that BDE209 (from the deca-mix PBDE technical product) may be debrominated in the environment to yield lower brominated BDE congeners, particularly as a large reservoir of BDE209 is accumulating in sediments.

In the future, there may be a move towards polymeric BFRs, with the idea that, as large molecules, they are less likely to migrate out of end-use products and so to disperse into the environment [77]. The potential impacts of such compounds remain to be assessed.

References

1. Imm P, Knobeloch L, Buelow C, Anderson HA (2009) Household exposures to polybrominated diphenyl ethers (PBDEs) in a Wisconsin cohort. Environ Health Perspect 117:1890–1895
2. Khalaf H, Larsson A, Berg H, McCrindle R, Arsenault G, Olsson P-E (2009) Diastereomers of the brominated flame retardant 1, 2-dibromo-4-(1, 2-dibromoethyl)cyclohexane induce androgen receptor activation in the HepG2 hepatocellular carcinoma cell line and the LNCaP prostate cancer cell line. Environ Health Perspect 117:1853–1859
3. Rice DC, Thompson WD, Reeve EA, Onos KD, Assadollahzadeh M, Markowski VP (2009) Behavioural changes in aging but not young mice after neonatal exposure to the polybrominated flame retardant decaBDE. Environ Health Perspect 117:1903–1911
4. Roze E, Meijer L, Bakker A, van Braeckel KN, Sauer PJJ, Bos AF (2009) Prenatal exposure to organohalogens, including brominated flame retardants, influence motor, cognitive, and behavioural performance at school age. Environ Health Perspect 117:1953–1958
5. Tagliaferri S, Caglieri A, Goldoni M, Pinelli S, Alinovi R, Poli D, Pellacani C, Giordano G, Mutti A, Costa LG (2010) Low concentrations of the brominated flame retardants BDE-47 and BDE-99 induce syb ergistic oxidative stress-mediated neurotoxicity in human neuroblastoma cells. Toxicol in Vitro 24:116–122
6. Law RJ (2009) Brominated flame retardants. In: Harrad SJ (ed) Persistent organic pollutants. Wiley, New York. ISBN:978-1-4051-6930-1, pp 5–24
7. Law RJ, Herzke D, Harrad S, Morris S, Bersuder P, Allchin CR (2008) Levels and trends of HBCD and BDEs in the European and Asian environments, with some information for other BFRs. Chemosphere 73:223–241
8. Yogui GT, Sericano JL (2009) Polybrominated diphenyl ether flame retardants in the U.S. marine environment: a review. Environ Int 35:655–666

9. Andersson Ö, Blomkvist G (1981) Polybrominated aromatic pollutants found in fish in Sweden. Chemosphere 10:1051–1060
10. Leonards P, López P, de Boer J (2008) Analysis and occurrence of new brominated flame retardants in the environment. Organohalogen Compd 70:926–929
11. Covaci A, Nadeem A, Abdallah MA-E, Harrad S, Law RJ, Herzke D (2010) Human exposure to novel brominated flame retardants. In: Proceedings of the conference BFR2010
12. Covaci A, Nadeem A, Abdallah MA-E, Harrad S, Law RJ, Herzke D (2010) Knowledge gaps in the analysis of "novel" brominated flame retardants. In: Proceedings of the conference BFR2010
13. Herzke D, Harju M, Heimstad E, Sandanger T, Posner S, Wania F (2010) Emerging "new" brominated flame retardants: sources and transport. In: Proceedings of the conference BFR2010
14. Law RJ, Covaci A, Harrad S, Herzke D, Nadeem A, Abdallah MA-E (2010) "Novel" brominated flame retardants in the environment: a review. In: Proceedings of the conference BFR2010
15. Muir DCG, Wit CA (2010) Trends of legacy and new persistent organic pollutants in the circumpolar Arctic: overview, conclusions, and recommendations. Sci Total Environ 408:2852–2853
16. Hung H, Kallenborn R, Breivik K, Su Y, Brorström-Lundén E, Olafsdottir K, Thorlacius JM, Leppänen S, Bossi R, Skov H, Manø S, Patton GW, Stern G, Sverko E, Fellin P (2010) Atmospheric monitoring of organic pollutants in the Arctic under the Arctic monitoring and assessment programme (AMAP): 1993–2006. Sci Total Environ 408:2854–2873
17. Venier M, Hites RA (2008) Flame retardants in the atmosphere near the Great Lakes. Environ Sci Technol 42:4745–4751
18. Venier M, Hites RA (2008) Atmospheric deposition of PBDEs to the Great Lakes featuring a Monte Carlo analysis of errors. Environ Sci Technol 42:9058–9064
19. Su Y, Hung H, Brice KA, Su K, Alexandrou N, Blanchard P, Chan E, Sverko E, Fellin P (2009) Air concentrations of polybrominated diphenyl ethers (PBDEs) in 2002–2004 at a rural site in the Great Lakes. Atmos Environ 43:6230–6237
20. Noël M, Dangerfield N, Hourston RAS, Belzer W, Shaw P, Yunker MB, Ross PS (2009) Do trans-Pacific air masses deliver PBDEs to coastal British Columbia, Canada? Environ Pollut 157:3404–3412
21. Iacovidou E, Mandalakis M, Stephanou EG (2009) Occurrence and diurnal variation of polychlorinated biphenyls and polybrominated diphenyl ethers in the background atmosphere of Eastern Mediterranean. Chemosphere 77:1161–1167
22. Zhong B-Z, Guan Y-F, Li S-M, Zeng EY (2009) Occurrence of polybrominated diphenyl ethers in air and precipitation of the Pearl River Delta, South China: annual washout ratios and depositional rates. Environ Sci Technol 43:9142–9147
23. Wang L-C, His H-C, Wang Y-F, Lin S-L, Chang-Chien G-P (2010) Distribution of polybrominated diphenyl ethers (PBDEs) and polybrominated dibenzo-p-dioxins and dibenzofurans (PBDD/Fs) in municipal solid wastes incinerators. Environ Pollut 158:1595–1602
24. Mandalakis M, Stephanou EG, Horii Y, Kannan K (2008) Emerging contaminants in car interiors: evaluating the impact of airborne PBDEs and PBDD/Fs. Environ Sci Technol 42:6431–6436
25. Lagalante AF, Oswald TD, Calvosa FC (2009) Polybrominated diphenyl ether (PBDE) levels in dust from previously owned automobiles at United States dealerships. Environ Int 35:539–544
26. Harrad S, Ibarra C, Abdallah MA-E, Boon R, Neels H, Covaci A (2008) Concentrations of brominated flame retardants in dust from United Kingdom cars, homes and offices: causes of variability and implications for human exposure. Environ Int 34:1170–1175
27. Huang Y, Chen L, Peng X, Xu Z, Ye Z (2010) PBDEs in indoor dust in south-central China: characteristics and implications. Chemosphere 78:169–174
28. Toms L-ML, Bartkow ME, Symons R, Paepke O, Mueller JF (2009) Assessment of polybrominated diphenyl ethers (PBDEs) in samples collected from indoor environments in South East Queensland, Australia. Chemosphere 76:173–178

29. Takigami H, Suzuki G, Hirai Y, Ishikawa Y, Sunami M, Sakai S-I (2009) Flame retardants in indoor dust and air of a hotel in Japan. Environ Int 35:688–693
30. Takigami H, Suzuki G, Hirai Y, Sakai S-I (2009) Brominated flame retardants and other polyhalogenated compounds in indoor air and dust from two houses in Japan. Chemosphere 76:270–277
31. Toms L-ML, Hearn L, Kennedy K, Harden F, Bartkow M, Temme C, Mueller JF (2009) Concentrations of polybrominated diphenyl ethers (PBDEs) in matched samples of human milk, dust and indoor air. Environ Int 35:864–869
32. Fromme H, Körner W, Shahin N, Wanner A, Albrecht M, Boehmer S, Parlar H, Mayer R, Liebl B, Bolte G (2009) Human exposure to polybrominated diphenyl ethers (PBDE), as evidenced by data from a duplicate diet study, indoor air, house dust, and biomonitoring in Germany. Environ Int 35:1125–1135
33. Abdallah MA-E, Harrad S (2009) Personal exposure to HBCDs and its degradation products via ingestion of indoor dust. Environ Int 35:870–876
34. Harrad S, Abdallah MA-E, Rose NL, Turner SD, Davidson TA (2009) Current-use brominated flame retardants in water, sediment, and fish from English lakes. Environ Sci Technol 43:9077–9083
35. Webster L, Russell M, Adefehinti F, Dalgarno EJ, Moffat CF (2008) Preliminary assessment of polybrominated diphenyl ethers (PBDEs) in the Scottish aquatic environment, including the firth of Clyde. J Environ Monit 10:463–473
36. Zhang X-L, Luo X-J, Chen S-J, Wu J-P, Mai B-X (2009) Spatial distribution and vertical profile of polybrominated diphenyl ethers, tetrabromobisphenol-A, and decabromodiphenylethane in river sediment from an industrialized region of South China. Environ Pollut 157:1917–1923
37. Sun K, Zhao Y, Gao B, Liu X, Zhang Z, Xing B (2009) Organochlorine pesticides and polybrominated diphenyl ethers in irrigated soils of Beijing, China: levels, inventory and fate. Chemosphere 77:1199–1205
38. Luo X-J, Zhang X-L, Chen S-J, Mai B-X (2010) Free and bound polybrominated diphenyl ethers and tetrabromobisphenol A in freshwater sediments. Mar Pollut Bull 60:718–724
39. Haukås M, Hylland K, Berge JA, Nygård T, Mariussen E (2009) Spatial diastereomer patterns of hexabromocyclododecane (HBCD) in a Norwegian fjord. Sci Total Environ 407:5907–5913
40. Hong SH, Munschy C, Kannan N, Tixier C, Tronczynski J, Héas-Moisan K, Shim WJ (2009) PCDD/F, PBDE, and nonylphenol contamination in a semi-enclosed bay (Masan Bay, South Korea) and a Mediterranean lagoon (Thau, France). Chemosphere 77:854–862
41. Johannessen SC, Macdonald RW, Wright CA, Burd B, Shaw DP, van Roodselaar A (2008) Joined by geochemistry, divided by history: PCBs and PBDEs in Strait of Georgia sediments. Mar Environ Res 66:S112–S120
42. Tanabe S (2008) Temporal trends of brominated flame retardants in coastal waters of Japan and South China: retrospective monitoring study using archived samples from *es*-bank, Ehime University, Japan. Mar Pollut Bull 57:267–274
43. Kohler M, Zennegg M, Bogdal C, Gerecke AC, Schmid P, Heeb NV, Sturm M, Vonmont H, Kohler H-PE, Giger W (2008) Temporal trends, congener patterns, and sources of octa-, nona- and decabromodiphenyl ethers (PBDE) and hexabromocyclododecanes (HBCD) in Swioss lake sediments. Environ Sci Technol 42:6378–6384
44. Jin J, Liu W, Wang Y, Tang XY (2008) Levels and distribution of polybrominated diphenyl ethers in plant, shellfish and sediment samples from Laizhou Bay in China. Chemosphere 71:1043–1050
45. Wang X, Ren N, Qi H, Ma W, Li Y (2009) Levels and distribution of brominated flame retardants in the soil of Harbin in China. J Environ Sci 21:1541–1546
46. Zou M-Y, Ran Y, Gong J, Mai B-X, Zeng EY (2007) Polybrominated diphenyl ethers in watershed soils of the Pearl River Delta, China: occurrence, inventory and fate. Environ Sci Technol 41:8262–8267

47. Vane CH, Ma Y-J, Chen S-J, Mai B-X (2010) Increasing polybrominated diphenyl ether (PBDE) contamination in sediment cores from the inner Clyde Estuary, UK. Environ Geochem Health 32:13–21
48. Li Q, Yan C, Luo Z, Zhang X (2010) Occurrence and levels of polybrominated diphenyl ethers (PBDEs) in recent sediments and marine organisms from Xiamen offshore areas, China. Mar Pollut Bull 60:464–469
49. Petreas M, Oros D (2009) Polybrominated diphenyl ethers in California wastestreams. Chemosphere 74:996–1001
50. Ricklund N, Kierkegaard A, McLachlan MS (2008) An international survey of decabromodiphenyl ethane (deBDethane) and decabromodiphenyl ether (decaBDE) in sewage sludge samples. Chemosphere 73:1799–1804
51. Clarke B, Porter N, Symons R, Marriott P, Ades P, Stevenson G, Blackbeard J (2008) Polybrominated diphenyl ethers and polybrominated biphenyls in Australian sewage sludge. Chemosphere 73:980–989
52. Peng X, Tang C, Yu Y, Tan J, Huang Q, Wu J, Chen S, Mai B (2009) Concentrations, transport, fate, and releases of polybrominated diphenyl ethers in sewage treatment plants in the Pearl River Delta, South China. Environ Int 35:303–309
53. Law RJ, Allchin CR, de Boer J, Covaci A, Herzke D, Lepom P, Morris S, Tronczynski J, de Wit CA (2006) Levels and trends of brominated flame retardants in the European environment. Chemosphere 64:187–208
54. Gottschall N, Topp E, Edwards M, Russell P, Payne M, Kleywegt S, Curnoe W, Lapen DR (2010) Polybrominated diphenyl ethers, perfluorinated alkylated substances, and metals in tile drainage and groundwater following applications of municipal biosolids to agricultural fields. Sci Total Environ 408:873–883
55. Xia K, Hundal LS, Kumar K, Armbrust K, Cox AE, Granato TC (2010) Triclocarban, triclosan, polybrominated diphenyl ethers, and 4-nonylphenol in biosolids and in soil receiving 33-year biosolids application. Environ Toxicol Chem 29:597–605
56. Clarke BO, Porter NA, Symons RK, Marriott PJ, Stevenson GJ, Blackbeard JR (2010) Investigating the distribution of polybrominated diphenyl ethers through an Australian wastewater treatment plant. Sci Total Environ 408:1604–1611
57. Guan Y-F, Sojinu OSS, Li S-M, Zeng EY (2009) Fate of polybrominated diphenyl ethers in the environment of the Pearl River Estuary, South China. Environ Pollut 157:2166–2172
58. Oram JJ, McKee LJ, Werme CE, Connor MS, Oros DR, Grace R, Rodigari F (2008) A mass budget of polybrominated diphenyl ethers in San Francisco Bay, CA. Environ Int 34: 1137–1147
59. Xu J, Xian Q, Yu H, Feng J (2009) Levels and distribution of polybrominated diphenyl ethers (PBDEs) in the freshwater environment surrounding a PBDE manufacturing plant in China. Environ Pollut 157:1911–1916
60. Allchin CR, Law RJ, Morris S (1999) Polybrominated diphenylethers (PBDEs) in sediments and biota downstream of potential sources in the UK. Environ Pollut 105:197–207
61. Ma J, Addink R, Yun S, Cheng J, Wang W, Kannan K (2009) Polybrominated dibenzo-*p*-dioxins/dibenzofurans and polybrominated diphenyl ethers in soil, vegetation, workshop-floor dust, and electronic shredder residue from an electronic waste recycling facility and in soil from a chemical industrial complex in Eastern China. Environ Sci Technol 43:7350–7356
62. Zhao Y-X, Qin X-F, Li Y, Liu P-Y, Tian M, Yan S-S, Qin Z-F, Xu X-B, Yang Y-J (2009) Diffusion of polybrominated diphenyl ether (PBDE) from an e-waste recycling area to the surrounding regions in southeast China. Chemosphere 76:1470–1476
63. Zhang X, Yang F, Luo C, Wen S, Zhang X, Xu Y (2009) Bioaccumulative characteristics of hexabromocyclododecanes in freshwater species from an electronic waste recycling area in China. Chemosphere 76:1572–1578
64. Luo X-J, Liu J, Luo Y, Zhang X-L, Wu J-P, Lin Z, Chen S-J, Mai B-X, Yang Z-Y (2009) Polybrominated diphenyl ethers (PBDEs) in free-range domestic fowl from an e-waste

recycling site in South China: levels, profile and human dietary exposure. Environ Int 35: 253–258
65. Luo X-J, Zhang X-L, Liu J, Wu J-P, Luo Y, Chen S-J, Mai B-X, Yang Z-Y (2009) Persistent halogenated compounds in waterbirds from an e-waste recycling region in South China. Environ Sci Technol 43:306–311
66. Wu J-P, Luo X-J, Zhang Y, Luo Y, Chen S-J, Mai B-X, Yang Z-Y (2008) Bioaccumulation of polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) in wild aquatic species from an electronic waste (e-waste) recycling site in South China. Environ Int 34:1109–1113
67. Wu J-P, Luo X-J, Zhang Y, Chen S-J, Mai B-X, Guan Y-T, Yang Z-Y (2009) Residues of polybrominated diphenyl ethers in frogs (*Rana limnocharis*) from a contaminated site, South China. Environ Sci Technol 43:5212–5217
68. Qin X, Xia X, Li Y, Zhao Y, Yang Z, Fu S, Tian M, Zhao X, Qin Z, Xu X, Yang Y (2009) Ecotoxicological effects of mixed pollutants resulted from e-wastes recycling and bioaccumulation of polybrominated diphenyl ethers in Chinese loach (*Misgurnus anguillicaudatus*). J Environ Sci 21:1695–1701
69. Robinson BH (2009) E-waste: an assessment of global production and environmental impacts. Sci Total Environ 408:183–191
70. Frazzoli C, Orisakwe OE, Dragone R, Mantovani A (2010) Diagnostic health risk assessment of electronic waste on the general population in developing countries' scenarios. Environ Impact Assess Rev (in press)
71. Han W, Feng J, Gu Z, Chen D, Wu M, Fu J (2009) Polybrominated diphenyl ethers in the atmosphere of Taizhou, a major e-waste dismantling area in China. Bull Environ Contam Toxicol 83:783–788
72. Tang X, Shen C, Shi D, Cheema SA, Khan MI, Zhang C, Chen Y (2010) Heavy metal and persistent organic compound contamination in soil from Wenling: an emerging e-waste recycling city in Taizhou area, China. J Hazard Mater 173:653–660
73. Zhao X-R, Qin Z-F, Yang Z-Z, Zhao Q, Zhao Y-X, Qin X-F, Zhang Y-C, Ruan X-L, Zhang Y-F, Xu X-B (2010) Dual body burdens of polychlorinated biphenyls and polybrominated diphenyl ethers among local residents in an e-waste recycling region in southeast China. Chemosphere 78:659–666
74. Wang L-C, Wang Y-F, Hsi H-C, Chang-Chien G-P (2010) Characterizing the emissions of polybrominated diphenyl ethers (PBDEs) and polybrominated dibenzo-*p*-dioxins and dibenzofurans from metallurgical processes. Environ Sci Technol 44:1240–1246
75. Wang Y, Yang R, Wang T, Zhang Q, Li Y, Jiang G (2010) Assessment of polychlorinated biphenyls and polybrominated diphenyl ethers in Tibetan butter. Chemosphere 78:772–777
76. Law RJ (2009) Tetrabromobisphenol-A: investigating the worst-case scenario. Mar Pollut Bull 58:459–460
77. Gouteux B, Alaee M, Mabury SA, Pacepavicius G, Muir DCG (2008) Polymeric brominated flame retardants: are they a relevant source of emerging brominated aromatic compounds in the environment? Environ Sci Technol 42:9039–9044

Bioaccumulation of Brominated Flame Retardants

Angel Antelo Domínguez, Robin J. Law, Dorte Herzke, and Jacob de Boer

Abstract Brominated flame retardants (BFRs) account for the second largest market group of flame retardants currently in use. Since their detection in wildlife samples collected far from local sources, environmental concern about the use of BFRs has grown. Further research in biotic and abiotic matrices revealed the bioavailability of these chemicals in the terrestrial and aquatic ecosystems. Together with their persistency and potential long-range transport, bioaccumulation in wildlife and the potential for trophic magnification indicate serious risks for many organisms. In addition to the polybrominated diphenylethers, hexabromocyclododecane and tetrabromobisphenol A, other BFRs have entered the market in recent years. Not all BFRs show similar behaviour. Their structure and properties, and the metabolic processes taking place within the exposed organisms, are of great importance in determining their bioaccumulation profile.

Keywords Bioaccumulation, Bioavailability, Biomagnification, Brominated flame retardants, Trophic chain

Contents

A. Antelo Domínguez and J. de Boer (✉)
Institute for Environmental Studies, VU University, De Boelelaan 1087, 1081 HV Amsterdam, The Netherlands
e-mail: jacob.de.boer@ivm.vu.nl

R.J. Law
The Centre for Environment, Fisheries and Aquaculture Science, Cefas Lowestoft Laboratory, Pakefield Road, Lowestoft, Suffolk NR33 0HT, UK

D. Herzke
Norwegian Institute for Air Research, The Polar Environmental Centre, 9296 Tromsø, Norway

E. Eljarrat and D. Barceló (eds.), *Brominated Flame Retardants*,
Hdb Env Chem (2011) 16: 141–185, DOI 10.1007/698_2010_95,

1 Introduction

In December 2006, a new European Union regulation (1907/2006; EC, 2006) stated the policy to be applied in the evaluation of potentially hazardous chemical substances. The principal aim of this new framework was to improve the existing legislation that regulates the chemicals industry in the EU, through a system of Registration, Evaluation and Authorization of Chemicals (REACH). The REACH regulation is based on the precautionary principle, which means that the lack of information about new chemicals or chemicals currently in use, and their possible toxicological effects, could not be a reason for the continued production and use of chemical substances. Information concerning their physicochemical and toxicological properties is therefore required before a substance is approved for sale [1]. The European Chemicals Agency (ECHA) plays an important role within the REACH framework. It coordinates the in-depth evaluation of high production volume chemicals (HPVCs) and toxic chemicals and runs a public database in which hazard information is provided. Important parameters are production, long-range atmospheric transport associated with particulate matter, persistency and bioaccumulation. Based on these criteria, several brominated flame retardants (BFRs) are of concern [2].

Flame retardants (FRs) are a group of structurally diverse chemicals that comprise more than 175 different types, divided into four major groups: inorganic, organophosphorous, nitrogen-containing and halogenated FRs. The main criteria for the usage of a compound as FR are stability during the lifetime of the product, compatibility with the polymer and fire-retarding properties. As a result, BFRs have been widely applied by the industry because they show a higher radical trapping efficiency, a lower decomposition temperature and more compatibility with plastics than most other FRs [3]. Of the FRs globally used, 39% are based on bromine, which is estimated at 200,000 tonnes of BFRs produced per year [4]. There are more than 75 different aliphatic, aromatic and cyclo-aliphatic compounds that have been developed for use as BFRs.

The main commercial BFRs currently in use are tetrabromobisphenol A (TBBP-A), hexabromocyclododecane (HBCD) and polybrominated diphenyl ethers (PBDEs), TBBP-A being the one with the highest production volume (130,000 tonnes per year [5]). For this reason, most of the studies regarding the occurrence of BFRs in the environment to date have involved PBDEs, TBBP-A and HBCD, while other

brominated compounds used for flame retardation have remained in the background. Similar to the polychlorinated biphenyls (PCBs) and organochlorine pesticides (OCPs), defined as persistent organic pollutants (POPs) within the Stockholm Convention, some PBDE congeners and HBCD appear to have persistent characteristics, and their bioaccumulation properties in aquatic and terrestrial organisms indicate the need for more strict control and regulation. In 2009, penta-mix and octa-mix BDEs were placed on the Stockholm Convention POPs list. Apart from the parent compounds, potential degradation products formed during usage or after release to the environment should also be taken into account. Decomposition of plastics may lead to the formation of bromophenols, bromotoluenes and aliphatic bromides, increasing the number of brominated compounds in the environment [6, 7]. Mono-, di- and tri-substituted bromoanilines have also been reported as intermediates in the formulation of FRs incorporated within plastic materials [8].

1.1 Characteristics of Selected BFRs

1.1.1 Tetrabromobisphenol A

TBBP-A is produced via bromination of bisphenol A in an organic solvent. It is mainly used as a reactive intermediate in the production of epoxy resins, but it is also transformed into derivatives such as dimethyl TBBP-A or *bis*-(2-hydroxyethyl ether) TBBP-A [3]. The presence of TBBP-A was not expected in the environment due to its covalent bond to the polymer, but it has been detected in sediments and organisms in the North Sea [9]. A rapid excretion of TBBP-A and metabolites from aquatic organisms and mammals was reported [10]. Although its presence in biota and sediments is generally low compared with the PBDEs and HBCD [11], its similarity in chemical structure to thyroxine (T4) is of special concern as it was demonstrated in in vitro studies to have the ability to interfere with thyroid hormone homeostasis [12]. TBBP-A is not readily biodegradable but can undergo primary biodegradation to form several products, including bisphenol-A. Photochemical degradation of TBBP-A may yield mono- or di-substituted bromophenols which could be bio-transformed into their corresponding bromoanisoles [13, 14]. Several studies indicate that TBBP-A can generate brominated dibenzo-*p*-dioxins and dibenzofurans although the scale of this production seems to be very low and to occur only under certain pyrolysis conditions [15]. In the human health risk assessment report (RAR), no health effects of concern were identified from the primary use of TBBP-A [2].

1.1.2 Polybrominated Diphenyl Ethers

Of the 209 theoretical congeners, only a subset of the possible brominated diphenyl ethers (BDEs) congeners is commonly found in the environment. Lower BDE congeners derived from the penta-mix and octa-mix commercial products are

the predominant BDEs in the aquatic environment, whereas the terrestrial ecosystem accumulates more of the higher brominated congeners, such as BDE209 [11, 16–18]. Due to the different size of the congener molecules and their degree of bromination, which implies variation in properties such as hydrophobicity and lipophilicity, individual BDE congeners show diverse behaviour in the environment.

Comprehensive risk assessments have been conducted within the European Union for the three commercial PBDE formulations, the penta-, octa- and deca-mix products. It was concluded that the technical mixtures penta- and octa-mixes should be banned and that additional data should be provided for the deca-mix [2]. The major components of penta-BDE are the BDE47 and BDE99, whereas the major component of the octa-BDE is the heptabrominated congener BDE183. The penta-BDE components have been widely found in sediments and at different levels in food webs. This demonstrates their ability to enter the ecosystem and, due to the higher rates of uptake and retention compared to elimination, their potential to bioaccumulate to the top of the food chain [19].

1.1.3 Deca-Brominated Diphenyl Ether

The Deca-brominated diphenyl ether (Deca-BDE) technical mixture is the commercial PBDE mixture with the highest production volume currently. Its major component, BDE209, has been found in different matrices, particularly sediments and some terrestrial biota, but to a lesser extent in aquatic organisms [3, 16]. There is a special concern regarding its potential for debromination which could yield lower brominated compounds with stronger bioaccumulation characteristics than the BDE209 itself. It has been shown in laboratory experiments that BDEs can be photochemically degraded by UV or sunlight in organic and aqueous solvents and in soil and sediments, resulting in the formation of less brominated BDEs. The degradation rates generally increase with an increasing degree of bromination [20–24]. However, it is unclear to what extent this degradation occurs in the natural environment as shielding effects may often limit the amount of UV light reaching the BDE molecules. Following advice from environmental agencies, industries in the USA will voluntary phase out the deca-BDE product within the next few years [5].

1.1.4 Hexabromocyclododecane

The commercial mixture of HBCD comprises mainly three diastereomers with the γ-HBCD as the dominant compound. Two other stereoisomers (δ, ε) have been detected at very low concentrations in the technical mixture [24]. All three diastereomers can occur as enantiomers. Although γ-HBCD is the predominant diastereomer in the technical mixture, the α-HBCD isomer is generally found to

dominate in biological samples, which suggests a possible selective metabolism of individual isomers or a diastereomer rearrangement [9, 25]. Thermal decomposition has been observed for HBCD at 170–190°C, with slower rates for α- and β-HBCD than for the γ-diastereomer [26].

HBCD has been detected in freshwater and marine biota. The high concentrations found in top predators such as marine mammals and birds of prey suggest a strong biomagnification potential [27, 28]. Its detection in bird eggs and porpoise blubber illustrates the potential of HBCD for maternal transfer [29]. HBCD has been reported to biodegrade in freshwater and wastewater through several dihaloelimination steps, resulting in 1,5,9-cyclododecatriene [30].

1.1.5 Decabromodiphenylethane

Decabromodiphenylethane (DBDPE) has been manufactured as an alternative to the deca-BDE formulation since the mid-1980s. Not much is known about this brominated compound as the main attention was focused on the aforementioned BFRs, but its similarity in structure to BDE 209 suggests a similar behaviour. Although there are few reports on the presence of DBDPE in the environment, it has already been detected in several matrices including sediments and fish, but at lower concentrations than BDE209 [31, 32]. DBDPE can be thermally degraded to bromotoluenes and photolytically debrominated to nona- and octa-BDE congeners [33].

1.1.6 Polybrominated Biphenyls

Polybrominated biphenyls (PBBs) are a group of chemicals that were widely used in the past as fire retardants. The accidental introduction of the chemical into the food chain of Michigan in 1973 led to the quarantine of farms, the destruction of millions of animals and dairy products, and serious human health problems [34]. Nowadays, PBBs are controlled in Europe under the Restriction of Hazardous Substances Directive, which limits their use in electrical and electronic products to be sold within the EU [35].

2 Occurrence and Levels in Wildlife

A multitude of studies on PBDEs in wildlife has resulted in a large database of concentrations in all sorts of organisms. Although not exhaustive, an overview of the most important studies is given below.

2.1 Birds and Birds' Eggs

2.1.1 Aquatic Birds

Predatory birds are known to respond to relatively low levels of organohalogen compounds. The concentrations of these contaminants in birds may vary according to the species and the chemical compound involved [36]. Liver samples from cormorants [37, 38] and guillemot eggs from the Baltic Sea [39] showed higher concentrations of BDE47 and BDE99, compared to higher brominated congeners.

In eggs of eider ducks and greater black-backed gulls sampled from a contaminated Norwegian fjord, Haukås et al. [40] determined HBCD concentrations along a transect away from a known point source. Mean sum HBCD concentrations at the four locations in eider ducks declined from 140 ± 50 to 15 ± 5.0 μg kg^{-1} lipid weight. In the gulls, concentrations at all locations were similar, ca. 150 μg kg^{-1} lipid weight, possibly reflecting overlapping feeding areas.

Dauwe et al. reported PBDEs in eggs of Northern lapwing and Mediterranean gulls near the harbour of Antwerp (Belgium) [41]. Lapwing eggs had the highest median concentrations of BDEs (109 μg kg^{-1} lipid weight). Mediterranean gulls feed during breeding on ground-dwelling invertebrates on agricultural fields which differ from the marine food items in the rest of the year. Mediterranean gull eggs had the lowest median concentrations of Σ7PBDEs (25 μg kg^{-1} lipid weight). These birds are migratory and their wintering grounds may be less polluted with PBDEs than their breeding sites.

Verboven et al. reported Σ38BDE levels in plasma of 15 female and male glaucous gulls from Bjørnøya, Norway, collected in 2006 [42]. Female glaucous gulls showed a mean concentration of 7 μg kg^{-1} wet weight and males of 19.5 μg kg^{-1} wet weight. Verrault et al. [43] also reported data for Σ38PBDE in plasma from 42 glaucous gull collected in the same year. Similar sumPBDE levels (8.5 μg kg^{-1} wet weight for females and 19.6 μg kg^{-1} wet weight for males) were found in that study also.

BDEs were analysed in dead and dying glaucous gulls at Bjørnøya (Svalbard) by Sagerup et al. [44]. Σ11BDE concentrations were four to ten times higher in liver than in the brain, 13,000 μg kg^{-1} lipid weight and 1,800 μg kg^{-1} lipid weight, respectively. The brain concentration was 12% of the liver concentration for the tribrominated congener BDE28 and only 2% for the nona-brominated congener BDE207. The hepatic levels of ΣBDEs were 10–40 times higher in that previously reported in randomly sampled glaucous gulls from the Barents Sea area.

Ivory gull eggs from the Russian and Norwegian Arctic were investigated by Miljeteig et al. [45]. Thirty-five eggs were sampled from individual ivory gull nests within four colonies in Svalbard: Svenskøya (78° 47′ N, 26° 36′ E, in 2007, and in northwestern Russia in 2006), Nagurskoe (80° 48′ N, 47° 37′ E), Kluyv Cape (81° 39′ N, 62° 11′ E, in Franz Josef Land) and Domashny (79° 30′ N, 91° 05′ E, in Severnaya Zemlya). Σ7BDE concentrations in the eggs from Svalbard varied between 101 and 221 μg kg^{-1} lipid weight and were lower than those from the Russian locations

Nagurskoe and Kluyv Cape, which had concentrations of 302 and 287 μg kg^{-1} lipid weight, respectively. The Domashny colonies gave a median concentration of 51 μg kg^{-1} lipid weight, being the least contaminated. BDE47 was the dominant congener in all samples.

A population of lesser black-backed gulls was investigated by Bustnes et al. [46], determining Σ10BDE concentrations in whole blood samples. Breeding lesser black-backed gulls were caught during two distinct sampling periods from a colony on the coast of northern Norway. Only BDE47 could be detected in the samples, with a mean concentration of 1.9 μg kg^{-1} wet weight.

Herzke et al. analysed samples from two marine bird species, European shag and common eider sampled at a coastal site in Norway close to urban activity and at a remote site [47]. Six different PBDE congeners could be detected in the shag eggs. BDE 47 and 100 were the main contributors, with concentrations of 24 and 27 μg kg^{-1} lipid weight, respectively. A Σ6BDE concentration of 90 μg kg^{-1} lipid weight was found. The common eider eggs were less contaminated, with BDE47 as the dominant congener, followed by BDE99 and BDE100. The Σ6BDE concentrations were 5.5 μg kg^{-1} g lipid weight at the remote site and 48 μg kg^{-1} lipid weight at the urban site in 2004.

To assess whether the fluctuating wing asymmetry and hepatic concentrations of POPs are associated with European shag chicks, Jenssen et al. also determined BDEs [48]. Of eight BDE congeners determined, only BDE47 and BDE100 could be detected in livers of 21-day-old chicks from Sklinna, Norway. BDE47 concentrations varied from not detected to 3 μg kg^{-1} lipid weight, and BDE100 was detected in only one sample.

Guillemot eggs from North-Western Europe and the Baltic Sea were studied by Jörundsdóttir et al. [49]. Guillemot eggs were collected from Iceland (Vestmannaeyjar, 2002, 63° 24′ N, 20° 18′ W), from Sweden (Stora Karlsö, 2003, 57° 18′ N, 18° E), from the Faroe Islands (Sandøy, 2003, 61° 48′ N, 6° 48′ W) and from three locations in Norway (Sklinna, 65° 12′ N, 11° E, Hjelmsøya, 2005, 71° 6′ N, 24° 42′ E and Bjørnøya, 2005, 74° 24′ N, 19° E). In the North Atlantic, eggs from Iceland contain the highest concentrations of PBDEs. The Norwegian eggs contain the lowest amounts of PBDEs of all the egg samples analysed. Eggs from the Baltic Proper have up to an order of magnitude higher concentration of PBDEs than eggs from the North Atlantic. Σ4PBDE ranged from 51.6 μg kg^{-1} lipid weight in Iceland, 30.7 μg kg^{-1} lipid weight on the Farøe Islands, 12.4 μg kg^{-1} lipid weight in Norway and 147 μg kg^{-1} lipid weight in Sweden.

Hebert et al. [50] investigated the intra-specific differences in the food webs used by individual seabirds. Annual Herring gull egg collections (one egg from each of 10–13 nests) were made at Strachan Island (45° 02′ N, 74° 82′ W) in Lake St Lawrence from 1986 to 2005 (except in 1987). Concentrations of individual contaminants varied greatly between the least and most contaminated eggs. Concentration ranges for contaminants measured above detection limits in all samples were Σ29BDE (206–902 μg kg^{-1} wet weight).

In pooled samples of herring gull eggs from the Great Lakes, Gauthier et al. [51] studied temporal trends in BDE concentrations (particularly BDE209) over the

period 1982–2006. Concentrations of BDE209 in 2006 were 4.5–20 μg kg^{-1} wet weight. Octa- and nona-BDE concentrations doubled more slowly – doubling times of 3.0–11 and 2.4–5.3 years, respectively. The source of the octa- and nona-BDE congeners (e.g. BDE197 and BDE207) were the result of the debromination of BDE209, either metabolically by the herring gulls or before uptake via their diet. Congeners deriving mainly from the penta-mix and octa-mix formulations, in contrast, have shown rapid increases in concentration up to 2,000 and no trend subsequently. In an additional report, Gauthier et al. [49] described Σ7BDE levels from Herring gull egg pools collected in 2006 from seven colonies on the Laurentian Great Lakes (sum of BDE28, BDE47, BDE99, BDE100, BDE153, BDE154 and BDE183). The levels varied between 288 and 1,140 μg kg^{-1} wet weight (% lipid 7.7–10.7).

Custer et al. investigated archived great blue heron eggs collected from Indiana Dunes National Lakeshore, Indiana, USA in 1993 [52]. The ranking of PBDE congener concentrations by percent concentration (BDE47 > BDE99 > BDE100 > BDE153 > BDE154 > BDE28 > BDE183) was consistent with use of the penta-mix PBDE formulation. Total PBDE concentrations in great blue heron eggs from Indiana Dunes were elevated and probably reflect local contamination from urban and industrial inputs into Lake Michigan. PBDE concentrations were within the range of those associated with altered reproductive behaviour in other avian species and, based on trends in other Great Lakes birds, are probably higher today than in 1993.

Concentrations and time trends of PBDEs in aquatic bird eggs from San Francisco Bay, California, USA were investigated during the period 2000–2003 by She et al. [53]. Caspian and Forster's terns showed no change in Σ5PBDE concentration over time. Congener patterns in the two species from year to year are similar, with BDE47 dominating, followed by BDE99 > BDE100 > BDE153 > BDE154. The median ΣBDE concentrations in Caspian tern eggs were 2,410, 4,730, 3,720 and 2,880 μg kg^{-1} lipid weight, for 2000–2003, respectively. The median ΣBDE concentrations in Forster's tern eggs were 1,820, 4,380, 5,460 and 3,600 μg kg^{-1} lipid weight, for 2000–2003, respectively. The median Σ5BDE concentrations in least tern eggs collected in 2001 and 2002 were 5,060 and 5,170 μg kg^{-1} lipid weight, respectively. The median ΣBDE concentration in Clapper rail eggs collected in 2001 was 379 μg kg^{-1} lipid weight.

A spatial and temporal trend study of PBDEs carried out since the mid-1970s for herring gull eggs in the Great Lakes from North America showed higher concentrations of BDE47 followed by BDE99, BDE100, BDE153, BDE154, BDE28 and BDE183, in this bird species that feeds mainly on alewife and rainbow smelt [54].

Muscle tissue of herring gull was analysed by Wan et al. [55] to assess the trophodynamics of PBDEs in the marine food web of Bohai Bay, North China. BDE47 was the dominant congener, with a mean concentration of 1.6 μg kg^{-1} wet weight, followed by BDE100, BDE153 and BDE99 all with mean concentrations around 0.3 μg kg^{-1} wet weight. The reported mean Σ13BDE concentration was 3.3 μg kg^{-1} wet weight (33 μg kg^{-1} lipid weight), much lower than values reported for herring gulls from Europe and Canada.

Levels and pattern of PBDEs in eggs of Antarctic seabirds were investigated by Yogui and Sericano [56] (Fig. 1). Eggs of chinstrap penguin and South Polar skua were collected during the breeding season of 2004–2005, while eggs of gentoo penguin were collected in 2005–2006 at Admiralty Bay, King George Island. Σ29BDE levels ranged from 6.8 μg kg^{-1} lipid weight for Chinstrap penguin and 8.1 μg kg^{-1} lipid weight for Gentoo penguin, to 146 μg kg^{-1} lipid weight for South Polar skua. South Polar skuas occupy a higher trophic level than chinstrap penguins, since the nototheniid fish *P. antarcticum* that they eat is a zooplankton feeder that forages on krill. Gentoo penguins occupy an intermediate trophic position closer to that of chinstrap penguins. The level of BDEs in eggs of the three species is not exclusively explained by their diets during the breeding season. It is likely a result of several factors such as trophic level and type of prey items taken during both the breeding and non-breeding seasons. If BDE contamination was due to local sources only, gentoo eggs would be expected to exhibit intermediate concentrations significantly higher than those of chinstrap eggs. The higher contamination levels in South Polar skuas probably result from exposure during the non-breeding season when they migrate northward to the waters of the northern hemisphere.

Gao et al. [57] investigated BDEs, DBDPE and a PBB congener (BB153) in eggs of six species of wild aquatic birds. Egg samples ($n = 67$) were collected from the Yellow River Delta National Nature Reserve in China in May 2008. The sampled species included Saunders's gull, common tern, Kentish plover, black-winged stilt, oriental pratincole and common coot. With the exception of oriental pratincole,

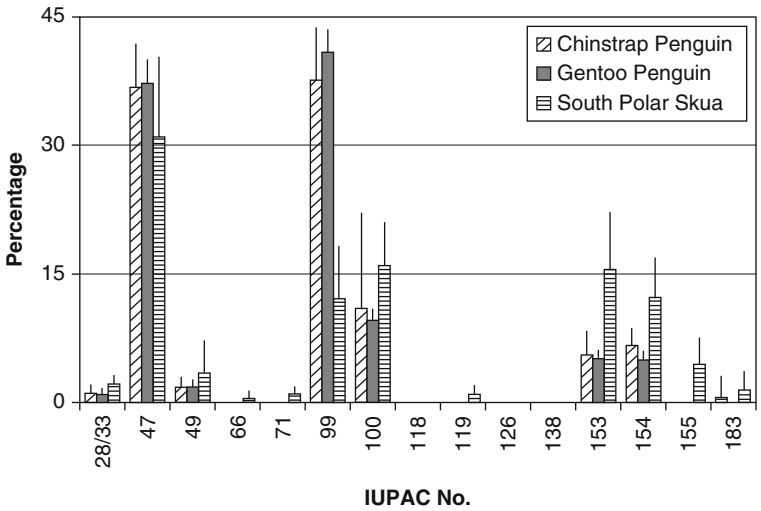


Fig. 1 Per cent distribution of BDE congeners in seabird eggs collected from nesting sites at King George Island, Antarctica. *Error bars* represent standard deviation [56]. Reprinted from Levels and pattern of polybrominated diphenyl ethers in eggs of Antarctic seabirds: endemic versus migratory species. Yogui GT, Sericano JL, Environ Pollut 157:975–980, 2009, with permission of Elsevier

BDE47 showed the highest abundance in all species of wild aquatic birds, comprising 34% of total BDE concentrations, followed by BDE99 and BDE153 in nearly equal proportions. The oriental pratinocole eggs were dominated by BDE209. Median concentrations of DBDPE and BB153 in all avian species were in the range of not detectable (ND) – 1.7 and ND – 0.7 μg kg^{-1} lipid weight, respectively.

Pectoral muscle samples of nine avian species, which were collected from the open sea and Japanese coastal and inland areas during 1994–2001, were analysed for BFR by Kunisue et al. [58]. BDEs were detected in all the avian samples. Among open sea birds, concentrations of BDEs in the black-footed albatross were the highest (60–210 μg kg^{-1} lipid weight), followed by the Laysan albatross (6.2–73 μg kg^{-1} lipid weight) and the northern fulmar (3.3–6.5 μg kg^{-1} lipid weight). As for Japanese coastal and inland birds, the goshawk accumulated the highest concentrations of Σ13BDEs (33,000 μg kg^{-1} lipid weight) > Steller's sea eagle (11,000 μg kg^{-1} lipid weight) > jungle crow (290–4,000 μg kg^{-1} lipid weight) ≈ golden eagle (270–2,300 μg kg^{-1} lipid weight) > common cormorant (230–820 μg kg^{-1} lipid weight) > black-tailed gull (220–530 μg kg^{-1} lipid weight). Small sample sizes for some species prevented any further inter-species comparison. In Japanese coastal and inland birds, relatively higher residue levels of BDE47 were found in fish-eating species, such as the Steller's sea eagle, black-tailed gull and common cormorant. On the other hand, in inland predators such as the goshawk and golden eagle, and jungle crow, a dedicated inland omnivore, BDE153 and higher brominated congeners were predominant, highlighting once more the contrast between uptake of BDEs in aquatic and terrestrial food chains (Fig. 2).

Luo et al. [19] investigated various waterbird species from an extensive e-waste recycling region in South China. Muscle samples from five bird species, including *Rallidae* (white-breasted waterhen, slaty-breasted rail, ruddy-breasted crake); *Ardeidae* (Chinese-pond heron) and *Scolopacidae* families (common snipe) were collected between 2005 and 2007 from Qingyuan County. The median Σ13BDE concentrations in five bird species ranged from 37 to 2,200 μg kg^{-1} lipid weight. BDE47, BDE99, BDE100, BDE153, BDE154 and BDE183 were detected in all the samples, and BDE28 and BDE209 were detected in less than 50% of the samples. The Chinese-pond heron was the most contaminated species, with a Σ13BDE concentration of 2,200 μg kg^{-1} lipid weight. BB153 was detected in 93% of the samples, at concentrations ranging from 1 to 2,800 μg kg^{-1} lipid weight.

PBDEs were measured in eggs of two Ardeid species, the little egret and black-crowned night heron from three port cities along the South China coast, Hong Kong, Xiamen and Quanzhou. ΣBDE levels were highest in Hong Kong, 480 μg kg^{-1} lipid weight, followed by Quanzhou, 220 μg kg^{-1} lipid weight and Xiamen, 40 μg kg^{-1} lipid weight [59].

PBDEs and HBCD in bird eggs from South Africa were analysed by Polder et al. [60]. During the period from November 2004 to March 2005, 43 unhatched eggs from eight different bird species were collected at five different localities in South Africa. BDEs were detected in eggs of all the studied species and in all locations. Highest concentrations of Σ8BDEs (61–396 μg kg^{-1} lipid weight) were measured

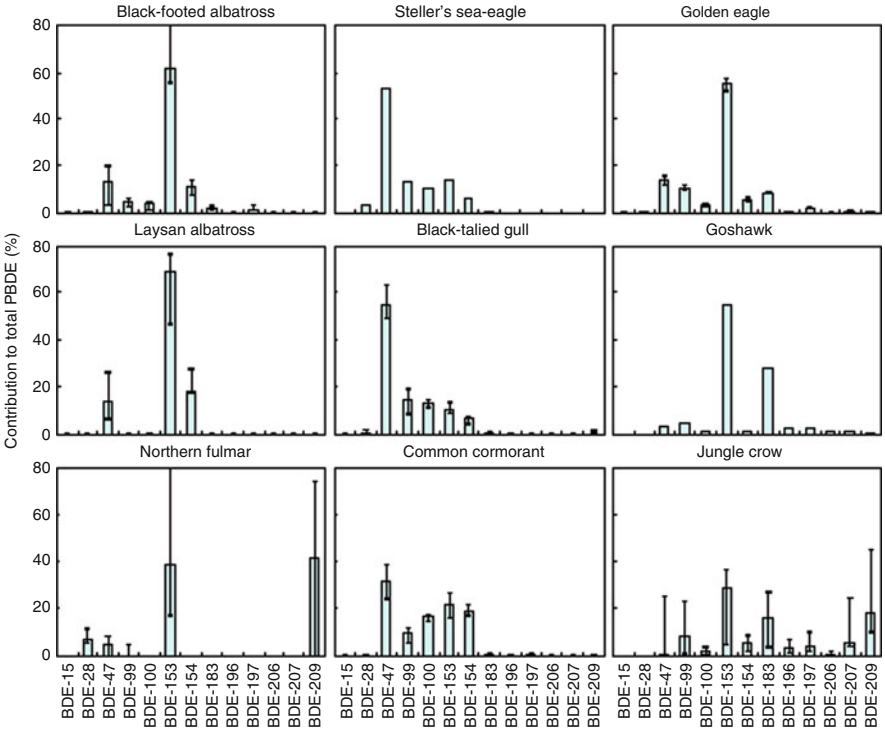


Fig. 2 Composition of PBDEs in avian species from Japan [58]. Reprinted from Spatial trends of polybrominated diphenyl ethers in avian species: utilization of stored samples in the Environmental Specimen Bank of Ehime University (es-Bank). Environ Pollut 154:272–282, 2008, with permission of Elsevier

in eggs of the African sacred ibis. The lowest ΣBDE concentrations were measured in eggs of cattle egrets (2.3 μg kg^{-1} lipid weight). Interestingly, only the little grebe, the white-fronted plover and the kelp gull showed a PBDE pattern dominated by BDE47. The profiles in the other bird species were dominated by either BDE154 (African darter and reed cormorant) or BDE183 (cattle egret, sacred ibis, crowned plover). HBCD was found in three species, at concentrations varying between 1.6 and 71 μg kg^{-1} lipid weight.

2.1.2 Terrestrial Birds

Whether BDEs can reduce the reproductive success of ospreys in Oregon and Washington, USA, was studied by Henny et al. who determined BDE concentrations in eggs [61]. Findings for the 89 osprey eggs collected between 2002 and 2006 indicate that the middle Willamette River eggs contained the highest geometric mean Σ12BDE concentrations and usually had the highest individual congener

concentrations. Eggs collected from the forested and sparsely populated headwater reservoirs of the Willamette River contained the lowest concentrations. ΣBDE concentrations in osprey eggs collected from the Columbia River in 2004 increased in a downstream pattern from 157 μg kg^{-1} wet weight to 403 μg kg^{-1} wet weight. BDE47 was the dominant congener in osprey eggs, followed by BDE100, BDE99, BDE154/BB153, BDE153 and BDE28. When the data including all of the ΣBDE concentrations <1,000 μg kg^{-1} (Willamette River in 2006 and Columbia River in 2007) were evaluated separately, the ten nests from the Willamette River in 2006 showed a negative relationship between productivity and ΣBDE concentrations ($Z = -2.4093$, $P = 0.008$). A negative relationship was also indicated for the 20 nests from the Columbia River in 2007 ($Z = -1.5809$, $P = 0.057$). McKernan et al. [62] suggested the lowest observable effect level may be as low as or 1,800 μg kg^{-1} wet weight of Σ12BDEs in eggs.

Time-trends and congener profiles of BDEs in Californian peregrine falcons were investigated by Park et al. [63] during the period 1986–2007. Over the past 22 years, BDE levels more than tripled in the eggs during each decade. For BDEs, eggs collected in large cities showed markedly different patterns to those in eggs from coastal locations: BDE209 and the higher brominated BDE congeners (hexa- to nona-brominated) were the dominant congeners in eggs from cities, while BDE47 and BDE99 were dominant in coastal eggs. In many of the birds that yielded multiple eggs over time, BDE patterns changed over time: the high proportions of BDE209 and higher brominated BDEs (short half-lives) in young birds contrasted with increasingly higher proportions of BDE153 (long half-life) and other lower brominated PBDEs as the birds aged (Fig. 3). These data are consistent with metabolic debromination of BDE209 to the lower brominated BDE congeners, with accumulation over time of BDE153. Diet (prey birds) may explain the urban BDE congener pattern, as the patterns in urban pigeons and peregrines were similar, with high proportions of BDE209 and the higher brominated BDEs. In summary, these data indicate that BDE209 is taken up by wildlife (particularly in urban locations) and undergoes metabolic debromination to the lower brominated BDE congeners.

An additional study on peregrine falcons focused on urban and rural trends in the Northeastern USA [64]. A total of 23 peregrine falcon eggs were obtained between 1993 and 2002 from 13 nests, encompassing 11 locations in the Chesapeake Bay region, USA. The maximum Σ11BDE concentration in an individual egg, from an urban highway bridge site, was 354 μg kg^{-1}. This egg also exhibited the highest BDE209 burden (48.2 μg kg^{-1}). The congeners BDE153, BDE99 and BDE100 constituted 26.0%, 24.8% and 13.1%, respectively, of ΣBDEs. BDE47 constituted only 4.4% of Σ11BDEs in the eggs in this study. The median BDE209 concentration was 6.3 μg kg^{-1}. The sum of the octa- to nona-brominated congeners (BDE196, BDE197, BDE206, BDE207 and BDE208) contributed, on average, 14% of Σ11BDEs, exceeding the contribution from BDE209 (5.9%). Median BDE209 concentrations were significantly correlated ($p < 0.01$, Spearman $R = 0.690$) with the human population density of the area surrounding the nest. ΣBDE concentrations were not correlated with human population density.

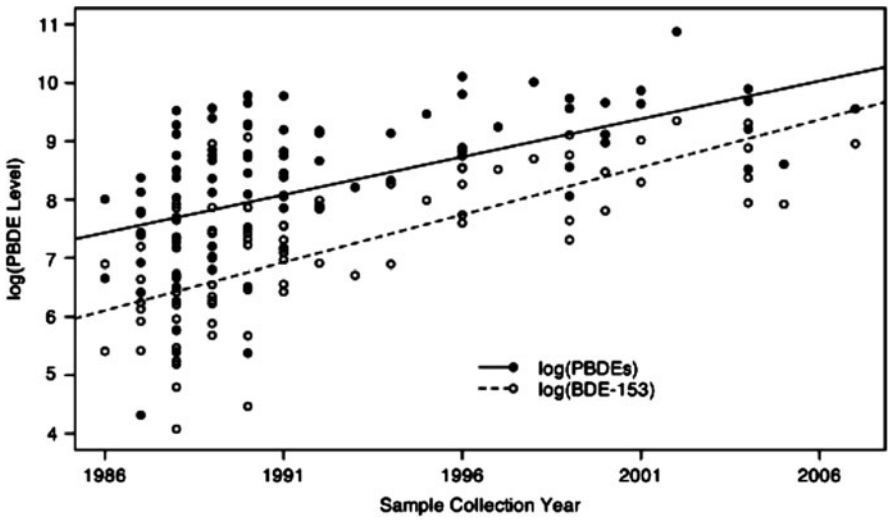


Fig. 3 Temporal changes in the log (natural logarithm) of levels (μg kg^{-1} lipid weight) of ΣBDEs and BDE153 in peregrine falcon eggs from California ($n = 90$) [63]. Reprinted (and adapted) from Time-trends and congener profiles of PBDEs and PCBs in California Peregrine Falcons (*Falco peregrinus*). Park, J.S., Holden, A., Chu, V., Kim, M., Rhee, A., Patel, P., Shi, Y.T., Linthicum, J., Walton, B.J., McKeown, K., Jewell, N.P., Hooper, K., Environmental Science and Technology 43, 8744–8751. 2009, Copyright American Chemical Society

BDEs in Peregrine Falcon Eggs from the Northeastern USA were studied by Chen et al. [65]. Eggs were collected from 1996 to 2006, excluding 1997 and 1998. Σ31BDE concentrations ranged from 74.5 to 6,610 μg kg^{-1} wet weight, with a median of 440 μg kg^{-1} wet weight, showing clearly higher levels than in eggs collected from the west coast, in California. These levels were generally also higher than those observed in European peregrine eggs, but comparable to those seen in North American seabird eggs. Congener patterns were dominated by BDE153, followed by BDE99, BDE183, BDE209, BDE197, BDE207, BDE154, BDE100 and BDE196, with lower contributions from BDE47, BDE208, BDE203, BDE201, BDE206, BDE202, BDE138 and BDE119, similar to eggs from California. Urban and rural falcon eggs contained similar total BDE concentrations but different congener profiles. Urban eggs exhibited higher BDE209 concentrations and greater percentages of other highly brominated congeners. BDE209 was detectable in all eggs, at concentrations ranging from 1.4 to 420 μg kg^{-1} wet weight. Five octa- and three nona-brominated congeners were also frequently detected, some likely derived from the biodegradation of BDE209. Temporal analyses indicated no significant changes in concentrations of total BDEs, or of most individual congeners during the study period. An exception was BDE209, which exhibited a significant increase, with a doubling time of 5 years.

Adult American kestrels exposed to environmentally relevant levels of the PBDE mixture DE-71 were investigated by Fernie et al. in two studies [66, 67].

Captive American kestrels were exposed via their diet to environmentally relevant concentrations of DE-71 and to HBCD. This exposure resulted in delayed egg laying and smaller eggs being laid, caused thinner eggshells and differential weight loss during embryonic development, and reduced fertility and reproductive success. The thickness of the eggshell declined as the concentrations of all measured BDE congeners (except BDE183 and BDE209) and of α-HBCD increased; increasing concentrations of BDE153, BDE154, BDE28 and BDE17 delayed egg laying, reduced eggshell mass (and ΣBDEs) and reduced fledging success (BDE153 and BDE154 only). As uptake of DE-71 continued following pairing, the timing of the courtship behaviours shown by the treated birds differed markedly from that of the control birds. Exposure to low and high levels of DE-71 changed the appropriate timing of the birds' copulatory behaviour, nest box inspections, pair-bonding behaviours and food consumption patterns. Perhaps, most critically, as the birds were continuously exposed to DE-71 during the courtship period, the treatment birds failed to copulate, participate in pair-bonding sexual behaviours and investigate their nest boxes, neither at appropriate times nor as frequently as the control birds.

The enantiomer-specific accumulation of HBCD in eggs of predatory birds was investigated by Janák et al. [68]. Eggs of peregrine falcon, white-tailed sea eagle, guillemot and common tern sampled in Sweden were analysed. Only the α-HBCD diastereomer was found in the eggs of peregrine falcon and white-tailed sea eagle and it was the predominant diastereomer in terns and guillemots. Clear differences in the enantiomer fraction (EFα) were found between the different species analysed, indicating species-specific stereoselective mechanisms for uptake and metabolism of the enantiomers of α-HBCD. Sum HBCD levels varied between 80 and 3,100 μg kg^{-1} lipid weight.

BDE congener patterns, HBCD and BB153 in eggs of peregrine falcons breeding in Sweden were investigated by Johansson et al. [69]. Geometric mean concentrations of Σ13BDEs, HBCD and the hexabrominated biphenyl (BB153) were 3,100, 140 and 81 μg kg^{-1} lipid weight for the southern population; 2,500, 110 and 84 μg kg^{-1} lipid weight for the northern population; and 47, not detected, and 8 μg kg^{-1} lipid weight for the captive population. The BDE congener pattern was dominated by BDE153, BDE99 and BDE100. The average brood size for individual females from the southern population decreased with increasing concentrations of Σ13BDE in the eggs (log-linear regression $p < 0.01$).

Sonne et al. described summed BDE concentrations in plasma of raptor chicks sampled in Northern Norway. Σ8BDE concentrations varied between 2.8, 7.3 and 2.0 ng ml^{-1} for golden eagle, goshawk and white-tailed sea eagle, respectively [70].

Concentrations of BDEs in common magpie feathers were determined by Jaspers et al. [71] while assessing regional differences in contamination. BDE47 and BDE99 could be detected in all samples collected at a rural and an urban location in Flanders, Belgium. BDE47 had a higher contribution in feathers from the urban area ($p < 0.05$), while BDE99 was the most prominent congener in feathers from the rural areas (0.3 μg kg^{-1} dry weight and 0.11 μg kg^{-1} dry weight for BDE47 and 0.17 and 0.19 for BDE99, respectively, in urban and rural locations). The analysis

of preen gland samples of the same species showed Σ6BDE levels of 13 μg kg^{-1} lipid weight (3.2 and 4.8 μg kg^{-1} lipid weight for BDE47 and BDE99, respectively), indicating that the preen gland might be an important elimination route for BDEs in birds.

Three studies by Van den Steen et al. focused on the use of great tit and starlings to monitor BFRs and their effects [72–74]. Eggs from 22 locations were sampled across Europe. The concentrations of Σ7BDE ranged from 4.0 ± 0.7 to 136 ± 19 μg kg^{-1} lipid weight. Σ7BDE concentrations differed significantly among the sampling locations (one-way ANOVA: $F_{21,129} = 16.67$, $p < 0.001$). Σ7BDE concentrations were significantly higher in the urban sampling locations than in the rural and remote locations (urban > rural > remote). Eggs from the rural sampling locations showed significantly higher Σ7BDE levels compared to the eggs from remote sampling locations. Eggs from the urban sampling locations showed significantly higher concentrations compared to the remote locations but not compared to the rural locations. Second, eight complete first clutches with known laying order were collected in 2006 from two sites near Antwerp (Belgium). Σ7BDE concentrations decreased in relation to the laying order from 68 ± 10 to 53 ± 11 μg kg^{-1} lipid weight, but this was not statistically significant. Mean ΣBDE concentrations were significantly lower in eggs of replacement clutches compared to first clutches. And finally, in an exposure study with PBDEs in female European starlings, toxicokinetics and reproductive effects were investigated. Female European starlings were exposed to a pentabromodiphenyl ether mixture through subcutaneous implants, and levels and profiles of BDEs together with reproductive effects were examined. Σ7BDE levels increased significantly in the serum of the exposed females from 218 ± 43 to 23,400 ± 2,035 pg ml^{-1}. ΣBDE concentrations in the eggs of the exposed group ranged from 130 ± 12 to 220 ± 37 μg kg^{-1} wet weight. The profile in serum after egg laying was very similar to that observed in eggs. There were no detectable levels of OH-BDEs in either serum or eggs. Fewer females of the exposed group initiated egg laying compared to the control group, although the difference was not significant. In addition, egg weight and volume were significantly higher in the exposed group. These results suggest that, at the investigated exposure levels (150 μg ΣPBDEs per bird), PBDEs may have a negative effect on reproductive performance.

Covaci et al. [75] studied BDEs and HBCD in the eggs of free-range chickens from Belgium sampled in 2006–2007, thereby addressing both environmental and food concerns simultaneously. Concentrations of both BFRs were relatively low and comparable to those seen elsewhere. Σ6BDE concentrations ranged from not detected up to 32 μg kg^{-1} lipid weight; those of HBCD from not detected up to 62 μg kg^{-1} lipid weight with a lower detection frequency. When present, BDE209 was the major congener (45% of Σ6BDE), otherwise BDE47 and BDE99 predominated. Soil seemed to be the major, but not the sole, source of the BFRs in hens' eggs.

The BDE congener profile observed in sparrow hawks, buzzards and blackbirds from Switzerland was dominated by BDE47, BDE99, BDE100 and BDE153, which was found to be in agreement with previous studies in birds of prey from Australia and Flanders [76–78].

A study in terrestrial birds of prey from China showed the presence of BDE209 in almost 80% of the samples, which confirms the bioaccumulation ability of this congener [79]. Starling muscle tissue [74] and peregrine falcon eggs [80] from terrestrial ecosystems showed higher concentrations of BDEs 153, 154, 100, 99, 183 and 209 compared to BDE47. Similar patterns were found in eggs from a study comparing peregrine falcons feeding from species belonging to terrestrial and aquatic food chains, but the hypothesis that higher brominated congeners would be present to the greatest extent in the terrestrial food chain was not supported [28].

2.2 Fish and Shellfish

In 11 species of fish from the River Scheldt in Belgium, Roosens et al. [81] reported concentrations of BDEs and HBCD. The sum of tri- to hepta-BDE congeners (2,270 ± 2,260 μg kg^{-1} lipid weight; range 660–11,500 μg kg^{-1} lipid weight) and total HBCDs (4,500 ± 3,000 μg kg^{-1} lipid weight; range 390–12,100 μg kg^{-1} lipid weight) were 10-fold higher than those usually reported for freshwater systems, indicating local point sources. Eels showed a considerable decrease in levels of both BDEs and HBCD from 2000 to 2006.

In Zebra mussels from Lake Maggiore in Italy, Binelli et al. [82] reported Σ14BDE concentrations from 40 to 447 μg kg^{-1} lipid weight, similar to those found in environments polluted by deposition or atmospheric transport. The congener profile showed BDE47 > BDE99 > BDE100 > BDE209, closely resembling patterns observed in freshwater ecosystems worldwide.

In shore crabs sampled from a contaminated Norwegian fjord, Haukås et al. [33] determined HBCD concentrations along a transect away from a known point source. Mean ΣHBCD concentrations at the four locations declined from 300 ± 220 to 26 ± 6.8 μg kg^{-1} lipid weight. In lugworms and mussels, concentrations declined from 7,000 ± 2,000 μg kg^{-1} lipid weight to not detected and 1,400 ± 110 μg kg^{-1} lipid weight to not detected, respectively.

In three species of deepwater fish (caught at >1,000 m depth in 2006) off the west coast of Scotland, Russell et al. [83] reported Σ17BDE concentrations from 12 to 51 μg kg^{-1} lipid weight. In wild and rope-grown mussels from Scottish coastal waters taken since 1999, Σ9BDE concentrations were not detected to 3.7 μg kg^{-1} wet weight, with the highest concentration in Aberdeen in summer 2008 [84]. Σ17BDE concentrations in flatfish muscle from 11 locations around Scotland were up to 1.7 μg kg^{-1} wet weight, while in muscle of brown trout from freshwater lochs the maximum concentration was 1.2 μg kg^{-1} wet weight [85]. In the same study, Σ17BDE concentrations of 4.1–536 μg kg^{-1} wet weight were recorded in the livers of fish from the former sewage sludge disposal site at Garroch Head in the Firth of Clyde.

Harrad et al. [86] determined HBCD and TBBP-A in fish collected in 2008 from nine English lakes. Concentrations ranged from 14 to 290 μg kg^{-1} lipid weight and <0.3–1.7 μg kg^{-1} lipid weight, respectively.

In three fish species from the southern Baltic Sea, Szlinder-Richert et al. [87] recorded mean Σ7BDE concentrations of 1.2 (herring), 1.6 (sprat) and 2.5 (salmon) μg kg^{-1} wet weight. BDE47 predominated in all samples, and BDE concentrations in herring were similar to those observed in herring from the northern Baltic Sea but lower than in those from the Belgian North Sea. In salmon, BDE concentrations were similar to those in samples from the northern and northeastern Baltic Sea but similar to those found in fish from the central part.

Samples of marine and freshwater mussels from different locations showed a similar pattern of BDEs congeners, with predominance of the lower brominated ones (BDE47 and BDE99) [88]. In a study on common frogs from Scandinavia, more than 90% of the liver samples revealed the presence of BDE47, and less than 50% that of BDE99 [89].

In four species of Antarctic fish, Borghesi et al. [90] reported ΣBDE concentrations from 0.09 to 0.44 μg kg^{-1} wet weight. In tuna from the Mediterranean Sea, concentrations were 15 μg kg^{-1} wet weight, 100–1,000× higher. Lower brominated congeners prevailed in Antarctic species while, in tuna, tetra- and penta-BDE congeners dominated, consistent with the major source to the Antarctic being long-range atmospheric transport. In swordfish from the Mediterranean, Corsolini et al. [91] reported Σ19BDE concentrations of 2.2 ± 3.3 μg kg^{-1} wet weight in liver and 0.6 ± 0.6 μg kg^{-1} wet weight in muscle tissue.

In two fish species, two crab species and three bivalve species from Tokyo Bay, Japan, Σ20BDE concentrations were 97 and 192, 92 and 97, and 17–66 μg kg^{-1} lipid weight, [92]. Hong et al. [93] determined BDEs in mussels from two locations in France and South Korea. Mean Σ13BDE concentrations were 13 μg kg^{-1} dry weight in Masan Bay, South Korea, and 0.9 μg kg^{-1} dry weight in Thau lagoon, France. The authors suggested that these data indicated a growing pollution problem in Asia, and in South Korea in particular.

Twelve species of deep-sea fishes collected in 2005 off the coast of Japan were analysed for BDEs and HBCD [94]. The fish were caught at depths from 410 to 900 m, and so remote from land-based sources. The concern of the authors was that the deep-sea might act as an ultimate sink for such compounds. Σ14BDE concentrations ranged from 1.3 to 53 μg kg^{-1} lipid weight, and HBCD from <0.05 to 110 μg kg^{-1} lipid weight. A significant positive correlation was found between $\delta^{15}N$ and lipid-normalized concentrations of BDEs showing their high biomagnification potential for food web uptake, though this was not the case for HBCD.

Bivalves (mussels and oysters) in coastal waters from Japan (22 locations) were sampled and analysed for BDEs and HBCD [95]. HBCD and Σ14BDE concentrations ranged from 12 to 5,200 μg kg^{-1} lipid weight and 3.1–86 μg kg^{-1} lipid weight, respectively. The authors noted that HBCD concentrations were among the highest levels reported from Asia and Europe. Estimated uptake levels for human consumers from oysters and mussels as seafood for HBCD and

Σ14BDEs were 0.45–34 ngkg^{-1} body weight and 0.58–6.8 ngkg^{-1} body weight, respectively.

To determine the potential input sources of PBDEs to fish farms in south China, Zhang et al. [96] sampled seven environmental matrices in 2006–2007. Tri- to deca-BDE congeners were detected in all samples, at mean Σ46BDE concentrations (including BDE209) of 5.7 ± 3.6 ngl^{-1} in pond water, 15 ± 11 μg kg^{-1} dry weight in pond sediments, 12 ± 3.8 μg kg^{-1} dry weight in bank soil, 21 ± 20 μg kg^{-1} lipid weight in fish and 93 ± 62 μg kg^{-1} lipid weight in fish feed. BDE209 was the dominant congener in all samples other than fish, where BDE47 predominated. As in other studies, fish feed (in this case, along with pond water) was the dominant source of BDEs in farmed fish.

Fish and invertebrates collected from the Pearl River Delta (PRD) region in China during 2005–2007 were analysed for BDEs [97]. Σ7BDE concentrations ranged from 6.2 to 208 μg kg^{-1} lipid weight, a decrease relative to those seen in 2004. In two species of fish and in winkles from the vicinity of a local source from e-waste recycling, Zhang et al. [96] reported ΣHBCD concentrations of 377 and 1,790, and 186 μg kg^{-1} lipid weight, respectively. Gao et al. [57] determined BDEs in 16 species of aquatic biota, including fish, crab and shrimp, from the lower Yangtze River in East China sampled in 2004–2007. Σ12BDE concentrations were 3.5–604 μg kg^{-1} lipid weight (mean 44 μg kg^{-1} lipid weight), low to average on a global scale.

Jin et al. [98] determined BDEs in five species of shellfish sampled in 2006 from Laizhou Bay, China. Σ11BDE concentrations (including BDE209) in the shellfish ranged from 230 to 720 μg kg^{-1} lipid weight.

Σ23BDE concentrations were determined in seafood from China as part of a market study [99]. In fatty fish, concentrations ranged from 0.04 to 0.91 μg kg^{-1} wet weight, and in shellfish, from 0.02 to 0.35 μg kg^{-1} wet weight. Van Leeuwen et al. [100] determined BDEs and HBCD in farmed fish and shrimp from Southeast Asia, Europe and South America. Concentrations were generally very low. Carnivorous species contained high concentrations than omnivorous species. In another diet study, Miyake et al. [101] determined BDEs in seafood samples from two cities in China, Guangzhou and Zhoushan. Guangzhou is one of the largest cities in China and has experienced rapid economic growth since 1979. Zhoushan is a coastal city and port less influenced by industry and not opened for economic development until 1988. Mean Σ10BDE concentrations in the two cities were: fish, 46 and 6.7 μg kg^{-1} lipid weight; crab, 11 and 3.0 μg kg^{-1} lipid weight; cephalopods, 9.2 and 8.3 μg kg^{-1} lipid weight; shrimp, 28 and 7.4 μg kg^{-1} lipid weight; bivalves, 14 and 11 μg kg^{-1} lipid weight; respectively.

Li et al. [102] determined BDEs in ten species of fish and shellfish from Yuandang Lagoon, Xiamen Island, China. Σ8BDE concentrations ranged from 0.3 to 1.3 μg kg^{-1} lipid weight and were higher in crabs and clams than in fish, probably because benthic organisms are in closer contact with contaminated sediments. BDE congener patterns also differed: fish contained mainly lower brominated BDEs with BDE209 not detected, while higher brominated BDE congeners (including BDE209) were observed in crabs and clams.

Shaw et al. [103] determined BDEs in seven species of teleost fish comprising the major prey items of harbour seals in the NW Atlantic. Σ16BDE concentrations in whole fish samples (as eaten by seals) ranged from 18 to 94 μg kg^{-1} lipid weight (62 ± 34 μg kg^{-1} lipid weight); total HBCD concentrations from 2.4 to 38 μg kg^{-1} lipid weight (17 ± 10 μg kg^{-1} lipid weight). Σ16BDE concentrations were ca. 100-fold higher than the levels in fish.

In muscle tissue of wild Chinook salmon from Chile, Montory et al. [104] reported Σ14BDE concentrations between 0.3 and 1.05 μg kg^{-1} wet weight, similar to levels reported for the northern hemisphere. Sloan et al. [105] reported Σ10BDE concentrations in juvenile Chinook salmon from the Columbia River and Estuary and Puget Sound, NW USA. The mean Σ10BDE concentrations in fish from the various urban and nonurban sites sampled ranged from 0.35 to 2.8 μg kg^{-1} lipid weight. Levels of PBDEs in hatchery fish were significantly lower than those in the wild fish.

Concentrations of TBBP-A and HBCD were determined in sharks (bull shark and Atlantic sharpnose shark) from US waters by Johnson-Restrepo et al. [106]. The highest concentrations of TBBP-A and HBCD were found in bull shark, 36 and 413 μg kg^{-1} lipid weight, respectively.

In lake trout from Lake Ontario, Canada, sampled between 1979 and 2004, Σ6BDE concentrations (BDE28–BDE154) increased significantly from 1979 until the mid-1990s, then levelled off or decreased to 2004 [107]. In contrast, concentrations of BDE209 increased by a factor of 4 between 1998 and 2004. Concentrations of total HBCD showed some decline and pentabromoethyl benzene (PBEB) showed no consistent trend over the period studied; 1,2-*bis*(2,4,6,tribromophenoxy)ethane (BTBPE) showed a rising trend until ca. 1993 and then concentrations decreased to 2004.

Blocksom et al. [108] determined BDEs in whole fish from three major US rivers (upper Mississippi, Missouri and Ohio) in 2004–2005 with the aim of estimating human and wildlife exposure risks from fish consumption. Σ6BDE concentrations were highest in fish in the Missouri and Ohio rivers (>1,000 μg kg^{-1} lipid weight) with BDE47 dominating. Concentrations were positively correlated to fish size, lipid content, trophic guild and proximity to urban areas.

The Hawaiian Islands are located in the middle of the Pacific Ocean and are geographically isolated. PBDEs have been determined in the muscle tissue of wild tilapia from the vicinity of Honolulu and Waikiki [109]. Σ8BDE concentrations at three sampling sites were 567 ± 54, 232 ± 18 and 686 ± 79 μg kg^{-1} lipid weight. Although few industries have been developed in the islands, these PBDE concentrations are still relatively high. BDE183 and BDE209 were not detected in these samples.

Losada et al. [110] determined BDEs in six species of marine fish, one species of crab and squid from Sydney Harbour, Australia. Mean Σ10BDE concentrations ranged from 6.4 μg kg^{-1} lipid weight in squid to 115 μg kg^{-1} lipid weight in flounder. Blue swimmer crab and squid had lower concentrations than the fish species. BDE47 was the dominant congener; BDE183 was not detected and BDE209 was not determined.

Elevated levels of BDEs in farmed compared to those observed in wild salmon have previously been ascribed to the levels in their feed, usually derived from fish meal and oil [111]. Berntssen et al. [112] have assessed the impact of replacing these with novel alternative feeds based on ingredients of plant origin with a minor inclusion of krill. In their study, the use of the alternative feed reduced Σ10BDE levels by approximately two-thirds. In an earlier study, in Atlantic salmon fed on fish oil, rapeseed oil or a 1:1 mixture of the two oils, mean Σ7BDE concentrations were 2.2, 1.1 and 1.7 μg kg^{-1} wet weight, respectively, indicating a lower level of contamination in the oil of vegetable origin.

Maternal transfer was also observed for all BFRs detected in female zebra fish and for the metabolites. The egg/fish concentration ratios were significantly above 1 for several compounds. Generally, high egg/fish ratios were observed for BFRs with high log K_{ow} values. These compounds seemed to be more efficiently transferred to eggs [113].

2.3 Marine Mammals

The detection of BDE congeners in sperm whale tissues, feeding offshore and in deep water, and the particularly high concentrations found in dolphins and seals highlighted the ubiquity and bioavailability of these chemicals in the marine ecosystem [114]. A wide range of marine mammals has been investigated since with a similar BDE congener pattern [114–124] (Fig. 4). A large number of harbour porpoises from England and Wales were analysed for 14 tri- to hepta-BDEs, and the major congeners detected were BDE47, BDE99 and BDE100. Porpoise foetuses were also analysed and BDEs were also detected, demonstrating transplacental transfer from mother to offspring [125]. Three BDE congeners were analysed in 11 stranded harbour seals from San Francisco Bay between 1989 and 1998, showing that the contribution of BDE47 to the sum of the congener concentrations ranged between 62% and 94% [126]. Long-finned pilot whales from the Faroe Island showed higher BDE concentrations in juvenile animals, which were ascribed to lactational transfer [127]. A study out of BDEs in blubber samples from Baikal seals detected a gender difference for the concentrations of BDEs and HBCD. The transfer of these contaminants from mother to pup during gestation and lactation was suggested as the cause of this difference [128].

Liver samples from ten species of cetaceans stranded 1994–2006 in Southeast Brazil were analysed for BDEs [130]. Σ9BDE concentrations were 3–5,960 μg kg^{-1} lipid weight, similar to those observed in Northern Hemisphere dolphins. A positive correlation was observed between Σ9BDE concentrations and year of stranding, indicating rising concentrations.

Von der Recke and Vetter [131] studied PBBs in blubber of seals and harbour porpoises (as well as in fish) originating from the North Sea, the Baltic Sea, and the coastal waters of Iceland and North America. Hexa-BB congeners dominated, followed by penta-BBs and hepta-BBs, while octa-BBs were detected only

Species	Location	BDE	Reference
Grey seal	Baltic Sea	730 419	[115] [116]
Ringed seal	Svalbard Canadian Arctic	51 26–50*	[115] [117]
Harbour seal	North Sea San Francisco Bay	600–6,000 67–7,140	[114] [126]
Caspian seal	Azerbayan	BDE47: 15 (ww)	[125]
Bottlenose dolphin	Gulf of Mexico	8,000	[118]
Striped dolphin	Mediterranean Sea	726–8,130	[120]
Indo-Pacific humpback dolphin	India	10–12*	[128]
Spinner dolphin	Philippines	2,600–5,400*	[129]
Harbour porpoise	Br. Columbia England & Wales Pacific	350–2,300* 440–7,670* 860–3,160*	[140] [121] [129]
Beluga	Canadian Arctic	81–160*	[117]
Long-finned pilot whale	Faroe Islands	843–3,160*	[127]
Minke whale	Netherlands	870	[114]
Melon headed whale	Queensland Japan	36 (ww) 190–510	[125] [133]
Killer whale	UK Shiretoko	490–2,000, max. 16,200* (ww) 170–540*	[123] [122]

Fig. 4 Overview of concentrations of PBDEs in marine mammals and sample location around the world. Concentrations given in ng g^{-1} lipid weight unless otherwise stated. ΣBDE = sum of BDEs 47, 99 and 100. * More congeners included

occasionally and nona-BBs and BB209 not at all. The hexa-BB pattern in samples from Iceland was a mixture of those seen in samples from North America and continental Europe. BB153 dominated, and BB155 and BB154 were also prominent. The patterns of some congeners indicated degradation of more highly

brominated products. Concentrations of individual BB congeners or of the sum of those congeners determined were not reported.

Tanabe [132] summarized a number of studies using archived marine mammal tissue samples from a specimen bank. In recent years, HBCD concentrations seemed to exceed those of ΣBDEs in samples from Japan, presumably reflecting a change in usage following controls. ΣBDE levels peaked in the 1990s (as for sediments above) and then stabilized. In finless porpoises from the South China Sea, ΣBDE levels were much higher than those of HBCD both in past and recent years, implying a lower consumption of HBCD than of PBDEs in China.

Kajiwara et al. [133] determined BDEs in blubber of melon-headed whales from Japan sampled in 1982–2006. In 2006, Σ10BDE concentrations were 190–510 μg kg^{-1} lipid weight, as against 7.5–30 μg kg^{-1} lipid weight in 1982. Maternal transfer was estimated to be 85% of the mother's body burden. In striped dolphins (1978–2003), Isobe et al. [134] determined BDEs and HBCD in blubber of striped dolphins from Japan 1978–2003. Σ11BDE concentrations ranged from 13 to 850 μg kg^{-1} lipid weight, and HBCD concentrations from 10 to 940 μg kg^{-1} lipid weight. In both instances, the highest concentrations were seen in 2003, suggesting growing consumption in recent years.

In muscle-blubber biopsy samples from 21 Galapagos sea lions collected from the Galapagos Islands (1,000 km off the coast of Ecuador) in 2005, Alava et al. [135] determined BDEs. Only traces of BDEs were detected in one male pup.

Schiavone et al. [136] studied BDEs in Antarctic fur seals collected on the Antarctic Peninsula in 2004. The mean Σ9BDE concentration was 11 μg kg^{-1} lipid weight – in fact, only BDE47 and BDE66 were above the limit of detection.

Peck et al. [137] determined HBCD in blubber and liver of Atlantic white-sided dolphins that stranded on the east coast of the USA during 1993–2004. α-HBCD concentrations in blubber and liver ranged from 19 to 380 μg kg^{-1} lipid weight and 2.9 to 140 μg kg^{-1} lipid weight, respectively. These were lower than HBCD concentrations in cetaceans from Western Europe, and than concentrations of BDEs reported earlier in a subset of the same animals. Concentrations of TBBP-A and HBCD were determined in blubber of bottlenose dolphins from US waters by Johnson-Restrepo et al. [100]. The mean concentrations of TBBP-A and HBCD were 86 and 413 μg kg^{-1} lipid weight, respectively. In the Hawaiian Islands, Ylitalo et al. [138] determined BDEs in false killer whales from Hawaii. Σ10BDE concentrations ranged from not detected to 2,900 μg kg^{-1} wet weight, with adult females having lower concentrations than adult males and juveniles. Meng et al. [139] studied BDEs in Cliformia sea lion, harbour seal and Northern elephant seal from California. Σ14BDE concentrations were 0.06–236, 0.32–7.2 and 0.04–2.0 μg kg^{-1} lipid weight, respectively. Ikonomou and Addison [140] measured BDE concentrations in the blubber of five mother–pup pairs of grey seals from Nova Scotia sampled in 1995, and of 20 harbour seals from British Columbia sampled in 1991–1992. Σ10BDE concentrations in maternal grey seals averaged 112 ± 55 μg kg^{-1} lipid weight and were over twice the concentrations measured in their pups. Lower brominated congeners transferred more efficiently than hepta-BDEs and larger congeners. Σ10BDE concentrations in harbour seals

from the Strait of Georgia were 319 ± 132 μg kg^{-1} lipid weight, while those in harbour seals from the more remote Quatsino Sound were 28 ± 12 μg kg^{-1} lipid weight. In a study in central west Greenland, Vorkamp et al. [141] determined BDEs in archived samples of ringed seal blubber over the period 1982–2006. Median Σ11BDE concentrations ranged from 2.2 to 8.5 μg kg^{-1} lipid weight. Levels were lower than those observed previously in seals from east Greenland in a similar time trend study [142].

Lam et al. [143] looked at concentrations of HBCD and BDEs in Indo-Pacific humpback dolphins and finless porpoises from Hong Kong, during 2002–2007 and 2003–2008, respectively. The concentrations of ΣHBCD and Σ14BDE were 4.1–519 and 103–51,100 μg kg^{-1} lipid weight, respectively. A significant increasing trend in HBCD concentrations was seen in dolphins from 1997 to 2007, with an estimated annual rate of increase of 9%. No trend was observed for BDEs. This may reflect increasing use of HBCD in response to controls on the PBDE products. Three "novel" BFRs compounds were studied: hexachlorocyclopentadienyldibromocyclooctane (HCDBCO) was not detected; while 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (TBB) and *bis*(2-ethylhexyl)-tetrabromophthalate (TBPH) were detected at maximum concentrations of 70 and 3,860 μg kg^{-1} lipid weight, respectively. Levels of HBCD and TBPH were comparable in porpoise samples.

In ringed seals from East Greenland, Letcher et al. [144] determined BDEs, BBs and HBCD and their metabolites. Mean Σ13BDE concentrations were 149 ± 87 μg kg^{-1} lipid weight, and the mean concentration of BB101 was 0.25 ± 0.12 μg kg^{-1} lipid weight. The mean α-HBCD concentration was 19 ± 2 μg kg^{-1} lipid weight.

Houde et al. [145] determined BDEs and their hydroxylated analogues in plasma of bottlenose dolphins from the east coast of the USA. Significantly lower Σ12BDE concentrations were found in animals from Florida than in those from South Carolina (5.5 ± 4.6 μg kg^{-1} wet weight and 30 ± 40 μg kg^{-1} wet weight, respectively). Similarly, Σ16OH-BDE were 1.15 ± 0.7 and 0.6 ± 0.4 μg kg^{-1} wet weight in South Carolina and Florida, respectively. A significant proportion might be a consequence of naturally produced MeO- and OH-BDEs. In Europe, Weijs et al. [146] determined BDEs and OH-BDEs in serum of captive harbour seals and harbour porpoises from 2006 to 2008. Median Σ6BDE concentrations were 130 $pgml^{-1}$ in seals and 1,300 $pgml^{-1}$ in porpoises. OH-BDEs were not detected in either species.

Fair et al. [147] reported concentrations of BDEs in bottlenose dolphins sampled in 2003–2005 from two estuarine areas in the southeastern USA, Charleston in South Carolina and the Indian River Lagoon in Florida. Σ13BDE concentrations ranged from 295 to 22,800 and 196 to 3,790 μg kg^{-1} lipid weight, respectively. Concentrations in bottlenose dolphins from Charleston were among the highest recorded in marine mammals in the world to date.

Montie et al. [148] studied BDEs and OH-BDEs in cerebrospinal fluid and cerebellum grey matter of short-beaked common dolphins and Atlantic white-sided dolphins from the east coast of the USA. In cerebrospinal fluid, Σ33BDE concentrations were 0.3 and 0.9 μg kg^{-1} wet weight in female common dolphins,

0.7 and 1.6 μg kg^{-1} wet weight in male white-sided dolphins and 13 ± 16 μg kg^{-1} wet weight in female white-sided dolphins. Concentrations of HO-BDEs were very low, maximum 0.3 μg kg^{-1} wet weight. In grey matter of white-sided dolphins, concentrations of Σ14OH-BDEs were 4.2–8.9 μg kg^{-1} wet weight.

2.4 Turtles

Few data are available for turtles, but Swarthout et al. [149] reported Σ27BDE concentrations in blood samples from two species of turtles (Kemp's ridley and green sea turtles) sampled in the Gulf of Mexico in 2001–2002. BDEs were detected in all 58 turtles analysed, and BDE47, BDE99, BDE100, BDE153 and BDE154 were the dominant congeners (deriving from the penta-mix PBDE product). Summed concentrations ranged from 0.0002 to 0.0015 μg kg^{-1} wet weight.

2.5 Terrestrial Animals

Verreault et al. [150] determined BDEs in adipose tissue from captive sledge dogs in Greenland. Σ36BDE concentrations were 42 ± 0.7 μg kg^{-1} wet weight in an exposed group (fed on minke whale blubber) compared to 2.1 ± 0.4 μg kg^{-1} wet weight in a control group fed on pork fat.

Concentrations of higher brominated BDE congeners in terrestrial animals have been found to be relatively high, which indicates their bioaccumulation capacity in these animals. Higher brominated BDE congeners were also bioaccumulated in the meat and body fat of cows [151]. BDE 209 was found to be the most abundant congener in studies on the terrestrial top predators red fox and grizzly bears. Grizzly bears consuming salmon had a congener profile dominated by the lower brominated BDEs [17, 18].

These variations in the pattern of the BDEs congeners depending on the ecosystem emphasize the importance of the bioavailability of the BFRs and their potential degradation.

3 Bioaccumulation and Bioavailability

Bioavailability and bioaccumulation are intrinsically connected with each other and directly related to the interaction of chemical substances with the abiotic and biotic environment. The bioavailability of chemical contaminants in the environment depends on several factors including structure and physicochemical properties of a compound, its main sources of production, its ability to be transported to different environments and the nature of the medium in which these chemicals are found.

There are different emission routes through which a contaminant can reach the environment. This may be during production, product formulation, application, its lifetime usage and its disposal after the end of their in-service life. Once released into the environment, they can be adsorbed to particulate matter depending on their water solubility and binding affinity to particles. Consequently, they may be transported through the aquatic environment or travel far from the emission source while attached to dust particles with a high spatial mobility.

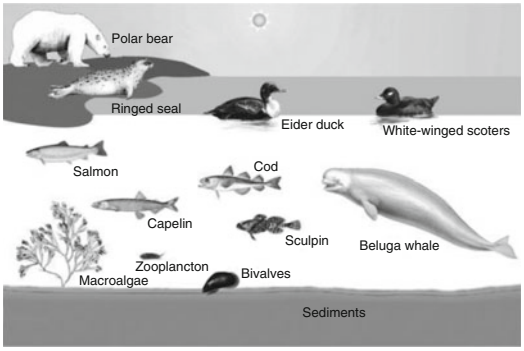
The bioconcentration factor (BCF) is defined as the accumulation of a compound through the respiratory system or dermal contact after exposure to the medium, measured in laboratory tests. It results in a higher concentration of the substance within an organism than in its surrounding environmental medium, such as water or air. This factor is correlated to the water solubility of a chemical and its vaporization rate, referring to the maximum solute concentration possible at equilibrium, and the octanol–water partition coefficient (K_{ow}), referring to the ratio of the concentration of a chemical in *n*-octanol and in water at equilibrium at a specific temperature and pressure [152]. The quantification of process rates and partition coefficients of organic pollutants in air, water, soil and biota is an important step in defining the level of organic contaminants in environmental systems and their potential impact on environmental quality.

A specific way of determining the bioconcentration of a substance is by calculating the biota-soil accumulation factor (BSAF), which relates the concentration of the chemical in the organism on a lipid weight basis to its concentration in the surrounding soil on an organic carbon basis.

The bioaccumulation factor (BAF) is defined as the ratio between the concentration of a compound in an organism and the concentration in the surrounding environment at steady state after exposure from any source. The level to which a substance is bioaccumulated depends on the rate and mode of uptake, through inhalation (respiratory system: lungs or gills) or ingestion along with food, through contact with the epidermis (skin), and the elimination rate. It is also important to consider the possible transformation of the substance by metabolic processes, the lipid content of the organism and other environmental factors. BCF and BAF are often determined as the ratio between the concentration of a compound (on a lipid weight basis) in an organism and its concentration in the surrounding water.

As a general rule, the more hydrophobic (lipophilic) a substance, the higher the expected BAF will be in organisms. Lipophilic substances are less likely to be diluted or excreted in urine, and so can accumulate in fatty tissues. However, it has been shown that an increasing degree of halogenation with a related increase in the molecular size and K_{ow} lowers the absorption efficiency of a halogenated compound in fish [153]. It has been argued that this reduced dietary absorption of large super hydrophobic substances (such as BDE209) was due to the physically restricting size of the molecule which hinders its passage through the membrane via the gills or the gut [154].

As a consequence of the persistence and bioaccumulation potential of chemicals, and due to the interaction between the different trophic levels in a selected ecosystem, a chemical may biomagnify in a food web. When a chemical is bioaccumulated



ORGANISM	δ15N (‰)	TROPHIC LEVEL
Macroalgae *(Fucus gardneri)**	6.1 ± 0.2	1.0
Zooplancton *(Calanus hyperboreus)***	7.9 ± 0.1	2.0
Bivalves *(Mytilus eduils)***	9.1 ± 0.7	2.3
Salmon *(Salmo salar)**	11.9 ± 1.2	3.1
Capelin *(Mallotus villosus)**	12.8 ± 0.13	3.3
Arctic cod *(Boreogadus saida)**	13.5 ± 0.5	3.5
Sculpin *(Myoxocephalus scorpioides)**	14.1 ± 0.9	3.6
Eider duck *(Somateria mollissima)**	12.1 ± 0.5	3.5
White-winged scoters *(Melanitta fusca)**	13.8 ± 0.8	3.9
Beluga whale *(Delphinapterus leucas)**	15.3 ± 0.7	4.0
Ringed seal *(Pusa hispida)***	17.5 ± 0.2	4.5
Polar bear *(Ursus maritimus)***	21.1 ± 0.3	5.5

* Data obtained from Kelly et al.(2008) [156]
** Data obtained from Hobson et al.(2002) [155]

Fig. 5 Representation of trophic levels of a Canadian Arctic marine food web by stable isotope characterisation (mean + SD)

in an organism from a low trophic level, such as an invertebrate species, it may result in a buildup in the adipose tissue of successive trophic levels such as fish, birds or marine mammals. When eaten by another organism, fats carrying the contaminant are absorbed in the gut, and the chemical will accumulate in the fat of the predator.

To improve the food web characterization, a stable nitrogen isotope analysis technique has been developed, assessing predator–prey interactions and organism trophic levels by determining the $\delta_{15}N$, the concentration ratio of $_{15}N/_{14}N$, expressed relative to a standard (i.e. atmospheric N_2). This ratio increases with increasing trophic levels due to the preferential excretion of the lighter $_{14}N$ isotope [155, 156] (Fig. 5).

There are several ways to calculate the biomagnification of a chemical. One of them is by determining the biomagnification factor (BMF), which accounts for the ratio of lipid-normalized contaminant concentrations in predator and prey. Biomagnification occurs when BMFs are greater than 1, indicating that predators are less capable of metabolizing these compounds compared with their prey.

The trophic magnification factor (TMF) is the average biomagnification at several trophic levels, and it can be derived from the slope of the line in a plot of concentrations in an organism vs the trophic level.

$$\text{BAF, BCF} = \frac{C_{\text{organism}}}{C_{\text{water/air}}} \quad \text{BSAF} = \frac{C_{\text{organism}}}{C_{\text{soil}}} \quad \text{BMF} = \frac{C_{\text{predator}}}{C_{\text{prey}}}$$

3.1 Bioaccumulation Studies

Some BFR levels in wildlife and humans have substantially increased since the 1980 [157]. The evidence of bioaccumulation in wildlife and its potential trophic magnification ability has been investigated since, with interesting conclusions

regarding to the principal congeners bioavailability and its behaviour once they interact with the environment [158, 159].

The different concentrations of the BFRs detected along the food webs from separate locations are usually related to several factors such as the proximity to a production source and the potential degradation of BFRs in different matrices. Concentrations of PBDEs detected in temperate environment marine mammals were about 1,000 times higher than the ones found in Arctic environment, which evidences the decrease in concentration as a function of the distance from release sources and also their ubiquity in apparently less-exposed areas due to their transportation ability [159].

When focusing on a particular ecosystem, difficulties arise establishing the food chain interactions regarding to the predatory–prey preferences and the species-specific differences in the ability to metabolize and biotransform BFR compounds. These differences may change the congener profile in the organism showing congeners that are not detected in the environmental media and leading to a trophic enrichment of less brominated congeners [160, 161]. The dietary absorption efficiency also influences the biomagnification of BFRs along food webs which could lead to an underestimation of their BMF at higher trophic levels.

The bioaccumulation potential of BFRs has been investigated in several aquatic food webs. Gustafsson et al. [162] estimated BAFs in laboratory studies from water to Baltic blue mussels (*Mytilus edulis*), showing that BDE47 and BDE99 are very accumulative in this species with values of 1.3 and 1.4×10^6 followed by BDE153 (0.22×10^6). In a field study in the Netherlands, BCFs of PBDEs in blue mussels collected from several sites along the coast and in the Scheldt estuary were determined. It was concluded that BDE47, BDE28, BDE99, BDE100 and BDE153 bioaccumulate to a significant extent [163]. A study along the river Viskan (Sweden) detected high fish (pike) to sediment ratios for BDE47, BDE99, BDE100 and HBCD, indicating the bioavailability of these compounds. The low concentrations of octa- and nona-BDE congeners suggested limited bioavailability for these congeners [164].

In a study on Baltic and North Atlantic Sea food webs, several BDEs were analysed in zooplankton (copepods), planktivorous fish (sprat, small and large herring) and predatory fish (salmon) [165]. BDE47 appeared to biomagnify to the largest extent, showing higher assimilation efficiencies compared to BDE99 and BDE153, which was in agreement with previous studies of uptake in fish [166, 167]. The BMFs for all BDEs studied were positive, meaning that all congeners have the ability to biomagnify in this food web. However, the BMFs of the tetra- and penta-BDEs were higher than those of the tri-BDEs and hexa-BDEs reported in a previous study [168].

A trophic characterisation of PBDEs in a North Sea food web was carried out by Boon et al. [158]. Invertebrate sentinel species were investigated together with predatory gadoid fish species and marine mammals representing the higher trophic levels of this food web. All six major BDE congeners present in the penta-BDE formulation were detected, whereas no evidence of the octa-BDE formulation was found, as its major congener, BDE183, was not detected. Since BDE209 was the main BDE congener usually found in sediments from

the area, the main reason for its low concentrations in biota was concluded to be either due to a low uptake rate for this very large molecule (log K_{ow} 9–10), and so would be predominantly particle bound, or to a rapid excretion after biotransformation. The major biomagnification step in this study was found to occur from fish to marine mammals. Another study carried out in a North Sea estuary food web showed evidence of the bioaccumulation of α-HBCD [9]. It was argued that the higher water solubility of the α-isomer compared to the other two isomers could be the cause of the preferential uptake of α-HBCD in aquatic organisms, or that a rapid elimination from the organism of the β- and γ-isomer was occurring. TBBP-A was detected in lower concentrations than HBCD and appeared to have a lower bioaccumulation potential. Due to its more polar nature, TBBP-A may more easily be metabolized and eliminated from the aquatic organisms. This was confirmed by the low accumulation potential observed for the TBBP-A in a study involving uptake efficiency in zebrafish [169]. The bioaccumulation of HBCD in rainbow trout showed high levels after dietary uptake, with different values depending on the diastereomer determined. The highest BMF was found for α-HBCD (BMF = 9.2) followed by the γ- and β-diastereomer (BMF = 4.3) [170]. In aquatic invertebrates, marine fish, birds and marine mammals, the presence of the HBCD is mainly as its α-diastereomer, and the concentration of this isomer was found to increase with increasing trophic level [171]. Uptakes and elimination rates in zebrafish were recently determined for BDE28, BDE183 and BDE209, and the highest uptake was observed for BDE28, whereas the lowest was observed for BDE209 [172]. Bioaccumulation and trophic magnification were determined for several PBDEs in a Canadian Arctic marine food web [156]. The results showed that only BDE47 had a TMF above 1. The food web was characterized using stable nitrogen isotope analysis, involving zooplankton, invertebrate species and different fish, eider ducks and marine mammal species. Another study carried out to determine the biomagnification of PBDEs in a Canadian Arctic marine food web showed a similar pattern of trophic magnification for BDE47 and a low TMF for BDE209, with decreasing values at higher trophic levels [173]. A similar study was carried out for a freshwater food web in South China where three PBDEs were investigated [174]. There, BDE47, BDE100 and BDE153 showed a TMF significantly above 1.

The biomagnification potential of PBDEs was studied in a polar bear food chain from the Norwegian Arctic. The BDE47 BMFs for polar bear (assuming ringed seal as the prey species) were relatively low, between 1 and 7 [159, 160]. However, mean BMFs for BDE153 in polar bears (bear/ringed seal) from the Canadian Arctic and Alaska ranged between 91 and 130 [159], even though it has been reported that polar bears have a large capacity to metabolize organohalogenated compounds [175]. BDE153 is apparently one of the most stable BDEs. Relatively high BMFs for BDE47, BDE99 and BDE100 (between 20 and 60) were reported for beluga whales from Svalbard in the Arctic Ocean [160]. In the northwest Atlantic, no biomagnification was detected for several tetra-BDE congeners (BDE49, BDE66 and BDE75) in a study involving harbour seals. This suggests that this species may possess an efficient metabolism for these congeners [103].

In a Florida coastal marine food web, the highest BMFs for several BDE congeners were measured from forage fish to bottlenose dolphins and bull sharks [106]. Even though BDE209 has shown a lack of biomagnification in studies concerning marine mammals, a biomagnification of this congener in bull sharks was observed, which was explained by their habitat and feeding habits.

The correct characterization of contaminants in different food webs makes their behaviour in the environment more understandable. Trophic magnification can lead to chronic exposure and toxicological effects in organisms, such as endocrine disruption. The potential risk to human exposure considering our omnivorous diet is of special concern. BFRs have already been detected in human tissues, including adipose tissue, blood serum and milk [176–178].

4 Biotransformation

Environmental factors, such as temperature and pH, may influence the mobility and bioavailability of contaminants. The compounds already existing in the environment could favour chemical reactions leading to different compounds, presenting different toxicological risks. Biological processes may cause an increase in bioaccumulation, allowing the entrance of these compounds into the food chain of a specific ecosystem. Biodegradation processes, often mediated by microorganisms, may facilitate the elimination of contaminants from the environment, but can also lead to the formation of more toxic and bioaccumulative compounds.

There are several reactions that can take place once the chemical is deposited in soil, sediments or water which can modify the bioavailability of these chemicals. Abiotic oxidation, reductive debromination, hydrolysis, elimination and substitution reactions may change the structure, its characteristics and properties, and alter its congener profile in the ecosystem. Once inside organisms, several biotransformation processes may occur. Highly brominated BDEs have been shown to be susceptible to substitution of one or more bromines by a methoxy group, while lower brominated BDE congeners were resistant to this reaction [179]. Biotransformation processes can increase BDE elimination rates or lead to the bioformation of lower brominated congeners via debromination of higher brominated ones [180, 181]. Reductive debromination of BDEs has been confirmed in several species of fish, occurring with both highly and lower brominated congeners as precursors. The presence of hydroxylated metabolites has been detected in pike following dietary exposure to ^{14}C-BDE47, although no lower brominated BDE congeners were produced [182].

4.1 Polybrominated Diphenyl Ethers

BDEs are subject to atmospheric transportation adsorbed to dust particles, and their deposition rates are influenced by their structures. It has been estimated that 90% of

BDE47 that enters the troposphere may be removed by photolysis before being deposited, and that the loss of BDE209 from the atmosphere and its enhancement in sediments samples around the world is highly influenced by wet and dry deposition processes [183]. BDEs are highly hydrophobic compounds with high octanol/water partition coefficient values which indicate their potential bioaccumulation ability. The log K_{ow} increases with the degree of bromination which makes BDE209 the most hydrophobic BDE congener. Log K_{ow} values are in the range of 5.9–6.2 for tetra-BDEs; 6.5–7.0 for penta-BDEs; 8.4–8.9 for octa-BDEs and 10 for deca-BDE [184]. While the log K_{ow} values increase with the number of bromine substituents, the water solubility and vapour pressures decrease. Therefore, the highly brominated congeners are less likely to be found either dissolved in water or in the vapour phase. BDE209 solubility is extremely low and its ubiquity in soil and sediments illustrates the high binding affinity to particles. However, their adsorption to particles in air and particulate matter in water allow these chemicals to undergo long-range atmospheric transport. The vapour pressures range from 0.160 Pa (BDE1) to 5.7×10^{-7} Pa (BDE190) at room temperature, and it has been demonstrated that congeners with bromine substitution in the *ortho*-positions to the ether bond have higher vapour pressures [185]. The higher vapour pressures of the lower brominated BDE congeners facilitate aerial transport. The halogenation pattern also influences the boiling points that range from 310 to 430°C [186] and melting points from 20 to 300°C [187].

The key reaction during the biodegradation of halogenated organic compounds is the halogen removal step, which is known to occur under several dehalogenation enzymatic mechanisms, either aerobically or anaerobically [4]. BDEs may undergo anaerobic reductive debromination by isolated bacteria and mixed cultures, in sediments and in sewage sludge [188–191]. Uptake and biotransformation of highly brominated BDE congeners have been demonstrated in fish, resulting in the formation of lower brominated BDE congeners that have the potential to be both more persistent and bioaccumulative than the parent compounds. Rainbow trout exposed to the commercial deca-BDE mixture via diet showed a range of hexa- to nona-BDEs in their congener profile, with increasing levels influenced by the length of exposure [192]. Several species of fish exposed to octa- and deca-BDE mixtures supplied via water and food showed the presence of lower brominated congeners after exposure [193]. In the same study, a comparative in vitro analysis of degradation of BDE209 by liver microsomes from rainbow trout and carp revealed a more efficient debromination in carp than in trout, which shows that absorption efficiency and metabolic capacity are dependent on the fish species.

There are several difficulties when assessing the possible debromination pathways of the different BDE congeners. The bioaccumulation of a specific congener may be the result of the biotransformation from higher brominated congeners and its resistance to further degradation. Preferential *meta* debromination processes and specific accumulation of certain BDE congeners in fish have also been observed (Fig. 6).

The substantial accumulation of BDE47 and, to a lesser extent, of BDE99 in aquatic biota is an evidence of their stability due to the lack of *meta* bromine atoms [194–196]. A comparison of BDE congener profiles between fish from the Antarctic

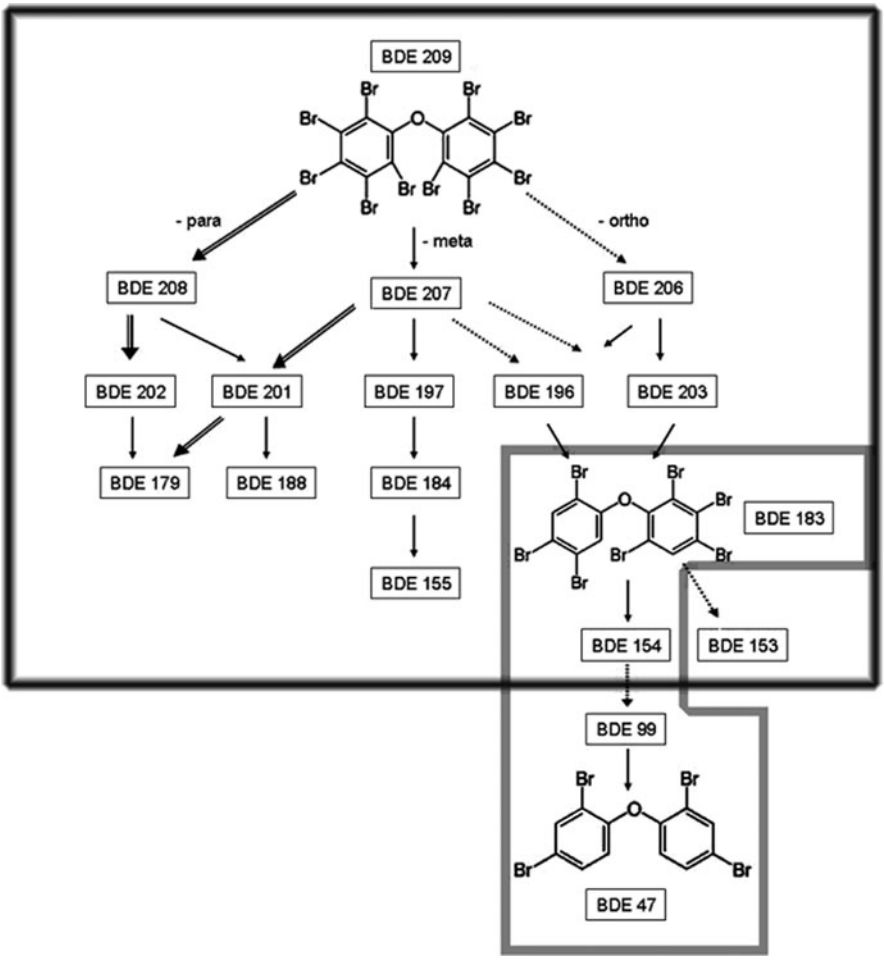


Fig. 6 Main congeners detected in fish after metabolic debromination of BDE209, BDE183 and BDE99. The different *arrows* represent the tentative debromination at the *ortho*-, *meta*- and *para*-positions [190–192]

and the Mediterranean Sea showed a difference in the ratio BDE47:BDE99 which was attributed to the lower ability of the icefish to metabolize the penta-BDE by debromination [197]. The accumulation of BDE99 was concluded to be at least partly dependent upon the differences in metabolic capacity between species [198]. However, the generally lower accumulation of BDE99 compared to BDE47 can be related either to a preferential excretion of BDE99 [196] or to a rapid absorption and conversion into hydroxy- and debrominated hydroxy metabolites [199]. Higher levels of BDE100 than BDE153 and BDE154 detected in tuna from the Mediterranean Sea may be attributed to hexa-BDE congener debromination processes [197]. BDE congeners with substituents in the *ortho*-position appear to be more recalcitrant in fish.

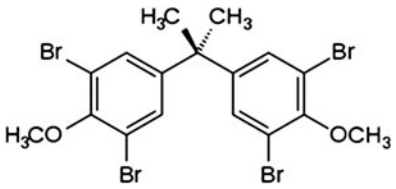


Fig. 7 Structure of TBBP-A *di-o*-methyl ether

The metabolic debromination of BDE209 was investigated in a study involving the European starling. This terrestrial bird species showed the ability to debrominate BDE209 to octa- and nona-BDE congeners, and to lesser extent hexa-BDEs [200]. The low levels of BDE209 in aquatic food webs compared with terrestrial animals may be attributable to a lower uptake, but the potential debromination of PBDEs in fish after dietary exposure, as observed in several studies, should also be considered when investigating their BAF.

4.2 Tetrabromobisphenol A

TBBP-A can undergo substitution reactions in the environment. Methylation of TBBP-A by microorganisms may cause the formation of a dimethylated derivative of TBBP-A in sediments (MeTA) [201]. MeTA has log K_{ow} of 6.4 [184] making it more lipophilic than the parent compound which has a log K_{ow} of 4.5 [202]. TBBP-A can also be microbially metabolized in a process involving reductive debromination under anaerobic conditions, resulting in bisphenol-A [203].

The possibility of *o*-methylating TBBP-A has been also tested under aerobic conditions, giving a highly lipophilic derivative with higher bioaccumulation potential (TBBP-A *di-O*-methyl ether [14]) (Fig. 7).

TBBP-A has been subjected to photolytical decomposition when exposed to UV light, resulting in different breakdown products such as di- and tri-bromobisphenol A and several bromophenols [11]. pH variations in the matrix change the solubility of TBBP-A in the environment, which may make its mobility in soil favourable and increase its potential for groundwater contamination [204].

4.3 Hexabromocyclododecane

The differences in structure of the individual HBCD diastereomers result in differences in polarity and, consequently, in water solubility. The variation of these properties will influence the bioavailability and the rates of biological uptake and metabolism of an organism [171]. Due to the low water solubility of the HBCD, hydrolysis could be assumed to be an insignificant degradation route. However, HBCD is susceptible of biodegradation in aerobic and anaerobic soil and aquatic sediments, resulting in the loss of two bromines from vicinal carbons with the

subsequent formation of a double bond between neighbouring carbon atoms [205, 206]. Experiments carried out for the evaluation of HBCD degradation under different conditions showed that there were differences in the degradation rates of the three diastereomers, and that the fastest degradation occurred under anaerobic conditions [207]. In sediment degradation tests, α-HBCD degraded more slowly than the other diastereomers [208].

The technical HBCD mixture has low water solubility (lower for the γ-diastereomer), and its log K_{ow} is 5.62 [209]. Juvenile rainbow trout were exposed to α-, β- and γ-HBCD for 56 days with a 112 days depuration period [210]. The analysis of muscle and liver samples did not show the presence of debrominated or hydroxylated metabolites. However, it was observed that the HBCD diastereomer pattern changed in biological samples. Muscle tissues of fish exposed solely to β-HBCD showed a shift to α- and γ-HBCD. Fish exposed to γ-HBCD showed the α-congener as the major diastereomer, and fish exposed to α-HBCD did not show any diastereomeric shift. A study of metabolization rates in microsomal liver preparations of common dab showed diastereomer and enantiomer-selective metabolism, with α-HBCD the least bio-transformed of the three main diastereomers [210]. Several hydroxylated metabolites of HBCD and pentabromocyclododecene (PBCDe) were identified in tern eggs and in the blubber of harbour seals [211]. In the same study, four different groups of hydroxylated metabolites were detected in rats after exposure to HBCD, and debromination to penta- and tetrabromocyclododecene was suggested as a metabolic pathway.

The blubber of female harbour porpoises and common dolphins stranded on western European coasts was investigated to determine the presence of HBCD. All samples analysed contained exclusively the α-diastereomer of HBCD. It was also seen that microsomal preparations of liver samples of harbour porpoises studied in vitro were capable of metabolizing β- and γ-HBCD when incubated in the presence of NADPH as an electron donor [26]. Three bromine-containing metabolites derived from β-HBCD could be observed, while two were found for γ-HBCD, including hydroxyl-metabolites. Therefore, biotransformation by the cytochrome P-450 system is also expected to occur in other marine mammals, thus explaining the higher rate of occurrence of α-HBCD in blubber samples.

References

1. Spencer Williams E, Panko J, Paustenbach DJ (2009) The European Union's REACH regulation: a review of its history and requirements. Crit Rev Toxicol 39:553–575
2. Kemmlein S, Herzke D, Law RJ (2009) Brominated flame retardants in the European chemicals policy of REACH – regulation and determination in materials. J Chromatogr A 1216:320–333
3. Alaee M, Arias P, Sjödin A, Bergmand Å (2003) An overview of commercially used brominated flame retardants, their applications, their use patterns in different countries/regions and possible modes of release. Environ Int 29:683–689

4. Segev O, Kushmaro A, Brenner A (2009) Environmental impact of flame retardants (persistence and biodegradability). Int J Environ Res Public Health 6:478–491
5. Bromine Science and Environmental Forum. www.bsef.com. Accessed 1 June 2010
6. Polo M, Llompart M, García Jares C, Gomes-Noya G, Bollain MH, Cela R (2006) Development of a solid-phase microextraction method for the analysis of phenolic flame retardants in water samples. J Chromatogr A 1124:11
7. Jakab E, Uddin Md A, Bhaskar T, Sakata Y (2003) Thermal decomposition of flame-retarded high impact polystyrene. J Anal Appl Pyrolysis 83:68–69
8. Toa Gosei Chem Ind Ltd (TOAG-C) Patent number JP5105725-A, JP3021454-B2
9. Morris S, Allchin CR, Zegers BN, Belpaire C, de Boer J et al (2004) Distribution and fate of HBCD and TBBP A brominated flame retardants in North Sea Estuaries and aquatic food webs. Environ Sci Technol 38:5497–5504
10. Scientific Committee on Health and Environmental Risks (SCHER), scientific opinion on the risk assessment report on 2,2-,6,6-tetrabromo-4,4-isopropilidene diphenol (tetrabromobisphenol A), environmental part, CAS 79-94-7, European Commission Health & Consumer Protection Directorate (2008)
11. de Wit CA (2002) An overview of brominated flame retardants in the environment. Chemosphere 46:583–624
12. Vos JG, Becher G, van den Berg M, de Boer J, Leonards PEG (2003) Brominated flame retardants and endocrine disruption. Pure Appl Chem 75:2039–2046
13. Eriksson J, Rahm S, Green N, Bergman A, Jakobsson E (2004) Determination of the flame retardant tetrabromobisphenol A in air samples by liquid chromatography–mass spectrometry. Chemosphere 54:117
14. Allard AS, Remberger M, Neilson AH (1987) Bacterial O-methylation of halogen-substituted phenols. Appl Environ Microbiol 53:839
15. EU RAR (2006) European Commission, Joint Research Centre, European Chemicals Bureau – European Union Risk Assessment Report (tetrabromobisphenol-A or TBBP-A), 4th priority list, vol 63
16. Law RJ, Herzke D, Harrad S, Morris S, Bersuder P, Allchin CR (2008) Levels and trends of HBCD and BDEs in the European and Asian environments, with some information for other BFRs. Chemosphere 73:223–241
17. Voorspoels S, Covaci A, Lepom P, Escutena S (2006) Remarkable findings concerning PBDEs in the terrestrial top-predator Red Fox (*Vulpes vulpes*). Environ Sci Technol 40:2937–2943
18. Christensen JR, MacDuffee M, MacDoanld RW, Whiticar M, Ross P (2005) Persistent organic pollutants in British Columbia grizzly bears: consequence of divergent diets. Environ Sci Technol 39:6952–6960
19. Luo X-J, Liu J, Luo Y, Zhang X-L, Wu J-P, Lin Z, Chen S-J, Mai B-X, Yang Z-Y (2009) Polybrominated diphenyl ethers (PBDEs) in free-range domestic fowl from an e-waste recycling site in South China: levels, profile and human dietary exposure. Environ Int 35:253–258
20. Rayne S, Ikonomou MG, MacMurray DW (2003) Anaerobic microbial and photochemical degradation of 4,4′-dibromodiphenyl ether. Water Res 37:551–560
21. Eriksson J, Green N, Marsh G, Bergman A (2004) Photochemical decomposition of 15 polybrominated diphenyl ether congeners in methanol/water. Environ Sci Technol 38:3119–3125
22. Söderström G, Sellström U, de Wit CA, Tysklind M (2004) Photolytic debromination of decabromodiphenyl ether. Environ Sci Technol 38:127–132
23. von der Recke R, Vetter W (2007) Photolytic transformation of polybrominated biphenyls leading to the structures of unknown hexa- to nonabromo-congeners. J Chromatogr A 1167:184–194
24. Fang L, Huang J, Yu G, Wang L (2007) Photochemical degradation of six polybrominated diphenyl ether congeners under ultraviolet irradiation in hexane. Chemosphere 71:258–267

25. Covaci A, Gerecke AC, Law RJ, Voorspoels S, Kohler M, Heeb NV, Leslie H, Allchin CR, de Boer J (2006) Hexabromocyclododecane (HBCDs) in the environment and humans: a review. Environ Sci Technol 40:3679
26. Peled M, Scharia R, Sondack D (1995) Thermal rearrangement of hexabromo-cyclododecane (HBCD). In: Desmurs JR, Gérard B, Goldstein MJ (eds) Industrial Chemistry Library. Advances in organo-bromine chemistry II. Elsevier, Amsterdam
27. Zegers BN, Mets A, van Bomel R, Minkenberg C, Hamers T, Kamstra JH, Pierce G, Reid B, Patterson T, Boon JP (2005) Levels of hexabromocyclododecane in harbour porpoises and common dolphins from Western European Seas, with evidence for stereoisomer-specific biotransformation by cytochrome P450. Environ Sci Technol 39:2095–2100
28. Johansson AK, Sellström U, Lindberg P, Bignert A, de Wit CA (2009) Polybrominated diphenyl ether congener patterns, hexabromocyclododecane, and brominated biphenyl 153 in eggs of peregrine falcons (*Falco peregrinus*) breeding in Sweden. Environ Sci Technol 28:9–17
29. Temporal trends of brominated flame retardants, cyclododeca-1,5,9-triene and mercury eggs of four bird species from Northern Norway and Svalvard. Report of the Norwegian Pollution Control Authority 942/2005 (SFT). 1–39. ISBN: 82-7655-497-0
30. Davis JW, Gonsior SJ, Markham DA, Friederich U, Hunziker RW, Ariano JM (2006) Biodegradation and product identification of [C-14] hexabromocyclododecane in wastewater sludge and freshwater aquatic sediment. Environ Sci Technol 40:5395
31. Kierkegaard A, Björklund J, Fridén U (2004) Identification of the flame retardant decabromodiphenyl ethane in the environment. Environ Sci Technol 38:3247
32. Law K, Halldorson T, Danell R, Stern G, Gewurtz S, Alaee M, Marvin C, Whittle M, Tomy G (2006) Bioaccumulation and trophic transfer of some brominated flame retardants in a Lake Winnipeg (Canada) food web. Environ Toxicol Chem 25:2177–2186
33. Kierkegaard A, Sellström U, MacLachlan MS (2009) Environmental analysis of higher brominated diphenyl ethers and decabromodiphenyl ethane. J Chromatogr A 1216:364–375
34. Carter LJ (1976) Michigan's PBB incident: chemical mix-up leads to disaster. Science 4236:240–243
35. RoHS 2002/95/EC (2002) European Union (EU) Directive 2002/95/EC on the restriction of the use of certain hazardous substances in electrical and electronic equipment (lead (Pb), cadmium (Cd), mercury (Hg), hexavalent chromium (Cr+6), polybrominated biphenyls (PBB) and polybrominated diphenylethers (PBDE))
36. Herzke D, Berger U, Kallenborn R, Nygård T, Vetter W (2005) Brominated flame retardants and other organobromines in Norwegian predatory bird eggs. Chemosphere 61:441–449
37. Allchin CR, Morris S, Bennett M, Law RJ, Russel I (2000) Polybrominated dyphenyl ether residues in cormorant (*Phalacrocorax carbo*) livers from England, UK. Organohalogen Compd 47:190–193
38. Law RJ, Allchin CR, Bennett ME, Morris S, Rogan E (2002) Polybrominated diphenyl ethers in two species of marine top predators from England and Wales. Chemosphere 46:673–681
39. Sellström U (1999) Determination of some polybrominated flame retardants in biota, sediments and sewage sludge. Doctoral dissertation, University of Stockholm, Sweden
40. Haukås M, Hylland K, Berge JA, Nygård T, Mariussen E (2009) Spatial diastereomer patterns of hexabromocyclododecane (HBCD) in a Norwegian fjord. Sci Total Environ 407:5907–5913
41. Dauwe T, van den Steen E, Jaspers V, Maes K, Covaci A, Eens M (2009) Interspecific differences in concentrations and congener profiles of chlorinated and brominated organic pollutants in three insectivorous bird species. Environ Int 35(2):369–375
42. Verboven N, Verreault J, Letcher RJ, Gabrielsen GW, Evans NP (2009) Nest temperature and parental behaviour of Arctic-breeding glaucous gulls exposed to persistent organic pollutants. Anim Behav 77:411–418
43. Verreault J, Verboven N, Gabrielsen GW, Letcher RJ, Chastel O (2008) Changes in prolactin in a highly organohalogen contaminated Arctic top predator seabird, the glaucous gull. Gen Comp Endocrinol 156:569–576

44. Sagerup K, Helgason LB, Polder A, Strom H, Josefsen TD, Skaare JU, Gabrielsen GW (2009) Persistent organic pollutants and mercury in dead and dying glaucous gulls (*Larus hyperboreus*) at Bjornoya (Svalbard). Sci Total Environ 407:6009–6016
45. Miljeteig C, Strom H, Gavrilo MV, Volkov A, Jenssen BM, Gabrielsen GW (2009) High levels of contaminants in Ivory Gull *Pagophila eburnea* eggs from the Russian and Norwegian Arctic. Environ Sci Technol 43:5521–5528
46. Bustnes JO, Borgå K, Erikstad KE, Lorentsen SH, Herzke D (2008) Perfluorinated, brominated, and chlorinated contaminants in a population of lesser black-backed gulls (*Larus fuscus*). Environ Toxicol Chem 27:1383–1392
47. Herzke D, Nygård T, Berger U, Huber S, Røv N (2009) Perfluorinated and other persistent halogenated organic compounds in European shag (*Phalacrocorax aristotelis*) and common eider (*Somateria mollissima*) from Norway: a suburban to remote pollutant gradient. Sci Total Environ 408:340–348
48. Jenssen BM, Aarnes JB, Murvoll KM, Herzke D, Nygård T (2010) Fluctuating wing asymmetry and hepatic concentrations of persistent organic pollutants are associated in European shag (*Phalacrocorax aristotelis*) chicks. Sci Total Environ 408:578–585
49. Jörundsdóttir H, Bignert A, Svavarsson J, Nygård T, Weihe P, Bergman Å (2009) Assessment of emerging and traditional halogenated contaminants in guillemot (*Uria aalge*) egg from North-Western Europe and the Baltic Sea. Sci Total Environ 407:4174–4183
50. Hebert CE, Weseloh DVC, Gauthier LT, Arts MT, Letcher RJ (2009) Biochemical tracers reveal intra-specific differences in the food webs utilized by individual seabirds. Oecologia 160:15–23
51. Gauthier LT, Potter D, Hebert CE, Letcher RJ (2009) Temporal trends and spatial distribution of non-polybrominated diphenyl ether flame retardants in the eggs of colonial populations of Great Lakes herring gulls. Environ Sci Technol 43:312–317
52. Custer TW, Kannan K, Tao L, Saxena AR, Route B (2009) Perfluorinated compounds and polybrominated diphenyl ethers in great blue heron eggs from Indiana Dunes National Lakeshore, Indiana. J Great Lakes Res 35:401–405
53. She JW, Holden A, Adelsbach TL, Tanner M, Schwarzbach SE, Yee JL, Hooper K (2008) Concentrations and time trends of polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) in aquatic bird eggs from San Francisco Bay, CA 2000–2003. Chemosphere 73:S201–S209
54. Norstrom RJ, Simon M, Moisey J, Wakeford B, Weseloh DVC (2002) Geographical distribution (2000) and temporal trends (1981–2000) of brominated diphenyl ethers in Great Lakes herring gull eggs. Environ Sci Technol 36:4783–4789
55. Wan YI, Hu JY, Zhang K, An LH (2008) Trophodynamics of polybrominated diphenyl ethers in the marine food web of Bohai Bay, North China. Environ Sci Technol 42:1078–1083
56. Yogui GT, Sericano JL (2009) Levels and pattern of polybrominated diphenyl ethers in eggs of Antarctic seabirds: endemic versus migratory species. Environ Pollut 157:975–980
57. Gao Z, Xu J, Xian Q, Feng J, Chen X, Yu H (2009) Polybrominated diphenyl ethers (PBDEs) in aquatic biota from the lower reach of the Yangtze River, East China. Chemosphere 75:1273–1279
58. Kunisue T, Higaki Y, Isobe T, Takahashi S, Subramanian A, Tanabe S (2008) Spatial trends of polybrominated diphenyl ethers in avian species: utilization of stored samples in the Environmental Specimen Bank of Ehime University (es-Bank). Environ Pollut 154:272–282
59. Lam JCW, Murphy MB, Wang Y, Tanabe S, Giesy JP, Lam PKS (2008) Risk assessment of organohalogenated compounds in water bird eggs from South China. Environ Sci Technol 42:6296–6302
60. Polder A, Venter B, Skaare JU, Bouwman H (2008) Polybrominated diphenyl ethers and HBCD in bird eggs of South Africa. Chemosphere 73:148–154

61. Henny CJ, Kaiser JL, Grove RA, Johnson BL, Letcher RJ (2009) Polybrominated diphenyl ether flame retardants in eggs may reduce reproductive success of ospreys in Oregon and Washington, USA. Ecotoxicology 18:802–813
62. McKernan MA, Rattner BA, Hale RC, Ottinger MA (2009) Toxicity of polybrominated diphenyl ethers (DE-71) in chicken (*Gallus gallus*), mallard (*Anas platyrhynchos*), and American kestrel (*Falco sparverius*) embryos and hatchlings. Environ Toxicol Chem 28:1007–1017
63. Park JS, Holden A, Chu V, Kim M, Rhee A, Patel P, Shi YT, Linthicum J, Walton BJ, McKeown K, Jewell NP, Hooper K (2009) Time-trends and congener profiles of PBDEs and PCBs in California peregrine falcons (*Falco peregrinus*). Environ Sci Technol 43:8744–8751
64. Potter KE, Watts BD, La Guardia MJ, Harvey EP, Hale RC (2009) Polybrominated diphenyl ether flame retardants in Chesapeake Bay Region, USA, peregrine falcon (*Falco Peregrinus*) eggs: urban/rural trends. Environ Toxicol Chem 28:973–981
65. Chen D, La Guardia MJ, Harvey E, Amaral M, Wohlfort K, Hale RC (2008) Polybrominated diphenyl ethers in peregrine falcon (*Falco peregrinus*) eggs from the Northeastern US. Environ Sci Technol 42:7594–7600
66. Fernie KJ, Shutt JL, Letcher RJ, Ritchie IJ, Bird DM (2009) Environmentally relevant concentrations of DE-71 and HBCD alter eggshell thickness and reproductive success of American kestrels. Environ Sci Technol 43:2124–2130
67. Fernie KJ, Shutt JL, Letcher RJ, Ritchie JI, Sullivan K, Bird DM (2008) Changes in reproductive courtship behaviors of adult American kestrels (*Falco sparverius*) exposed to environmentally relevant levels of the polybrominated diphenyl ether mixture, DE-71. Toxicol Sci 102:171–178
68. Janák K, Sellström U, Johansson AK, Becher G, de Wit CA, Lindberg P, Helander B (2008) Enantiomer-specific accumulation of hexabromocyclododecanes in eggs of predatory birds. Chemosphere 73:S193–S200
69. Johansson AK, Sellström U, Lindberg P, Bignert A, de Wit CA (2009) Polybrominated diphenyl ether congener patterns, hexabromocyclododecane, and brominated biphenyl 153 in eggs of peregrine falcons (*Falco peregrinus*) breeding in Sweden. Environ Toxicol Chem 28:9–17
70. Sonne C, Bustnes JO, Herzke D, Jaspers VLB, Covaci A, Halley DJ, Moum T, Eulaers I, Eens M, Ims RA, Hanssen SA, Erikstad KE, Johnsen T, Schnug L, Riget FF, Jensen AL (2010) Relationships between organohalogen contaminants and blood plasma clinical-chemical parameters in chicks of three raptor species from Northern Norway. Ecotoxicol Environ Saf 73:7–17
71. Jaspers VLB, Covaci A, Deleu P, Eens M (2008) Preen oil as the main source of external contamination with organic pollutants onto feathers of the common magpie (*Pica pica*). Environ Int 34:741–748
72. Van den Steen E, Eens M, Covaci A, Dirtu AC, Jaspers VLB, Neels H, Pinxten R (2009) An exposure study with polybrominated diphenyl ethers (PBDEs) in female European starlings (*Sturnus vulgaris*): toxicokinetics and reproductive effects. Environ Pollut 157:430–436
73. Van den Steen E, Eens M, Jaspers VLB, Covaci A, Pinxten R (2009) Effects of laying order and experimentally increased egg production on organic pollutants in eggs of a terrestrial songbird species, the great tit (*Parus major*). Sci Total Environ 407:4764–4770
74. Van den Steen E, Pinxten R, Jaspers VLB, Covaci A, Barba E, Carere C, Cichon M, Dubiec A, Eeva T, Heeb P, Kempenaers B, Lifjeld JT, Lubjuhn T, Mand R, Massa B, Nilsson JA, Norte AC, Orell M, Podzemny P, Sanz JJ, Senar JC, Soler JJ, Sorace A, Torok J, Visser ME, Winkel W, Eens M (2009) Brominated flame retardants and organochlorines in the European environment using great tit eggs as a biomonitoring tool. Environ Int 35:310–317
75. Covaci A, Roosens L, Dirtu AC, Waegeneers N, van Overmeire I, Neels H, Goeyens L (2009) Brominated flame retardants in Belgian home-produced eggs: levels and contamination sources. Sci Total Environ 407:4387–4396
76. Naert C, Van Peteghem C, Kupper J, Jenni L, Naegeli H (2007) Distribution of polychlorinated biphenyls and polybrominated diphenyl ethers in birds of prey from Switzerland. Chemosphere 68:977–987

77. Symons R, Burniston D, Piro N, Stevenson G, Yates A (2004) A study of the presence of brominated flame retardants in Australian fauna. Organohalogen Compd 66:3959–3965
78. Voorspoels S, Covaci A, Schepens P (2004) Brominated flame retardants in birds of prey from Flanders, Belgium. Organohalogen Compd 66:3884–3892
79. Chen D, Mai B, Song J, Sun Q, Luo Y, Luo X, Zeng EY, Hale RC (2007) Polybrominated diphenyl ethers in birds of prey from Northern China. Environ Sci Technol 41:1828–1833
80. Sellström U, Lindberg P, Häggberg L, de Wit CA (2001) Higher brominated PBDEs found in eggs of peregrine falcons (*Falco peregrinus*) breeding in Sweden. In: Proceedings of the second international workshop on brominated flame retardants BFR2001, Stockholm University, Sweden, 14–16 May, pp 159–162
81. Roosens L, Dirtu AC, Goemans G, Belpaire C, Gheorghe A, Neels H, Blust R, Covaci A (2008) Brominated flame retardants and polychlorinated biphenyls in fish from the River Scheldt, Belgium. Environ Int 34:976–983
82. Binelli A, Guzzella L, Roscioli C (2008) Levels and congener profiles of polybrominated diphenyl ethers (PBDEs) in Zebra mussels (*D. polymorpha*) from Lake Maggiore (Italy). Environ Pollut 153:610–617
83. Russell M, Webster L, Walsham P, Packer G, Moffat CF (2008) Brominated flame retardants in deep water fish collected off the west coast of Scotland. Organohalogen Compd 70:255–258
84. Webster L, Russell M, Walsham P, Phillips LA, Packer G, Hussy I, Scurfield JA, Dalgarno EJ, Moffat CF (2009) An assessment of persistent organic pollutants (POPs) in wild and rope grown blue mussels (*Mytilus edulis*) from Scottish coastal waters. J Environ Monit 11:1169–1184
85. Webster L, Russell M, Adefehinti F, Dalgarno EJ, Moffat CF (2008) Preliminary assessment of polybrominated diphenyl ethers (PBDEs) in the Scottish aquatic environment, including the Firth of Clyde. J Environ Monit 10:463–473
86. Harrad S, Abdallah MA-E, Rose NL, Turner SD, Davidson TA (2009) Current-use brominated flame retardants in water, sediment, and fish from English lakes. Environ Sci Technol 43:9077–9083
87. Szlinder-Richert J, Barska I, Usydus Z, Grabic R (2010) Polybrominated diphenyl ethers (PBDEs) in selected fish species from the southern Baltic Sea. Chemosphere 78:695–700
88. de Boer J, Wester PG, van der Horst A, Leonards PEG (2003) Polybrominated diphenyl ethers in influents, suspended particulate matter, sediments, sewage treatment plant and effluents and biota from the Netherlands. Environ Pollut 122:63–74
89. Ter Schure AFH, Larsson P, Merilä J, Jönsson KI (2002) Latitudinal fractionation of polybrominated diphenyl ethers and polychlorinated biphenyls in frogs (*Rana temporaria*). Environ Sci Technol 36:5057–5061
90. Borghesi N, Corsolini S, Leonards P, Brandsma S, de Boer J, Focardi S (2009) Polybrominated diphenyl ether contamination levels in fish from the Antarctic and the Mediterranean Sea. Chemosphere 77:693–698
91. Corsolini S, Guerranti C, Perra G, Focardi S (2008) Polybrominated diphenyl ethers, perfluorinated compounds and chlorinated pesticides in swordfish (*Xiphias gladius*) from the Mediterranean Sea. Environ Sci Technol 42:4344–4349
92. Mizukawa K, Takada H, Takeuchi I, Ikemoto T, Omori K, Tsuchiya K (2009) Bioconcentration and biomagnification of polybrominated diphenyl ethers (PBDEs) through lower-trophic-level coastal marine food web. Mar Pollut Bull 58:1217–1224
93. Hong SH, Munschy C, Kannan N, Tixier C, Tronczynski J, Héas-Moisan K, Shim WJ (2009) PCDD/F, PBDE, and nonylphenol contamination in a semi-enclosed bay (Masan Bay, South Korea) and a Mediterranean lagoon (Thau, France). Chemosphere 77:854–862
94. Takahashi S, Oshihoi T, Ramu K, Isobe T, Ohmori K, Kubodera T, Tanabe S (2010) Organohalogen compounds in deep-sea fishes from the western North Pacific, off-Tohoku, Japan: contamination status and bioaccumulation profiles. Mar Pollut Bull 60:187–196
95. Ueno D, Isobe T, Ramu K, Tanabe S, Alaee M, Marvin C, Inoue K, Someya T, Miyajima T, Kodama H, Nakata H (2010) Spatial distribution of hexabromocyclododecanes (HBCDs),

polybrominated diphenyl ethers (PBDEs) and organochlorines in bivalves from Japanese coastal waters. Chemosphere 78:1213–1219
96. Zhang B-Z, Ni H-G, Guan Y-F, Zeng EY (2010) Occurrence, bioaccumulation and potential sources of polybrominated diphenyl ethers in typical freshwater cultured fish ponds of South China. Environ Pollut 158:1876–1882
97. Yu M, Luo X-J, Wu J-P, Chen S-J, Mai B-X (2009) Bioaccumulation and trophic transfer of polybrominated diphenyl ethers (PBDEs) in biota from the Pearl River Estuary, South China. Environ Int 35:1090–1095
98. Jin J, Wang Y, Yang C, Hu J, Liu W, Cui J, Tang X (2009) Polybrominated diphenyl ethers in the serum and breast milk of the resident population from production area, China. Environ Int 35:1048–1052
99. Shen H, Yu C, Ying Y, Zhao Y, Wu Y, Han J, Xu Q (2009) Levels and congener profiles of PCDD/Fs, PCBs and PBDEs in seafood from China. Chemosphere 77:1206–1211
100. Van Leeuwen SPJ, Van Velzen MJM, Swart CP, Van der Veen I, Traag WA, de Boer J (2009) Halogenated contaminants in farmed salmon, trout, tilapia, pangasius, and shrimp. Environ Sci Technol 43:4009–4015
101. Miyake Y, Jiang Q, Yuan W, Hanari N, Okazawa T, Wyrzykowska B, So MK, Lam PKS, Yamashita N (2008) Preliminary health risk assessment for polybrominated diphenyl ethers and polybrominated dibenzo-*p*-dioxins/furans in seafood from Guangzhou and Zhoushan, China. Mar Pollut Bull 57:357–364
102. Li Q, Yan C, Luo Z, Zhang X (2010) Occurrence and levels of polybrominated diphenyl ethers (PBDEs) in recent sediments and marine organisms from Xiamen offshore areas, China. Mar Pollut Bull 60:464–469
103. Shaw SD, Berger ML, Brenner D, Kannan K, Lohmann N, Päpke O (2009) Bioaccumulation of polybrominated diphenyl ethers and hexabromocyclododecane in the northwest Atlantic marine food web. Sci Total Environ 407:3323–3329
104. Montory M, Habit E, Fernandez P, Grimalt JO, Barra R (2010) PCBs and PBDEs in wild Chinook salmon (*Oncorhyncus tshawytscha*) in the Northern Patagonia, Chile. Chemosphere 78:1193–1199
105. Sloan CA, Anulacion BF, Bolton JL, Boyd D, Olson OP, Sol SY, Ylitalo GM, Johnson LL (2010) Polybrominated diphenyl ethers in outmigrant juvenile Chinook salmon from the Lower Columbia River and Estuary and Puget Sound, Washington. Arch Environ Contam Toxicol 58:403–414
106. Johnson-Restrepo B, Kannan K, Addink R, Adams DH (2005) Polybrominated diphenyl ethers and polychlorinated biphenyls in a marine food web of coastal Florida. Environ Sci Technol 39:8243–8250
107. Ismail N, Gewurtz SB, Pleskach K, Whittle DM, Helm PA, Marvin CH, Tomy GT (2009) Brominated and chlorinated flame retardants in Lake Ontario, Canada, lake trout (*Salvelinus namaycush*) between 1979 and 2004 and possible influences of food-web changes. Environ Toxicol Chem 28:910–920
108. Blocksom KA, Walters DM, Jicha TM, Lazorchak JM, Angradi TR, Bolgrien DW (2010) Persistent organic pollutants in fish tissue in the mid-continental great rivers of the United States. Sci Total Environ 408:1180–1189
109. Yang F, Aguirre AA, Jin S, Wilcox B, Rougée L, Xu Y, Lu Y (2008) Detection of polybrominated diphenyl ethers in tilapia (*Oreochromis mossambicus*) from O'ahu, Hawai'i. J Environ Monit 10:432–434
110. Losada S, Roach A, Roosens L, Santos FJ, Galceran MT, Vetter W, Neels H, Covaci A (2009) Biomagnification of anthropogenic and naturally-produced organobrominated compounds in a marine food web from Sydney Harbour, Australia. Environ Int 35:1142–1149
111. Hites RA, Foran JA, Schwager SJ, Knuth BA, Hamilton MC, Carpenter DO (2004) Global assessment of polybrominated diphenyl ethers in farmed and wild salmon. Environ Sci Technol 38:4945–4949

112. Berntssen MHG, Julshamn K, Lundebye A-K (2010) Chemical contaminants in aquafeeds and Atlantic salmon (*Salmo salar*) following the use of traditional- versus alternative feed ingredients. Chemosphere 78:637–646
113. Niholm JR, Norman A, Norrgren L, Haglund P, Anderson PL (2008) Maternal transfer of brominated compounds in zebrafish (*Danio rerio*). Chemosphere 73:203–208
114. de Boer J, Wester PG, Klamer HJC, Lewis WE, Boon JP (1998) Do flame retardants threaten ocean life? Nature 394:28
115. Sellström U, Jansson B, Kierkegaard A, de Wit CA, Odsjö T, Olsson M (1993) Polybrominated dyphenyl ethers (PBDE) in biological samples from the Swedish environment. Chemosphere 26:1703–1718
116. Haglund PS, Zook DR, Buser HR, Hu J (1997) Identification and quantification of polybrominated diphenyl ethers and methoxy-polybrominated diphenyl ethers in Baltic biota. Environ Sci Technol 31:3281–3287
117. Alaee M, Luross J, Sergeant DB, Muir DCG, Whittle DM, Solomon K (1999) Distribution of polybrominated diphenyl ethers in the Canadian environment. Organohalogen Compd 40:347–350
118. Kuehl DW, Haebler R (1995) Organochlorine, organobromine, metal, and selenium residues in bottlenose dolphins (*Tursiops truncatus*) collected during an unusual mortality event in the Gulf of Mexico. Arch Environ Contam Toxicol 28:494–499
119. Ikonomou MG, Fisher M, He T, Addison RF, Smith T (2000) Congener patterns, spatial temporal trends of polybrominated diphenyl ethers in biota samples from the Canadian west coast and the Northwest Territories. Organohalogen Compd 47:77–80
120. Pettersson A, van Bavel B, Engwall M, Jimenez B (2004) Polybrominated diphenylethers and methoxylated tetrabromodiphenylethers in cetaceans from the Mediterranean Sea. Arch Environ Contam Toxicol 47:542–550
121. Law RJ, Allchin CR, Bennet ME, Morris S (2000) Polybrominated diphenyl ethers in the blubber of harbour porpoises (*Phocoena phocoena* L.) stranded in the coast of England and Wales. Organohalogen Compd 47:249–252
122. Kajiwara N, Kunisue T, Kamikawa S, Ochi Y, Yano S, Tanabe S (2006) Organohalogen and organotin compounds in killer whales mass-stranded in the Shiretoko Peninsula, Hokkaido, Japan. Mar Pollut Bull 52:1066–1076
123. Law RJ, Allchin CR, Mead LK (2005) Brominated diphenyl ethers in the blubber of twelve species of marine mammals stranded in the UK. Mar Pollut Bull 50:356–359
124. Law RJ, Allchin CR, de Boer J, Covaci A, Herzke D, Lepom P, Morris S, Tronczynski J, de Wit CA (2006) Levels and trends of brominated flame retardants in the European environment. Chemosphere 64:187–208
125. Law RJ, Alaee M, Allchin CR, Boon JP, Lebeuf M, Lepom P, Stern GA (2003) Levels and trends of polybrominated diphenylethers and other brominated flame retardants in wildlife. Environ Int 29:757–770
126. She J, Winkler J, Visita P, McKinney M, Petreas M (2000) Analysis of PBDEs in seal blubber and human breast adipose tissue samples. Organohalogen Compd 47:53–56
127. Lindström G, Wingfors H, Dam M, van Bavel B (1999) Identification of 19 polybrominated diphenyl ethers (PBDEs) in long-finned pilot whale (*Globicephala melas*) from the Atlantic. Arch Environ Contam Toxicol 36:355–363
128. Isobe T, Ochi Y, Imaeda D, Sakai H, Hirawaka S, Tsydenova O, Amano M, Petrov E, Batoev V, Iwata H, Takahashi S, Tanabe S (2009) Contamination status of brominated flame retardants (BFRs) in Baikal seals (*Pusa sibirica*). In: Interdisciplinary studies on environ chem-environ research in Asia, pp 119–124
129. Kajiwara N, Kamikawa S, Ramu K, Ueno D, Yamada TK, Subramanian A, Lam PKS, Jefferson TA, Prudente M, Chung K-H, Tanabe S (2006) Geographical distribution of polybrominated diphenyl ethers (PBDEs) and organochlorines in small cetaceans from Asian waters. Chemosphere 64:287–295

130. Dorneles PR, Lailson-Brito J, Dirtu AC, Weijs L, Azevedo AF, Torres JPM, Malm O, Neels H, Blust R, Das K, Covaci A (2010) Anthropogenic and naturally-produced organobrominated compounds in marine mammals from Brazil. Environ Int 36:60–67
131. Von der Recke R, Vetter W (2008) Congener pattern of hexabromobiphenyls in marine biota from different proveniences. Sci Total Environ 393:358–366
132. Tanabe S (2008) Temporal trends of brominated flame retardants in coastal waters of Japan and South China: retrospective monitoring study using archived samples from *es*-bank, Ehime University, Japan. Mar Pollut Bull 57:267–274
133. Kajiwara N, Kamikawa S, Amano M, Hayano A, Yamada TK, Miyazaki N, Tanabe S (2008) Polybrominated diphenyl ethers (PBDEs) and organochlorines in melon-headed whales, *Peponocephala electra*, mass stranded along the Japanese coasts: maternal transfer and temporal trend. Environ Pollut 156:106–114
134. Isobe T, Ochi Y, Ramu K, Yamamoto T, Tajima Y, Yamada TK, Amano M, Miyazaki N, Takahashi S, Tanabe S (2009) Organohalogen contaminants in striped dolphins (*Stenella coeruleoalba*) from Japan: present contamination status, body distribution and temporal trends (1978–2003). Mar Pollut Bull 58:396–401
135. Alava JJ, Ikonomou MG, Ross PS, Costa D, Salazar S, Aurioles-Gamboa D, Gobas FAPC (2009) Polychlorinated biphenyls and polybrominated diphenyl ethers in Galapagos sea lions (*Zalophus wollebaeki*). Environ Toxicol Chem 28:2271–2282
136. Schiavone A, Kannan K, Horii Y, Focardi S, Corsolini S (2009) Occurrence of brominated flame retardants, polycyclic musks, and chlorinated naphthalenes in seal blubber from Antarctica: comparison to organochlorines. Mar Pollut Bull 58:1406–1419
137. Peck AM, Pugh RS, Moors A, Ellisor MB, Porter BJ, Becker PR, Kucklick JR (2008) Hexabromocyclododecane in white-sided dolphins: temporal trend and stereoisomer distribution in tissues. Environ Sci Technol 42:2650–2655
138. Ylitalo G, Baird RW, Yanagida GK, Webster DL, Chivers SJ, Bolton JL, Schorr GS, McSweeney DJ (2009) High levels of persistent organic pollutants measured in blubber of island-associated false killer whales (*Pseudorca crassidens*) around the main Hawaiian Islands. Mar Pollut Bull 58:1932–1937
139. Meng X-Z, Blasius ME, Gossett RW, Maruya KA (2009) Polybrominated diphenyl ethers in pinnipeds stranded along the southern California coast. Environ Pollut 157:2731–2736
140. Ikonomou MG, Addison RF (2008) Polybrominated diphenyl ethers (PBDEs) in seal populations from eastern and western Canada: an assessment of the processes and factors controlling PBDE distribution in seals. Mar Environ Res 66:225–230
141. Vorkamp K, Rigét FF, Glasius M, Muir DCG, Dietz R (2008) Levels and trends of persistent organic pollutants in ringed seals (*Phoca hispida*) from central west Greenland, with particular focus on polybrominated diphenyl ethers (PBDEs). Environ Int 34:499–508
142. Rigét F, Vorkamp K, Dietz R, Rastogi SC (2006) Temporal trend studies on polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) in ringed seals from east Greenland. J Environ Monit 8:1000–1005
143. Lam JCW, Lau RKF, Murphy MB, Lam PKS (2009) Temporal trends of hexabromocyclododecanes (HBCDs) and polybrominated diphenyl ethers (PBDEs) and detection of two novel flame retardants in marine mammals from Hong Kong, South China. Environ Sci Technol 43:6944–6949
144. Letcher RJ, Gebbink WA, Sonne C, Born EW, McKinney MA, Dietz R (2009) Bioaccumulation and biotransformation of brominated and chlorinated contaminants and their metabolites in ringed seals (*Pusa hispida*) and polar bears (*Ursus maritimus*) from East Greenland. Environ Int 35:118–1124
145. Houde M, Pacepavicius G, Darling C, Fair PA, Alaee M, Bossart GD, Solomon KR, Letcher RJ, Bergman Å, Marsh G, Muir DCG (2009) Polybrominated diphenyl ethers and their hydroxylated analogs in plasma of bottlenose dolphins (*Tursiops truncatus*) from the United States east coast. Environ Toxicol Chem 28:2061–2068

146. Weijs L, Das K, Siebert U, van Elk N, Jauniaux T, Neels H, Blust R, Covaci A (2009) Concentrations of chlorinated and brominated contaminants and their metabolites in serum of harbour seals and harbour porpoises. Environ Int 35:842–850
147. Fair PA, Adams J, Mitchum G, Hulsey TC, Reif JS, Houde M, Muir D, Wirth E, Wetzel D, Zolman E, McFee W, Bossart GD (2010) Contaminant blubber burdens in Atlantic bottlenose dolphins (*Tursiops truncatus*) from two southeastern US estuarine areas: concentrations and patterns of PCBs, pesticides, PBDEs, PFCs, and PAHs. Sci Total Environ 408:1577–1597
148. Montie EW, Reddy CM, Gebbink WA, Touhey KE, Hahn ME, Letcher RJ (2009) Organohalogen contaminants and metabolites in cerebrospinal fluid and cerebellum gray matter in short-beaked common dolphins and Atlantic white-sided dolphins from the western North Atlantic. Environ Pollut 157:2345–2358
149. Swarthout RF, Keller JM, Peden-Adams M, Landry AM, Fair PA, Kucklick JR (2010) Organohalogen contaminants in blood of Kemp's ridley (*Lepidochelys kempii*) and green sea turtles (*Chelonia mydas*) from the Gulf of Mexico. Chemosphere 78:731–741
150. Verrault J, Letcher RJ, Sonne C, Dietz R (2009) Dietary, age and trans-generational effects on the fate of organohalogen contaminants in captive sledge dogs in Greenland. Environ Int 35:56–62
151. Kierkegaard A, Asplund L, de Wit CA, McLachlan MS (2007) Fate of higher brominated PBDEs in lactating cows. Environ Sci Technol 41:417–423
152. Pontolillo J, Eganhouse RP (2001) The search for reliable aqueous solubility (Sw) and octanol–water partition coefficient (Kow) data for hydrophobic organic compounds: DDT and DDE as a case study. U.S. Geological Survey Water-Resources Investigations. Report 01-4201. Reston, Virginia
153. Muir DCG, Yarechewski AL (1988) Dietary accumulation of four chlorinated dioxin congeners by rainbow trout and fathead minnows. Environ Toxicol Chem 7:227–236
154. Opperhuizen A, Velde EWvd, Gobas FAPC, Liem DAK, Steen JMDvd, Hutzinger O (1985) Relationship between bioconcentration in fish and steric factors of hydrophobic chemicals. Chemosphere 14:1871–1896
155. Hobson KA, Fisk AT, Karnovsky NJ, Holst M, Gagnon JM, Fortier M (2002) A stable isotope (delta 13C, delta 15C) model for the North Water food web: implications for evaluating trophodynamics and the flow of energy and contaminants. Deep Sea Res II 49:5131–5150
156. Kelly BC, Ikonomou MG, Blair JD, Gobas FAPC (2008) Bioaccumulation behaviour of polybrominated diphenyl ethers (PBDEs) in a Canadian Arctic marine food web. Sci of the Total Environ 401:60–72
157. Ikonomou MG, Rayne S, Addison RF (2002) Exponential increase of the brominated flame retardants, polybrominated diphenyl ethers, in the Canadian Arctic from 1981 to 2000. Environ Sci Technol 36:1886–1892
158. Boon JP, Lewis WE, Tjoen ACMR, Allchin CR, Law RJ, de Boer J et al (2002) Levels of polybrominated diphenyl ether (PBDE) flame retardants in animals representing different trophic levels of the North Sea food web. Environ Sci Technol 36:4025–4032
159. Muir DC, Backus S, Derocher AE, Dietz R, Evans TJ, Gabrielsen GW, Nagy J, Norstrom RJ, Sonne C, Stirling I, Tayloe MK, Letcher RJ (2006) Brominated flame retardants in polar bears (*Ursus maritimus*) from Alaska, the Canadian Arctic, East Greenland, and Svalbard. Environ Sci Technol 40:449–455
160. Wolkers H, van Bavel B, Derocher AE, Wiig O, Kovacs KM, Lydersen C et al (2004) Congener specific accumulation and food chain transfer of polybrominated diphenyl ethers in two Arctic food chains. Environ Sci Technol 38:1667–1674
161. Sørmo EG, Jenssen BM, Lie E, Skaare JU (2009) Brominated flame retardants in aquatic organisms from the North Sea in comparison with biota from the high Arctic marine environment. Environ Toxicol Chem 28:2082–2090
162. Gustafsson K, Björk M, Burreau S, Gilek M (1999) Bioaccumulation kinetics of brominated flame retardants (polybrominated diphenyl ethers) in blue mussels (*Mytilus edulis*). Environ Toxicol Chem 18:1218–1224

163. Booij K, Zegers BN, Boon JP (2002) Levels of some polybrominated diphenyl ether (PBDE) flame retardants along the Dutch coast as derived from their accumulation in SPMDs and blue mussels (*Mytilus edulis*). Chemosphere 46:683–688
164. Sellström U, Kierkegaard A, de Wit CA, Jansson B (1998) Polybrominated diphenyl ethers and hexabromocyclododecane in sediment and fish from a Swedish river. Environ Toxicol Chem 17:1065–1072
165. Burreau S, Zebühr Y, Ishaq R, Broman D (2000) Comparison of the biomagnification of PBDEs in food chains from the Baltic Sea and the Northern Atlantic Sea. Organohalogen Compd 47:253–255
166. Burreau S, Axelman J, Broman D, Jakobsson E (1997) Dietary uptake in pike (*Esox lucius*) of some polychlorinated biphenyls, polychlorinated naphthalenes and polybrominated diphenyl ethers administered in natural diet. Environ Toxicol Chem 16:2508–2513
167. Andersson PL, Wågman N, Berg HA, Olsson P-E, Tysklind M (1999) Bio-magnification of structurally matched polychlorinated and polybrominated diphenyl ethers (PCDE/PBDE) in zebrafish (*Danio rerio*). Organohalogen Compd 43:9–12
168. Burreau S, Broman D, Zebühr Y (1999) Biomagnification quantification of PBDEs in fish using stable nitrogen isotopes. Organohalogen Compd 40:363–366
169. Kuiper RV, Brandhof EJvd, Leonards PEG, Ven LTMvd, Wester PW, Vos JG (2007) Toxicity of tetrabromobisphenol A (TBBPA) in zebrafish (*Danio rerio*) in a partial life-cycle test. Arch Toxicol 81:1–9
170. Law K, Palace VP, Halldorson T, Danell R, Wautier K, Evans B, Alaee M, Marvin C, Tomy GT (2006) Dietary accumulation of hexabromocyclododecane diastereoisomers in juvenile rainbow trout (*Oncorhynchus mykiss*) I: bioaccumulation parameters and evidence of bioisomerization. Environ Toxicol Chem 25:1757–1761
171. Heeb NV, Schweizer WB, Kohler M, Gerecke AC (2005) Structure elucidation of hexabromocyclododecanes – a class of compounds with a complex stereo-chemistry. Chemosphere 61:65–73
172. Nihlom JR, Norman A, Norrgren L, Haglund P, Andersson PL (2009) Uptake and biotransformation of structurally diverse brominated flame retardants in zebrafish (*Danio rerio*) after dietary exposure. Environ Toxicol Chem 28:1035–1042
173. Tommy GT, Pleskach K, Oswald T, Halldorson T, Helm PA, MacInnis G, Marvin CH (2008) Enantioselective bioaccumulation of hexabromocyclododecane and congener-specific accumulation of brominated diphenyl ethers in an eastern Canadian Arctic marine food web. Environ Sci Technol 42:3634–3639
174. Wu J-P, Luo X-J, Zhang Y, Yu M, Chen S-J, Mai B-X, Yang Z-Y (2009) Bio-magnification of polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls in a highly contaminated freshwater food web from South China. Environ Pollut 157:904–909
175. Letcher RJ, Norstrom RJ, Lin S, Ramsay MA, Bandiera SM (1996) Inmuno-quantitation and microsomal monooxygenase activities of hepatic cytochromes P4501A and P4502B and chlorinated hydrocarbon contaminant levels in polar bear (*Ursus maritimus*). Toxicol Appl Pharmacol 137:127–140
176. Strandman T, Koistinen J, Kiviranta H, Vuorinen PJ, Tuomisto J, Vartiainen T (1999) Levels of some polybrominated diphenyl ethers (PBDEs) in fish and human adipose tissue in Finland. Organohalogen Compd 40:355–358
177. Sjödin A, Hagmar L, Klasson-Wehler E, Bergman Å (1999) Flame retardant exposure – polybrominated diphenyl ethers (PBDEs) in blood from Swedish workers. Environ Health Perspect 107:643–648
178. Ryan JJ, Patry B (2000) Determination of brominated diphenyl ethers (BDEs) and levels in Canadian human milks. Organohalogen Compd 47:57–60
179. Rahm S, Green N, Norrgran J, Bergman Å (2005) Hydrolysis of environmental contaminants as an experimental tool for indication of their persistency. Environ Sci Technol 39:3128–3133
180. Tomy GT, Palace VP, Halldorson T, Braekevelt E, Danell R, Wautier K et al (2004) Bioaccumulation, biotransformation, and biochemical effects of brominated diphenyl ethers in juvenile lake trout (*Salvelinus namaycush*). Environ Sci Technol 38:1496–1504

181. Stapleton HM, Alaee M, Letcher RJ, Baker JE (2004) Debromination of the flame retardant decabromodiphenyl ether by juvenile carp (*Cyprinus carpio*) following dietary exposure. Environ Sci Technol 37:112–119
182. Kierkegaard A, Burreau S, Marsh G, Klasson-Wehler E, de Wit CA, Asplund L (2001) Metabolism and distribution of 2,2′,4,4′-tetrabromo[14C]diphenylether in pike (*Esox lucius*) after dietary exposure. Organohalogen Compd 52:58–61
183. Raff J, Hites R (2007) Deposition versus photochemical removal of PBDEs from Lake Superior air. Environ Sci Technol 41:6725–6731
184. Watanabe I, Tatsukawa R (1990) Anthropogenic brominated aromatics in the Japanese environment. In: Freij L (ed) Proceedings, workshop on brominated aromatic flame retardants, Skokloster, Sweden, 24–26 October 1989. Swedish National Chemicals Inspectorate (KemI), Solna, Sweden, pp 63–70
185. Wong A, Lei YD, Alaee M, Wania F (2001) Vapour pressures of polybrominated diphenyl ethers. J Chem Eng Data 46:239–242
186. de Boer J, Boer K, Boon JP (2000) Polybrominated biphenyls and diphenylethers. In: Springer Verlag (ed) The handbook of environmental chemistry, Part K: New types of persistent halogenated compounds, vol 3, pp 62–71
187. WHO/ICPS (1994) EHC 162, Brominated flame retardants. International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland
188. He J, Robrock KR, Alvarez-Cohen L (2006) Microbial reductive debromination of polybrominated diphenyl ethers (PBDEs). Environ Sci Technol 40:4429–4434
189. Gerecke AC, Hartmann PC, Heeb NV, Kohler HP, Giger W, Schmid P, Zennegg M, Kohler M (2005) Anaerobic degradation of decabromodiphenyl ether. Environ Sci Technol 39:1078–1083
190. Robrock KR, Korytar P, Alvarez Cohen L (2008) Pathways for the anaerobic microbial debromination of polybrominated diphenyl ethers. Environ Sci Technol 42:2845–2852
191. Tokarz JA, Ahn MY, Leng J, Filley TR, Nies L (2008) Reductive debromination of polybrominated diphenyl ethers in anaerobic sediment and a biomimetic system. Environ Sci Technol 42:2845–2852
192. Kierkegaard A, Balk L, Tjärnlund U, de Wit CA, Jansson B (1999) Dietary uptake and biological effects of decabromodiphenyl ether in the rainbow trout (*Oncorhynchus mykiss*). Environ Sci Technol 33:1613–1617
193. Stapleton HM, Brazil B, Holbrook RD, Mitchelmore CL, Benedict R, Kon-stantinov A, Potter D (2006) In vivo and in vitro debromination of decabromodiphenyl ether (BDE 209) by juvenile rainbow trout and common carp. Environ Sci Technol 40:4653–4658
194. Stapleton HM, Letcher RJ, Baker RA (2004) Debromination of polybrominated diphenyl congeners BDE99 and BDE183 in the intestinal tract of the common carp (*Cyprinus carpio*). Environ Sci Technol 38:1054–1061
195. Vives I, Grimalt JO, La Corte S, Guillamón M, Barceló D (2004) Polybromodiphenyl ether flame retardants in fish from lakes in European high mountains and Greenland. Environ Sci Technol 38:2338–2344
196. Isosaari P, Lundebye AK, Ritchie G, Lie Ø, Kiviranta H, Vartiainen T (2005) Dietary accumulation efficiencies and biotransformation of polybrominated diphenyl ethers in Atlantic salmon (*Salmo salar*). Food Addit Contam 22:829–837
197. Borghesi N, Corsolini S, Leonards P, Brandsma S, de Boer J, Focardiet S (2009) Polybrominated diphenyl ether contamination levels in fish from the Antarctic and the Mediterranean Sea. Chemosphere 77:693–698
198. Voorspoels S, Covaci A, Schepens P (2003) Polybrominated diphenyl ethers in marine species from the Belgian North Sea and the Western Scheldt estuary; levels, profiles, and distribution. Environ Sci Technol 37:4348–4357
199. Hakk H, Larsen G, Klasson Wehler E (2002) Tissue disposition, excretion and metabolism of 2,2′,4,4′,5-pentabromodiphenyl ether (BDE-99) in the male Sprague–Dawley rat. Xenobiotica 32:369–382

200. Van den Steen E, Covaci A, Jaspers VLB, Dauwe T, Voorspoels S, Eens M, Pinxten R (2007) Accumulation, tissue-specific distribution and debromination of decabromodiphenyl ether (BDE 209) in European starlings (*Sturnus vulgaris*). Environ Pollut 148:648–653
201. Sellström U, Jansson B (1995) Analysis of tetrabromobisphenol A in a product and environmental samples. Chemosphere 31:3085–3092
202. WHO/ICPS (1995) EHC 172, Tetrabromobisphenol-A. International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland
203. Ronen AZ, Abeliovich A (2000) Anaerobic–aerobic process for microbial degradation of tetrabromobisphenol. Appl Environ Microbiol 66:2372–2377
204. Hakk H, Letcher RJ (2003) Metabolism in the toxicokinetics and fate of brominated flame retardants – a review. Environ Int 29:801–828
205. Davis JW, Gonsior S, Marty G, Ariano J (2005) The transformation of hexabromocyclododecane in aerobic and anaerobic soils and aquatic sediments. Water Res 39:1075–1084
206. Davis JW, Gonsior S, Markham DA, Friederich U, Hunziker RW, Arianob J (2006) Biodegradation and product identification of [14C] hexabromocyclododecane in wastewater sludge and freshwater aquatic sediments. Environ Sci Technol 40:5395–5401
207. Gerecke AC, Giger W, Hartmann PC, Heeb NV, Kohler HEP, Schmid P, Zennegg M, Kohler M (2006) Anaerobic degradation of brominated flame retardants in sewage sludge. Chemosphere 64:311–317
208. Davis JW, Gonsior SJ, Marty G, Friederich U, Ariano JM (2004) Investigation of the biodegradation of [14C] hexabromocyclododecane in sludge, sediment, and soil. In: Third international workshop on brominated flame retardants, Toronto, Canada, pp 239–244
209. MacGregor JA, Nixon WB (1997) Hexabromocyclododecane (HBCD): determination of n-octanol/water partition coefficient. Wildlife International Ltd, Easton, MD, 439C-104:68
210. Janak K, Covaci A, Voorspoels S, Becher G (2005) Hexabromocyclododecane in marine species from the western Scheldt estuary: diastereoisomer- and enantiomer-specific accumulation. Environ Sci Technol 39:1987–1994
211. Brandsma SH, van der Ven LTM, de Boer J, Leonards PEG (2009) Identification of hydroxylated metabolites of hexabromocyclododecane in wildlife and 28-days exposed Wistar rats. Environ Sci Technol 43:6058–6063

Degradation of Brominated Flame Retardants

E. Eljarrat, M.L. Feo, and D. Barceló

Abstract In this chapter, an overview of the degradation processes of brominated flame retardants is presented, including both chemical and biological processes. BFRs could be affected by different types of reactions, being the photochemical reactions the most widely studied and reported. Also, among the different BFR families, PBDEs, and in particular the deca-BDE, are those that have more studies and therefore more data on degradation pathways and degradation products. Degradation processes may change the structure of the contaminants, as well as its characteristics and properties. In this sense, it is very important to know the potential degradation products, as well as their environmental behavior and toxicology. Research regarding the transformation processes of BFRs and its products is needed for both environmental remediation and health assessments. Conclusions and future perspectives are outlined.

Keywords Biodegradation, Brominated flame retardants, Hexabromocyclododecane, Photodegradation, Polybrominated diphenylethers, Tetrabromobisphenol A, Thermal degradation

Contents

E. Eljarrat (✉) and M.L. Feo
Department of Environmental Chemistry, IDAEA, CSIC, Jordi Girona 18-26, 08034 Barcelona, Spain
e-mail: eeeqam@cid.csic.es

D. Barceló
Department of Environmental Chemistry, IDAEA, CSIC, Jordi Girona 18-26, 08034 Barcelona, Spain
and
Catalan Institute for Water Research (ICRA), Parc Científic i Tecnològic de la Universitat de Girona, Pic de Peguera 15, 17003 Girona, Spain

E. Eljarrat and D. Barceló (eds.), *Brominated Flame Retardants*,
Hdb Env Chem (2011) 16: 187–202, DOI 10.1007/698_2010_96,

Abbreviations

BFR	Brominated flame retardant
BPA	Bisphenol A
GC	Gas chromatography
HBCD	Hexabromocyclododecane
MS	Mass spectrometry
PBB	Polybrominated biphenyl
PBDD	Polybrominated dibenzo-*p*-dioxins
PBDE	Polybrominated diphenyl ether
PBDF	Polybrominated dibenzofuran
PCB	Polychlorinated biphenyl
POP	Persistent organic pollutant
TBBPA	Tetrabromobisphenol A
WWTP	Wastewater treatment plant

1 Introduction

Persistent organic pollutants (POPs), such as brominated flame retardants (BFRs), are organic compounds that are resistant to environmental degradation through chemical, biological, and photolytic processes. Because of this, they have been observed to persist in the environment, to be capable of long-range transport, to bioaccumulate in human and animal tissue, to biomagnify in food chains, and to have potential significant impacts on human health and the environment. However, there are a number of reactions that can take place once the BFRs are released to the different environmental compartments (air, water, soil, sediment).

While physicochemical properties, long-range transport, bioaccumulation, and toxicity of potential environmental contaminants are described, at least to some extent, the persistence of chemicals is in general less well understood. In order to conduct proper risk assessments for BFRs, more knowledge is needed on their persistence, especially the half-lives of such compounds. Degradation half-life time ($t_{1/2}$) is an important parameter to characterize the extent of degradation. Wania and Dugani [1] reported the $t_{1/2}$ values for several polybrominated diphenyl ethers (PBDE) congeners at ~150 days except for BDE-28 (~60 days). The United Nations

Environment Program on POPs has established criteria for identifying new POPs, and according to these criteria, a substance is classified as persistent if it has a half-life in soil or sediment of >180 days [2]. Under the European Union REACH chemical legislation, the half-life of a substance must be >120 days in freshwater sediment or soil to fulfill the persistent criteria, and to fulfill the very persistent criteria, the half-life must be >180 days in soil or sediment [3].

Depending on the chemical structure, it is possible to identify major potential reaction pathways. Many factors influence the degradation of contaminants, including the presence of light, level of oxygen, temperature, pH, humidity, and microorganism species composition. BFRs could be affected by abiotic oxidation, reductive debromination, hydrolysis, elimination, and substitution reactions. These processes may change the structure of the contaminant, as well as its characteristics and properties. In this sense, it is very important to take care on degradation products. For instance, European Union risk assessment [4] on BDE-209 concluded recently that there is a need for further information on the degradation of BDE-209 into more toxic and bioaccumulative compounds (e.g., reductive debromination to lower brominated congeners).

This chapter discusses some of the environmental degradation resulting from widespread urban chemical release to soil, surface water, sediments, groundwater, and air. Moreover, some degradation studies carried out for developing effective remediation processes for BFRs were also included.

2 Chemical Degradation

The perbromination of BFRs such as PBDEs makes it vulnerable to a range of chemical reactions, such as substitution, reduction, and photolysis. The latter two reaction pathways are leading to, among other products being formed, lower PBDE congeners. From a chemical point of view, deca-BDE-209 is a labile molecule. BDE-209 reacts readily with nucleophiles [5], it is reduced by hydride reagents such as sodium borohydride [6], and it is rapidly photolyzed under UV-B and UV-C irradiation [7]. Data available suggest that photochemical degradation is the main transformation process for PBDEs in the environment. Thus, it is important to understand the photochemical behavior of PBDEs, including both photodegradation kinetics and photoproducts.

2.1 Photochemical Degradation

A large number of halogen-containing organic compounds have been reported to undergo photochemical transformations, both under experimental and natural conditions as reviewed by Méallier [8], Pagni and Sigman [9], and Richard and Grabner [10]. In the environment, photochemical transformations proceed by direct

photolysis under the action of solar light and occur in the atmosphere and in surface waters. However, the low volatility and low solubility of many organohalogen compounds make it difficult to study their photolysis in these media in the laboratory. To overcome these constraints, a variety of procedures for measuring the photolysis reactions of organohalogen pollutants have been reported, although differences in the use of solvents, apparatus, and wavelengths can lead to different results being obtained for the same compound.

2.1.1 Polybrominated Diphenyl Ethers

PBDEs belong to the group of organobromine compounds that absorb light in the UV-A spectra. The energy supplied by UV light often results in loss of bromine and thereby also a possibility for rearrangements. Photolytic degradation of organobromines is a well-known type of reaction in basic chemistry. The rate of degradation of PBDEs by UV light in the sunlight region is dependent on the degree of bromination. Hence, lower PBDEs degrade slower than highly brominated congeners. Degradation rates of 15 PBDE congeners, dissolved in 80% methanol exposed to UV light, were determined by Eriksson et al. [11] showing decreasing rates with decreased bromination degree of the diphenyl ethers. The observed rate difference is up to 700 times between the slowest reacting PBDE studied (tetra-BDE-77) and the fastest (deca-BDE-209). Much of these differences can be explained by their absorbance behavior since the higher PBDEs absorb at longer wavelengths. Hexa-BDEs to octa-BDEs and di-BDFs to penta-BDFs were shown. One product was also identified as a methoxylated tetra-BDF.

Many studies have shown that BDE-209 is labile to light, and photolysis is an important degradation pathway for the compound in the environment. The main photoproducts of BDE-209 are lower brominated PBDEs and polybrominated dibenzofurans (PBDFs), which are more persistent, bioavailable, and toxic. The first study, performed in the late 1980s by Watanabe and Tatsukawa [12], indicated the formation of debrominated diphenyl ethers. Octa-BDEs down to tri-BDEs were reported as major products. Furthermore, mono-BDFs to hexa-BDFs were reported as products in their study as well as tetra- and penta-bromobenzenes. Ohta et al. [13] dissolved deca-BDE in toluene to detect a large number of lower PBDEs, mainly mono-BDEs to nona-BDEs. Deca-BDE dissolved in toluene or adsorbed to silica gel, sand, sediment, or soil and subjected to UV light reported similar transformations without matrix-related effects on the product profile (PBDEs and PBDFs) but with effects on BDE-209 degradation rate [7]. Great differences of BDE-209 photolytic rates were found among these different media. The half-life of BDE-209 adsorbed on soil was 600 times longer than that on silica gel. Similarly, it has been shown that sand particles coated with humic acid may decrease degradation rates of deca-BDE when irradiated with UV light [14]. In contrast, Ahn et al. [15] showed increased photolytic transformation rates when deca-BDE was adsorbed to clay minerals (montmorillonite and kaolinte), probably due to the electron-donating ability of the clay minerals.

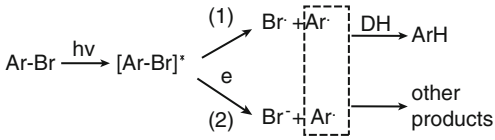


Fig. 1 Photolytic mechanism of BDE-209. Reproduced from [16]

According to the previous studies, the possible mechanism of BDE-209 photolysis can be proposed as shown in Fig. 1 [16]. The excited BDE-209 molecule ([Ar–Br]*) can undergo debromination processes via C–Br homolysis (step 1) or by the attack of electron donor (step 2). Then the generated aryl radical can get a hydrogen atom from the hydrogen donor (DH) (step 3), or undergo other pathways such as polymerization to form products. Thus, besides the hydrogen-donating and electron-donating efficiency of the reaction media, properties of BDE-209 in different media may affect the photolytic rate, such as the energy for BDE-209 to be exited and the difficulty for C–Br bonds to cleave.

Photolysis of deca-BDE yields a wide span of products, from nona-BDEs to hydroxylated bromobenzenes. The photolytic half-life for BDE-209 is longer on more complex matrices, i.e., sediment and soil. The slow rate of photodebromination on soil may cause a continuous production of lower brominated PBDEs, such as BDE-154 and BDE-183, which are more stable to photolytic degradation and more bioaccumulative due to smaller molecular size and lower K_{ow}. Recommendations and perspectives BDE-209, the main constituent of deca-BDE mixture, is primarily forming debrominated diphenyl ethers with higher persistence, which are more bioaccumulative than the starting material when subjected to UV light. Hence, deca-BDE should be considered as a source of these PBDE congeners in the environment.

2.1.2 Hexabromocyclododecane

The information on photodegradation processes of hexabromocyclododecane (HBCD) is very scarce. Recently, the photochemical properties of α-, β-, and γ-HBCD have been investigated [17]. As a result of this study, the UV absorption spectra of the three HBCD diastereosiomers were provided, as well as a detailed assignment of the UV spectral features. The photodegradation and photostereoisomerization trends of HBCDs under the UV illumination with wavelengths shorter than 240 nm were predicted. The study also demonstrated the photostereoisomerization trends. However, more attention should be paid to the photochemical properties for HBCDs.

2.1.3 Tetrabromobisphenol A

A large number of halogen-containing organic compounds have been reported to undergo photochemical transformations, under both experimental and natural conditions. For phenolic compounds, such as tetrabromobisphenol A (TBBPA), the

rate of photodegradation is highly dependent on the pH [10] as the absorption of the associated and dissociated forms can be very different. Photolytic decomposition of TBBPA in the environment occurs in the atmosphere and in surface waters. Eriksson et al. [11] have reported that, at pH values below its p*K*a of ~7.4, the quantum yield of TBBPA photodecomposition decreases with decreasing pH, while at pH values above its p*K*a, photodecomposition is independent of pH. There are several reported studies on TBBPA decomposition pathways [11, 18, 19], which suggest that the most important routes involve debromination and scission reactions that yield phenols. Radical reactions are thought to be responsible for the formation of the intermediates in the TBBPA decomposition pathways.

Eriksson et al. [11] developed a method for studies of the phototransformation at UV irradiation of aqueous solutions of TBBPA and related compounds at various pHs. They found that the rate of decomposition of TBBPA was six times higher at pH 8 than at pH 6. Identification of the degradation products of TBBPA and Tri-BBPA, by gas chromatography (GC)–mass spectrometry (MS) analysis and by comparison to synthesized reference compounds, indicated that TBBPA and Tri-BBPA decompose via different mechanisms. Three isopropylphenol derivatives, 4-isopropyl-2,6-dibromophenol, 4-isopropylene-2,6-dibromophenol, and 4-(2-hydroxyisopropyl)-2,6-dibromophenol, were identified as major degradation products of TBBPA, while the major degradation product of Tri-BBPA was tentatively identified as 2-(2,4-cyclopentadienyl)-2-(3,5-dibromo-4-hydroxyphenyl)propane (Fig. 2).

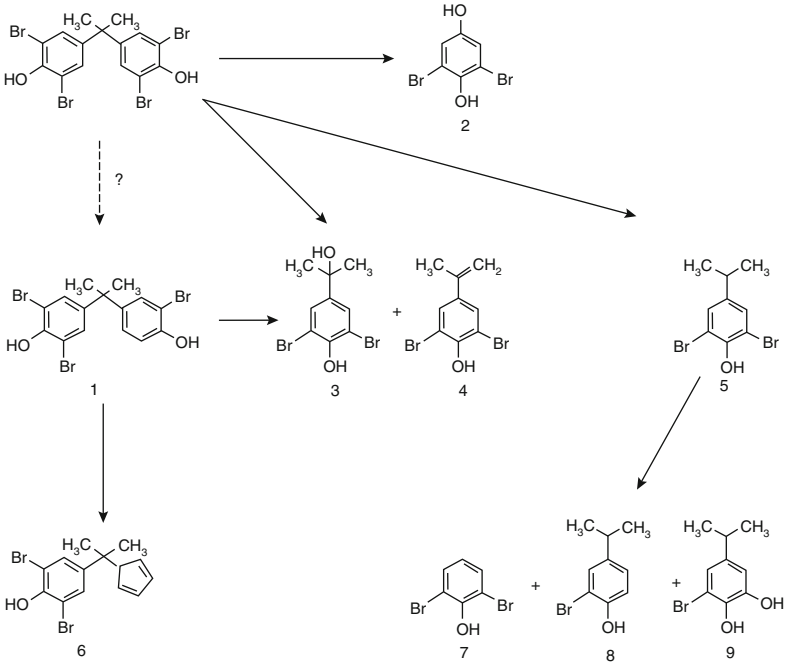


Fig. 2 Proposed degradation path for TBBPA. Reproduced from [11]

In the environment, photochemical transformations proceed by direct photolysis under the action of solar light. In sensitized redox processes under aerobic conditions, the active reaction intermediates participating in the transformation of the pollutant may be the electronically excited sensitizer molecule or the solvated electron as well as reactive oxygen species such as singlet oxygen ($^1O_2$) or the superoxide anion radical ($O_2^{\bullet -}$) [20, 21]. Han et al. [22] explored the possibility of photosensitized degradation of TBBPA mediated by singlet oxygen or free radicals. While direct photodegradation may be environmentally important, particularly in alkaline waters, the authors suggest that reaction with $^1O_2$ may be an alternative pathway. Because TBBPA is a stable compound that at neutral pH does not absorb much of the atmosphere-filtered solar radiation, its photosensitized oxidation by $^1O_2$ may be the key reaction initiating or mediating TBBPA degradation in the natural environment. Han et al. [22] concluded that because the quantum yield of generation of self-sensitized singlet oxygen by TBBPA is low, it is unlikely to play a role in the degradation of the retardant. However, previous studies have shown that there are environmental sources of singlet oxygen such as the humic acids [23] which could contribute to the destruction of TBBPA.

2.2 Thermal Degradation

Some studies have focused on the thermolysis of certain BFRs. Results showed the formation of polybrominated dibenzo-*p*-dioxins (PBDDs) and PBDFs. In particular, experiments using brominated aromatics that could be considered as PBDD/PBDF precursors, such as PBDEs or polybrominated biphenyls (PBBs), resulted in high yields of PBDDs/PBDFs. Weber and Kuch [24] discussed four categories of thermal processes according to their potential for PBDD/PBDF generation: thermal stress, pyrolysis/gasification, insufficient combustion conditions, and controlled combustion conditions.

Under thermal stress situations, as they may occur in production or recycling processes, PBDDs/PBDFs precursors like PBDEs can have a relevant potential for PBDD/PBDF formation via a simple elimination. From a mechanistic point of view, the formation of PBDFs from PBDEs requires only an intramolecular elimination of Br_2 or HBr. It is generally observed that the yield of PBDD/PBDFs in pyrolytic residues decreases from penta-BDEs, octa-BDEs, to deca-BDEs. Luijk et al. [25] suggested that the higher yield of PBDFs from low brominated PBDEs is due to the energetically favorable elimination of HBr in lower brominated DPE (requirement of an hydrogen position in *ortho*-position of the PBDEs), compared to the energetically less favorable elimination of two bromine substituents in highly brominated DE. An alternative explanation for the low PBDD/PBDF formation potential of higher brominated PBDEs may be the steric hindrance in the formation of CC bond, when bromine substitution results in 1,9-substituted PBDF: the bromine substituents in 1,9 position in PBDFs cause a "steric crowding." Therefore, the formation of PBDFs with a hydrogen substituent in 9-position is favored (requirement of a hydrogen position in *meta*-position of PBDEs) (Fig. 3).

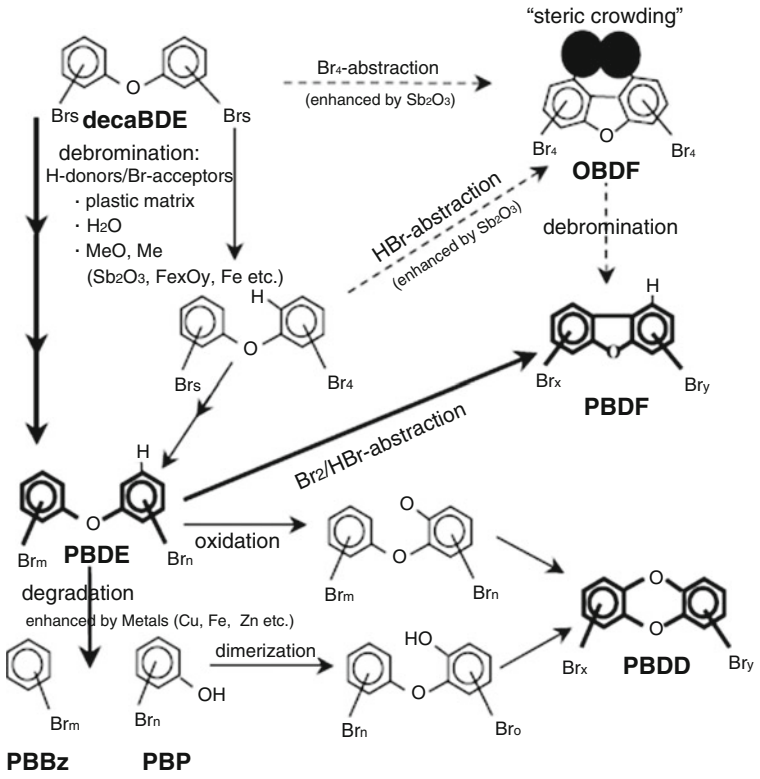


Fig. 3 Formation pathways of PBDDs and PBDFs from deca-BDE during thermal degradation. Reproduced from [24]

For most BFRs, formation of PBDDs/PBDFs by a simple elimination or condensation step is not possible. TBBPA is one example in this respect. Although formation of PBDDs and PBDFs has been observed during thermolysis of TBBPA [26], the yields were orders of magnitudes lower compared to PBDEs or bromophenols. Dettmer [27] investigated the thermal degradation of TBBPA during thermal degradation and observed the formation of large amounts of brominated phenols (up to 17%) and to a lesser amount brominated benzenes (up to 0.5%). The amount of brominated phenols and benzenes detected in the condensates showed a good quantitative correlation to the amount of PBDDs and PBDFs formed. The formation of PBDDs/PBDFs from TBBPA proceeds therefore, most probably, in two steps: (a) the generation of precursors (polybrominated phenols and polybrominated benzenes) during thermal degradation/incineration of the polymer/TBBPA and (b) dimerization/condensation of the precursors.

Under insufficient combustion conditions as they are present in, e.g., accidental fires and uncontrolled burning as well as gasification/pyrolysis processes, considerable amounts of PBDDs/PBDFs can be formed from BFRs, preferably via the

precursor pathway. In contrast, under controlled combustion conditions, BFRs and PBDDs/PBDFs can be destroyed with high efficiency.

3 Biological Degradation

BFRs have been shown to be susceptible to several metabolic processes including oxidative debromination, reductive debromination, oxidative CYP enzyme-mediated biotransformation, and Phase II conjugation (glucuronidation and sulfation) [28]. Thus, biodegradation can be one of the most important processes that reduce concentrations of organic chemicals in the environment. Aerobic biodegradation processes can predominate in surface waters, surface soils, and the aeration basins of wastewater treatment plants (WWTPs). Anaerobic processes, in contrast, can occur in aquatic sediments, groundwater, and anaerobic digestion units of WWTPs. Anaerobic degradation in sediments, soils, and sewage sludge has been frequently reported for organohalogen compounds other than BFRs. Reductive dehalogenation (e.g., substitution of Br or Cl by a hydrogen atom) has been shown to be an important mechanism [29, 30]. Thereby, halogenated compounds serve as electron acceptors in respiratory or cometabolic processes. Examples include reduction of polychlorinated biphenyls (PCBs) and PBBs in anaerobic sediment enrichment cultures [31, 32].

Biotransformation, an alternative to degradation, alters the compound without making substantial changes to the carbon skeleton of the substrate. Microbial O-methylation is one such biotransformation reaction commonly observed for many halogenated phenolic compounds [33]. The microbial biotransformation products may differ greatly in their chemical characteristics (e.g., water solubility, partitioning onto solids) and more importantly their bioaccumulation potential and toxicity. Thus, it is important to know the different biotransformation mechanisms to elucidate potential risks to environmental and human health due to transformation products.

3.1 Polybrominated Diphenyl Ethers

Debromination of deca-BDE and octa-BDE mixture was observed with anaerobic bacteria including *Sulfurospirillum multivorans* and *Dehalococcoides* species [34] (Fig. 4). Hepta- and octa-BDEs were produced by the *S. multivorans* culture when it was exposed to deca-BDE, although no debromination was observed with the octa-BDE mixture. In contrast, a variety of hepta- through di-BDEs were produced by *Dehalococcoides*-containing cultures exposed to octa-BDE mixture, despite the fact that none of these cultures could debrominate deca-BDE. The more toxic hexa-BDE-154, penta-BDE-99, tetra-BDE-49, and tetra-BDE-47 were identified among the debromination products.

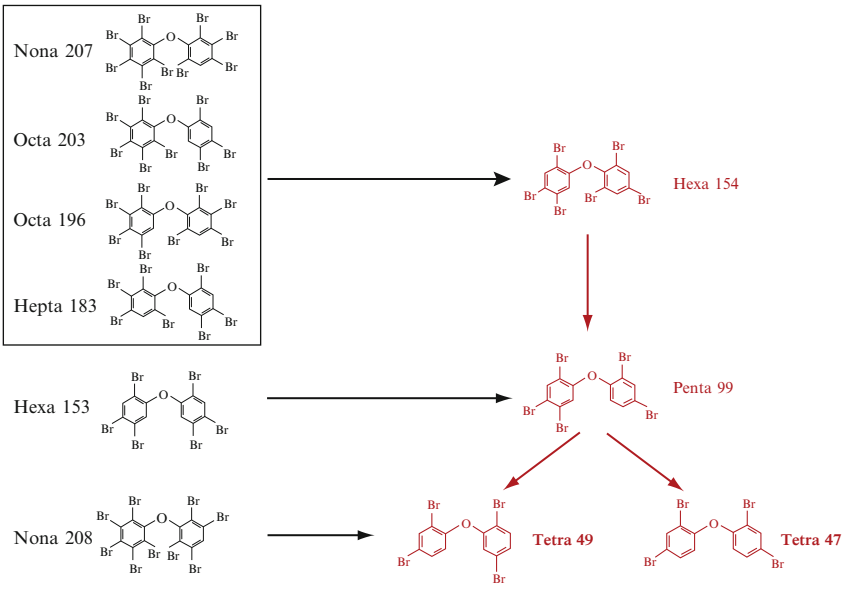


Fig. 4 Identified PBDE substrates (*black*) and debromination products (*red*) detected for ANAS195 amended with the octa-BDE mixture. *Arrows* connect substrates with potential debromination products assuming no isomerization. Reproduced from [34]

Kim et al. [35] reported an aerobic degradation pathway for diphenyl ether used for the biotransformation of selected PBDEs by an isolated *Sphingomonas* strain. *Sphingomonas* sp. PH-07 was isolated from activated sludge samples of a WWTP using diphenyl ether as sole carbon and energy source. In liquid cultures, this strain mineralized 1 g of diphenyl ether per liter completely within 6 days. The metabolites detected and identified corresponded with a feasible degradative pathway. However, the strain PH-07 even catabolized several brominated congeners such as mono-, di-, and tri-PBDEs thereby producing the corresponding metabolites.

The debromination pathways of seven PBDEs (BDE-47, -99, -153, -183, -196, -197, and -203) by three different cultures of anaerobic dehalogenating bacteria were investigated by Robroch et al. [36] (Fig. 5). Dehalogenating cultures evaluated were a trichloroethene-enriched consortium containing multiple *Dehalococcoides* species and two pure cultures, *Dehalobacter restrictus* PER-K23 and *Desulfitobacterium hafniense* PCP-1. All studied congeners were debrominated to some extent by the three cultures and all exhibited similar debromination pathways with preferential removal of *para* and *meta* bromines. Debromination of the highly brominated congeners was extremely slow, with usually less than 10% of nanomolar concentrations of PBDEs transformed after 3 months. In contrast, debromination of the lesser brominated congeners, such as penta-BDE-99 and tetra-BDE- 47, was faster,

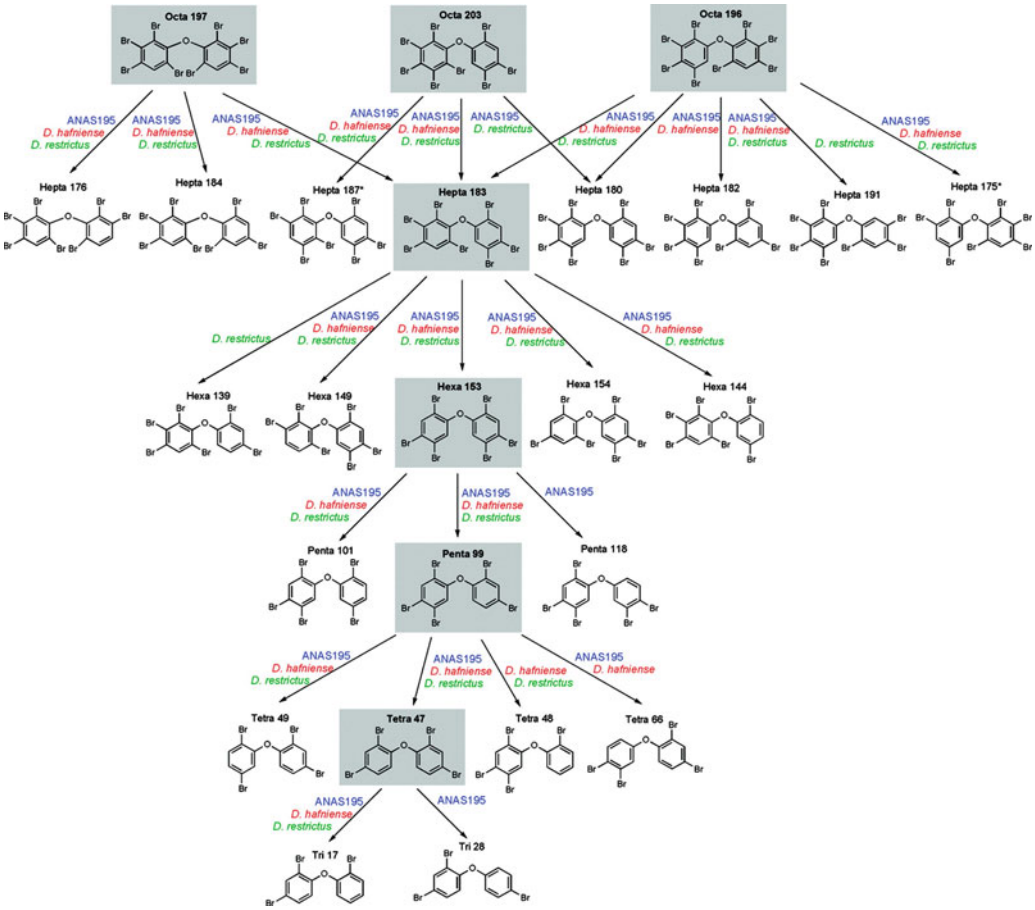


Fig. 5 PBDE debromination pathway by different cultures. Highlighted molecules are those that were applied as initial substrate. The cultures that produced each congener are listed by the reaction *arrows*. *Asterisk* (*) indicates congener that is presumptively identified due to lack of available standards. Reproduced from [36]

with some cultures completely debrominating nanomolar levels of tetra-BDE-47 within weeks.

White rot fungi are known to degrade a wide variety of recalcitrant pollutants. Zhou et al. [37] studied for the first time BDE-209 transformation by fungi. White rot fungi can rapidly oxidize and mineralize a broad spectrum of diverse aromatic compounds, such as PCBs, which have similar structures as PBDEs. However, the biodegradation of PBDEs is limited by their low bioavailability resulting from extremely low water solubility. Many researches have examined the possibility of enhancing the bioavailability of low solubility and highly sorptive compounds by adding a "solubilization" agent such as a surfactant or cyclodextrin to the system. Tween 80 is a kind of nonionic surfactant which was used widely in the degradation

of hydrophobic or insoluble organic compounds. Cyclodextrins are cyclic, non-reducing maltooligosaccharides produced from the enzymatic degradation of starch and related compounds by certain bacteria that contain the cyclodextrin glycosyltransferases. Zhou et al. [37] showed that BDE-209 could be degraded by white rot fungi. Tween 80 at appropriate concentration was found capable of significantly enhancing the biodegradation of BDE-209 by white rot fungi. But Tween 80 at a high concentration will restrain the fungal growth and the degradation of BDE-209. Cyclodextrins could also improve the BDE-209 degradation by white rot fungi. It is a promising bioavailability-enhancing agent for the treatment of BDE-209 contaminations, not only for its positive effects on the BDE-209 degradation, but also for its partial biodegradability, nontoxicity, and relatively low cost.

3.2 Hexabromocyclododecane

Anaerobic degradation of technical HBCD mixture has been reported by Davis et al. [38]. Soil and sediment microcosms were used to evaluate the environmental lifetime of HBCD under realistic environmental concentrations. HBCD loss was observed in both viable and abiotic soils and sediments, although the rates were appreciable faster in the viable reaction mixtures. Biologically mediated transformation processes (i.e., biotransformation) accelerated the rate of loss of HBCD when compared to the biologically inhibited (i.e., heat-treated) soils and sediments. Biotransformation half-lives for HBCD were determined to be 63 and 6.9 days in the aerobic and anaerobic soils, respectively, while biotransformation half-lives for HBCD in the two river systems ranged from 11 to 32 days and 1.1 to 1.5 days under aerobic and anaerobic conditions, respectively. Brominated degradation products were not detected in any of the soils or sediment microcosms during the course of this study.

In a later work, Davis et al. [39] identified major intermediate metabolites formed during HBCD biodegradation. Substantial biological transformation of α-, β-, and γ-HBCD diastereomers was observed in wastewater (i.e., digester) sludge and in freshwater aquatic sediment microcosms prepared under aerobic and anaerobic conditions. Concomitant with the loss of HBCD in these matrixes, there was a concurrent production of three products. These metabolites were identified as tetrabromocyclododecene, dibromocyclododecadiene, and cyclododecatriene. These results demonstrate that microorganisms naturally occurring in aquatic sediments and anaerobic digester sludge mediate complete debromination of HBCD.

Gerecke et al. [40] studied the degradation of HBCD under anaerobic conditions in digested sewage sludge. The half-life of technical HBCD mixture was 0.66 day. Moreover, experiments with (±)-α-, (±)-β-, and (±)-γ-HBCD incubated in separate experiments showed that (±)-β- and (±)-γ-HBCD degraded more rapidly than (±)-α-HBCD by an estimated factor of 1.6 and 1.8, respectively. The fact that (±)-α-HBCD exhibited an almost doubled half-life compared to (±)-β-HBCD

and (±)-γ-HBCD is an important finding with respect to the discussion on the persistence of individual HBCD diastereoisomers and the reports on strong relative enrichment of α-HBCD in biota. Finally, no statistically significant enantioselective degradation of α-, β-, or γ-HBCD was found.

3.3 Tetrabromobisphenol A

Various redox zones exist in estuarine sediments, depending upon the location and pollutant input. Nitrate-reducing, sulfate-reducing, iron(III)-reducing, and methanogenic conditions could be encountered within sediment layers. Dehalogenation, a process through which dehalogenating bacteria utilize halogenated compounds as electron acceptors, can be enhanced or inhibited by other electron acceptors present in the sediment [41]. For example, studies have found that under sulfate-reducing conditions (the primary electron-accepting process in the top layers of marine and estuarine sediments), the process of dehalogenation may be inhibited. Dehalogenation may be suppressed by the following: direct inhibition of dehalogenases by sulfate, sulfite, or hydrogen sulfide; preferential use of sulfate (over the halogenated compound) as an electron acceptor within the same organism; or successful competitive exclusion of dehalogenating bacteria through competition for electron donor by sulfate-reducing bacteria [42]. Biotransformation of TBBPA, and their ultimate biodehalogenation product, bisphenol A (BPA), was examined in anoxic estuarine sediments [43]. Dehalogenation of TBBPA was examined under conditions promoting either methanogenesis or sulfate reduction as the primary terminal electron-accepting process. Complete dehalogenation of TBBPA to BPA with no further degradation of BPA was observed under both methanogenic and sulfate-reducing conditions. Dehalogenation of TBBPA under both methanogenic and sulfate-reducing conditions resulted in the accumulation of a persistent dichlorinated bisphenol A isomer, while no BPA was formed. The dehalogenation of TBBPA and the potential for accumulation of BPA in anoxic sediments are significant, given the widespread use of these chemicals. The persistence of BPA in anoxic sediments under a variety of electron-accepting conditions is thus a concern. BPA has been detected in anoxic marine sediments [44], and it will likely persist for an extended period of time. Formation of BPA through the dehalogenation of TBBPA could potentially increase concentrations of this compound in anoxic environments. Combined, the concerns regarding the potential estrogenic effects of BPA and the largely unknown effects of TBBPA, and the potential for the accumulation of BPA under anoxic conditions justify vigilance and the continued study of the environmental fate of this flame retardant.

Although TBBPA dimethyl ether is not produced in industry, it has been detected in samples of terrestrial and aquatic sediments, as well as biological samples. It was hypothesized that the TBBPA dimethyl ether may be a product of microbial transformation. Allard et al. [45] first demonstrated that bacterial cultures

were capable of O-methylating TBBPA although the reaction proceeded at a relatively slow rate. George and Häggblom [46] showed that two mycobacterium isolates known for their ability to O-methylate chlorophenols transform TBBPA to the corresponding mono- and dimethylated ethers. Additionally, this study demonstrated the microbially mediated O-methylation of TBBPA in sediment microcosms, suggesting that O-methylation of TBBPA may be an environmentally significant process. With the addition of two hydrophobic methyl groups, TBBPA dimethyl ether is more lipophilic than its parent compound. This characteristic increases its potential for bioconcentration in fatty tissue. Currently, little is known about the toxicology of TBBPA mono- and dimethylated ether. Given the suspected prevalence of bacterial O-methylation, additional environmental and toxicological data should be collected for these derivatives.

4 Conclusions

Large variations were found in the degradability among the different BFRs, and generally, degradation was faster in aerobic than in anaerobic conditions. The degradation rates of PBDEs were not significant, or low, in both aerobic and anaerobic conditions. TBBPA also degraded slowly in anaerobic soil. However, degradation rates in the environment will also be affected by factors such as temperature, presence of light, humidity, and the microorganism flora.

The degradation process more widely studied is the photochemical degradation. Different studies revealed the degradation rates, degradation pathways, and degradation products. It is important to pay attention to these new chemicals formed under different processes. Degradation products are formed and often have similar properties as the original substances (persistence, bioaccumulation potential, toxicity), and may accumulate in the system. If a degradation product is, at the same time, present in the environment in relevant quantities and has high bioaccumulation potential and toxicity, not taking this degradation product into account might lead to an underestimation of the hazard and risk of the parent compound. For example, PBDDs and PBDFs are degradation products of thermal PBDE degradation, and they have greater toxicity than PBDEs themselves. Another example is the BPA, resulting from the TBBPA degradation, and a well-known endocrine disruptor. Thus, the transformation products of BFRs may prove to be important for health risk evaluation. Further research regarding the transformations of BFRs is needed for both environmental remediation and health assessments.

As was reviewed in this chapter, some data related with chemical and biological degradation of selected BFRs, such as PBDEs, HBCD, or TBBPA, are available. However, in addition to these more studied BFRs, other BFRs have entered the market in recent years (see chapter by de Wit, this volume) [47], and they are being found in the environment. Thus, more data on these new BFRs are needed to evaluate their degradation rates as well as their degradation products.

Acknowledgments This research work was founded by the Spanish Ministry of Science and Innovation through the projects CEMAGUA (CGL2007-64551/HID) and Consolider-Ingenio 2010 (CSD2009-00065), by the CSIC through the project Intramural (ref. 200880I096) and by the Fundación BBVA under the BROMACUA project (Evaluación del impacto ambiental de los retardantes de llama bromados en ecosistemas acuáticos de América Latina). María Luisa Feo acknowledges CSIC for providing training and specialization of staff investigator through the JAE-Doc program.

References

1. Wania F, Dugani CB (2003) Environ Toxicol Chem 22:1252
2. UNEP (2001) Final act of the conference of plenipotentiaries on the Stockholm convention on persistent organic pollutants. United Nations Environment Program, Geneva, Switzerland
3. European Union (2006) Annex XIII. Criteria for the identification of persistent, bioaccumulative and toxic substances, and very persistent and very bioaccumulative substances. Official Journal of the European Union L396, 383–385. Brussels, Belgium
4. Hansen BG, Munn SJ, de Bruijn J, Luotamo M, Pakalin S, Berthault F, Vegro S, Pellegrini G, Allanou R, Scheer S (eds) (2002) EUR 20402 ENsEuropean Union Risk Assessment Report bis(pentabromophenyl) Ether, Volume 17; European Commission, Luxembourg
5. Rahm S, Jakobsson E (2001) Reactivity of brominated diphenyl ethers vs. methane thiolate. Proceedings of the second international workshop on brominated flame retardants, Stockholm. Swedish National Chemicals Inspectorate, Solna, Sweden, pp 227–228
6. Eriksson J, Eriksson L, Marsh G, Bergman A (2003) Organohalogen Compd 61:191
7. Söderström G, Sellström U, de Wit CA, Tysklind M (2004) Environ Sci Technol 38:127
8. Méallier P (1999) Phototransformation of pesticides in aqueous solution. In: Boule P (ed) Environmental photochemistry, vol 2, part l. Springer Verlag, Berlin, Heidelberg, Germany, p 241
9. Pagni RM, Sigman ME (1999) The photochemistry of PAHs and PCBs in water and on solids. In: Boule P (ed) Environmental photochemistry, vol 2, part l. Springer Verlag, Berlin, Heidelberg, Germany, p 139
10. Richard C, Grabner G (1999) Mechanism of phototransformation of phenol and derivatives in aqueous solution. In: Boule P (ed) Environmental photochemistry, vol 2, part l. Springer Verlag, Berlin, Heidelberg, Germany, p 218
11. Eriksson J, Rahm S, Green N, Bergman A, Jakobsson E (2004) Chemosphere 54:117
12. Watanabe I, Tatsukawa R (1987) Bull Environ Contam Toxicol 39:953
13. Ohta S, Nishimura H, Nakao T, Aozasa O, Miyata H (2001) Organohalogen Compounds 52:321
14. Hua I, Kang N, Jafvert CT, Fabrega-Duque JR (2003) Environ Toxicol Chem 22:798
15. Ahn MY, Filley TR, Jafvert CT, Nies L, Hua I, Bezares-Cruz J (2006) Environ Sci Technol 40:215
16. Xie Q, Chen J, Shao J, Chen C, Zhao H, Hao C (2009) Chemosphere 76:1486
17. Zhao Y, Zhang X, Sojinu S (2010) Chemosphere 80:150
18. Barontini F, Cozzani V, Marsanich K, Raffa V, Petarca L (2004) J Anal Appl Pyrolysis 72:41
19. Marsanich K, Zanelli S, Barontini F, Cozzani V (2004) Thermochim Acta 421:95
20. Haag WR, Hoigne J (1986) Water Chlorination 5:1011
21. Baxter RM, Carey JH (1983) Nature 306:575
22. Han SK, Bilski P, Karriker B, Sik RH, Chignell CF (2008) Environ Sci Technol 42:166
23. Sandvik SLH, Bilski P, Pakulski JD, Chignell CF, Coffin RB (2000) Mar Chem 69:139
24. Weber R, Kuch B (2003) Environ Int 29:699
25. Luijk R, Wever H, Olie K, Govers HAJ (1991) Chemosphere 23:1173
26. Wichmann H, Dettmer FT, Bahadir M (2002) Chemosphere 47:349

27. Dettmer FT (2001) Bromorganische Flammschutzmittel-Analytische Anforderungen und thermische Bildung von polybromierten Dibenzo-p-dioxinen und Dibenzofuranen. Dissertation, University of Braunschweig
28. Hakk H, Letcher RJ (2003) Environ Int 29:801
29. Suflita JM, Horowitz A, Shelton DR, Tiedje JM (1982) Science 218:1115
30. Fetzner S (1998) Appl Microbiol Biotechnol 50:633
31. Bedard DL, van Dort HM, May RJ, Smullen LA (1997) Environ Sci Technol 31:3308
32. Abraham WR, Nogales B, Golyshin PN, Pieper DH, Timmis KN (2002) Curr Opin Microbiol 5:246
33. Häggblom MM (1992) FEMS Microbiol Rev 9:29
34. He JZ, Robrock KR, Alvarez-Cohen L (2006) Environ Sci Technol 40:4429
35. Kim YM, Nam IH, Murugesan K, Schmidt S, Crowley DE, Chang YS (2007) Appl Microbiol Biotechnol 77:187
36. Robrock K, Korytar P, Alvarez-Cohen L (2008) Environ Sci Technol 42:2845
37. Zhou J, Jiang W, Ding J, Zhang X, Gao S (2007) Chemosphere 70:172
38. Davis, JW, Gonisor SJ, Marty G, Friederich U, Ariano JM (2004) Investigation of the biodegradation of [14C]hexabromocyclododecane in sludge, sediment, and soil. In: The third international workshop on brominated flame retardants. Book of Abstracts, p 239
39. Davis JW, Gonsior SJ, Markham DA, Friederich U, Hunziker RW, Ariano JM (2006) Environ Sci Technol 40:5395
40. Gerecke AC, Giger W, Hartmann PC, Heeb NV, Kohler HPE, Schmid P, Zennegg M, Kohler M (2006) Chemosphere 64:311
41. Häggblom MM, Milligan PW (2000) Anaerobic degradation of halogenated pesticides: influence of alternate electron acceptors. In: Bollag JM, Stotzky G (eds) Soil biochemistry, vol 10. Marcel Dekker, New York, pp 1–34
42. Gerritse J, Drzyzga O, Kloetstra G, Keijmel M, Wiersum LP, Hutson R, Collins MD, Gottschal JC (1999) Appl Environ Microbiol 65:5212
43. Voordeckers JW, Fennell DE, Jones K, Häggblom MM (2002) Environ Sci Technol 36:696
44. Khim JS, Kannan K, Villeneuve DL, Koh CH, Giesy JP (1999) Environ Sci Technol 33:4199
45. Allard A, Remberger M, Neilson AH (1987) Appl Environ Microbiol 53:839
46. George KW, Haggblom M (2008) Environ Sci Technol 42:5555
47. de Wit CA, Kierkegaard A, Ricklund N, Sellström U (2010) Emerging brominated flame retardants (BFRs) in the environment. In: Eljarrat E, Barceló D (eds) Brominated flame retardants, The handbook of environmental chemistry. Springer-Verlag, Berlin Heidelberg

Human Exposure to Brominated Flame Retardants

Leisa-Maree L. Toms, Laurence Hearn, Andreas Sjödin, and Jochen F. Mueller

Abstract Human polybrominated diphenyl ether (PBDE) exposure occurs through a range of pathways including: ingestion of dust including hand-to-mouth contact; inhalation (air/particulate matter); and ingestion via food including the unique nutrition sources of human milk and placental transfer. While inhalation has been deemed a minor source of exposure, ingestion of food and dust make greater contributions to overall PBDE body burden with intake via dust reported to be much higher in infants than in adults.

PBDEs have been detected in samples of human milk, blood serum, cord blood, and adipose tissue worldwide. Concentrations have been found to be highest in populations from North America, followed by Australia, Europe, and Asia. While factors such as gender and parity may not affect concentrations, occupational exposure and age (infants and children) are associated with higher PBDE concentrations. In contrast to "traditional" persistent organic pollutants, there is an inverse relationship between PBDE body burden and age. Predicted body burden calculated using available information on intake and elimination rates of BFRs appears to underestimate measured human body burden data obtained through analysis of BFRs in blood or human milk. This may be due to unknown exposure or inaccurate elimination data. Further exposure studies should focus on younger age groups and an investigation of human PBDE half-lives.

Keywords Adipose tissue, Blood, Body burden, Exposure, Half-lives, Human milk

---

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

L.-M.L. Toms, J.F. Mueller (✉), L. Hearn
The University of Queensland National Research Centre for Environmental Toxicology, 39 Kessels Road, Coopers Plains, 4108, QLD, Australia
e-mail: j.mueller@uq.edu.au

A. Sjödin
Center for Disease Control and Prevention, 4770 Buford Hwy, MS F-17, Atlanta, GA 30341-3724, USA

E. Eljarrat and D. Barceló (eds.), *Brominated Flame Retardants*,
Hdb Env Chem (2011) 16: 203–240, DOI 10.1007/698_2010_90,

Contents

1 Introduction

Over the last few decades, data on brominated flame retardants (BFRs), in particular polybrominated diphenyl ethers (PBDEs), have increased worldwide. In comparison with "traditional" persistent organic pollutants (POPs), the exposure modes of BFRs in humans are less well defined, although dietary sources, inhalation, and dust ingestion have all been reported (e.g., [1–3]). The human body burden (i.e., concentration of chemical in a given person at a given time) is a function of all intake and elimination processes (half-lives) of the chemicals. Both intake and elimination processes are relative to body size and can vary between individuals substantially. In this chapter, we aim to provide an overview of human exposure to BFRs and factors that may affect human exposure. Furthermore, we aim to evaluate whether human body burden data obtained through analysis of BFRs in blood or human milk is in agreement with predicted body burden calculated using available information on intake and elimination rates of BFRs.

2 Exposure Pathways

Human PBDE exposure occurs through a range of pathways (Fig. 1) including:

- Ingestion of dust including hand-to-mouth contact
- Inhalation (air/particulate matter) and
- Ingestion via food, mainly fatty fish, meat, dairy products, and the unique nutrition sources of human milk and placental transfer

2.1 Dust

Human exposure to PBDEs is suggested to occur via ingestion of dust. Relatively high levels of PBDEs have been extensively reported in house dust [3–13] and to a

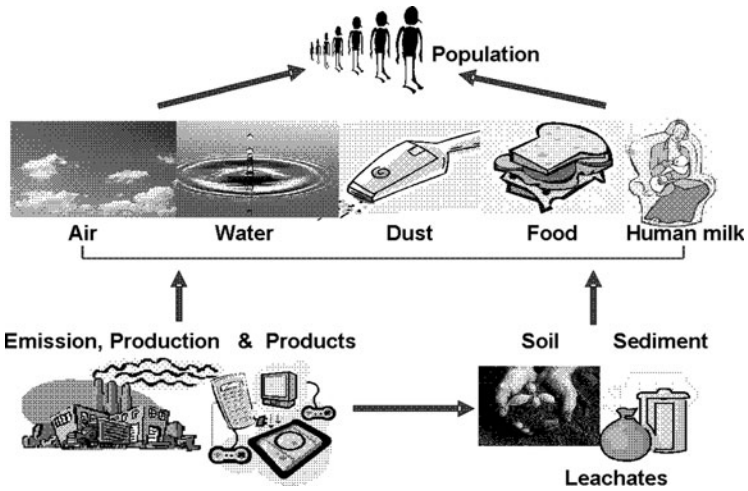


Fig. 1 Schematic overview of sources and pathways of brominated flame retardants

lesser extent, office dust [9] and microenvironments, such as cars [14] and planes [15]. Based on the extent of PBDE contamination in dust, dust ingestion is considered by some to potentially be the major route of exposure to PBDEs for the general population [3, 16–18]. The presence of PBDEs in dust has been attributed to consumer products; however, the mechanism of transfer remains poorly understood. For example, while chamber experiments have documented volatilization of the more volatile lower brominated PBDE congeners from both foam and electronics [19, 20], this work does not explain the predominance of BDE-209, a nonvolatile compound at room temperature, in dust samples reported by most international studies [3–13]. Other mechanisms, which may explain PBDE, particularly BDE-209, transfer from product to dust include direct partitioning between PBDEs in polymers and dust, and physical weathering or abrasion [3, 21–24].

Comparisons of PBDE concentrations in household dust from studies conducted in many countries indicate that for house dust typically the US, Canada, and the UK contain the highest measured amounts of total PBDEs [6–8] (Fig. 2). Reported levels of BDE-47 in dust samples ($n = 40$) from Australia, US, UK, and Germany [8] provided a good correlation, although heavily influenced by US data, with previously reported BDE-47 body burdens measured in serum and human milk from the investigated countries [25–30].

Intracountry variation in PBDE contamination of house dust samples has also been reported [9, 31]. PBDE concentrations in dust (and hence human exposure via this pathway) have been reported to be 4–10 times higher in California than in other North American regions [31]. This elevation of PBDE levels in dust samples appears to be reflected in serum levels of BDE-47, the dominant congener in serum, which were approximately 2-fold higher in Californian residents compared to the rest of the US general population ($p = 0.003$). This apparent regional PBDE

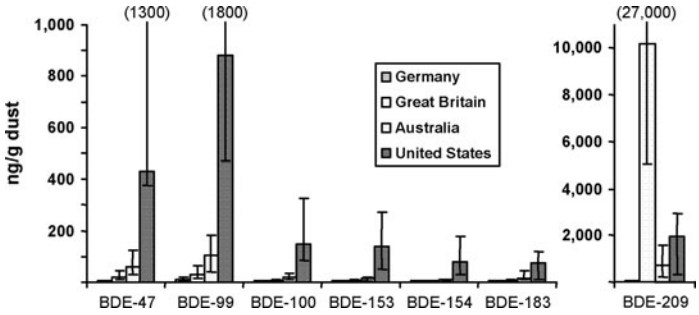


Fig. 2 Median concentrations (ng/g dust) of polybrominated diphenyl ethers (PBDEs) in dust samples from four countries ($n = 10$/country) with quartile ranges indicated. Reprinted from [8] Copyright (2008), with permission from Elsevier

concentration gradient may be a consequence of the state's stringent furniture flammability standards [31]. In addition, variations in fire safety regulations between countries may explain the relatively high BDE-209 levels detected in UK dust samples, which has particularly stringent fire safety regulations compared to the rest of Europe [6, 7].

Correlation between PBDEs in house dust and human uptake using matched human blood and house dust samples has been assessed in some studies. In the US, a strong correlation ($r = 0.65$–0.89, $p < 0.05$) was detected between dust concentrations of congeners BDE-47, -99, and -100, and matched serum samples ($n = 24$) [13]. In another matched sample study in the US [32] ($n = 38$), total pentaBDE congener levels were not significant predictors of blood sera levels.

European matched sample studies [33–35] found no correlation, which may be due to the much lower PBDE contamination in dust and the human population in Europe. Other studies have used matched human milk and dust samples [10–12, 36, 37]. Only the US-based study by Wu et al. [37] reported a positive correlation between PBDE concentrations in human milk and house dust samples ($n = 11$) ($r = 0.76$, $p = 0.003$, not including BDE-209). In this study, participants in homes with high levels of PBDEs in dust had human milk concentrations 2.6 times higher than those in homes with low levels.

Several studies have estimated intake of PBDEs for the general population and evaluated house dust ingestion as a significant pathway to total PBDE body burden [17, 18, 38–40]. Intake estimates vary by age with differing amounts of dust ingested by infants, children, and adults, as shown in Table 1.

For adults, Stapleton et al. [2] estimated that the intake of ΣPBDEs via household dust in US adults was approximately 3.3 ng/day (assuming adults ingest 0.0056 g/day dust) [2] based on 16 dust samples collected in 2004. A similar average uptake was estimated by [3] for the population in Canada with 7.5 ng/day (assuming adults ingest 0.00416 g/day dust) based on 74 dust samples collected in 2002–2003. A multimedia urban model using exposure via soil/dust from [42] estimated adult daily PBDE intake to range from 2 to 5,000 ng/day [43, 44]. In the UK, Harrad et al. [6, 7] estimated intake of tri-hexa-BDEs and BDE-209 via

Table 1 Estimated range of polybrominated diphenyl ether (PBDE) intake from dust (ng/day/person) for three different age groups; adult and 2.5- and 6-year-old children [8]

Age group	Country	Estimated dust intake (mg/day)[a]	Estimated daily intake range of PBDEs through dust (ng/day/person)				
			BDE47	BDE99	BDE153	BDE183	BDE209
Adult	Germany	0.56–110	<1–2	<1–4	<1–2	<1–13	<1 – 45
	UK	0.56–110	<1–20	<1–33	<1–6	<1–2	<1 – 6,000
	Australia	0.56–110	<1–150	<1–380	<1–46	<1–11	<1 – 1,400
	US	0.56–110	<1–330	<1–400	<1–72	<1–440	<1 –2,300
2.5-year-old	Germany	50–100	<1–2	<1–4	<1–2	<1–12	<1 –41
	UK	50–100	<1–18	<1–30	<1–5	<1–2	45 –5,400
	Australia	50–100	1–140	1–340	<1–41	<1–10	1–1,300
	US	50–100	12–300	3–370	<1–65	<1–400	6–2,100
6-year-old	Germany	3	<1–<1	<1–<1	<1–<1	<1–<1	<1–1
	UK	3	<1–<1	<1–<1	<1–<1	<1–<1	3–160
	Australia	3	<1–4	<1–10	<1–1	<1–<1	<1–38
	US	3	<1–9	<1–11	<1–2	<1–12	<1–62

[a]Data from exposure factors handbook [41]

Abbreviations: *BDE-47* 2,2′,4,4′-tetrabrominated diphenyl ether; *BDE-99* 2,2′,4,4′,5-tetraBDE; *BDE-153* 2,2′,4,4′,5,5′-hexaBDE; *BDE-183* 2,2′,3,4,4′,5′,6-heptaBDE; *BDE-209* decaBDE; *PBDE* polybrominated diphenyl ether

Maximum daily intake (DI) calculated from highest observed PBDE dust concentration and the high estimate of dust intake (Protection Agency (EPA), 1997). The lower DI calculated assuming minimum concentration and dust intake

household, office and car dust to be 1.3 and 233 ng/day, respectively, based on 68 samples of dust collected in 2006–2007. In Singapore, Tan et al. [45] estimated PBDE intake to range from 4.8 to 116 ng/g for adults based on 31 samples. Australian intake based on the work of Sjödin et al. [8] was estimated to range from <1 to 150 and 1 to 1,300 ng/day for BDE-47 and -209, respectively.

Infants are thought to ingest more dust than adults because they are in close contact with the floor and tend to use their mouths for sensory perception. For infants, ingestion of PBDEs via dust has been estimated to be in the range of 120–1,180 ng/day in the US (assuming children ingest 0.02–0.2 g of dust/day) [2] compared with an average estimated intake of 99 ng/day in Canada (assuming infants ingest 0.055 g/day dust) [3] and 1–140 ng/day in Australia for 2.5-year-olds [8]. For toddlers, the estimated soil/dust intake using the multimedia urban model ranged between 1 and 19,000 ng/day [43, 44]. In Singapore, ingestion for 6-month to 2-year-olds ranged from 64 to 232 ng/day [45]. Recently, a report of PBDEs present on the skin surface of hands affirmed exposure to PBDE contaminated dust or consumer products. The median exposure estimates for children and adults were 1,380 and 154 ng ΣPBDEs/day, respectively, and were greater than for dietary intake [38–40].

Interpersonal variability associated with the amount of dust consumed by individuals suggests that exposures can vary considerably. Comparison of data from different studies should be made cautiously due to different dust ingestion rates used and the wide variation in PBDE concentrations in house dust. Similarly, the

metabolism of BDE-209 (the dominant congener in dust samples) in humans and possible biotransformation pathways need to be further investigated to fully evaluate the extent of PBDE uptake in the general population via dust ingestion. Despite the limitations, it appears that there is a general consensus that ingestion of dust contributes to overall PBDE body burden with intake via this pathway reported to be much higher in infants than in adults.

2.2 Air

PBDEs are distributed globally via atmospheric transport and are now ubiquitous in their global atmospheric distributions, with levels in air reported at remote sites [46–48], including the Artic [49, 50]. Oceanic background PBDE levels have also been reported over the open Pacific, Artic [51], Baltic [52], and Indian Oceans [53]. This makes inhalation another possible pathway of human exposure to PBDEs.

PBDE concentration gradients in ambient air have been detected between urban and rural regions [54–58]. Other studies have reported intracity variation in ambient air, identifying industrialized regions as PBDE hotspots [59, 60]. Several studies have also reported PBDE emissions to the atmosphere, near or at source-sites [48, 52, 61–64].

PBDE levels in air vary between countries and for outdoor air samples, levels reported from Canada [42, 65–67] and the US [65] are usually higher compared to Europe with the lowest concentrations reported from Asia, although high PBDE concentrations were detected in China at a site in a typical urban center although in the vicinity of industrial areas thought to be heavy users of PBDEs [59] (Fig. 3). For indoor air (Fig. 4), concentrations were highest in a study from domestic sites in Canada [42, 66, 67] but also high from English workplaces [1].

PBDE congener composition was dominated by BDE-47, -99 and -28, with the high variability in the congener profile of the indoor samples potentially explained by the range of sources and commercial mixtures used in treated products within the home environment [42]. Similar interhome variability in PBDE air levels was reported by [68], with PBDE levels in homes varying by more than two orders of magnitude. Other studies have compared office and home air [10–12, 69] and reported PBDE concentrations as being generally higher in office air than in home air; however, the difference was not significant.

Higher concentrations of PBDEs have been found in indoor compared to outdoor air [1, 10–12, 42, 66] and exposure via indoor air has been the subject of a number of investigations. The relatively high concentration of PBDEs indoors compared to outdoors is likely to be related to the usage and slow release of these chemicals from consumer products and building materials [19]. The atmospheric concentration in a given area is further influenced by many factors, such as ventilation rate and the age and type of sources in a building [42].

Human exposure via this pathway has been reported based on PBDE air concentrations detected from various countries. The mean adult inhalation of PBDEs

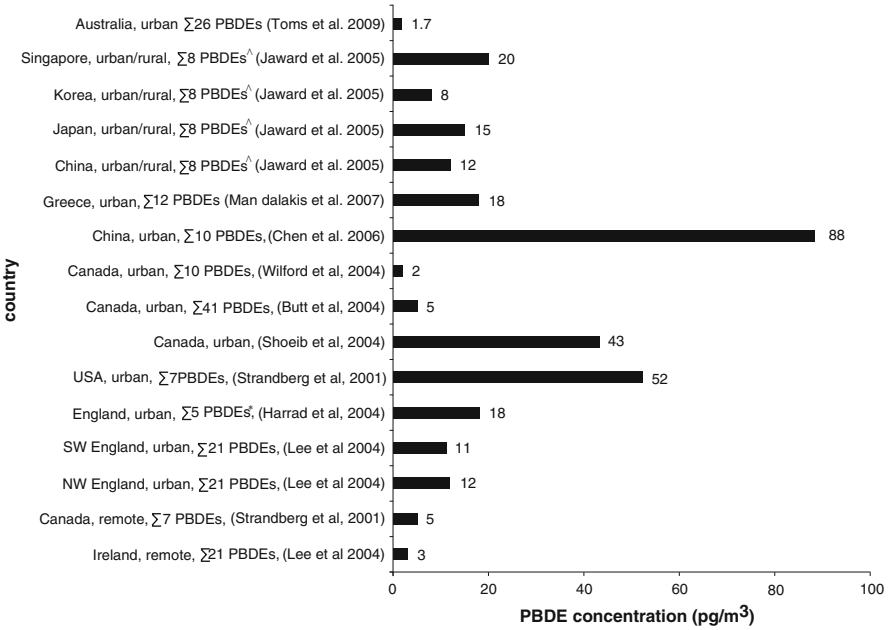


Fig. 3 PBDE concentrations (pg/m^3) in outdoor air from selected countries

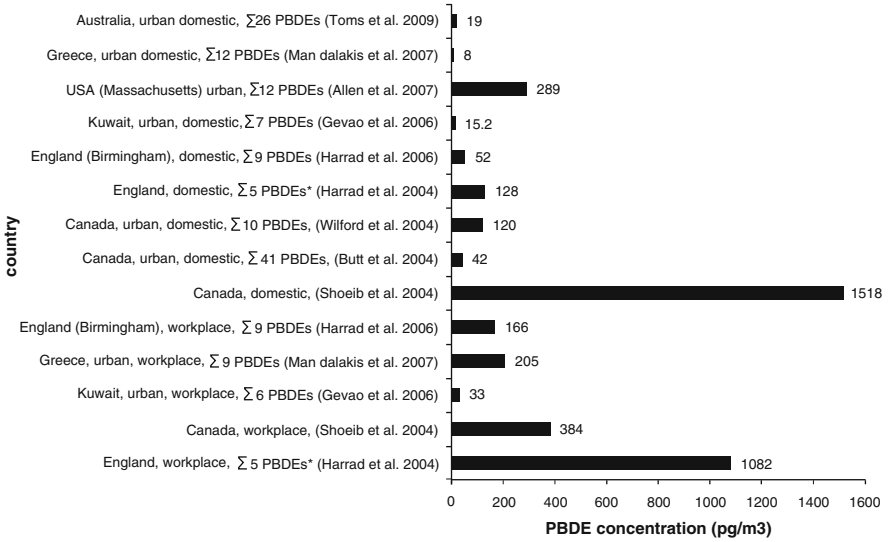


Fig. 4 PBDE concentrations (pg/m^3) in indoor air from selected countries

including indoor air (home and workplace) and outdoor air has been estimated to be approximately 0.4 ng/day in Kuwait [4, 5]; 1.9 ng/day (females) and 2 ng/day (males) in Canada [42]; 0.33 ng/day and 2.0 ng/day for children and adults, respectively, in Singapore [45]; 6.9 ng/day in the UK [1]; and in Australia 1.5 ng/day for adults [10–12]. Jones-Otazo [43, 44] used a multimedia urban model to estimate air inhalation for various age groups. For adults, the estimated daily intake was 10 ng/day and for toddlers it was around 2 ng/day [43, 44]. In addition, it has been shown that microenvironments such as car interiors contain high levels of airborne PBDEs and may cause additional exposure via inhalation [70, 71]. Overall, studies of total PBDE exposure deem inhalation as a minor source [17, 72].

2.3 Food Including Human Milk

2.3.1 Food

The ability of selected PBDEs to bioaccumulate means that both aquatic and terrestrial foods are potential exposure sources. For POPs that exhibit similar physical–chemical properties to PBDEs, food is the dominant exposure source [73]. It is noteworthy though that the magnitude of PBDE exposure via food has been subject to debate [1, 17, 43, 44, 74, 75].

PBDEs have been detected in many food products and higher intake has been found via oils and fats, seafood, meat and meat products, eggs and dairy products compared to vegetables, fruits, and tubers ([76–82]). Interestingly, data from Finland showed a greater contribution from beverages, spices, and sweets to the daily PBDE intake than from meat and eggs [83].

Uptake of BDEs via the terrestrial food chain appears to be less relevant than for some of the traditional POPs, such as dioxin-like chemicals, partially due to comparatively low concentrations in ambient air. It is feasible that foods may be contaminated during or after processing in indoor environments, whereas cooking processes can result in a reduction of concentrations [74, 75, 84].

High concentrations of PBDEs in fish and seafood have been reported and separate studies have found both positive (in Japan [85]; the USA [86]; Norway [87, 88]) and negative (in Sweden [89] and the USA [28]) associations between fish/seafood consumption and body burden. An investigation of almost 2,000 participants from the National Health and Nutrition Examination Survey (NHANES) by Fraser et al. [90] reported ΣPBDE serum concentrations among vegetarians were 23% ($p = 0.006$) lower than among omnivores as assessed by 24-h food recall (Fig. 5). In addition, serum PBDE concentrations were associated with consumption of poultry fat (ΣPBDEs, $p = 0.0005$) and red meat (BDE-153, $p = 0.005$), with no associations for dairy or fish.

Daily dietary intake of PBDEs has been estimated for a range of different countries (Table 2). Estimates indicate mean dietary intake ranging from 15 to

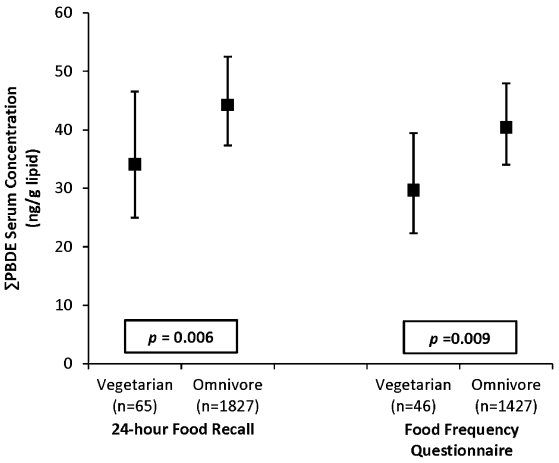


Fig. 5 Geometric mean ΣPBDE concentrations in vegetarians and omnivores based on two distinct dietary assessments: 24 h food recall and 1-year food frequency questionnaire. Means are adjusted for race/ethnicity, sex, age, age^2, PIR (poverty index ratio), and BMI. Error bars represent 95% CIs. For 24FR, $p = 0.006$; for FFQ, $p = 0.009$ taken from [90]. Reproduced with permission from *Environmental Health Perspectives*

Table 2 Daily dietary intake of PBDEs by country

Country (year food collected)	Intake ΣPBDEs (ng/day)	Reference
Australia (2004)	90[a]	[80]
Japan (1995)	94	[91]
Finland (1997–1999)	44	[83]
Spain (2000)	97	[76]
Spain (2003–2005)	39[b]	[79]
Spain (2006)	75	[81]
Sweden (unknown)	27	[92]
Sweden (1999)	51	[78]
Norway (unknown)	66[c]	[87]
Norway (2004–2005)	2549[d]	[88]
US (2001)	15–45	[93]
US (2003–2004)	54[e]	[74, 75]
US (2008–2009)	50	[94, 95]
U.K. (1999–2000)	91	[1]
The Netherlands (2003–2004)	32	[96]

[a]Adult females
[b]Food from animal origin only
[c]Median of 1.1 ng/kg bw/day, lower bound for a body weight of 60 kg
[d]Fish consumed from contaminated lake contribute 98.7% of total dietary exposure
[e]Based on 0.9 ng/kg bw/day for a body weight of 60 kg

100 ng/day with lowest intake from one US study [93] and highest intake from Norway [88], which focused on fish from a contaminated lake.

Variation in PBDE concentrations within food types has been observed [94, 95] and studies using large sample sizes are required to obtain representative data. Comparisons should be made with caution due to varying congeners used to calculate ΣPBDEs and varying food products used for dietary intake. There are few studies reporting causal relationships between PBDE dietary intake and human

blood serum concentrations. The available data do not provide good evidence that differences in human body burden between populations from different countries is related to differences in dietary intake.

2.3.2 Human Milk

For the fetus and infant, two unique forms of nutrition exist: human milk and nutrients via placental transfer (see Sect. 2.3.3). Exposure to PBDEs via human milk can be calculated using the PBDE concentration detected in the mother's milk and the amount of milk consumed by the infant.

Analysis of human milk is often used for assessing human body burden of lipophilic POPs such as PBDEs because of its relatively high lipid content (~3.5–4%) and noninvasive collection methods. It has been used to determine PBDE body burden from numerous countries since the late 1980s (Krueger 1988 in [97]). A review of the literature reveals PBDE concentrations in human milk range from <1 ng/g lipid in Asian countries, such as Indonesia, [98], Japan [85, 99–101], and Taiwan [102] and European countries including Sweden [97, 103–106], Finland [107], Germany [108–110], Italy [111], The Faroe Islands [112], and the Netherlands [113] to approximately 10 ng/g lipid in Australia [30] and in excess of 70 ng/g lipid in samples collected in Canada [114] and the USA [25, 37, 115, 116] (Fig. 6).

Carrizo and Grimalt et al. [127] note that breastfeeding is an important contributor to PBDE intake in the first years of growth, with BDE-47 concentration in the blood of 4-year-old children who were breastfed as infants almost five times that of

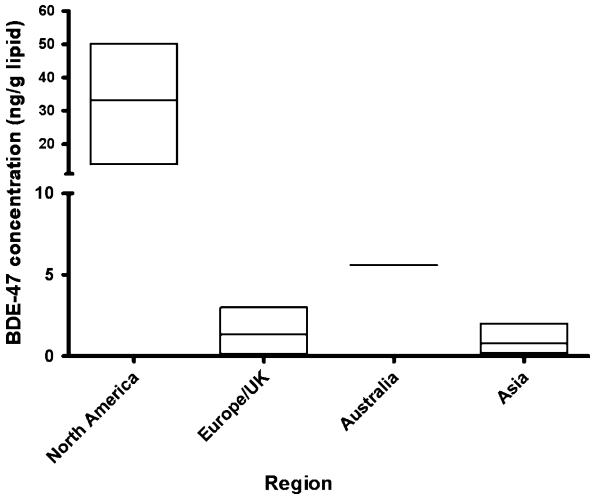


Fig. 6 Range (minimum to maximum) of BDE-47 concentrations in human milk by region (data taken from Table 3)

children who were formula fed. It should, however, be noted that the World Health Organization recommends breastfeeding in spite of the transient risk posed by POPs in human milk [128].

Selected studies have investigated the factors that contribute to individual concentrations of PBDEs in human milk. PBDE concentrations have been shown to vary by maternal weight, age, and over the course of breastfeeding, but not by parity or race [119]; while another study showed PBDE concentrations varied by parity, education, having a cohabitant employed as an electrician, and ventilation [124]. The duration of breastfeeding appears to have little effects on the concentrations of PBDEs in human milk [25, 119, 129, 130] (Table 3).

2.3.3 Cord Blood

Prior to exposure via human milk, the fetus receives a load of PBDEs via placental transfer. PBDEs have been detected in cord blood with ΣPBDEs ranging from approximately 1 to 39 ng/g lipid (Table 4). Lower brominated diphenyl ethers have been detected in cord blood at concentrations, similar to those in maternal blood (e.g., [133, 135]). Higher brominated diphenyl ethers were also detected in cord blood but at much lower concentrations indicating that lower brominated congeners were better able to undergo placental transfer [131, 132].

3 Metabolism

Following PBDE exposure, the body excretes the chemicals through metabolic processes. From the limited data published on PBDE half-lives in humans, the estimated durations for selected congeners are: BDE-47 (1.8 years), BDE-99 (2.9 years), BDE-100 (1.6 years), BDE-153 (6.5 years) [137]; BDE-183 (94 days [138, 139], ~90 days [140]), and BDE-209 (15 days [138, 139], ~7 days [140]). The half-lives reported by [138–140] result from investigation of occupationally exposed individuals, while the data from [137] are based on animal studies. There is currently a paucity of data on human half-lives of PBDEs and further investigation in this area is required.

4 Body Burden

Human body burden of PBDEs will be discussed with respect to concentrations in human blood and adipose tissue, as human milk (a matrix often used as an indicator of body burden) has been discussed in Sect. 2.3.2.

Analysis of blood and adipose tissue from various countries indicated that in contrast to “traditional” POPs, such as dioxin-like compounds, the concentrations

Table 3 Examples of PBDE concentrations (ng/g lipid) in human milk by country (from 1998 onward)

Country	Sampling year	No. of samples	Comments	ΣPBDE	BDE-47	BDE-209	Reference
North America							
Canada	2001–2002	20		42.8	18#	na	[117]
USA	2002	47		73.9	40.8	0.92	[25]
USA	2003	40		96	50.1	0.8	[118]
USA	2004	38	Massachusetts	76	42.1	nd	[115]
USA	2004–2005	46	Massachusetts	30.2	13.9	nd	[37]
USA	2007	29	Texas	39.7	24	na	[94, 95]
USA	2004–2006	301	North Carolina	51	28	na	[119]
Europe							
Germany	2000	7		na	0.65#	na	[108]
Germany	2002	79		3.75	1.63	na	[109]
Germany	2005	42	12th Week postpartum	1.9	0.67	na	[110]
Germany	2005	42	16th Week postpartum	2.03	0.66	na	[110]
Italy (Rome)	1998–2000	10		4.1	1.9	na	[111]
Italy (Venice)	1998–2000	6	Low fish consumers	2.8	1.5	na	[111]
Russia (Arkhangelsk)	2002	23		1.07	0.36	0.35	[120]
Russia (Buryatia)	2003–2004	10		0.96	0.14	na	[121]
Russia (Murmansk)	2000	14		1.16	0.65	na	[120]
Spain	2002	15	Catalonia	2.4	nr	na	[122]
Sweden	1996–2001	124		3.79	2.24	na	[106]
Sweden	1996–1999	93		4.01	2.35	na	[97]
Sweden	1998	40		3.88	2.29	na	[105]
Sweden	1999	40		3.46	1.97	na	
Sweden	2000	40		2.79	1.7	na	
Sweden	1996–2006	276		2.9	1.5	na	[123]
The Faroe Islands	1998–1999	1 (pool = 10)		7.2	1.7	na	[112]
Norway	2000–2001	10	Northern Norway	3.2	1.26	0.13	[120]
Norway	2003–2009	393		0.99	2.1	0.32	[124]
The Netherlands	1998	103		na	1.53	na	[113]
UK							

UK	2001–2003	52		6.6	3	na	[125]
Australia							
Australia	2002–2003						
Asia							
Indonesia	2001–2003	30		2.2	0.39	0.27	[98]
Japan	1998	35		2.31	1.03	na	[99]
Japan	1999	30		1.45	0.62	na	
Japan	2000	27		1.39	0.53	na	
Japan	1999	13		0.73–291	0.2–187	na	
Japan	2004	105		1.34	0.68	na	[100]
Japan	2005	89		1.74	0.41	0.12	[101]
Japan	Unknown	12		1.3	na	na	[85]
Taiwain	2000–2001	20		3.93	1.52	0.27	[102]
Vietnam	2007	20	Hanoi	0.42	0.19	na	[126]
China	2007	25	Beijing	1.9	0.89	na	
Korea	2007	29	Seoul	3.7	2.0	na	
Japan	2007–2008	20	Kyoto	1.4	0.58	na	
Japan	2007	20	Sendai (Miyagi)	1.7	0.76	na	
Japan	2007	20	Takayama (Gifu)	1.3	0.57	na	

na not available

Table 4 Examples of PBDE concentrations (median) in ng/g lipid cord blood from various countries

Country	Year	Sample size	ΣPBDEs	BDE-47	BDE-209	Reference
Australia	2006–2007	*n* = 3 pools (eight samples in each pool)	24	12	n/a	[10–12]
China	Unknown	21	3.9	1.4	n/a	[131]
Sweden	2000–2001	15	1.69	0.98	n/a	[132]
Spain	2003–2004	44 (Vallecas district)	15	3.3	2.2	[133]
		48 (Getafe district)	13.3	3.2	1.4	
Denmark	2007	50	1.22	0.47	n/a	[134]
US	2001	12	39	25	n/a	[135]
Korea	2007	108	8.2	6.1	n/a	[136]

n/a not available

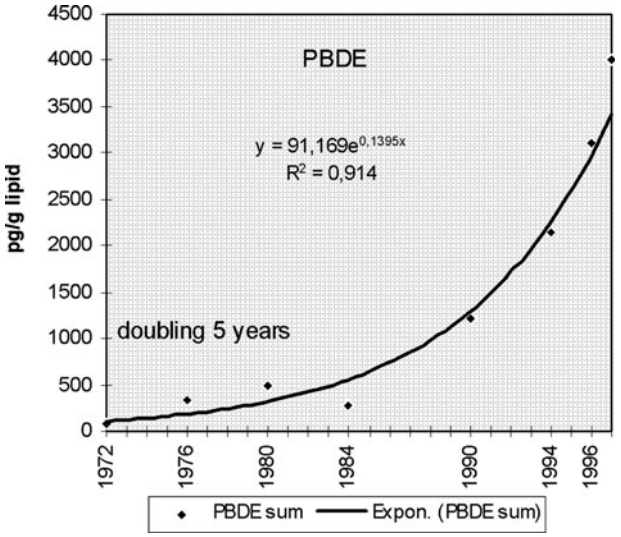


Fig. 7 Concentrations of PBDE (sum eight congeners) in pooled human breast milk samples from different time periods [143] taken from de Wit (2002). Reprinted from [192] Copyright (2002), with permission from Elsevier

of PBDEs in human populations increased from the 1970s [16], with a peak reported in Swedish and American samples in the late 1990s [104, 106, 141, 142] (Fig. 7). It was the report of PBDE concentrations in human milk doubling every 5 years in the late 1990s in Sweden [143] that lead to a sudden interest in human exposure to BFRs worldwide [144]. Differences in study designs (individual versus pooled samples), analytical techniques, and included congeners means comparisons of PBDE concentrations between studies should be made with caution.

4.1 Adipose Tissue

Adipose tissue has been used in limited studies to assess PBDE body burden. Samples are often obtained from deceased persons and therefore, sample collection may be limited by ethical implications and sample size; and the cause of death/disease may confound results. In addition, these factors may limit the investigation of variables, which may affect PBDE concentrations. ΣPBDE concentrations in adipose tissue are reported to range from approximately 1 ng/g lipid in Japan [145], France [146], and Singapore [147], approximately 4 ng/g lipid in Sweden [105], Spain [148], and Belgium [149] and up to 75 ng/g lipid in the US [150–152] (see Table 5).

4.2 Blood

Sampling and analysis of human blood has been widely used to assess human body burden of PBDEs and allow comparison of body burdens in different subpopulations (i.e., genders or different age groups). Internationally, PBDE concentrations in

Table 5 Examples of PBDE concentrations in adipose tissue from various countries (1998 onward)

Country	Sampling year	No. of samples	Comments	Sum PBDE	BDE-47	BDE-209	Reference
Belgium	2000	20	Males and females (mean)	4.75	1.45	na	[153]
Belgium	2003–2005	25	Males and females (mean)	5.3	1.2	na	[149]
Japan	2000	10	Females (median)	1.3	0.5	na	[145]
Singapore	2003–2004	16	Females (mean)	3.63	2.89	na	[147]
Spain	Unknown	13	Males and females (mean)	4.12	1.36	na	[148]
Sweden	1994	5	Males and females (mean)	na	2.4	na	[105]
USA (California)	1996–1998	32	Females (mean)	na	28.9	na	[150]
USA (New York)	2003–2004	52	Males and females (median)	75	29.3	na	[151, 152]
France	2004–2006	86	Females (median)	2.7	0.7	0.8	[146]
Italy	2005–2006	12	Males and females	11	6	na	[154]
Brazil	2004–2005	25	Females	1.54	0.39	na	[155]

na not available

blood from adult populations range from approximately 2 ng/g lipid in Japan [156, 157], to approximately 5 ng/g lipid in European countries including Germany [158], Norway [159], Spain [133], Sweden [160, 161], and the Faroe Islands [162]; the United Kingdom [163] and New Zealand [164]. Higher levels of approximately 10 ng/g lipid in Australia [10–12] and more than 100 ng/g lipid in Canada [165, 166] and the USA [28, 86, 135, 141, 150, 167–170] have been reported.

Variables including geographical region, occupational exposure, gender, and age (in particular for infants and children) have been assessed in relation to PBDE concentrations. It should be noted that for PBDEs, high variability between individuals has been reported previously [25, 117, 171]. For example, in a US cohort of 2,060 individual serum samples from NHANES, the reported median concentration of BDE-47 was 19.2 ng/g lipid, while the maximum concentration was 2,350 ng/g lipid [172]. The reasons for this variability are likely due to exposure and/ or an individual's capacity for metabolism and excretion of these chemicals.

4.2.1 Geographic Trends

Overall, PBDE concentrations in human blood serum of adults appear to be highest in the US and Canada followed by Australia, Asia, and Europe (Fig. 8). In Australia, intracountry differences for the general population are not apparent [72], and those studies showing differences between regions in one country are related to high exposure, e.g., E-waste sites [173] and varying fire regulations, e.g., California, US [31]. The geographical differences in PBDE serum concentration are related to

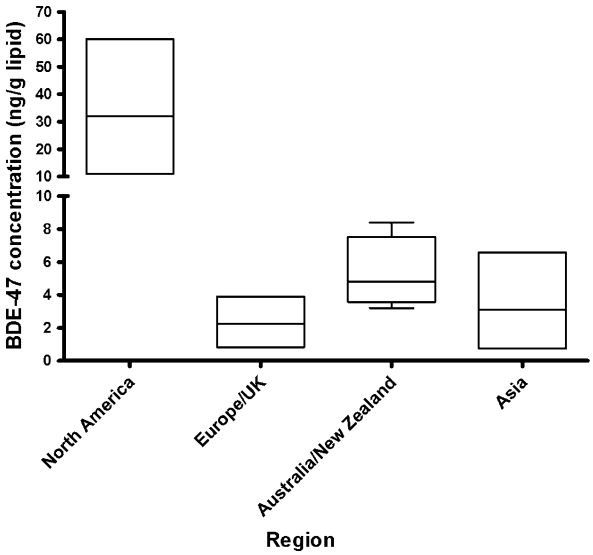


Fig. 8 Range (minimum to maximum) of BDE-47 concentrations in human blood serum by region

exposure and may reflect volume of usage, that is, by 2001 around 50% of the global production of penta-, octa-, and deca-BDE commercial products were used in the Americas, followed by 37% in Asia and 12% in Europe [174]. In Australia, in 2003/04 approximately 210 tons of penta-, octa-, and deca-BDE products were imported in chemical form accounting for less than 1% of global production [175]. This, however, is not reflected in blood serum concentrations in Australia. In addition, duration of usage varies by region. In 2004 and 2005, in the US and in Japan, respectively, industry began to voluntarily phase out production of penta- and octa-BDE commercial products [176]. In the same year, the use of penta- and octa-BDE commercial products at concentrations greater than 0.1% was banned in the European Union. In 11 States of the US, such a ban was effective between 2006 and 2008 [177] and in Australia, importation of these products ceased in 2005 [176]. Deca-BDE commercial product will be phased out in the US by 2012 (U.S. [178]).

Data from Fig. 8 for North America [28, 86, 135, 141, 150, 165–170, 172]; Europe/UK [133, 158–163]; Australia/ New Zealand [10–12, 164, 179]; and Asia [131, 156, 157, 180, 181].

4.2.2 Gender Trends

Higher PBDE concentrations in males compared to females have been reported previously [148, 156, 158, 159] and appears to be due to placental transfer and elimination during lactation. In contrast, other studies have reported either no difference or higher concentrations in females [133, 167, 168].

4.2.3 Congener Profiles

The congener profile in human blood serum and human milk samples is generally dominated by BDE-47, followed by BDE-153, BDE-99, and BDE-100, with other BDE congeners usually contributing less than 10% to total PBDEs. This profile has been found in studies of human blood from Australia, New Zealand, North America, and Europe [72, 141, 159, 164, 167, 168]. Limited studies have shown BDE-153 [112] or BDE-209 [156, 181] as the dominant congener. Variations in congener profile may be related to degradation, exposure, and/or analytical differences.

In cord blood, the profile is often dominated by BDE-47, followed by BDEs −99, −153, and −100 [10–12, 133]; however, others have found BDE-153 in higher concentrations than BDE-99 [131, 132].

4.2.4 Occupational Exposure

Persons working in certain industries are predisposed to a potentially higher PBDE body burden due to exposure to contaminated air and dust in the workplace (Table 6). The release of PBDEs can be accelerated from industrial settings during PBDE manufacture; addition to products and subsequent recycling, and disposal of

Table 6 Concentration of various PBDE congeners measured in workers serum (ng/g^{-1}Lipid) relative to reference group/s (Median unless stated otherwise)

	Study/Country	PBDE congeners (Median ng/g^{-1} lipid)	Main variation in PBDE congener relevant to referent group/s	Reference Group A	Reference Group B
Recycling E-waste	[173][a]/China	Workers and inhabitants of Guiyu town (dismantling electronic equipment) 600 ($n = 26$)	BDE-209	Residents from nearby region 170 ($n = 21$)	NA
	[182][b]/China	Dismantling electronic equipment 126.0 ($n = 20$)	BDE-209	Residents from nearby region (50 km away from E-waste region) 35.0 ($n = 15$)	General population (All female) 10.4 ($n = 20$)
	[138, 139][c]/ Sweden	Dismantling electronic equipment 16.8 ($n = 19$)	BDE-183	White collar workers 11.5 ($n = 8$)	NA
	[41][d]/Sweden	Dismantling electronic equipment 26.0 ($n = 19$)	BDE-183	Hospital cleaners 3.3 ($n = 20$)	Computer clerks 4.1 ($n = 20$)
	[183][e]/Norway	8.8 (Mean) (n = 5)	BDE-183	Circuit board producers 3.9 (Mean) ($n = 5$)	Laboratory personnel 3.0 (Mean) ($n = 5$)
Computer technician	[184][f]/Sweden	6.9 ($n = 19$)	BDE-153	Hospital cleaners 2.6 ($n = 20$)	Computer clerks 3.0 ($n = 20$) / Never breast-feeding cleaners and clerks 4.2 ($n = 20$)
Foam recycling and carpet installation	[38–40][g]/U.S.A	Foam recycling workers 160.0 ($n = 12$) / Carpet layers 178.0 ($n = 3$)	BDE-47	Control group 19.3 ($n = 5$)	NA
	[161][h]/Sweden	Rubber workers	BDE-209	Abattoir workers	NA

Manufacturing or handling flame-retarded rubber		35.0 (n = 20)		2.4 (n = 17)	
Incinerator workers	[180][i]/Korea	Incinerator workers (men) 17.7 (n = 30)	None	Residents living nearby the source (within 1 km) 14.7 (n = 51)	Control- Residents living distant from source (6–20 km) (n = 11) 18.2

n indicates the Number of persons; *NA* not applicable

[a]Total 16 congeners were identified including BDE 153, 183, 196, 197, 203, 206, 207, 208, 209

[b]BDE 28, 47, 99, 100, 153, 154, 183, 196, 203, 207, 208, 209

[c]BDE 47, 99, 100, 153, 183, 209

[d]BDE 47, 77, 85, 99, 100, 128, 138, 153, 154, 183, 209

[e]BDE 28, 47, 99, 100, 153, 154, 183

[f]BDE 47, 153, 154, 183, 209

[g]BDE 17, 28, 47, 66, 99, 100, 153, 154, 183

[h]Total of 12 congeners were identified including BDE 47, 100, 153, 183, 203, 206, 207, 208, 209. This table reports median values for BDE 209 only

[i]BDE 15, 28, 33, 47, 49, 66, 85, 99, 100, 140, 153, 154, 183

consumer products containing these flame retardants, with elevated PBDE levels reported in air [61, 63, 64] and dust [62] in close proximity to such facilities.

Elevated levels of PBDEs in workers' blood samples relative to a reference group have been reported in various occupations, including dismantling electronic waste (E-waste) [41, 138, 139, 173], foam recycling and carpet installation [38–40], computer technicians [184] and the manufacturing or handling of flame retarded rubber [161]. A very high median PBDE level, 600 ng/g lipid in serum, attributed to occupational exposure [173] has been found in China, where entire regions have been devoted to the recycling of E-waste. It is worth noting that the median PBDE level in serum of the referent group who lived 50 km from the occupational group was as high as 170 ng/g lipid. The magnitude of this industry combined with limited occupational protection of workers and relatively primitive methods of dismantling electronic equipment has led to an increase in PBDE contamination on a much broader scale [173].

Also, elevated PBDE levels in blood samples of workers at a contaminated workplace and variation in congener patterns reflective of differential exposure may be expected when compared to a reference group, although this is not always the case. The ΣPBDE levels in serum samples of foam recycling workers and carpet installers in the US had median values of 160 and 178 ng/g lipid, respectively. This was an order of magnitude greater than the control group median value of 19.3 ng/g lipid. No differences in congener patterns were observed for the primary BDE congeners 47, 99, 100, and 153, which contributed approximately 90% of the total PBDE serum concentrations measured [38–40]. Considering the long half-life of BDE-47 and the relatively high background concentrations in the US general population, congener patterns may be obfuscated. It is worth noting that in this study an individual from the control group was found to have the highest measurement of ΣPBDEs in her serum. Concentrations of bromobiphenyl 153 (BB-153) and chlorobiphenyl 153 (CB-153) were not significantly different among the different groups; however, the ratio between BB-153/BDE-47 and CB-153/BDE-47 was significantly lower in foam recycling workers and carpet installers, suggesting the higher PBDE levels measured were attributable to the workplace.

Evidence of a congener pattern different to a referent group has been reported in workers dismantling electronic equipment in Sweden [41]. Significantly higher concentrations of each of the individual PBDE congeners analyzed were found, with particularly high concentrations of BDE-183 relative to the control group on a molar basis. In addition, the CB-153/BDE-183 ratio was significantly lower in the serum of the workers at the dismantling plant as compared to referent groups. In Holland, another study investigating electronic dismantlers reported BDE-183 was only identified in workers dismantling electronic equipment [183], although levels of BDE-183 in this study were approximately an order of magnitude lower than that reported in the Swedish study.

Other studies have reported congener patterns which differed in occupational exposed groups relative to reference groups through the higher brominated congeners, octa-, nona-, and BDE-209 [161, 173, 182]. Rubber mixers, who incorporated commercial deca-BDE as an additive in flame-retarded rubber, and some cable manufacturers in the same facility had serum concentrations of BDE-209 up to

50- to 100-fold higher than those in the reference groups. The median CB-153 concentrations in rubber workers and referents were in the same range.

Indoor air PBDE concentrations and hence, exposure, in a workplace setting can be impacted by processes within the facility. Cahill [63] reported PBDE air concentrations in the dismantling hall of the electronics recycling facility were highly dependent on the degree of shredding activity. It has also been demonstrated by introducing standard industrial hygiene measures such as structural process planning, good ventilation, and good cleaning procedures, work-related exposure to PBDEs, particularly the higher brominated congeners, can be reduced [138, 139].

4.2.5 Infants and Children

PBDEs have been detected in human blood of adults from many countries and these studies frequently show no trend in PBDE concentration by age [62, 133, 164, 170, 180]. However, once samples from infants and children are included in analysis, an inverse trend with age becomes apparent (Fig. 9) with highest concentrations in 2- to 5-year-olds.

International pediatric PBDE data are limited (Table 7). Data from a Norwegian study showed that the concentrations of PBDEs in blood serum from a pool of 14 children 0–4 years of age was 1.6–3.5 times higher (BDE-47 concentration 6.2 ng/g

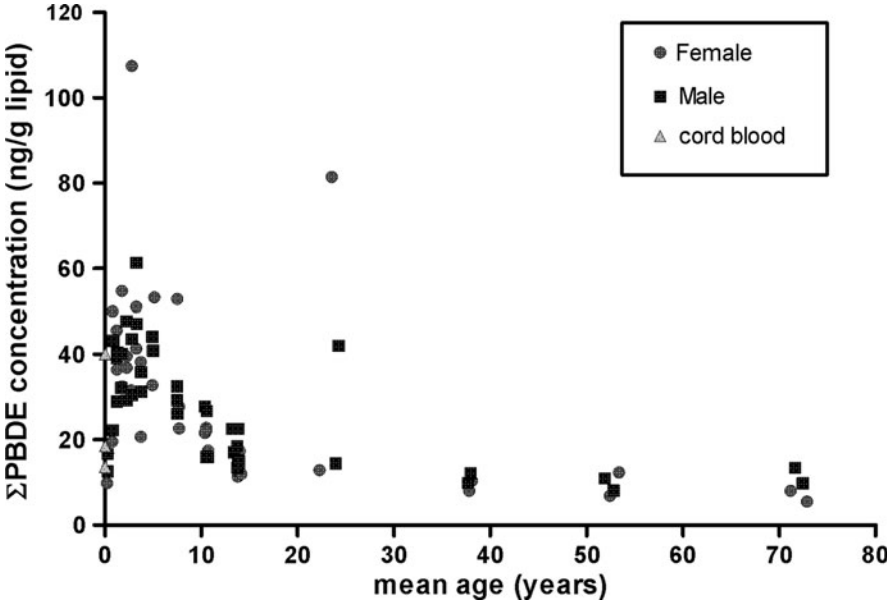


Fig. 9 ΣPBDE concentrations (ng/g lipid) by mean age (0–80 years) and gender. Each data point represents up to 30 individual blood samples [10–12]. Reproduced with permission from *Environmental Health Perspectives*

Table 7 Summary of studies reporting on PBDE levels in young children and mothers around the world [185]

Study location	Year of sample collection	Child population	Adult population	Individual samples?	Paired samples	Finding	Ref
Faroe Island	1994–1995 (mothers) 2001–2002 (children)	42 children age 7	57 Maternal serum samples collected during pregnancy	Yes	Yes	No association found between individual moms and children. Total PBDE concentrations are similar for both groups, but congener profile is different with BDE-153 dominant in children	(*162*)
Norway	2002	49 Children in 2 pooled samples grouped by age	60 Adults in 3 pooled samples grouped by age	No	NA[a]	0- to 4-year-old pool highest for every congener except BDE-209 (Σ_7PBDE = 9.7 ng/g lw) vs ~6 ng/g lw in 5 to 14 years old, and $\leq$3.6 ng/g lw in older age groups	(*191*)
Australia	2002–2005 (adults) 2004–2005 (children)	4 Pools, containing blood from 100 children 0 to 4 years, 15 pools each from 24–100 children 5 to 15 years	69 Pools, each generally 100 people, 4 age groups (16–30, 31–45, 46–60, >60 years)	No	No	Highest concentrations in 0- to 4- year-olds. PBDEs 2.6 to 4 times higher than older age groups.	(*72*)
United States	2003–2004	277 Age 12 to 19	1758 Age 20+	Yes	No	Younger group had highest concentrations of all congeners, and lower	(*172*)

						concentrations of BB-153.	
California, U.S.	2004	2 Young children	2 Parents	Yes	Yes	Children's concentrations were 2 to 7 times higher for tetra- to hexa-congeners and 2 to 10 times higher for BDE-209	(*169*)
United States	2006	20 Children age 1.5 to 4	20 Mothers	Yes	Yes	Children significantly higher for major tetra-, to hexa- congeners, average 3-fold elevation in children.	(*185*)
Australia	2006–2007	Cord blood and 12 age groups for <16 years	4 Age groups	No	NA[a]	PBDE concentrations increased from birth through 2.6–3 years and then decreased through adulthood. Levels in the 2- to 5-year-old age groups were roughly double those from 13 to 30 years old and four times higher than older adults.	(*10*)

[a]*NA* not available

lipid) than that obtained from other pooled age groups aged 4–60 years (mean BDE-47 concentration 2.1 ng/g lipid) [159]. A study of a family of four from California, US, found BDE-47 concentrations to be greatest in the 18-month-old infant (245 ng/g lipid) followed by the 5-year-old child (137 ng/g lipid) and the parents (32 and 60 ng/g lipid for the father and mother, respectively) [169]. In another US study, the mean BDE-47 concentrations collected from 6- to 11-year-olds, Mexican-Americans, non-Hispanic blacks, and non-Hispanic whites in 2001–2002 ranged from 60 to 105 ng/g lipid for males and 65 to 110 ng/g lipid for females, while for adults aged 20 to greater than 60 years, the range was 20–60 ng/g lipid (data not shown). These findings contrast with those of a study from the Faroe Islands, where no difference was observed between the serum PBDE concentrations in 42 seven-year-olds (median BDE-47 concentration 0.87 ng/g lipid) versus their mothers (median BDE-47 concentration 1.3 ng/g lipid) [162].

In summary, it is important to recognize that for PBDEs more than for any other chemicals listed under the Stockholm convention it is apparent that with the potential exception of occupationally exposed groups, young children have the highest exposure in the population.

4.2.6 Predicted BFR Body Burden

When limited data are available on POPs in humans, researchers have used models to predict chemical concentrations and/ or assess exposure based on input and clearance data [186, 187]. For PBDEs, data have been modeled to assess exposure pathways and dose estimates [43, 44, 72, 188, 189]. A simple model using Australian exposure data and half-life data from the literature [137] was used to predict PBDE human concentration trends for formula and breastfed infants over an 80-year life span. These predicted concentrations were then compared to measured data from the Australian population (Fig. 10). The model indicated that the elevated concentrations

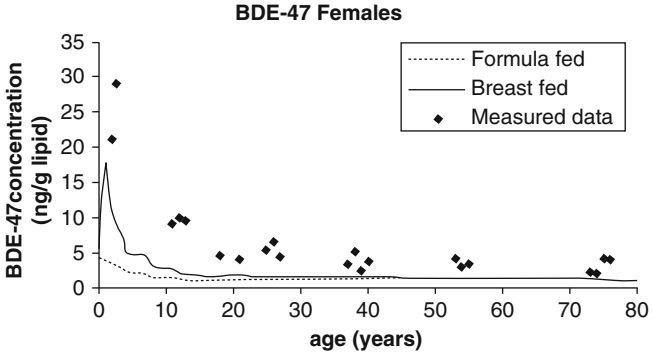


Fig. 10 Measured (each data point represents a pool of 30 individual human blood serum samples) versus predicted concentrations of BDE-47 (ng/g lipid) for formula and breastfed infants. Reprinted "in part" with permission from [72] Copyright 2008 American Chemical Society

in infants were primarily due to maternal transfer and human milk consumption with inhalation and ingestion of dust making a comparatively lower contribution [72].

The overall differences in measured and predicted data indicated that either:

1. Intake sources other than human milk, food, air, and dust contributed to the human concentrations of PBDEs or
2. The half-lives of PBDEs have been underestimated

These factors are particularly important for BDEs -47 and -153, which show the greatest difference. The model most accurately predicted concentrations measured in the >36 years age groups, indicating that known input and clearance data were more reflective of exposure [72]. Due to the length of half-lives for these PBDEs (19–78 months [137]), exposure in the older age groups must be constant to cause the stabilization of PBDE concentrations. It should be noted that data on human PBDE half-lives are limited and further assessment of these half-lives in humans is required for accurate risk assessment.

The use of pooled samples obtained from both formula and breastfed babies may also have resulted in the underestimation of the measured concentrations. In Australia, breastfeeding rates decrease from 85% at birth to 45% and 23% at 6 and 12 months, respectively [190], so the pooling of serum from the formula fed infants would reduce the mean PBDE concentrations in the pools, and may have resulted in underestimation of measured values in breastfed babies. We can also assume that breastfed babies have even higher concentrations than indicated by the measured data, reinforcing the idea that some input or clearance data are missing for this age group. Other potential sources in the young age group, not accounted for in the model, include increased exposure from: mouthing and sucking either products treated with PBDEs or covered in dust contaminated with PBDEs from the indoor environment, or their hands on which PBDEs have recently been shown to be present [38–40]; and exposure to child-specific products, such as car seats, prams, mattresses, and toys, which may also be a source of PBDEs.

In assessing the predictive value of the model, it is also important to consider variation in an individual's response to PBDE exposure. Overall body burden of PBDEs may be determined by individual metabolic differences that affect rates of retention/ sequestration [43, 44] as well as occupational exposure [138, 139], and these factors were not accounted for by the model. This may be particularly evident in children and young adults. In contrast, measured values reflect the overall concentration as a function of an individual's input, metabolism, and degradation. The sample collection was structured with the aim of obtaining a representative sample of the Australian population. However, due to the use of deidentified samples and pooling, occupational or dietary (including human milk) exposures were unknown and resulted in the determination of mean concentrations. Hence, the minimum and maximum PBDE concentrations in the population were not determined. Continued monitoring of PBDE exposure as a function of age will further validate the accuracy of this model and enable the identification and perhaps

reduction of specific sources and pathways of exposure of PBDEs for infants and young children.

5 Conclusion

Exposure to BFRs, in particular PBDEs occur predominantly via dust and food ingestion with a minor contribution from inhalation. PBDEs have been detected in samples of human milk, blood, adipose tissue, and cord blood from countries around the world. Concentrations have been shown to be highest in populations from North America followed by Australia, New Zealand, Asia, and Europe. While factors such as gender and parity may not affect concentrations, occupational exposure and age (infants and children) are associated with higher PBDE concentrations. Predicted body burden calculated using available information on intake and elimination rates of BFRs appears to underestimate human body burden data obtained through analysis of BFRs in blood or human milk. This may be due to unknown exposure or inaccurate elimination data. Further exposure studies should focus on younger age groups and an investigation of human PBDE half-lives.

References

1. Harrad S, Wijesekera R, Hunter S, Halliwell C, Baker R (2004) Preliminary assessment of U.K. human dietary and inhalation exposure to polybrominated diphenyl ethers. Environ Sci Technol 38:2345–2350
2. Stapleton HM, Dodder NG, Offenberg JH, Schantz MM, Wise SA (2005) Polybrominated diphenyl ethers in house dust and clothes dryer lint. Environ Sci Technol 39:925–931
3. Wilford B, Shoeib M, Harner T, Zhu J, Jones KC (2005) Polybrominated diphenyl ethers in indoor dust in Ottawa, Canada: implications for sources and exposure. Environ Sci Technol 39:7027–7035
4. Gevao B, Al-Bahloul M, Al-Ghadban AN, Al-Omair LA, Zafar J, Helaleh M (2006) House dust as a source of human exposure to polybrominated diphenyl ethers in Kuwait. Chemosphere 64:603–608
5. Gevao B, Al-Bahloul M, Al-Ghadban AN, Ali L, Al-Omair A, Helaleh M, Al-Matrouk K, Zafar J (2006) Polybrominated diphenyl ethers in indoor air in Kuwait: implications for human exposure. Atmos Environ 40:1419–1426
6. Harrad S, Ibarra C, Abdallah MA, Boon R, Neels H, Covaci A (2008) Concentrations of brominated flame retardants in dust from United Kingdom cars, homes, and offices: causes of variability and implications for human exposure. Environ Int 34:1170–1175
7. Harrad S, Ibarra C, Diamond M, Melymuk L, Robson M, Douwes J, Roosens L, Dirtu AC, Covaci A (2008) Polybrominated diphenyl ethers in domestic indoor dust from Canada, New Zealand, United Kingdom and United States. Environ Int 34:232–238

8. Sjödin A, Paepke O, McGahee EE, Focant J-F, Jones RS, Wang R, Pless-Mulloli T, Toms LML, Herrman T, Mueller JF, Needham L, Patterson D Jr (2008) Concentration of polybrominated diphenyl ethers (PBDEs) in household dust from various countries – is dust a major source of exposure? Chemosphere 73:S131–S136
9. Huang Y, Chen L, Peng X, Xu Z, Ye Z (2009) PBDEs in indoor dust in South-Central China: characteristics and implications. Chemosphere 78:169–174
10. Toms LML, Sjödin A, Harden F, Hobson P, Jones R, Edenfield E, Mueller JF (2009) Concentrations of polybrominated diphenyl ethers (PBDEs) in pooled human serum are higher in children (aged 2-5 years) than in infants and adults. Environ Health Perspect 117:1461–1465
11. Toms LM, Bartkow ME, Symons R, Paepke O, Mueller JF (2009) Assessment of polybrominated diphenyl ethers (PBDEs) in samples collected from indoor environments in South East Queensland, Australia. Chemosphere 76:173–178
12. Toms LM, Hearn L, Kennedy K, Harden F, Bartkow M, Temme C, Mueller JF (2009) Concentrations of polybrominated diphenyl ethers (PBDEs) in matched samples of human milk, dust and indoor air. Environ Int 35:864–869
13. Johnson PI, Stapleton HM, Sjodin A, Meeker JD (2010) Relationships between polybrominated diphenyl ether concentrations in house dust and serum. Environ Sci Technol. 10.1021/es100697q
14. Cunha SC, Kalachova K, Pulkrabova J, Fernandes JO, Oliveira MBPP, Alves A, Hajslova J (2010) Polybrominated diphenyl ethers (PBDEs) contents in house and car dust of Portugal by pressurized liquid extraction (PLE) and gas chromatography-mass spectrometry (GC-MS). Chemosphere 78:1263–1271
15. Christiansson A, Hovander L, Athanassiadis I, Jakobsson K, Bergman A (2008) Polybrominated diphenyl ethers in aircraft cabins – a source of human exposure? Chemosphere 73:1654–1660
16. Hites RA (2004) Polybrominated diphenyl ethers in the environment and in people: a meta-analysis of concentrations. Environ Sci Technol 38:945–956
17. Lorber M (2008) Exposure of Americans to polybrominated diphenyl ethers. J Expo Sci Environ Epidemiol 18:2–19
18. Johnson-Restrepo B, Kannan K (2009) An assessment of sources and pathways of human exposure to polybrominated diphenyl ethers in the United States. Chemosphere 76:542–548
19. Kemmlein S, Hahn O, Jann O (2003) Emissions of organophosphate and brominated flame retardants from selected consumer products and building materials. Atmos Environ 37:5485–5493
20. Wilford BH, Thomas GO, Alcock RE, Jones KC, Anderson DR (2003) Polyurethane foam as a source of PBDEs to the environment. Organohalogen Compd 61:219–222
21. Hale RC, Guardia MJL, Harvey E, Mainor TM (2002) Potential role of fire retardant-treated polyurethane foam as a source of brominated diphenyl ethers to the US environment. Chemosphere 46:729–735
22. Lioy PJ (2006) Employing dynamical and chemical processes for contaminant mixtures outdoors to the indoor environment: the implications for total human exposure analysis and prevention. J Expo Sci Environ Epidemiol 16:207–224
23. Allen JG, McClean MD, Stapleton HM, Webster T (2008) Critical factors in assessing exposure to PBDEs via house dust. Environ Int 34:1085–1091
24. Weschler CJ, Nazaroff WW (2008) Semivolatile organic compounds in indoor environments. Atmos Environ 42:9018–9040
25. Schecter A, Pavuk M, Päpke O, Ryan J, Birnbaum L, Rosen R (2003) Polybrominated diphenyl ethers (PBDEs) in U.S. mothers' milk. Environ Health Perspect 111:1723–1729
26. Kalantzi OI, Martin FL, Thomas GO, Alcock RE, Tang HR, Drury SC, Carmichael PL, Nicholson JK, Jones KC (2004) Different levels of polybrominated diphenyl ethers (PBDEs)

and chlorinated compounds in breast milk from two UK regions. Environ Health Perspect 112:1085–1091
27. Vieth B, Herrmann T, Mielke H, Ostermann B, Paepke O, Rüdiger T (2004) PBDE levels in human milk: the situation in Germany and potential influencing factors – a controlled study. Organohalogen Compd 66:2643–2648
28. Morland KB, Landrigan PL, Sjodin A, Gobeille AK, Jones RS, McGahee EE, Needham L, Patterson D Jr (2005) Body burden of polybrominated diphenyl ethers among urban anglers. Environ Health Perspect 113:1689–1692
29. Wolff MS, Teitelbaum SL, Lioy PJ, Santella RM, Wang RY, Jones RL et al (2005) Exposures among pregnant women near the World Trade Center site on 11 September 2001. Environ Health Perspect 113:739–748
30. Toms LM, Harden FA, Symons RK, Burniston D, Furst P, Muller JF (2007) Polybrominated diphenyl ethers (PBDEs) in human milk from Australia. Chemosphere 68:797–803
31. Zota A, Rudel R, Morello-Frosch R, Brody JG (2008) Elevated house dust and serum concentrations of PBDEs in California: unintended consequences of furniture flammability standards? Environ Sci Technol 42:8158–8164
32. Imm P, Knobeloch L, Buelow C, Anderson H (2009) Household exposures to polybrominated diphenyl ethers (PBDEs) in a Wisconsin cohort. Paper presented at the 11th annual workshop on brominated flame retardants, Ottawa, Ontario, Canada, 2009
33. Karlsson M, Julander A, van Bavel B, Hardell L (2007) Levels of brominated flame retardants in blood in relation to levels in household air and dust. Environ Int 33:62–69
34. Fromme H, Korner W, Shahin N, Wanner A, Albrecht M, Boehmer S, Parlar H, Mayer R, Liebl B, Bolte G (2009) Human exposure to polybrominated diphenyl ethers (PBDE), as evidenced by data from a duplicate diet study, indoor air, house dust, and biomonitoring in Germany. Environ Int 35:1125–1135
35. Roosens L, Abdallah MA, Harrad S, Neels H, Covaci A (2009) Factors influencing concentrations of polybrominated diphenyl ethers (PBDEs) in students from Antwerp, Belgium. Environ Sci Technol 43:3535–3541
36. Sharp R, and S. Lunder (2004): In the dust. Toxic fire retardants in American homes environmental working group. http://www.ewg.org/reports/inthedust/index.php
37. Wu N, Herrmann T, Paepke O, Tickner J, Hale R, Harvey LE, La Guardia M, McClean MD, Webster TF (2007) Human exposure to PBDEs: associations of PBDE body burdens with food consumption and house dust concentrations. Environ Sci Technol 41:1584–1589
38. Stapleton HM, Allen JG, Kelly SM, Konstantinov A, Klosterhaus S, Watkins D, McClean MD, Webster TF (2008) Alternate and new brominated flame retardants detected in U.S. house dust. Environ Sci Technol 42:6910–6916
39. Stapleton HM, Kelly SM, Allen JG, McClean MD, Webster T (2008) Measurement of polybrominated diphenyl ethers on hand wipes: estimating exposure from hand-to-mouth contact. Environ Sci Technol 42:3329–3334
40. Stapleton HM, Sjodin A, Jones RS, Niehuser S, Zhang Y, Patterson DG Jr (2008) Serum levels of polybrominated diphenyl ethers (PBDEs) in foam recyclers and carpet installers working in the United States. Environ Sci Technol 42:3453–3458
41. Sjodin A, Hagmar L, Klasson-Wehler E, Kronholm-Diab K, Jakobsson E, Bergman A (1999) Flame retardant exposure: polybrominated diphenyl ethers in blood from Swedish workers. Environ Health Perspect 107:643–648
42. Wilford BH, Harner T, Zhu J, Shoeib M, Jones KC (2004) Passive sampling survey of polybrominated diphenyl ether flame retardants in indoor and outdoor air in Ottawa, Canada: implications for sources and exposure. Environ Sci Technol 38:5312–5318
43. Jones-Otazo H, Clarke J, Diamond M, Archbold J, Ferguson G, Harner T, Richardson GM, Ryan J, Wilford B (2005) Is house dust the missing exposure pathway for PBDEs? An analysis of the urban fate and human exposure to PBDEs. Environ Sci Technol 39:5121–5130

44. Jones-Otazo H, Clarke J, Diamond M, Archbold J, Harner T, Richardson M, Ryan J, Wilford B (2005) House dust is the main exposure pathway for PBDEs to humans. Organohalogen Compd 1585–1588
45. Tan J, Cheng SM, Loganath A, Chong YS, Obbard JP (2007) Polybrominated diphenyl ethers in house dust in Singapore. Chemosphere 66:985–992
46. Bossi R, Skov H, Vorkamp K, Christensen J, Rastogi SC, Egelø A, Petersen D (2008) Atmospheric concentrations of organochlorine pesticides, polybrominated diphenyl ethers and polychloronaphthalenes in Nuuk, South-West Greenland. Atmos Environ 42:7293–7303
47. Su Y, Hung H, Brice K, Su AK, Alexandrou N, Blanchard P, Chan E, Sverko E, Fellin P (2009) Air concentrations of polybrominated diphenyl ethers (PBDEs) in 2002-2004 at a rural site in the Great Lakes. Atmos Environ 43:6230–6237
48. Wang X-P, Gong P, Yao T-D, Jones KC (2010) Passive air sampling of organochlorine pesiticides, polychlorinated biphenyls, and polybrominated diphenyl ethers across the Tibetan Plateau. Environ Sci Technol 44:2988–2993
49. Alaee M, Cannon C, Muir D, Blanchard P, Brice K, Fellin P (2001) Spatial distribution and seasonal variation of PBDEs in Arctic and Great Lakes air. Organohalogen Compd 52:26–29
50. Su Y, Hung H, Sverko E, Fellin P, Henrik L (2007) Multi-year measurements of polybrominated diphenyl ethers (PBDEs) in the Arctic atmosphere. Atmos Environ 41:8725–8735
51. Wang XM, Ding X, Mai BX, Xie ZQ, Xiang CH, Sun LG, Sheng GY, Fu JM, Zeng EY (2005) Polybrominated diphenyl ethers in airborne particulates collected during a research expedition from the Bohai Sea to the Arctic. Environ Sci Technol 39:7803–7809
52. ter Schure AFH, Agrella C, Bokenstranda A, Svedera J, Larssona P, Zegers BN (2004) Polybrominated diphenyl ethers at a solid waste incineration plant II:atmospheric deposition. Atmos Environ 38:5149–5155
53. Wurl O, Potter JR, Durville C, Obbard JP (2006) Polybrominated diphenyl ethers (PBDEs) over the open Indian Ocean. Atmos Environ 40:5558–5565
54. Gouin T, Harner T, Daly GL, Wania F, Mackay D, Jones KC (2005) Variability of concentrations of polybrominated diphenyl ethers and polychlorinated biphenyls in air: implications for monitoring, modeling and control. Atmos Environ 39:151–166
55. Hoh E, Hites RA (2005) Brominated flame retardants in the atmosphere of the East-Central United States. Environ Sci Technol 39:7794–7802
56. Harner T, Shoeib M, Diamond M, Ikonomou M, Stern G (2006) Passive sampler derived air concentrations of PBDEs along an urban-rural transect: spatial and temporal trends. Chemosphere 64:262–267
57. Harrad S, Hunter S (2006) Concentrations of polybrominated diphenyl ethers in air and soil on a rural-urban transect across a major UK conurbation. Environ Sci Technol 40:4548–4553
58. Kennedy K, Hearn L, Toms LML, Thompson J, Bartkow M, Mueller JF (2008) Ambient atmospheric levels of PBDEs across urban and rural centres in Australia determined using polyurethane foam (PUF) passive air sampling. Organohalogen Compd 70:1621–1624
59. Chen LG, Mai BX, Bi XH, Chen SJ, Wang XM, Ran Y, Luo XJ, Sheng GY, Fu JM, Zeng EY (2006) Concentration levels, compositional profiles, and gas-particle partitioning of polybrominated diphenyl ethers in the atmosphere of an urban city in South China. Environ Sci Technol 40:1190–1196
60. Cetin B, Odabasi M (2008) Atmospheric concentrations and phase partitioning of polybrominated diphenyl ethers (PBDEs) in Izmir, Turkey. Chemosphere 71:1067–1078
61. Sjodin A, Patterson D Jr, Bergman A (2001) Brominated flame retardants in serum from U.S. blood donors. Environ Sci Technol 35:3830–3833
62. Julander A, Karlsson M, Hagstroem K, Ohlson CG, Engwall M, Bryngelsson I-L, Westberg H, Bavel Bv (2005) Polybrominated diphenyl ethers – plasma levels and thyroid status of workers at an electronic recycling facility. Int Arch Occup Environ Health 78:584–592

63. Cahill TM, Groskova D, Charles MJ, Sanborn JR, Denison MS, Baker L (2007) Atmospheric concentrations of polybrominated diphenyl ethers at near-source sites. Environ Sci Technol 41:6370–6377
64. Choi S-D, Baek S-Y, Chang Y-S (2008) Atmospheric levels and distribution of dioxin-like polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) in the vicinity of an iron and steel making plant. Atmos Environ 42:2479–2488
65. Strandberg B, Dodder NG, Basu I, Hites RA (2001) Concentrations and spatial variations of polybrominated diphenyl ethers and other organohalogen compounds in Great Lakes air. Environ Sci Technol 35:1078–1083
66. Butt CM, Diamond ML, Truong J, Ikonomou MG, Schure AFH (2004) Spatial distribution of polybrominated diphenyl ethers in Southern Ontario as measured in indoor and outdoor window organic films. Environ Sci Technol 38:724–731
67. Shoeib M, Harner T, Ikonomou K, Kannan K (2004) Indoor and outdoor air concentrations and phase partitioning of perfluoroalkyl sulfonamides and polybrominated diphenyl ethers. Environ Sci Technol 38:1313–1320
68. Allen JG, McClean MD, Stapleton HM, Nelson JW, Webster TF (2007) Personal exposure to polybrominated diphenyl ethers (PBDEs) in residential indoor air. Environ Sci Technol 41:4574–4579
69. Chen L, Mai B, Xu Z, Peng X, Han J, Ran Y, Shen G, Fu J (2008) In- and outdoor sources of polybrominated diphenyl ethers and their human inhalation exposure in Guangzhou, China. Atmos Environ 42:78–86
70. Harrad S, Hazrati S, Ibarra C (2006) Concentrations of polychlorinated biphenyls in indoor air and polybrominated diphenyl ethers in indoor air and dust in Birmingham, United Kingdom: implications for human exposure. Environ Sci Technol 40:4633–4638
71. Mandalakis M, Stephanou EG, Horii Y, Kannan K (2008) Emerging contaminants in car interiors: evaluating the impact of airborne PBDEs and PBDD/Fs. Environ Sci Technol 42:6431–6436
72. Toms LM, Harden F, Paepke O, Hobson P, Ryan JJ, Mueller JF (2008) Higher accumulation of polybrominated diphenyl ethers in infants than in adults. Environ Sci Technol 42:7510–7515
73. Liem A, Fuerst P, Rappe C (2000) Exposure of populations to dioxins and related compounds. Food Addit Contam 17:241–259
74. Schecter A, Paepke O, Harris TR, Tung KC, Musumba A, Olson J, Birnbaum L (2006) Polybrominated diphenyl ether (PBDE) levels in an expanded market basket survey of United States (U.S.) food and estimated PBDE dietary intake by age and gender. Environ Health Perspect 114:1515–1520
75. Schecter A, Paepke O, Tung K, Brown T, Musumba A (2006) Changes in polybrominated diphenyl ether (PBDE) levels in cooked food. Toxicol Environ Chem 88:207–211
76. Bocio A, Llobet JM, Domingo JL, Corbella J, Teixido A, Casas C (2003) Polybrominated diphenyl ethers (PBDEs) in food stuffs: human exposure through the diet. J Agric Food Chem 51:3191–3195
77. Schecter A, Paepke O, Ryan JJ, Tung K, Pavuk M, Staskal D, Birnbaum L, Quynh HT, Constable JD (2004) PBDEs in U.S. milk, blood, and food, and temporal trends for PBDEs, PCDDs, and PCBs in US blood. Organohalogen Compd 66:2834–2840
78. Darnerud PO, Atuma S, Aune M, Bjerselius R, Glynn A, Petersson Grawe K, Becker W (2006) Dietary intake estimations of organohalogen contaminants (dioxins, PCB, PBDE and chlorinated pesticides, e.g. DDT) based on Swedish market basket data. Food Chem Toxicol 44:1597–1606
79. Gomara B, Herrero L, Gonzalez MJ (2006) Survey of polybrominated diphenyl ether levels in Spanish commercial foodstuffs. Environ Sci Technol 40:7541–7547
80. Food Standards Australia and New Zealand (2007) Polybrominated diphenyl ethers (PBDE) in food in Australia. Food Standards, Canberra, p 49

81. Domingo JL, Marti-Cid R, Castell V, Llobet JM (2008) Human exposure to PBDEs through the diet in Catalonia, Spain: temporal trend. A review of recent literature on dietary PBDE intake. Toxicology 248:25–32
82. Schecter A, Harris TR, Shah N, Musumba A, Paepke O (2008) Brominated flame retardants in US food. Mol Nutr Food Res 52:266–272
83. Kiviranta H, Ovaskainen M-L, Vartiainen T (2004) Market basket study on dietary intake of PCDD/Fs, PCBs and PBDEs in Finland. Environ Int 30:923–932
84. Bayen S, Barlow P, Kee Lee H, Obbard JP (2005) Effect of cooking on the loss of persistent organic pollutants from Salmon. J Toxicol Environ Health A 68:253–265
85. Ohta S, Ishizuka D, Nishimura H, Nakao T, Aozasa O, Shimidzu Y, Ochiai F, Kida T, Nishi M, Miyata H (2002) Comparison of polybrominated diphenyl ethers in fish, vegetables, and meat and levels in human milk of nursing women in Japan. Chemosphere 46:689–696
86. Anderson H, Imm P, Knobeloch L, Turyk M, Mathew J, Buelow C, Persky V (2008) Polybrominated diphenyl ethers (PBDE) in serum: findings from a US cohort of consumers of sport-caught fish. Chemosphere 73(2):187–194
87. Knutsen HK, Kvalem HE, Thomsen C, Froshaug M, Haugen M, Becher G, Alexander J, Meltzer HM (2008) Dietary exposure to brominated flame retardants correlates with male blood levels in a selected group of Norwegians with a wide range of seafood consumption. Mol Nutr Food Res 52:217–227
88. Thomsen C, Knutsen HK, Liane VH, Froshaug M, Kvalem HE, Haugen M, Meltzer HM, Alexander J, Becher G (2008) Consumption of fish from a contaminated lake strongly affects the concentrations of polybrominated diphenyl ethers and hexabromocyclododecane in serum. Mol Nutr Food Res 52:228–237
89. Jakobsson K, Athanasiadou M, Christiansson A, Bergman A, Hagmar L (2005) Polybrominated diphenyl ethers (PBDEs) in serum from Swedish men 1988-2002. A longitudinal study. Organohalogen Compd 533–536
90. Fraser A, Webster T, McClean MD (2009) Diet contributes significantly to the body burdens of PBDEs in the general US population. Environ Health Perspect 117:1520–1525
91. Wada Y, Koizumi A, Yoshinaga T, Harada K, Inoue K, Morikawa A et al (2005) Secular trends and geographical variations in the dietary intake of polybrominated diphenyl ethers (PBDEs) using archived samples from the early 1980s and mid 1990s in Japan. J Occup Health 47:236–241
92. Lind Y, Atuma S, Aune M, Bjerselius R, Darnerud PO, Cnattingius S, Glynn A (2001) Polybrominated dihphenyl ethers (PBDEs) in breast milk from Uppsala women – extension and up-dating of data. In: Proceedings of the second international workshop on brominated flame retardants, The Swedish Chemical Society, Stockholm, Sweden, 14–16 May 2001, pp 117–120
93. Huwe JK, Larsen G (2005) Polychlorinated dioxins, furans, and biphenyls, and polybrominated diphenyl ethers in a US meat market basket and estimates of dietary intake. Environ Sci Technol 39:5606–5611
94. Schecter A, Colacino J, Sjodin A, Needham LL (2010) Partitioning of polybrominated diphenyl ethers (PBDEs) in serum and milk from the same mothers. Chemosphere 78:1279–1284
95. Schecter A, Haffner D, Colacino J, Patel K, Paepke O, Opel M (2010) Polybrominated diphenyl ethers (PBDEs) and hexabromocyclodecane (HBCD) in composite U.S. food samples. Environ Health Perspect 118:357–362
96. Bakker MI, de Winter-Sorkina R, de Mul A, Boon PE, van Donkersgoed G, van Klaveren JD, Baumann B, Hijman WC, Van Leeuwen SP, de Boer J, Zeilmaker M (2008) Dietary intake and risk evaluation of polybrominated diphenyl ethers in The Netherlands. Mol Nutr Food Res 52:204–216
97. Lind Y, Darnerud P, Atuma S, Aune M, Becker W, Bjerselius R, Cnattingius S, Glynn A (2003) Polybrominated diphenyl ethers in breast milk from Uppsala County, Sweden. Environ Res 93:186–194

98. Sudaryanto A, Kajiwara N, Takahashi S, Muawanah H, Tanabe S (2008) Geographical distribution and accumulation features of PBDEs in human breast milk from Indonesia. Environ Pollut 151:130–138
99. Akutsu K, Kitagawa M, Nakazawa H, Makino T, Iwazaki K, Oda H, Hori S (2003) Time-trend (1973-2000) of polybrominated diphenyl ethers in Japanese mother's milk. Chemosphere 53:645–654
100. Eslami B, Koizumi A, Ohta S, Inoue K, Aozasa O, Harada K, Yoshinaga T, Date C, Fujii S, Fujimine Y, Hachiya N, Hirosawa I, Koda S, Kusaka Y, Murata K, Nakatsuka H, Omae K, Saito N, Shimbo S, Takenaka K, Takeshita T, Todoriki H, Wada Y, Watanabe T, Ikeda M (2006) Large-scale evaluation of the current level of polybrominated diphenyl ethers (PBDEs) in breast milk from 13 regions of Japan. Chemosphere 63:554–561
101. Inoue K, Harada K, Takenaka K, Uehara S, Kono M, Shimizu T, Takasuga T, Senthilkumar K, Yamashita F, Koizumi A (2006) Levels and concentration ratios of polychlorinated biphenyls and polybrominated diphenyl ethers in serum and breast milk in Japanese mothers. Environ Health Perspect 114:1179–1185
102. Chao HR, Wang SL, Lee WJ, Wang YF, Papke O (2007) Levels of polybrominated diphenyl ethers (PBDEs) in breast milk from central Taiwan and their relation to infant birth outcome and maternal menstruation effects. Environ Int 33:239–245
103. Darnerud P, Atuma S, Aune M, Cnattingius S, Wernroth M, Wicklund-Glynn A (1998) Polybrominated diphenyl ethers (PBDEs) in breast milk from primiparous women in Uppsala county, Sweden. Organohalogen Compd 35:411–414
104. Meironyte D, Noren K (1999) Analysis of polybrominated diphenyl ethers in Swedish human milk. A time-related trend study, 1972–1997. J Toxicol Environ Health A 58:329–341
105. Meironyte Guvenius D, Noren K (2001) Polybrominated diphenyl ethers in Swedish human milk. The follow-up study. In: Proceedings of the second international workshop on brominated flame retardants, The Swedish Chemical Society, Stockholm, Sweden, 14–16 May 2001, pp 303–305
106. Darnerud P, Aune M, Atuma S, Becker W, Bjerselius R, Cnattingius S, Glynn A (2002) Time trend of polybrominated diphenyl ether (PBDE) levels in breast milk from Uppsala, Sweden, 1996–2001. Organohalogen Compd 58:233–236
107. Strandman T, Koistinen J, Vartiainen T (2000) Polybrominated diphenyl ethers (PBDEs) in placenta and human milk. Organohalogen Compd 47:61–64
108. Fürst P (2001) Organochlorine pesticides, dioxins, PCB and polybrominated biphenylethers in human milk from Germany in the course of time. Organohalogen Compd 52:185–188
109. Fürst P (2006) Dioxins, polychlorinated biphenyls and other organohalogen compounds in human milk. Levels, correlations, trends and exposure through breastfeeding. Mol Nutr Food Res 50:922–933
110. Raab U, Preiss U, Albrecht M, Shahin N, Parlar H, Fromme H (2008) Concentrations of polybrominated diphenyl ethers, organochlorine compounds and nitro musks in mother's milk from Germany (Bavaria). Chemosphere 72:87–94
111. Ingelido AM, Ballard T, Dellatte E, di Domenico A, Ferri F, Fulgenzi AR, Herrmann T, Iacovella N, Miniero R, Papke O, Porpora MG, De Felip E (2007) Polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) in milk from Italian women living in Rome and Venice. Chemosphere 67:S301–S306
112. Fängström B, Strid A, Athanassiadis I, Grandjean P, Weihe P, Bergman A (2004) A retrospective time trend study of PBDEs and PCBs in human milk from the Faroe Islands. Organohalogen Compd 66:2829–2832
113. Baumann B, Hijman W, van Beuzekom S, Hoogerbrugge R, Houweling D, Zeilmaker M (2003) PBDEs in human milk from the Dutch 1998 monitoring programme. Organohalogen Compd 61:187–190
114. Ryan J, Patry B (2000) Determination of brominated dipheyl ethers (BDEs) and levels in Canadian human milks. Organohalogen Compd 47:57–60

115. Johnson-Restrepo B, Addink R, Wong C, Arcaro K, Kannan K (2007) Polybrominated diphenyl ethers and organochlorine pesticides in human breast milk from Massachusetts, USA. J Environ Monit 9:1205–1212
116. She J, Holden A, Sharp M, Tanner M, Williams-Derry C, Hooper K (2007) Polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) in breast milk from the Pacific Northwest. Chemosphere 67:S307–S317
117. Ryan J, Patry B, Mills P, Beaudoin N (2002) Recent trends in levels of brominated diphenyl ethers (BDEs) in human milks from Canada. Organohalogen Compd 58:173–176
118. She J, Holden A, Sharp M, Derry C, Hooper K (2005) PBDEs are higher than PCBs in thirty percent breast milk samples from the Pacific Northwest. Organohalogen Compd 647–650
119. Daniels JL, Pan I-J, Jones R, Anderson S, Patterson D Jr, Needham LL, Sjodin A (2010) Individual characteristics associated with PBDE levels in US human milk samples. Environ Health Perspect 118:155–160
120. Polder A, Thomsen C, Lindstrom G, Loken KB, Skaare JU (2008) Levels and temporal trends of chlorinated pesticides, polychlorinated biphenyls and brominated flame retardants in individual human breast milk samples from Northern and Southern Norway. Chemosphere 73:14–23
121. Tsydenova OV, Sudaryanto A, Kajiwara N, Kunisue T, Batoev VB, Tanabe S (2007) Organohalogen compounds in human breast milk from Republic of Buryatia, Russia. Environ Pollut 146:225–232
122. Schuhmacher M, Kiviranta H, Vartiainen T, Domingo JL (2007) Concentrations of polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) in milk of women from Catalonia, Spain. Chemosphere 67:S295–S300
123. Lignell S, Aune M, Darnerud PO, Cnattingius S, Glynn A (2009) persistent organochlorine and organobromine compounds in mother's milk from Sweden 1996-2006: compound specific temporal trends. Environ Res 109:760–767
124. Thomsen C, Stigum H, Froshaug M, Broadwell SL, Becher G, Eggesbo M (2010) Determinants of brominated flame retardants in breast milk from a large scale Norwegian study. Environ Int 36:68–74
125. Kalantzi O, Alcock R, Martin F, Thomas G, Jones K (2003) Polybrominated diphenyl ethers (PBDEs) and selected organochlorines in human breast milk samples from the United Kingdom. Organohalogen Compd 61:9–12
126. Haraguchi K, Koizumi A, Inoue K, Harada KH, Hitomi T, Minata M, Tanabe M, Kato Y, Nishimura E, Yamamoto Y, Watanabe T, Takenaka K, Uehara S, Yang HR, Kim MY, Moon CS, Kim HS, Wang P, Liu A, Hung NN (2009) Levels and regional trends of persistent organochlorines and polybrominated diphenyl ethers in Asian breast milk demonstrate POPs signatures unique to individual countries. Environ Int 35:1072–1079
127. Carrizo D, Grimalt JO, Ribas-Fito N, Sunyer J, Torrent M (2007) Influence of breastfeeding in the accumulation of polybromodiphenyl ethers during the first years of child growth. Environ Sci Technol 41:4907–4912
128. World Health Organization (2007) Biomonitoring of Persistent Organic Pollutants (POPs). INFOSAN Information Note No. 02/2007 – Biomonitoring of POPs
129. Hooper K, She J, Sharp M, Chow J, Jewell N, Gephart R, Holden A (2007) Depuration of polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) in breast milk from California first-time mothers (primiparae). Environ Health Perspect 115:1271–1275
130. LaKind J, Berlin C, Sjodin A, Turner WE, Wang RY, Needham LL, Paul IM, Stokes JL, Naiman D, Patterson D Jr (2009) Do human milk concentrations of persistent organic chemicals really decline during lactation? Chemical concentrations during lactation and milk/serum partitioning. Environ Health Perspect 117:1625–1631
131. Bi X, Qu W, Sheng G, Zhang W, Mai B, Chen D, Yu L, Fu J (2006) Polybrominated diphenyl ethers in South China maternal and fetal blood and breast milk. Environ Pollut 144:1024–1030

132. Meironyte Guvenius D, Aronsson A, Ekman-Ordeberg G, Bergman A, Noren K (2003) Human prenatal and postnatal exposure to polybrominated diphenyl ethers, polychlorinated biphenyls, polychlorobiphenylols and pentachlorophenol. Environ Health Perspect 111:1235–1241
133. Gomara B, Herrero L, Ramos JJ, Mateo JR, Fernandez MA, Garcia JF, Gonzalez MJ (2007) Distribution of polybrominated diphenyl ethers in human umbilical cord serum, paternal serum, maternal serum, placentas, and breast milk from Madrid population, Spain. Environ Sci Technol 41:6961–6968
134. Frederiksen M, Thomsen M, Vorkamp K, Knudsen LE (2009) Patterns and concentration levels of polybrominated diphenyl ethers (PBDEs) in placental tissue of women in Denmark. Chemosphere 76:1464–1469
135. Mazdai A, Dobber NG, Abernathy MP, Hites RA, Bigsby RM (2003) Polybrominated diphenyl ethers in maternal and fetal blood samples (Children's Health). Environ Health Perspect 111:1249–1253
136. Kim TH, Lee YJ, Lee E, Patra N, Lee J, Kwack SJ, Kim KB, Chung KK, Han SY, Han JY, Lee BM, Kim HS (2009) Exposure assessment of polybrominated diphenyl ethers (PBDE) in umbilical cord blood of Korean infants. J Toxicol Environ Health A 72:1318–1326
137. Geyer HJ, Schramm K-W, Darnerud PO, Aune M, Feicht EA, Fried KW, Henkelmann B, Lenoir D, Schmid P, McDonald TA (2004) Terminal elimination half-lives of the brominated flame retardants TBBPA, HBCD, and lower brominated PBDEs in humans. Organohalogen Compd 66:3867–3872
138. Thuresson K, Bergman K, Rothenbacher K, Herrmann T, Sjolin S, Hagmar L, Papke O, Jakobsson K (2006) Polybrominated diphenyl ether exposure to electronics recycling workers– a follow up study. Chemosphere 64(11):1855–1861
139. Thuresson K, Hoglund P, Hagmar L, Sjodin A, Bergman A, Jakobsson K (2006) Apparent half-lives of hepta- to decabrominated diphenyl ethers in human serum as determined in occupationally exposed workers. Environ Health Perspect 114:176–181
140. Sjodin A, Patterson D Jr, Bergman A (2003) A review on human exposure to brominated flame retardants- particularly polybrominated diphenyl ethers. Environ Int 29:829–839
141. Sjodin A, Jones RS, Focant J-F, Lapeza CR, Wang RY, III EEM, Zhang Y, Turner WE, Slazyk B, Needham LL, Patterson D Jr (2004) Retrospective time-trend study of polybrominated diphenyl ether and polybrominated and polychlorinated diphenyl levels in human serum from the United States. Environ Health Perspect 112:654–658
142. Fängström B, Athanassiadis I, Odsjo T, Noren K, Bergman A (2008) Temporal trends of polybrominated diphenyl ethers and hexabromocyclodecane in milk from Stockholm mothers, 1980-2004. Mol Nutr Food Res 52:187–193
143. Noren K, Meironyte D (2000) Certain organochlorine and organobromine contaminants in Swedish human milk in perspective of past 20–30 years. Chemosphere 40:1111–1123
144. Alaee M (2006) Recent progress in understanding of the levels, trends, fate and effects of BFRs in the environment. Chemosphere 64:179–180
145. Choi J-W, Fujimaki S, Kitamura K, Hashimoto S, Ito H, Suzuki N, Sakai S-I, Morita M (2003) Polybrominated dibenzo-p-dioxins, dibenzofurans, and diphenyl ethers in Japanese human adipose tissue. Environ Sci Technol 37:817–821
146. Antignac JP, Cariou R, Zalko D, Berrebi A, Cravedi JP, Maume D, Marchand P, Monteau F, Riu A, Andre F, Le Bizec B (2009) Exposure assessment of French women and their newborn to brominated flame retardants: determination of tri- to deca- polybromodiphenylethers (PBDE) in maternal adipose tissue, serum, breast milk and cord serum. Environ Pollut 157:164–173
147. Li QQ, Loganath A, Chong YS, Obbard JP (2005) Determination and occurrence of polybrominated diphenyl ethers in maternal adipose tissue from inhabitants of Singapore. J Chromatogr B 819:253–257
148. Meneses M, Wingfors H, Schuhmacher M, Domingo J, Lindstrom G, Bavel Bv (1999) Polybrominated diphenyl ethers detected in human adipose tissue from Spain. Chemosphere 39:2271–2278

149. Covaci A, Voorspoels S, Roosens L, Jacobs W, Blust R, Neels H (2008) Polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) in human liver and adipose tissue samples from Belgium. Chemosphere 73:170–175
150. Petreas M, She J, Brown FR, Winkler J, Windham G, Rogers E, Zhao G, Bhatia R, Charles MJ (2003) High body burdens of 2, 2′, 4, 4′-tetrabromodiphenyl ether (BDE-47) in California women. Environ Health Perspect 111:1175–1180
151. Johnson-Restrepo B, Kannan K, Addink R, Adams DH (2005) Polybrominated diphenyl ethers and polychlorinated biphenyls in a marine foodweb of coastal Florida. Environ Sci Technol 39:8243–8250
152. Johnson-Restrepo B, Kannan K, Rapaport DP, Rodan BD (2005) Polybrominated diphenyl ethers and polychlorinated biphenyls in human adipose tissue from New York. Environ Sci Technol 39:5177–5182
153. Covaci A, De Boer J, Ryan JJ, Voorspoels S, Schepens P (2002) Distribution of organobrominated and organochlorinated contaminants in Belgian human adipose tissue. Environ Res Sect A 88:210–218
154. Schiavone A, Kannan K, Horii Y, Focardi S, Corsolini S (2010) Polybrominated diphenyl ethers, polychlorinated naphthalenes and polycyclic musks in human fat from Italy: comparison to polychlorinated biphenyls and organochlorine pesticides. Environ Pollut 158:599–606
155. Kalantzi OI, Brown FR, Caleffi M, Goth-Goldstein R, Petreas M (2009) Polybrominated diphenyl ethers and polychlorinated biphenyls in human breast adipose samples from Brazil. Environ Int 35:113–117
156. Takasuga T, Senthilkumar K, Takemori H, Ohi E, Tsuji H, Nagayama J (2004) Impact of fermented brown rice with *Aspergillus oryzae* (FEBRA) intake and concentrations of polybrominated diphenyl ethers (PBDEs) in blood of humans from Japan. Chemosphere 57:795–811
157. Koizumi A, Yoshinaga T, Harada K, Inoue K, Morikawa A, Muroi J, Inoue S, Eslami B, Fugii S, Fujimine Y, Hachiya N, Koda S, Kusaka Y, Murata K, Nakatsuka H, Omae K, Saito K, Shimbo S, Takenaka K, Takeshita T, Todoriki H, Wada Y, Watanabe T, Ikeda M (2005) Assessment of human exposure to polychlorinated biphenyls and polybrominated diphenyl ethers in Japan using archived samples from the early 1980s and mid-1990s. Environ Res 99:31–39
158. Schroter-Kermani C, Helm D, Herrmann T, Paepke O (2000) The German environmental specimen bank – application in trend monitoring of polybrominated diphenyl ethers in human blood. Organohalogen Compd 47:49–52
159. Thomsen C, Lundanes E, Becher G (2002) Brominated flame retardants in archived serum samples from Norway: a study on temporal trends and the role of age. Environ Sci Technol 36:1414–1418
160. van Bavel B, Hardell L, Kitti A, Liljedahl M, Karlsson M, Pettersson A, Tysklind M, Lindstrom G (2002) High levels of PBDEs in 5% of 220 blood samples from the Swedish population. Organohalogen Compd 58:161–164
161. Thuresson K, Bergman A, Jakobsson K (2005) Occupational exposure to commercial decabromodiphenyl ether in workers manufacturing or handling flame-retarded rubber. Environ Sci Technol 39:1980–1986
162. Fängström B, Hovander L, Bignert A, Athanassiadis I, Linderholm L, Grandjean P, Weihe P, Bergman A (2005) Concentrations of polybrominated diphenyl ethers, polychlorinated biphenyls and polychlorobiphenylols in serum from pregnant Faroese women and their children 7 years later. Environ Sci Technol 39:9457–9463
163. Thomas GO, Wilkinson M, Hodson S, Jones KC (2006) Organohalogen chemicals in human blood from the United Kingdom. Environ Pollut 141:30–41
164. Harrad S, Porter L (2007) Concentrations of polybrominated diphenyl ethers in blood serum from New Zealand. Chemosphere 66:2019–2023
165. Liberda E, Tsuji L, Nieboer E, Ryan J, Wainman B (2005) Determination of PBDE levels in a sub-artic aboriginal population. Organohalogen Compd 529–532

166. Sandanger TM, Sinotte M, Dumas P, Marchand M, Sandau CD, Pereg D, Berube S, Brisson J, Ayotte P (2007) Plasma concentrations of selected organobromine compounds and polychlorinated biphenyls in postmenopausal women of Quebec, Canada. Environ Health Perspect 115:1429–1434
167. Schecter A, Paepke O, Ryan J, Tung K, Olson J, Harris TR (2005) PBDEs in US human milk, archived and recent blood, fetal liver, partitioning between milk and blood, cooked and uncooked food and environmental specimens. Organohalogen Compd 651–653
168. Schecter A, Paepke O, Tung K, Joseph JE, Harris TR, Dahlgren J (2005) Polybrominated diphenyl ether flame retardants in the U.S. population: current levels, temporal trends, and comparison with dioxins, dibenzofurans, and polychlorinated biphenyls. J Occup Environ Med 47:199–211
169. Fischer D, Hooper K, Athanasiadou M, Athanassiadis I, Bergman A (2006) Children show highest levels of polybrominated diphenyl ethers (PBDEs) in a California family of four – a case study. Environ Health Perspect 114:1581–1584
170. Bradman A, Fenster L, Sjodin A, Jones RS, Patterson DG Jr, Eskenazi B (2007) Polybrominated diphenyl ether levels in the blood of pregnant women living in an agricultural community in California. Environ Health Perspect 115:71–74
171. Birnbaum LS, Cohen Hubal EA (2006) Polybrominated diphenyl ethers: a case study for using biomonitoring data to address risk assessment questions. Environ Health Perspect 114:1770–1775
172. Sjodin A, Wong L-Y, Jones RS, Park A, Zhang Y, Hodge C, Dipietro E, Mcclure C, Turner WE, Needham L, Patterson D Jr (2008) Serum concentrations of polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyl (PBB) in the United States population: 2003–2004. Environ Sci Technol 42:1377–1384
173. Bi X, Thomas GO, Jones KC, Qu W, Sheng G, Martin FL, Fu J (2007) Exposure of electronics dismantling workers to polybrominated diphenyl ethers, polychlorinated biphenyls, and organochlorine pesticides in South China. Environ Sci Technol 41:5647–5653
174. BSEF (2005) Brominated Science and Environmental Forum. http://www.bsef.com/bromine/faq/
175. NICNAS (2005) Summary of information on polybrominated flame retardants. Chemical Gazette, No. C 5
176. NICNAS (2007) Interim public health risk assessment report on certain PBDE congeners contained in commercial preparations of Pentabromodiphenyl ether and Octabromodiphenyl ether. http://www.nicnas.gov.au/Publications/CAR/Other/PBDE_PDF.pdf. Accessed 30 July 2008
177. Environmental Working Group (2008) Fire retardants in toddlers and their mothers. www.ewg.org/reports/pbdesintoddlers. Accessed 05 Sept 2008
178. U.S. Environmental Protection Agency (2009) DecaBDE Phase-out Initiative. http://www.epa.gov/oppt/existingchemicals/pubs/actionplans/deccadbe.html. Accessed 01 Feb 2010
179. Harden FA, Toms L-ML, Ryan JJ, Mueller JF (2004) Determination of the levels of polybrominated diphenylethers (PBDEs) in pooled blood sera obtained from Australians aged 31–45 years. In: Proceedings of the third international workshop on brominated flame retardants, Toronto, Canada, 6–9 June 2004, pp 59–62
180. Lee SJ, Ikonomou MG, Park H, Baek SY, Chang YS (2007) Polybrominated diphenyl ethers in blood from Korean incinerator workers and general population. Chemosphere 67:489–497
181. Zhu L, Ma B, Hites RA (2009) Brominated flame retardants in serum from the general population in northern China. Environ Sci Technol 43:6963–6968
182. Qu W, Bi X, Sheng G, Lu S, Fu J, Yuan J, Li L (2007) Exposure to polybrominated diphenyl ethers among workers at an electronic waste dismantling region in Guangdong, China. Environ Int 33:1029–1034
183. Thomsen C, Lundanes E, Becher G (2001) Brominated flame retardants in plasma samples from three different occupational groups in Norway. J Environ Monit 3:366–370

184. Jakobsson K, Thuresson K, Rylander L, Sjodin A, Hagmar L, Bergman A (2002) Exposure to polybrominated diphenyl ethers and tetrabromobisphenol A among computer technicians. Chemosphere 46:709–716
185. Lunder S, Hovander L, Athanassiadis I, Bergman A (2010) Significantly higher polybrominated diphenyl ether levels in young U.S. children than in their mothers. Environ Sci Technol 44:5256–5262
186. Cullen A (2002) Comparison of measured and predicted environmental PCB concentrations using simple compartmental models. Environ Sci Technol 36:2033–2038
187. Czub G, McLachlan MS (2004) A food chain model to predict the levels of lipophilic organic contaminants in humans. Environ Toxicol Chem 23:2356–2366
188. McDonald TA (2005) Polybrominated diphenylether levels among United States residents: daily intake and risk of harm to the developing brain and reproductive organs. Integr Environ Assess Manag 1:343–354
189. Lorber M (2007) Exposure of americans to polybrominated diphenyl ethers. J Expo Sci Environ Epidemiol 18(1):2–19
190. Australian Bureau of Statistics (2003) Breast feeding in Australia 2001 (4810.0.55.001). Canberra
191. Thomsen C, Liane, V. H.; Becher, G. Automated solid-phase extraction for the determination of polybrominated diphenyl ethers and polychlorinated biphenyls in serum–application on archived Norwegian samples from 1977 to 2003. J. Chromatogr., B: Anal. Technol. Biomed. Life Sci. 2007, 846 (1–2), 252–63
192. de Wit C (2002) An overview of brominated flame retardants in the environment. Chemosphere 46:583–624.

Emerging Brominated Flame Retardants in the Environment

Cynthia A. de Wit, Amelie Kierkegaard, Niklas Ricklund, and Ulla Sellström

Abstract A number of new brominated flame retardants (BFRs) are being found in the environment but the amount of data is still very small. The best studied emerging BFRs are 1,2-bis(2,4,6-tribromophenoxy)ethane and decabromodiphenyl ethane, with some data for hexabromobenzene, pentabromoethylbenzene, pentabromotoluene, tetrabromobisphenol A derivatives, bis(2-ethylhexyl) tetrabromophthalate, 2-ethylhexyltetrabromobenzoate, 1,2-dibromo-4-(1,2-dibromoethyl) cyclohexane, and 2,4,6-tribromophenol. Very little data are available for 2,4,6-tribromophenyl allyl ether, 2,3-dibromopropyl-2,4,6-tribromophenyl ether, hexachlorocyclopentadienyldibromocyclooctane, *tris*(2,3-dibromopropyl) isocyanurate, tetrabromophthalic anhydride, 1,2,5,6-tetrabromocyclooctane, and octabromo-1,3,3-trimethyl-1-phenylindane. Indoor air concentrations are generally higher than outdoor air concentrations, indicating emissions from flame-retarded products. Their presence in indoor air and dust indicates possible human exposure from this pathway, but there are little human data available to determine this. The presence of several of these BFRs in fish, birds, and mammals indicates that they are bioavailable and can be absorbed and bioaccumulated. Their presence in outdoor air and in the Arctic indicates that several are capable of long range atmospheric transport. More data on these new BFRs are needed in order to determine if they pose unacceptable risks to the environment and to human health.

Keywords 1,2,5,6-Tetrabromocyclooctane, 1,2-Bis(2,4,6-tribromophenoxy)ethane, 1,2-Dibromo-4-(1,2-dibromoethyl)cyclohexane, 2,3-Dibromopropyl-2,4,6-tribromophenyl ether, 2,4,6-Tribromophenol, 2,4,6-Tribromophenyl allyl ether, 2-Ethylhexyltetrabromobenzoate, Bis(2-ethylhexyl) tetrabromophthalate,

C.A. de Wit (✉), A. Kierkegaard, N. Ricklund, and U. Sellström
Department of Applied Environmental Science (ITM) Stockholm University, 10691 Stockholm, Sweden
e-mail: Cynthia.de.wit@itm.su.se

E. Eljarrat and D. Barceló (eds.), *Brominated Flame Retardants*,
Hdb Env Chem (2011) 16: 241–286, DOI 10.1007/698_2010_73,

Decabromodiphenyl ethane, Hexabromobenzene, Hexachlorocyclopenta dienyl-dibromocyclooctane, Octabromo-1,3,3-trimethyl-1-phenylindane, Pentabromoethylbenzene, Pentabromotoluene, Tetrabromobisphenol A derivatives, Tetra bromophthalic anhydride, *Tris*(2,3-dibromopropyl) isocyanurate

Contents

Abbreviations

ATE	2,4,6-Tribromophenyl allyl ether
BFR	Brominated flame retardant
BTBPE	1,2-Bis(2,4,6-tribromophenoxy)ethane
DBDPE	Decabromodiphenyl ethane
DPTE	2,3-Dibromopropyl-2,4,6-tribromophenyl ether
HBBz	Hexabromobenzene
HBCD	Hexabromocyclododecane
HCDBCO	Hexachlorocyclopentadienyldibromocyclooctane
OBIND	Octabromo-1,3,3-trimethyl-1-phenylindane

PBDE	Polybrominated diphenyl ether
PBEB	Pentabromoethylbenzene
PBT	Pentabromotoluene
TBB	2-Ethylhexyltetrabromobenzoate
TBBPA	Tetrabromobisphenol A
TBBPA-DAE	Tetrabromobisphenol A bis(allyl ether)
TBBPA-DBPE	Tetrabromobisphenol A (2,3-dibromopropyl ether)
TBBPA-DHEE	Tetrabromobisphenol A dihydroxyethyl ether
TBC	*Tris*(2,3-dibromopropyl) isocyanurate
TBCO	1,2,5,6-Tetrabromocyclooctane
TBECH	1,2-Dibromo-4-(1,2-dibromoethyl)cyclohexane
TBP	2,4,6-Tribromophenol
TBPA	Tetrabromophthalic anhydride
TBPH	Bis(2-ethylhexyl) tetrabromophthalate

1 Introduction

At least 75 brominated compounds are listed as flame retardants [1] but analytical focus has been on only a few including polybrominated diphenyl ethers (PBDEs), hexabromocyclododecane (HBCD), and tetrabromobisphenol A (TBBPA). Two of the PBDE technical products (PentaBDE, OctaBDE) are now being phased out or have been banned in North America and Europe. The remaining product (DecaBDE) is used more restrictively, and production, importation, and sales will be discontinued in the USA for all uses by the end of 2013 by the two major producers (Chemtura, Albemarle) and the largest US importer (ICL Industrial Products, Israel) [2–4]. Thus, other brominated flame retardants (BFRs) are finding increasing use as replacements for these BFRs. Some of these emerging BFRs are now being found in the environment, including in the Arctic, suggesting their potential for long range atmospheric transport [5]. This chapter is a review of the literature covering the environmental occurrence of a number of these less well-studied BFRs. Physico-chemical properties of these BFRs are given in Table 1 and their chemical structures are shown in Fig. 1.

2 1,2-Bis(2,4,6-tribromophenoxy)ethane

2.1 Background

1,2-Bis(2,4,6-tribromophenoxy)ethane (BTBPE) is an additive flame retardant marketed as FF-680 (Great Lakes Chemical Corporation, Arkansas, USA, now a part of Chemtura). BTBPE has been produced since the mid-1970s and is now

Table 1 Physico-chemical properties of emerging brominated flame retardants

Chemical	Abbreviation	CAS number	Molecular weight	Log K_{ow}	Log K_{aw}[a]	Vapor pressure 25°C	References
1,2-Bis(2,4,6-tribromophenoxy)ethane	BTBPE	37853-59-1	687.64	7.88	−5.17	3.88E-10	[90][b]
Decabromodiphenyl ethane	DBDPE	84852-53-9	971.22	11.1	−6.29	6.0E-15	[90][b]
Hexabromobenzene	HBBz	87-82-1	551.49	5.85	−3.03	1.14E-04	[90][b]
				6.07		3.17E-04	[139]
						7.5E-04	[140]
Pentabromoethylbenzene	PBEB	85-22-3	500.65	6.40	−2.92	3.2E-04	[90][b]
Pentabromotoluene	PBT	87-83-2	486.62	5.872	−2.92	1.22E-03	[90][b]
Tetrabromobisphenol A diallyl ether	TBBPA-DAE	25327-89-3	624.00	8.539	−4.43	1.83E-08	[90][b]
Tetrabromobisphenol A 2,3-dibromopropyl ether	TBBPA-DBPE	21850-44-2	943.61	10.422	−8.01	1.60E-07	[90][b]
						8.5E-13	[72][c]
Tetrabromobisphenol A dihydroxyethyl ether	TBBPA-DHEE	4162-45-2	631.98	6.78		5.2E-12	[72][c]
Bis(2-ethylhexyl) tetrabromophthalate	TBPH	26040-51-7	706.14	10.08	−5.95	1.55E-11	[90][b]
				11.95	−4.91	2.28E-09	[136][c]
2-Ethylhexyltetrabromobenzoate	TBB	183658-27-7	549.92	8.75	−3.59	4.57E-06	[136][c]
1,2-Dibromo-4-(1,2-dibromoethyl)cyclohexane	TBECH	3322-93-8	427.8	5.24	−2.77	1.40E-02	[136][c]
2,4,6-Tribromophenol	TBP	118-79-6	330.8	4.33	−2.3	0.41	[90][b]
2,4,6-Tribromophenyl allyl ether	ATE	3278-89-5	370.86	4.97	−2.41	4.90E-02	[90][b]
				5.4			[90]
Hexachlorocyclopentadienyldibromocyclooctane	HCDBCO	51936-55-1	536	7.91	−3.14	1.43E-05	[136][c]
Tris(2,3-dibromopropyl) isocyanurate	TBC	52434-90-9	728.69	7.37	−16.31	1.57E-13	[136][c]
Tetrabromophthalic anhydride	TBPA	632-79-1	463.7	3.78	−9.04	1.27E-09	[90][b]
1,2,5,6-tetrabromocyclooctane	TBCO	3194-57-8	427.80	4.42[b]		3.59E-05[b]	
Octabromo-1,3,3,-trimethyl-1-phenylindane	OBIND	155613-93-7	867.52	11.38[d]		2.18E-15[a]	

Log K_{ow} – octanol water partition coefficient; Log K_{aw} – air–water partition coefficient

[a]Log K_{aw} or other values predicted using SPARC Online Calculator

[b]Physico-chemical properties calculated using SciFinder (ACD/Labs Software V9.04)

[c]Physico-chemical properties calculated using US EPA EPI Suite V3.20

[d]Physico-chemical properties calculated using ACD Chemscetch

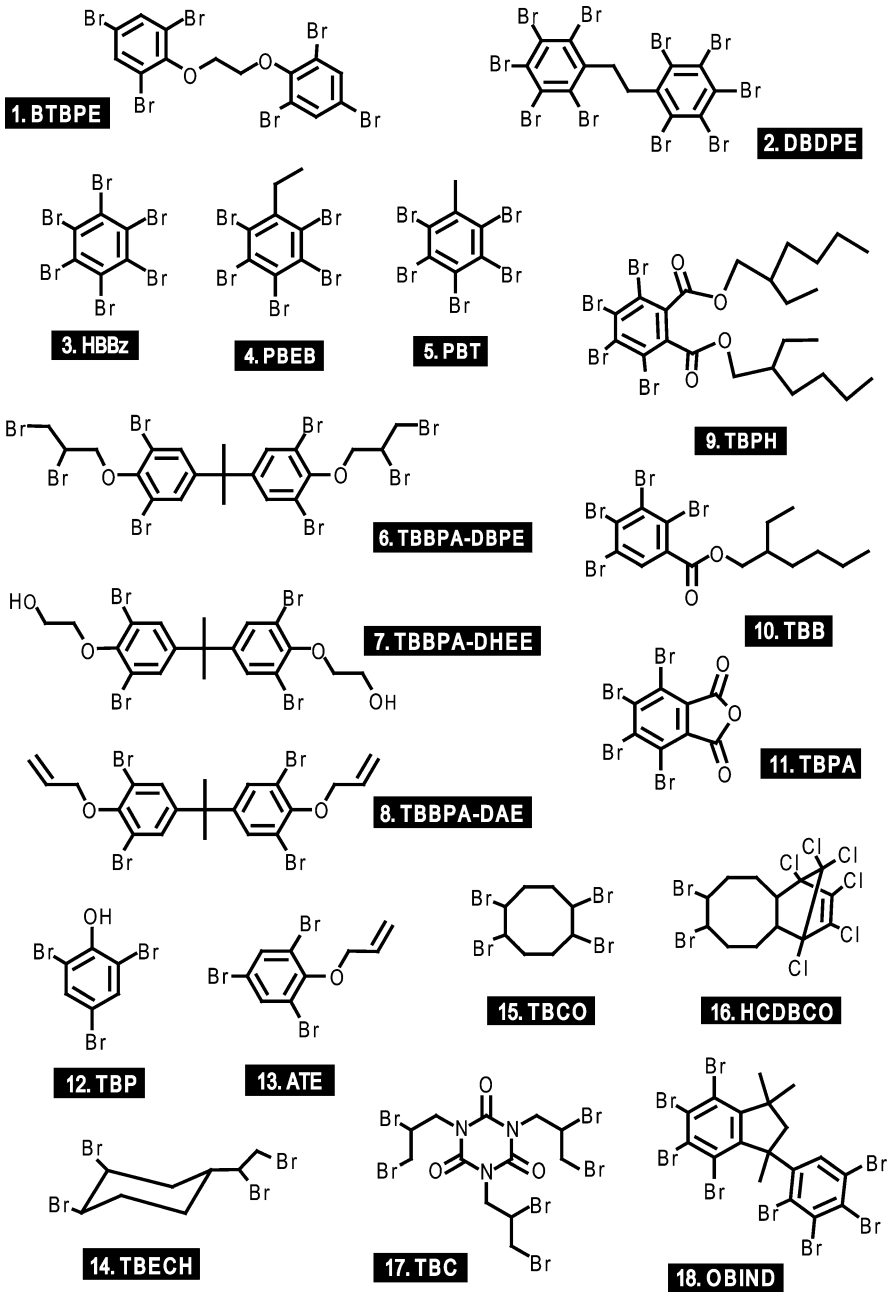


Fig. 1 1,2-bis(2,4,6-Tribromophenoxy)ethane (**1**), decabromodiphenyl ethane (**2**), Hexabromobenzene (**3**), Pentabromoethylbenzene (**4**), Pentabromotoluene (**5**), tetrabromobisphenol A (2,3-dibromopropyl ether) (**6**), tetrabromobisphenol A dihydroxyethyl ether (**7**), tetrabromobisphenol A bis(allyl ether) (**8**), bis(2-ethylhexyl) tetrabromophthalate (**9**), 2-ethylhexyltetrabromobenzoate

being used as a replacement for OctaBDE [6]. It is marketed for use in high impact polystyrene (HIPS), thermoplastics, and thermoset resins. Great Lakes Chemical Corp./Chemtura is the only producer of BTBPE in the USA, and they produced 4,500–22,500 metric tons/year from 1986 to 1994, with a decline to 450–4,500 tons/year after 1998 [6]. No information is available on more recent US production volumes but it can be surmised that they will increase as a result of the ban on OctaBDE. BTBPE is produced and used in China, as well, but information on production and use volumes is not available [7]. It is listed as a low production volume (LPV) chemical in the EU [8]. Worldwide production/usage was estimated to be 16,710 tons in 2001 [9]. BTBPE was first identified in the environment in the 1970s in samples taken at or near the Great Lakes Chemical Corp./Chemtura production facility in El Dorado, Arkansas, USA [10–12].

2.2 *Outdoor Air and Tree Bark*

In 1977, BTBPE was identified in air particulate samples taken using high-volume samplers on the grounds of a production site in El Dorado, Arkansas [11, 12]. The concentrations found ranged from not detectable level to 183 ng/m^3 [11].

More recently, high-volume air samples were taken at a number of sites in the east-central USA within the Integrated Atmospheric Deposition Network (IADN). In a first sampling campaign covering the time period 2002–2004, sampling sites included Chicago (Illinois), Sleeping Bear Dunes National Lakeshore (Michigan), Bloomington (Indiana), Rohwer (Arkansas), and Cocodrie (Louisiana) [6, 13]. BTBPE was found predominantly on particulates with a concentration range of 0.03–70 pg/m^3, and a mean of 3.4 pg/m^3, more than 100 times lower concentrations than seen in particulates sampled on the production site. The highest BTBPE concentrations were found in samples from the Arkansas site, which is only 150 km west of the Chemtura production plant and the authors speculate that these higher concentrations may be due to production facility emissions. The next highest BTBPE concentrations were found in air particulates from Chicago (mean 1.6 pg/m^3, range 0.025–11 pg/m^3), reflecting possible urban sources. Concentrations were lower at the other sites (rural) and were lowest at the remote site at Sleeping Bear Dunes National Lakeshore (mean 0.16 pg/m^3, range 0.03–1.4 pg/m^3) [6, 13]. In a second sampling campaign in 2005–2006, sampling sites included Chicago (Illinois), Sleeping Bear Dunes National Lakeshore and Eagle Harbor (Michigan), Cleveland (Ohio), and Sturgeon Point (New York) [14]. Highest concentrations were found in the samples from the urban site of Chicago (mean 1.2 pg/m^3) and lowest concentrations at the remote site of Eagle Harbor (mean

Fig. 1 (continued) (**10**), tetrabromophthalic anhydride (**11**), 2,4,6-tribromophenol (**12**), 2,4,6-tribromophenyl allyl ether (**13**), 1,2-dibromo-4-(1,2-dibromoethyl)cyclohexane (**14**), 1,2,5,6-tetrabromocyclooctane (**15**), Hexachlorocyclopentadienyldibromocyclooctane (**16**), *tris*(2,3-dibromopropyl) isocyanurate (**17**), octabromo-1,3,3-trimethyl-1-phenylindane (**18**)

0.5 pg/m^3). The BTBPE concentrations in both studies were similar to those for HBCD and some BDE congeners (BDE-47, -99, -209) in the same samples.

Other than the US, BTBPE has only been reported in air samples from Sweden and from Guangzhou City, in the Pearl River Delta (PRD) of southern China. Outdoor air samples from the city of Stockholm, Sweden, taken with a low volume sampler, had BTBPE concentrations below the limit of quantitation (3 pg/m^3) [15]. The PRD is a highly industrialized and urbanized area in China, with electronics and electrical equipment manufacturing and high usage of BFRs [16]. The mean BTBPE concentration in four high-volume air samples taken in Guangzhou City in 2007 was 30.7 pg/m^3 (range 3.8–67 pg/m^3) [7]. These higher BTBPE concentrations in Guangzhou City are similar to those seen in the air samples from Arkansas, USA, not far from a BTBPE production facility and indicate use of BTBPE in manufacturing facilities in the PRD. The concentrations of BTBPE were lower than those of the PBDEs.

In a sampling campaign of tree bark from 29 sites across North America in 2000–2001, BTBPE was detected in samples from only six of these sites, at concentrations of 0.68–24 ng/g lipid [17]. Sampling was done in rural residential areas away from roads. Interestingly, the samples with the highest BTBPE concentrations were from a site in Arkansas north of the Chemtura production facility (24 ng/g lipid), and several sites east, southeast, or northeast of this facility in the neighboring state of Mississippi (1.4, 1.5, and 1.9 ng/g lw). In another study, tree bark samples were collected in 2006 from 26 sites from the northeastern USA, and samples from 23 sites had BTBPE concentrations ranging from 0.40 to 17 ng/g lipid, with a mean of 3.2 ng/g lipid [18]. As there is only one production facility for BTBPE in the USA, located in the southcentral part of the country, the authors concluded that the presence of BTBPE on trees far from this source could only be explained by long range atmospheric transport and local use. BTBPE concentrations were lower than PBDE concentrations in both studies.

Qiu and Hites [18] also analyzed 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 ng/g lipid, respectively. BTBPE concentrations were much higher in tree bark from South Korea (56 ng/g lipid), and three sites in China (3.1–38 ng/g lipid). The highest concentration in China was found in Shenzheng, which is located in the PRD. Thus, results from tree bark spatial studies support the results of air sampling studies, indicating that BTBPE is capable of long range atmospheric transport and that production and use facilities are emission sources.

2.3 Soil and Outdoor Dust

In the 1970s, BTBPE was identified but not quantified in soil samples taken near the Chemtura production facility in El Dorado, Arkansas, USA [12]. More recently, BTBPE was found in soil samples taken from two areas in southern China, one in

the PRD and one near an electronics waste processing area in the agricultural area of Qingyuan City, north of the PRD [7]. The electronics waste area processes more than 1.7 million tons of e-waste per year imported to China from overseas. E-waste processing is done to recover metals using rudimentary methods in family workshops, including shredding, burning, and use of acids. Soil samples were collected from farmland near Guangzhou City, PRD, in 2007 and from the e-waste area in 2006. The mean BTBPE concentration was 0.05 ng/g dry weight (dw) (range 0.02–0.11 ng/g dw) for the PRD soils, but was much higher, 1.98 ng/g dw (range 0.07–6.2 ng/g dw) in the e-waste soils [7]. Outdoor dust samples collected from the ground surface near the e-waste workshops had a mean BTBPE concentration of 107 ng/g dw (range 14.6–232 ng/g dw), indicating that these workshops are probably a source of emissions to the nearby farmland. The concentrations of BTBPE were lower than those of PBDEs in the PRD samples, but were similar to PentaBDE concentrations at the e-waste site.

2.4 Indoor Air and Dust

BTBPE was included in analyses of indoor air at electronic recycling plants in Sweden [15, 19]. Sjödin et al. [15] found highest BTBPE concentrations in air samples taken near a shredder when BFR-containing plastics were shredded (140 and 150 ng/m^3). Lower concentrations were seen when shredding non-BFR-containing plastics (23 and 32 ng/m^3) and in the dismantling hall (mean 20 ng/m^3). These concentrations were in the same range as those of BDE-183 and -209, which were the predominant PBDEs found.

Petterson-Julander et al. [19] found similar BTBPE concentrations in personal air samples of electronic dismantlers at another electronics recycling plant (mean 22 ng/m^3). Personal air samples from other workers not directly exposed in the dismantling hall had lower BTBPE concentrations (mean 8.8 ng/m^3) and unexposed workers had the lowest concentration (0.8 ng/m^3). Again, concentrations of BTBPE were found to be in the same range as those of BDE-209 in all three groups. Expanding on this air sampling study, Julander et al. [20] used different types of air samplers to collect three different particle fractions (respirable, total, and inhalable dust) in air samples at this same electronics recycling plant. The highest BTBPE concentration ranged from 8.2 to 12.2 ng/m^3 in the inhalable fraction. BTBPE was also found in the total fraction (7.4–11.9 ng/m^3) with lowest concentrations in the respirable fraction (0.7–1.0 ng/m^3) [20]. Concentrations of BTBPE were somewhat higher than those of BDE-183, but much lower than those of BDE-209.

Sjödin et al. [15] also analyzed BTBPE in air samples from other indoor microenvironments (circuit board assembly, offices with computers, computer repair facilities, teaching halls). Concentrations were considerably lower and ranged from 41 pg/m^3 (circuit board assembly) to 3 pg/m^3 (teaching hall) and were similar to BDE-183 and -209 concentrations.

BTBPE was found in dust samples from five homes in Örebro, Sweden, with concentrations ranging from 2.5 to 8.2 ng/g dw, which were considerably lower than those of PBDEs [21]. Air samples were also analyzed, but BTBPE was not detected.

Researcher-collected dust samples were taken in 19 homes in Boston, Massachusetts, USA, in 2006, from the main living area, a bedroom, and also from the occupant's vacuum cleaner bag [22]. BTBPE concentrations ranged from 1.6 to 789 ng/g dw. Geometric mean BTBPE concentrations were 48.1 ng/g dw in the living area, 47.8 ng/g dw in the bedroom, and 17.7 ng/g dw in the vacuum cleaner dust [22]. BTBPE was not detected in the dust standard reference material (NIST SRM 2585) used. These concentrations were about ten times lower than HBCD concentrations found in the same samples. An additional 50 dust samples taken from vacuum cleaner bags between 2002 and 2007 from Boston houses also contained BTBPE [23]. BTBPE concentrations ranged from 1.4 to 950 ng/g dw with a geometric mean of 21 ng/g dw, which was eight times lower than the HBCD concentration and much lower than PBDE concentrations.

In the UK, Harrad et al. [24] collected dust samples from 30 homes, 18 offices, and 20 cars in 2006 and 2007. Average BTBPE concentrations were 120, 7.2, and 7.7 ng/g dw for homes, offices, and cars, respectively. The maximum concentration of 1,900 ng/g dw was also found in homes. BTBPE concentrations were generally lower than those of PBDEs. Estimated exposures via dust ingestion for adults and toddlers were as high as 13 and 69 ng/day, respectively, which were lower than those of tri-hexaBDEs.

BTBPE was also detected in dust samples from 25 homes in the Czech Republic but no concentrations were reported [25].

2.5 Children's Toys

China is a major manufacturer of children's toys, particularly in the Guangdong Province in southern China [26]. Sixty-nine toys were purchased in Guangzhou City in southern China in 2007 and 2008 and analyzed for a range of BFRs. The materials included hard plastic, foam, rubber/soft plastic, and textile stuffed toys [26]. BTBPE was found in hard plastic toys with a median concentration of 101 ng/g, which was lower than PBDE concentrations. BTBPE was also detected in some rubber/soft plastic toys, but was not detected in foam or stuffed toys. The estimated exposure of children to BTBPE from mouthing toys was calculated to be 0.024–0.82 ng/kg body weight-day.

2.6 Sewage Sludge

Sewage sludge samples were collected from Guangzhou City, PRD, in southern China in 2007 and analyzed for BTBPE [7]. BTBPE concentrations ranged from 0.31 to 1.66 ng/g dw with a mean of 0.88 ng/g dw.

2.7 Water and Sediment

In a bioaccumulation study of various BFRs, BTBPE was quantified in the dissolved phase of freshwater sampled in 2004 from the south basin of Lake Winnipeg, Canada [27]. The mean BTBPE concentration was 1.96 pg/L, which was lower than BDE-47 and -99 concentrations, but comparable to concentrations of BDE-100, -153, and 154.

Besides finding BTBPE in air samples near a production site in Arkansas, Zweidinger et al. [10] also found detectable levels in sediments from streams near the plant. BTBPE concentrations ranged from not detectable level to 466 ng/g.

BTBPE concentrations in surficial sediment samples collected in 2002 from Lake Winnipeg, Canada were below detection limits [27], but were 7.2 and 6.7 ng/g dw in samples taken in 2004 from Lake Michigan [6] and Lake Ontario [28]. For Lake Michigan, BTBPE concentrations were lower than PBDE concentrations, but were similar to PBDE concentrations for Lake Ontario. In the studies from Lakes Michigan and Ontario, analysis of BTBPE in different levels of sediment cores also showed rapidly increasing temporal trends from the mid-1970s (Michigan) or early 1980s (Ontario) as shown in Fig. 2.

Surficial sediment samples were collected from the Dongjiang River in the PRD area of southern China in 2002 and 2006 and analyzed for BTBPE and a range of other BFRs [7]. The samples from 2002 had a mean BTBPE concentration of

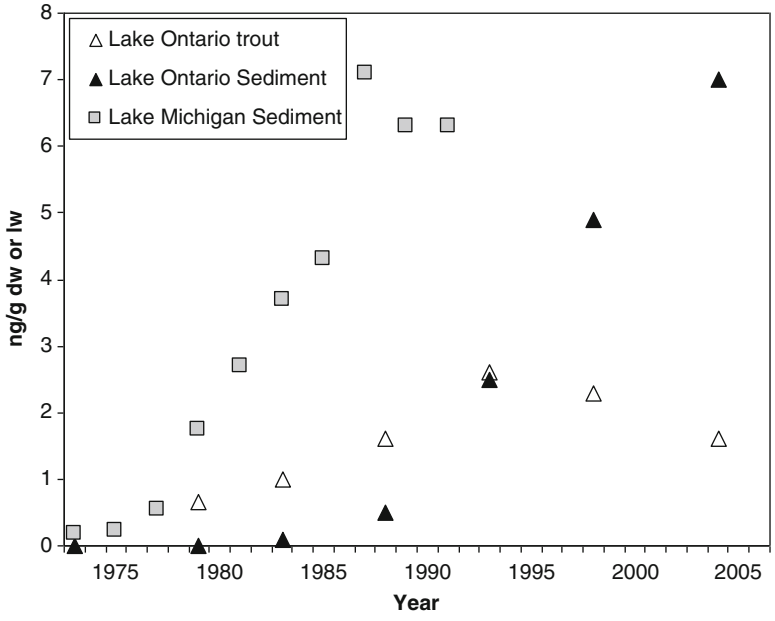


Fig. 2 Temporal trends of BTBPE in lake trout and sediment from Lake Ontario, and in sediment from Lake Michigan. Data from Ismail et al. [32], Hoh et al. [6], and Qiu et al. [28]

7.6 ng/g dw (range 0.27–21.9 ng/g dw), while the 2006 samples had a mean concentration of 1.3 ng/g dw (range 0.05–2.07 ng/g dw). The authors speculate that the lower BTBPE concentrations found in 2006, weighed together with results for a number of other BFRs in past or current use, may reflect changes in the use of different BFRs in the PRD area in recent years [7].

BTBPE was identified in sediments from two of four sites collected from the Western Scheldt along the coast of the Netherlands [29]. Concentrations at the two sites were 0.25 ng/g dw (Terneuzen) and 0.31 ng/g dw (Ouden Doel near the Belgian border). BTBPE was not detected in the suspended particulate matter collected from Terneuzen.

2.8 Invertebrates and Fish

Besides water and sediment, 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*) [27]. Biota were collected between 2000 and 2002. Mean BTBPE concentrations were 0.37 ng/g lipid weight (lw) in zooplankton, 1.3 ng/g lw in mussels, and from 0.13 to 0.95 ng/g lw in the different fish species, which were much lower than HBCD and PBDEs concentrations. The trophic magnification factor of BTBPE for the entire food web was 1.0, which was generally lower than that of most PBDEs and HBCD [27, 30]. Biomagnification factors (BMFs) calculated on the basis of lipid weight BTBPE concentrations in various predator/prey relationships indicated that BTBPE may bioaccumulate within certain feeding relationships, particularly for walleye [27]. BMFs for walleye ranged from 0.4 to 2.5 depending on the prey. The propensity of BTBPE to biomagnify was confirmed in a laboratory feeding study in juvenile rainbow trout (*Oncorhynchus mykiss*) [31]. BTBPE was taken up from the gut with an assimilation efficiency of 27% over the 49 day feeding period, resulting in a BMF of 2.3.

BTBPE concentrations were determined in Lake Ontario lake trout (*Salvelinus namaycush*) sampled from 1979 to 2004 [32]. Concentrations were found to increase exponentially from 1979 to 1993, doubling every 6 years, and then to level off or possibly decrease (Fig. 2). Mean BTBPE concentration in the 2004 sample was 1.6 ng/g lw, which is higher than that seen in fish in the Lake Winnipeg study [27]. Lake trout PBDE and HBCD concentrations were considerably higher than BTBPE concentrations.

In a study near an e-waste processing area in southern China, a few individuals of three farmed fish species were collected (carp (*Cyprinus carpio*), bighead carp (*Aristichthys nobilis*), tilapia (*Tilapia*)) from a pond 2 km away from the workshops and BTBPE analyzed in liver and muscle samples [7]. BTBPE was detectable in four of five muscle samples (range <0.012–0.15 ng/g lw), but found in only two of five liver samples (range <0.012–0.041 ng/g lw). These concentrations were much lower than those found for PBDEs.

BTBPE concentrations in the marine flatfish sole (*Solea solea*) collected along the French coastline in 2003 and 2004 ranged from 0.12 to 2.2 ng/g lw, which were lower than the concentrations found for PBDEs [33]. The highest BTBPE concentration was found in sole from the Seine estuary.

2.9 Birds

BTBPE was detected in California peregrine falcon (*Falco peregrinus*) eggs collected in 1999–2007; however, no concentrations were reported [34].

Eggs of herring gulls (*Larus argentatus*) from several colonies on the North American Great Lakes have been analyzed for BTBPE to discern spatial [35] and temporal trends from 1982 to 2006 [36]. In the spatial trend study, BTBPE was found in all colonies and mean concentrations ranged from 0.04 to 0.70 ng/g ww, with highest concentrations found in colonies along Niagara River above Niagara Falls [35]. These concentrations were much lower than those of PBDEs. In the temporal trend study, BTBPE was detected primarily in eggs from the mid-1990s to 2006, with no discernible trends [36]. The mean concentrations in 2006 for seven colonies ranged from <0.06 to 0.20 ng/g ww.

In a study near an e-waste processing area in southern China, several specimens of watercock (*Gallicrex cinerea*) were collected and muscle, liver, and kidney tissues analyzed for BTBPE [7]. Higher concentrations were found in liver (0.27–1.0 ng/g lw) and kidney (0.12–0.89 ng/g lw) than in muscle tissues (0.07–0.39 ng/g lw). Concentrations of BTBPE were much lower than those of PBDEs.

In the marine environment, BTBPE has been found in northern fulmar eggs (*Fulmarus glacialis*) from the Faroe Islands [37] and in glaucous gull eggs and plasma (*Larus hyperboreus*) from the Norwegian Arctic [9]. Mean concentrations were 0.11 ng/g lw (range <0.02–0.17 ng/g lw) in fulmar eggs collected in 2003, which was much lower than tri-decaBDE concentrations [37]. For glaucous gull samples collected in 2006, BTBPE was detected in only 5% of male glaucous gull plasma samples, 0% of female plasma, and 29% of egg yolk samples [9]. Plasma concentrations ranged from <0.20 to 0.26 ng/g ww and <0.27 to 0.96 ng/g wet weight (ww) in egg yolk and were much lower than concentrations of HBCD and PBDEs.

2.10 Mammals

Tomy et al. [38] analyzed several BFRs including BTBPE in blubber from Canadian Arctic beluga (*Delphinapterus leucas*) collected during 2002–2005 from several sites. BTBPE was found in a few samples with concentrations ranging from 0.1 to 2.5 ng/g lw. These concentrations were similar to those found for HBCD but lower than those for PBDEs.

BTBPE was also found in 10% of ringed seal (*Phoca hispida*) blubber samples from five locations in the Canadian Arctic collected in 2006, with concentrations ranging between <0.01 and 0.29 ng/g lw [39]. These concentrations were lower than those found for PBDEs.

2.11 Humans

BTBPE was not detected in human serum samples from Swedish electronic recycling workers [40], nor in household residents [21], although it was detected in air or dust in these environments. A number of BFRs were screened for in 128 serum samples from Tianjin, China [41]. Although PBDEs were found, no BTBPE was detected in any of the samples. In laboratory experiments with orally dosed rats, BTBPE exhibited limited absorption and metabolism, with the majority of the compound excreted in feces, which could explain the lack of accumulation in humans [42, 43].

3 Decabromodiphenyl Ethane

3.1 Background

Decabromodiphenyl ethane (DBDPE) is marketed as an alternative for technical DecaBDE. The molecular structures of the two chemicals resemble each other and they have similar applications, i.e., as additive brominated flame retardants in a wide range of polymeric materials. According to one of the producers, DBDPE has high thermal stability and does not tend to leak from its host polymer (i.e., it has low "blooming" characteristics) and its use is therefore encouraged in systems where recycling is anticipated (http://www.albemarle.com, accessed March 2010).

DBDPE became available on the market in the mid-1980s [44]. It has been marketed under the trade names Saytex 8010 (Albemarle, Arkansas, USA) and Firemaster 2100 (Chemtura). It is also produced in China by Shouguang Guangda Chemical Co., Ltd. (Shouguang, Shandong Province, http://www.sggdchem.com, accessed March 2010) and Shou Guang Longfa Chemical Co., Ltd. (Qindao, Shandong Province, http://www.longfachem.com, accessed March 2010). One reason for the commercialisation of DBDPE was that it meets the demands of the German dioxin ordinance, which imposes limits for chlorinated and brominated dioxins and furans in commercial products [45]. In contrast to its predecessor, DecaBDE, DBDPE does not have an ether bridge in its molecular structure. This makes it less prone to produce dioxins and furans under pyrolysis conditions, [46].

Information about production and sales are scarce. DBDPE is considered an LPV chemical in the EU [8]. In 2001, the imports to Europe of Saytex 8010 were

estimated to be a few thousand metric tons mainly to Germany [45]. In 2007 and 2008 two major expansions of the production of Saytex 8010 were completed according to one of the producers [47]. Shi et al. [7] reported that in China, in 2006, DBDPE was the second most highly used BFR after DecaBDE. The estimated domestic production volumes of DecaBDE and DBDPE were 20,000 and 12,000 metric tons, respectively. The annual DBDPE consumption in China has a yearly increase of 80% [48]. In Japan, the use of DBDPE increased continuously from 1993 to 2000 whereas the consumption of DecaBDE decreased over the same period. During 1997–1998, the annual consumption of DBDPE surpassed that of DecaBDE [49].

3.2 Outdoor Air and Tree Bark

DBDPE has been found in the particulate phase of air samples taken during the years 2005–2006 in the area of the Great Lakes in North America [14]. The mean levels at the five sampling sites ranged from 1.0 to 22 pg/m^3. The highest levels of DBDPE were found in Cleveland where a rough correlation to BDE-209 levels was observed, suggesting similar sources. For several PBDE congeners, levels fluctuated over time (i.e., levels increased during warm summer months) and were dependent on population density, but no such patterns were observed for DBDPE. A part of the explanation was likely the low number of detections and low levels of DBDPE.

Higher concentrations of DBDPE were measured in air samples (gas + particulates) collected in 2007 from the PRD, south China, with concentrations ranging from 400 to 3600 pg/m^3 [7]. These concentrations were higher than those found for PBDEs including BDE-209.

The presence of DBDPE in tree bark from North America has been reported in two studies [17, 18]. In the study of Zhu and Hites [17], levels up to 100 ng/g lw were found in tree bark collected during 2000–2001, but the detection frequency among the samples was low (∼7%). In this study, a manufacturing plant (in Arkansas) was suggested as a point source. In the study of Qiu and Hites [18], an average concentration of 8.5 ng/g lw was reported in samples collected in the northeastern US in 2006. There were no strong point sources of DBDPE influencing the levels in their data set. In the same study, average levels in tree bark samples from a few sites in other parts of the world were presented. DBDPE was not detected in samples from Canada, Germany, and Italy, but found at concentrations of 34 ng/g in South Korea, and up to 1,000 ng/g in China. In both studies, atmospheric deposition was believed to be the source of the DBDPE contamination.

3.3 Soil and Outdoor Dust

In Southern China, Shi et al. [7] found DBDPE along with other BFRs in soil from farmland situated in the highly industrialized PRD. Levels of DBDPE ranged from

18 to 36 ng/g dw. In this study, samples were also collected from an e-waste processing area, where DBDPE levels in dust and soil ranged between <2.5–140 ng/g dw and <2.5–4.6 ng/g dw, respectively. DBDPE had a higher relative abundance compared to the other BFRs analyzed in the samples from the PRD compared to the e-waste area. As an explanation, the PRD was suggested to be exposed to emissions that reflect more recent usage of BFRs in China. Conversely, the e-waste area may rather reveal previously used BFRs, e.g., lower brominated BDEs, which have limited usage during recent years.

3.4 Indoor Air and Dust

The occurrence of DBDPE has been studied in indoor environments in a handful of studies. In a Swedish dismantling facility for electronic equipment, Kierkegaard et al. [46] identified DBDPE in an air sample at a concentration of 0.7 ng/m^3. Petterson-Julander et al. [19] found geometric mean air concentrations ranging from 0.01 to 0.06 ng/m^3 in personal air samples from dismantlers and unexposed workers. Julander et al. [20] reported the presence of DBDPE in different particle size fractions of air samples from another Swedish electronic dismantling factory. DBDPE was found in all of the three different size fractions of dust that were collected with concentrations ranging from <0.02 to 0.79 ng/m^3. These concentrations were lower than those of PBDEs and BTBPE.

DBDPE was analyzed in air and dust from five Swedish households [21]. DBDPE was present in one air sample and four dust samples. The concentration in air was 23 pg/m^3, which was close to the detection limit, while the levels in dust were higher, from 21 to 120 ng/g dw. The dust DBDPE concentrations were in a similar range as BDE-47 and -99 concentrations, but somewhat lower than BDE-209 concentration. Together they comprised 85% of the total BFR levels.

In the UK, Harrad et al. [24] analyzed BFRs including DBDPE in dust from homes, offices, and cars. The average concentrations of DBDPE in these environments were 270, 170, and 400 ng/g dw, respectively. The DBDPE levels, as well as octa- to decaBDE levels, did not differ between the studied microenvironments, whereas the levels of tri-hexaBDEs were significantly higher in cars compared to homes. Estimated exposure via ingestion of dust for adults and toddlers (up to 44 and 190 ng/day, respectively) suggests that DBDPE intake is similar to that of tri-hexaBDEs.

In the USA, DBDPE was found in household dust from 19 homes in the Boston area collected from the main living area, the bedroom, and from the home vacuum cleaner bag [22]. The geometric means of DBDPE concentrations in the three different compartments were 138, 153, and 39.4 ng/g dw, respectively, but there was a large variation, ranging from <10 to 11,070 ng/g dw. Comparison with previous analysis of PBDEs in the same samples revealed a correlation between levels of BDE-209 and DBDPE; therefore, similar sources were suggested.

In Japan, DBDPE was recently detected in nearly all samples of indoor dust from a hotel, at levels up to 210 ng/g dw [50]. Levels were one or two orders of magnitude lower than those of PBDEs and HBCDs.

Positive identification of DBDPE in indoor dust has also been reported from the Czech Republic [25] and from the Netherlands [51].

3.5 *Children's Toys*

In a Chinese study of BFRs in children's toys, DBDPE was the second most prevalent BFR after decaBDE with a detection frequency of 40–90% in the different types of toys [26]. Compared to foam, rubber/soft plastic and stuffed toys, the hard plastic toys generally contained the highest levels of individual BFRs, with a median level of DBDPE at 5,540 ng/g. The estimated exposure of children to DBDPE from mouthing these toys was calculated to be 1.3–15 ng/kg body weight-day.

3.6 *Sewage Water and Sludge*

In a screening study of sewage sludge from 50 Swedish wastewater treatment plants (WWTPs), DBDPE was detected in 25 of the samples, with estimated concentrations up to 100 ng/g dw [46]. DBDPE was also positively identified in sludge from Spain at concentrations ranging from 0.2 to 90 ng/g dw [52, 53] and Canada with concentrations ranging from 5.6 to 32 ng/g dw [54].

Recently, an international survey of DBDPE in sewage sludge was performed [55]. Samples of sewage sludge from 11 different countries were analyzed for DBDPE and BDE-209. DBDPE was present in sludge from all countries and levels ranged from <0.58 to 220 ng/g dw. Diffuse leakage from the technosphere was suggested to be the primary source of DBDPE to the sludge, as suggested for other BFRs [56]. The concentration ratio of DBDPE to BDE-209 was calculated to estimate the relative usage of the two BFRs in the different countries. The ratio ranged from 0.0018 to 0.83 and was high in and around Germany, where imports of DBDPE are known to be high [45]. The high ratios found are indicative of a shift in consumption from DecaBDE to DBDPE. Lower ratios, possibly indicating lower DBDPE usage, were found in the USA and UK, which have traditionally been high consumers of the DecaBDE mixture.

A mass balance study of a WWTP in Sweden showed that DBDPE was delivered to the plant at the rate of 8.5 μg/day per person [57]. DBDPE was efficiently transferred from the sewage influent to the digested sludge, generating a mean level of 81 ng/g dw, while only a small fraction of the influent mass flow was emitted via the effluent water ($<1\%$). There was no evidence for losses by anaerobic

degradation. The behavior of DBDPE in the WWTP did not differ from that of BDE-209, for which mass flows were approximately one order of magnitude higher.

3.7 Landfills

DBDPE was analyzed in samples of leachate water and solid compost from five landfill sites in Spain [58]. DBDPE was found at three of these sites and levels in leachate and compost samples ranged from 1.2 to 35 ng/L and from 100 to 320 ng/g dw, respectively. Compared to the levels of BDE-209, the DBDPE concentrations were high in the compost samples, resulting in a DBDPE/BDE-209 ratio of 0.7–21.

3.8 Water and Sediment

The presence of DBDPE in the environment was initially identified in sediment from the Western Scheldt estuary in the Netherlands with DBDPE levels of 24 ng/g dw [46]. This is an industrialized area highly contaminated by decaBDE. Later, sediments from another two locations in the same area were analyzed, reporting DBDPE levels between 0.65 and 10 ng/g dw [29, 51]. The levels of BDE-209 were between one and two orders of magnitude higher.

Water and sediment from Lake Winnipeg were analyzed for DBDPE but concentrations were below the detection levels [27].

Recently, DBDPE was analyzed in sediments from isolated lakes and in a marine transect in Sweden [59]. Results from the analysis of the lake sediments showed that DBDPE was present in all of the 11 sampled lakes, at levels from 0.23 to 11 ng/g dw. The results indicate that the environmental contamination of DBDPE is widespread, and that long range transport and deposition may be important for the transport of DBDPE to remote areas. The marine sediment transect was from the city of Stockholm out through its archipelago [59]. The influence of local urban sources on DBDPE levels in the sediment decreased exponentially along the transect, starting at 10 ng/g dw. This was approximately only one order of magnitude lower than that measured in sludge from an adjacent WWTP [57]. In the transect, DBDPE levels dropped to half of their initial values within 14 km. Levels thereafter reached a low baseline, which was suggested to originate from atmospheric deposition.

DBDPE levels were reported in a study of 15 Chinese surficial river sediment samples and two sediment cores [48]. The samples were taken in the Dongjiang River, one of the main tributaries of the PRD area in Southern China. DBDPE was present in the surficial sediments at levels ranging from 19 to 430 ng/g dw. These levels exceeded the sum of tri- to heptaBDE concentrations (range 0.7–7.6 ng/g dw), but were lower compared to the sum of octa- to decaBDE concentrations (range 30–5,700 ng/g dw). The sediment cores showed that the levels of DBDPE as well as

those of TBBPA and tri- to heptaBDEs are increasing in the sediment layers, while the levels of octa- to nonaBDEs are decreasing, possibly reflecting a shift in usage from the DecaBDE formulation to DBDPE.

Shi et al. [7] compared DBDPE concentrations in river sediment from the same sites in the PRD in China between the years 2002 and 2006. The levels of DBDPE were clearly higher in the samples from 2006.

3.9 Invertebrates and Fish

In a study of a freshwater food web in Lake Winnipeg in Canada, zooplankton, mussels, and six species of fish, including predatory fish such as burbot and walleye were analyzed for DBDPE [27]. No detectable levels of DBDPE were found in zooplankton or mussels. However, the mean concentrations in the fish ranged from below the limit of detection to 1 ng/g lw. Lipid adjusted BMFs for 5 out of 13 possible predators to prey interactions were reported, and ranged from 0.2 to 9.2. BMFs above 1 were mainly found for the predatory species, burbot and walleye. For all 13 predator to prey interactions, the BMFs for BDE-209 were in the range of 0.1–34. Furthermore, the trophic magnification factor (TMF) obtained for DBDPE was 2.7, which was similar to that for BDE-209, i.e., 3.6 [30]. Both these TMFs were higher than those obtained for BDE-47, -99, -100, and BTBPE (1.5, 0.7, 1.6, and 1.0, respectively).

In another study of the Great Lakes, Lake Ontario lake trout collected between the years 1979 and 2004 were analyzed for different BFRs. DBDPE was below the detection limit in all samples [60].

Likewise, no DBDPE was detected (<3.8 ng/g lw) in liver and muscle samples of farmed fish (carp, bighead carp, tilapia) collected near an e-waste processing area in southern China [7].

In a study by Munschy et al. [33], various BFRs including DBDPE were analyzed in pooled muscle samples from the marine species, common sole. Sampling was performed in 2003 and 2004, at three sites representing nursery zones in coastal areas of France (English Channel and Biscay Bay). DBDPE was detected in all of the six samples, at levels in the range of 0.18–3.9 ng/g lw, with higher levels in the samples from 2004 compared to those from 2003. This pattern between years was also observed for hexabromobenzene (HBBz), while no pattern was observed for the other BFRs, namely tri-hexaBDEs, BDE-209, BTBPE, and BB-153.

3.10 Birds

There are a few recent studies where the presence of DBDPE in avian species has been reported. In North America, Gauthier et al. [36] analyzed DBDPE in herring gull eggs collected between the years 1982 and 2006 from seven sites around the

Great Lakes. The detection frequency among the samples was ~13% (10–13 eggs per pooled sample). DBDPE was only detected in samples from 1996 and later, but neither temporal trends nor spatial trends were possible to discern. At some sites, the DBDPE concentrations exceeded BDE-209 concentrations, with levels up to 288 ng/g ww.

Gao et al. [61] analyzed DBDPE in eggs from wild and captive birds (terrestrial and aquatic) in a nature reserve area in Northern China. The area is highly influenced by industrial discharges. Among the species studied, the highest level of 2.4 ng/g lw was found in the terrestrial ring-necked pheasant (*Phasanius colchicus*). Samples from the other birds contained levels in the range from not detectable level to 2.2 ng/g lw.

Tissue samples from three watercocks from near an e-waste recycling area in South China were analyzed for DBDPE [7]. DBDPE levels were in the range of 9.6–124 ng/g lw. Higher levels were found in liver and kidney compared to muscle. BDE-209 levels exceeded those of DBDPE by a factor of at least two in all samples.

In a study from the PRD in South China, 29 water birds of five different species were collected and muscle samples were analyzed for different persistent halogenated compounds [62]. DBDPE was present in all samples except one, at levels from 4 to 800 ng/g lw. The upper range is higher than what was found by Shi et al. [7] in watercock. In the birds analyzed by Luo et al. [62], the concentration of BDE-209 was approximately one order of magnitude higher. The authors suggest that leaching from local sources was responsible for the DBDPE contamination of the birds.

3.11 Mammals

Hu et al. [63] reported findings of DBDPE in various tissue samples (liver, kidney, brain, muscle) from captive giant (*Ailuropoda melanoleuca*) and red panda (*Ailurus fulgens*) (eight individuals of each species) from China, at levels from below the detection limit to 40.9 ng/g lw. In one gonad sample, the level was as high as 863 ng/g lw.

Blubber samples of ringed seal from five locations in the Canadian Arctic (collected in 2006), contained no detectable DBDPE [39].

3.12 Humans

In a recent study from China, 128 human serum samples were analyzed for PBDEs and non-PBDEs including DBDPE [41]. Although BDE-209 was present at levels up to 1,770 ng/g lw, DBDPE levels were below detectable levels (<15 ng/5–10 mL blood) in all samples. DBDPE was also below the detection limit (<1.03 ng/g lw) in plasma samples from residents of five homes in Örebro, Sweden [21].

4 Hexabromobenzene

4.1 Background

HBBz is an additive flame retardant, historically used in plastics, textiles, and woods [64], but also in paper and electric manufactured goods [65]. Information on producers and production volumes are scarce. Gauthier et al. [35] state that it is classified as an LPV chemical (1,000–5,000 tons) and that a large historical source of this compound in the USA was Velsicol Chemical Corporation, St. Louis, Missouri (now a part of Chemtura), which was shut down in the 1980s. In Japan, production of HBBz was 270 tons in 1983 [64]. Although the total consumption of BFRs in Japan increased between 1994 and 2001, the consumption of HBBz lay constant at about 350 tons/year [49]. In China, 600 tons of HBBz per year are produced at Shou Guang Longfa Chemical Co. Ltd. (Qindao, Shandong Province, http://www.longfachem.com, accessed March 2010). HBBz is marketed by the Japanese Nippoh Chemicals Corp. as FR-B and is also marketed by Dayang Chemicals in China.

Apart from being commercially produced, there are other possible sources for HBBz to the environment. HBBz was found to be the major product from pyrolysis of Octa- and DecaBDE technical products [66]. Polymeric BFRs could be possible sources of volatile brominated compounds even at low thermal stress. HBBz and other volatile brominated organics were released from a pentabromobenzyl acrylate oligomer (FR-1025, ICL Industrial Products, formerly Dead Sea Bromine Group, Israel) at room temperature [67]. The release rate increased as temperature increased (up to 100°C), suggesting that compounding of thermoplastics (done at higher temperatures) could lead to the release to the environment, although fugacity modeling indicated that concentrations found in outdoor air were better explained by its use as a flame retardant. The maximum temperature of 100°C in the study is well below the melting point for the polymer suggesting that the volatiles emitted were present in the polymer, either as unreacted monomers or as impurities.

4.2 Abiotic Samples

HBBz was detected at low levels (0.02–0.09 pg/m^3) in four outdoor air samples collected at a rural/suburban location in Canada in 2005 [67]. A low concentration of HBBz (0.48 ng/g dw) was also found in a sample of outdoor dust (from atmospheric deposition) in Germany [68].

The HBBz concentrations in indoor air in Tokyo, Japan, ranged from <470 to 710 pg/m^3 in houses and <470–950 pg/m^3 in office buildings [69]. In outdoor air sampled in connection with the indoor samples, no HBBz was found. HBBz was also detected in laboratory air (500 pg/m^3) and in migration samples from the floor (0.5 μg/m^2/h) [69].

HBBz was occasionally detected in dust samples from 25 Czech households but no concentration data were reported [25].

HBBz was detected but not analyzed quantitatively in four samples of scrap raw materials from an aluminum recycling plant in Finland [70].

None of the 126 water samples from multiple sites in Japan collected in 1989 and analyzed by the Environmental Agency of Japan had HBBz levels above the limit of quantitation (<50 ng/L) [49].

In sediment samples collected in 1982 and analyzed by the Environmental Agency of Japan, HBBz was detected in 3 out of 126 samples (range <0.9–4.3 ng/g dw) [49]. River sediment samples from Japan, collected during 1981–1983, contained HBBz at 6–60 ng/g dw and estuary sediments had lower concentrations (~0.5–6 ng/g dw) [65].

4.3 Biota

HBBz was not detected (<5 ng/g ww) in any of the 126 fish samples collected in 1982 and analyzed by the Environmental Agency of Japan [49]. No information on collection sites was given.

Six pooled samples of juvenile common sole from three nursery zones along the French Atlantic coast, collected in 2003 and 2004 were analyzed for a number of BFRs. HBBz was detected in all samples with a concentration range of 0.03–4.3 ng/g lw [33].

Nyholm conducted two studies where zebrafish (*Danio rerio*) were fed a mixture of BFRs, including HBBz, during 42 days. The first study was on maternal transfer to eggs [71]), and the second on male fish to study uptake, elimination, and possible biotransformation ([72]. HBBz levels were below (or just above) the limit of quantitation in both studies but a possible metabolite, TeBBz, was detected. It was concluded that the presence of TeBBz in eggs was due to maternal transfer from the female zebrafish rather than metabolism in the eggs [71]. The TeBBz levels increased in male zebrafish during the exposure period but it appeared to be rapidly eliminated when the fish were fed untreated food [72].

A subset of peregrine falcon eggs from California, previously analyzed for PBDEs, were analyzed for new BFRs. The eggs were collected during 1999–2007 and selected because of their high PBDE levels and/or were from the most recent years. According to the authors, HBBz was detected in most of the 19 eggs analyzed although at much lower levels than the PBDEs [34]. No concentration data were given.

Egg pools from seven colonies of herring gulls from the Laurentian Great Lakes of North America collected between 1982 and 2006 were analyzed for a number of BFRs to study spatial and temporal trends [35, 36]. HBBz was present in all samples (range 0.10–3.9 ng/g ww), although at much lower levels than the PBDEs (<0.2% of sumBDE). No temporal trends of HBBz were detected over the 25 year study period [36]. Comparable levels in eggs from across the Great Lakes

suggest low-level, common origins of exposure to HBBz, possibly via atmospheric transport.

The detection frequency of HBBz in male and female plasma and egg yolk samples of glaucous gulls collected in 2006 from the Norwegian Arctic was high [9]. The HBBz levels were the second highest of the non-BDE BFRs analyzed (after α-HBCD). The frequency of HBBz detections were higher in male (47%) compared to female (13%) plasma. The concentrations ranged from below the limit of quantitation to 0.15 ng/g ww in male, and 0.1 ng/g ww in female plasma. All egg yolk samples had detectable levels of HBBz with a mean of 1.1 ng/g ww (range 0.4–2.6 ng/g ww).

Low levels of HBBz were found in samples of polar bear adipose tissue collected from East Greenland, but no quantitative information was given [73].

4.4 Humans

While HBBz was detected in three samples of human adipose tissue from Japan (∼0.5–1.8 ng/g lw) [64], no detectable levels were found in a screening study of 37 human adipose tissue samples from Finland [74]. In the Japanese study, the possible metabolites of HBBz, Te- and PeBBz, were also detected, with TeBBz constituting about 60–80% of the sumBBz [64].

Higher concentrations of HBBz were detected in mother's milk and placenta in Denmark than in Finland [75]. Mean concentration in Danish milk was 0.050 ng/g lw (range 0.005–0.50 ng/g lw, 77% detections) and 0.037 ng/g lw in Finnish milk (range 0.012–0.120 ng/g lw, 48% detections). The Danish placenta samples had higher concentrations of HBBz (mean 0.880 ng/g lw, range 0.071–10 ng/g lw) than the Finnish (mean 0.120 ng/g lw, range 0.008–0.940), but the frequency of detection was lower, 18 and 30%, respectively. PeBBz was also detected in the samples, although at lower levels and frequencies than HBBz.

HBBz was detected in 26 out of 128 human blood serum samples from a typical industrial metropolis in North China [41]. The median concentration was 0.27 ng/g lw (mean 0.46 ng/g lw, range 0.11–1.5 ng/g ww).

5 Pentabromoethylbenzene

5.1 Background

The main applications of pentabromoethylbenzene (PBEB), used as an additive BFR, have been in thermoset polyester resins, circuit boards, textiles, adhesives, wire and cable coatings, and polyurethane foam [6, 76]. PBEB was produced by Dead Sea Bromine Group Ltd (now ICL Industrial Products) under the trade name FR-105

mainly in the 1970s and 1980s in the US [6]. After 1986, no US production or import volumes have been reported. In the EU, PBEB is classified as an LPV chemical [8], while in the OSPAR list of chemicals with rankings of persistence, liability to bioaccumulate, and toxicity it is marked as a chemical with no current production [77].

An additional identified source of PBEB emissions was from polymeric BFRs [67]. PBEB was released from the polymer at room temperature and the emissions increased several orders of magnitude when the polymer was exposed to thermal stress, a situation that normally occurs during compounding of thermoplastic polyesters. The prevalent concentrations of PBEB in air from the Great Lakes could, however, not be explained by the release from polymeric BFRs but are more likely to derive from the use of PBEB as an additive.

5.2 Abiotic Samples

Hoh et al. [6] found comparably high levels, 520 pg/m^3, of PBEB in air samples from Chicago in the summer of 2003. The concentrations exceeded that of the tri-decaBDEs, by almost one order of magnitude. The samples also contained a number of other early eluting brominated compounds identified as tetrabromochloroethylbenzene and tentatively congeners of tetrabromoethylbenzene. These compounds were also present in the analytical PBEB standard (98% purity) purchased for quantification which made the authors suggest them to be byproducts formed during synthesis and/or environmental debromination products. Both PBEB and its impurities were detectable but below the detection limit in other sampling sites studied during the same period as well as in Chicago air samples collected previously [6]. PBEB was also reported in air samples collected near Oxford in the south of England at a concentration of 30 pg/m^3, which exceeded the concentrations of ΣPBDEs [78]. Only one of four air samples from Egbert, 70 km north of Toronto, Canada contained PBEB [67]. The level was low (0.1 pg/m^3), and together with pentabromotoluene (PBT) and HBBz, the concentrations comprised only 1.5% of the BDE-47 concentration in the sample. PBEB was also occasionally present in dust collected in Czech households (no levels reported) [25].

Scrap samples of raw material from an aluminum recycling plant (filter dust, cyclone dust, and light fluff from an electronic crusher and a car shredder) contained PBEB but no concentrations were reported [70].

Although PBEB was detected in air samples, neither PBEB nor any of its proposed lower brominated byproducts were found in a sediment core taken in Lake Michigan [6].

5.3 Biota

A number of non-PBDE flame retardants were analyzed in archived Lake Ontario lake trout whole-body homogenates collected between 1974 and 2004 [32]. The

PBEB concentrations in the lake trout ranged from 17 to 320 ng/g lw, and showed no significant trend over the sampling period. The authors conclude that the lack of a decreasing trend after this period may support more recent emissions.

The dietary absorption efficiency of PBEB in rainbow trout after a single dose was 26% and the half-life was calculated to be 38 days [79].

Two studies report the presence of PBEB in avian species. PBEB was detected in herring gull eggs from six colonies from the North American Great Lakes and was present in all samples at concentrations up to 1.4 ng/g ww (7.6% lipid) [35]. Low levels of PBEB (up to 0.23 ng/g ww) were detected in egg yolk from glaucous gulls collected in the Norwegian Arctic [9]. The levels were about 15 times lower than in pooled herring gulls eggs reported by Gauthier et al. [35]. PBEB was detected in all yolk samples (n = 31) but represented only 0.04% of the sum of the 18 brominated substances. In contrast to PBT, PBEB was not identified in glaucous gull plasma samples. Still, its presence and detection frequency in yolk indicate that PBEB undergoes long range transport and that it is maternally transferred to eggs.

5.4 Humans

PBEB was included but not detected in a survey of BFRs in 128 serum samples from office cleaners, university students, and policemen from an industrial region in North China [41].

6 Pentabromotoluene

6.1 Background

PBT is an additive flame retardant used in unsaturated polyesters, polyethylene, polypropylenes, polystyrenes, textiles, and rubbers [76]. The production volume is categorized as moderate (1,000–5,000 tons/year). Commercial trade names are Flammex 5-BT from Berk Ltd. (U.K.) [80] and FR-105 from Ameribrom, a subsidiary of the Dead Sea Bromine Group (ICL Industrial Products) and Chemtura [35]. PBT is listed as an LPV chemical in the EU [8]. In China, 600 tons of PBT per year are produced at Shou Guang Longfa Chemical Co. Ltd. (Qindao, Shandong Province, http://www.longfachem.com, accessed March 2010).

Like HBBz and PBEB, PBT may be released from polymeric BFRs when exposed to thermal stress [67]. The rate at which PBT was released from the polymeric BFRs exceeded that of PBEB and HBBz. Furthermore, PBT may be formed from thermal decomposition of DBDPE. Cleavage of the aliphatic bridge and the evolution of PBT constituted the major pathway for the decomposition of

DBDPE treated polystyrene while the decomposition of BDE-209 resulted in ring closure forming brominated dibenzofurans [81]. Both pathways included partially debrominated homologues.

6.2 Abiotic Samples

Low levels of PBT (<0.01–0.02 pg/m^3) were detected in one of four air samples collected at the sampling station of Egbert, 70 km north of Toronto, Canada [67].

PBT was occasionally detected in dust from 26 Czech households [25].

The presence of PBT and its lower brominated homologues (di- and triBT) was positively confirmed in water from the Western Scheldt area in the Netherlands [82]. Generally the levels of the dibrominated toluenes exceeded PBT, which was quantified to be 2.4 ng/L in one of the four samples (<0.1 ng/L in the remaining samples).

A number of brominated and mixed brominated and chlorinated toluenes including PBT were detected in surface sediment samples from the Rivers Havel and Spree close to Berlin, Germany [83]. The concentrations for PBT ranged from <1 to 25 ng/g dw. Lower levels were measured in sediment and suspended particulate matter from the Western Scheldt area in the Netherlands [29]. PBT concentrations were in the range of 0.01–0.33 ng/g dw.

PBT was identified already in 1975 in sewage sludge from Sweden [80]. The levels ranged from 8,000 to ~180,000 ng/g dw, tentatively quantified versus the technical product. The sludge also contained two isomers of tetrabromotoluene, isomers that also were present in the technical product Flammex 5BT. Low levels of PBT (<100 ng/g) were found in soil amended with sludge and in barley.

6.3 Biota

Liver and muscle samples from perch and pike possibly exposed to PBT via effluents from a WWTP had PBT levels below the detection limit (<30 ng/g ww) [80]. The absorption efficiency of PBT was determined to be 18–28% after a single oral dose of a mixture of brominated and chlorinated chemicals and the half-life was 13–23 days in rainbow trout [79] and up to 83 days in Atlantic salmon [84]. PBT was among the non-PBDE BFRs detected in pooled herring gull eggs from the Great Lakes in North America [35]. The levels were the lowest of the non-PBDEs measured (0.004–0.02 ng/g ww) comprising less than 0.05% of the sum of BDE-47, -99, and -100.

PBT was detected in both egg yolk and plasma from glaucous gulls captured in the Norwegian Arctic [9]. The levels reported were <0.04–0.15 ng/g ww in plasma and <0.02–0.12 ng/g ww in egg yolk.

6.4 Humans

PBT was included in a screening study of Finnish human adipose tissue but was not detected in any of the samples [74].

7 Tetrabromobisphenol A Derivatives

7.1 Background

Tetrabromobisphenol A diallyl ether (TBBPA-DAE) is used as a reactive flame retardant in polystyrene foams but also as an additive flame retardant in expanded polystyrene and polystyrene foams. It is produced by Chemtura under the trade name BE-51 (http://www.chemtura.com, accessed March 2010). The US production volume in 2006 was <230 metric tons [85] and it is listed as an LPV chemical in the EU [8]. Tetrabromobisphenol A 2,3-dibromopropyl ether (TBBPA-DBPE) is used as an additive flame retardant in polyolefin resins and polystyrene [86]. It is produced under the trade names PE-68 (Chemtura) and FR-720 (ICL Industrial Products) [72]. US production in 2006 was <4,500 metric tons [85] and it is listed as an LPV chemical in the EU [8]. JiangSu HaoHua Fine Chemical Co., Ltd (Jiangsu Province) in China produces 3,000 metric tons/year (http://www.huadingchem.com, accessed March 2010). Weidong International Group, Ltd. (Weifang, Shandong Province, China) also produces TBBPA-DBPE (http://www.oceanchemical.en.ecplaza.net, accessed March 2010). Tetrabromobisphenol A dihydroxyethyl ether (TBBPA-DHEE) is used as an additive flame retardant in engineering polymers and coatings [87]. It is produced by Chemtura under the trade names BA-50P and BA-50 and has previously been produced by Teijin Chemicals Ltd. (Japan) under the trade name Fireguard 3600. The data base is inadequate for an evaluation or to support its use commercially [87]. No information on production volumes is available for TBBPA-DHEE for the US but it is listed as an LPV chemical in the EU [8].

TBBPA-DAE and TBBPA-DBPE are neutral compounds, DAE being very resistant towards hydrolysis and DBPE being rapidly dehydrohalogenated [88]. TBBPA-DHEE is a dihydroxylated compound, most probably not affected by environmentally relevant pH because of a likely high pK_a (∼15), [89]. The TBBPA family is very hydrophobic and, considering environmental partitioning, its members would preferably adsorb to solids [89]. If present in the atmosphere, TBBPA-DBPE and TBBPA-DAE will, because of their low volatility, be attached to particles and hence their atmospheric transport behavior will be determined by particle transport [90]. Their molecular size is much larger and volatility much lower than that of substances typically believed to have the potential to become Arctic contaminants, but were included in a list of substances potentially relevant for further investigation and monitoring because of their type of usage, both being

additive BFRs [90]. They are considered LPV compounds with low potential for long range atmospheric transport and low bioaccumulative potential as is generally the case with compounds having molecular weights close to or above 700 Da. Their overall persistence is probably high (estimated to >500 days [90]), because of their association with particles. They may have similar transport mechanisms in the environment as BDE-209 [91] and thus a likelihood of becoming global pollutants.

7.2 Abiotic Samples

Findings of these chemicals in environmental samples are scarce. TBBPA-DBPE was indicated qualitatively in indoor dust from Swedish homes [92]. It was also detected in outdoor dust (atmospheric deposition) collected from a metal surface near the artificial stream and pond system in Berlin-Marienfelde in Germany [68] at a higher concentration (1,300 ng/g dw) than BDE-209 (730 ng/g dw).

TBBPA-DBPE was below the detection limit in German sediment (<10 ng/g) and sewage sludge (<22 ng/g) [93] but was detected in sediment (<1.5–2,300 ng/g dw), outdoor air (130–1,240 pg/m^3), sewage sludge (240–8,900 ng/g dw), and soil (17–60 ng/g dw) from the PRD, in southern China, known for its electronic and electrical manufacturing [7]. The levels in sediments from 2006 were higher than in those taken in 2002 from the same sites. In outdoor dust and soil samples from an e-waste recycling area north of the PRD, the TBBPA-DBPE concentrations were below detection limits. The e-waste is to a large extent imported from abroad. The authors interpreted the different patterns of TBBPA-DBPE for the two areas as indication of different uses. The e-waste site is affected more by usage of older, now discontinued BFRs while the PRD samples reflect the introduction of replacement BFRs.

7.3 Biota

TBBPA-DAE was detected in 5 out of 30 Lake Ontario lake trout samples (0.2–1.7 ng/g ww) collected between 1997 and 2004 [60]. TBBPA-DBPE was analyzed for in watercock and three farmed fish species near an e-waste recycling area in southern China, but levels were below the detection limit [7].

Nyholm et al. [71, 72] conducted two studies where zebrafish were fed a mixture of BFRs, including TBBPA-DHEE and TBBPA-DBPE for 42 days. In the first study of maternal transfer to eggs, TBBPA-DHEE was not detected but TBBPA-DBPE was absorbed by the fish and transferred to the eggs (egg/fish ratio of >1 on lipid weight basis) [71]. In the second study on male fish, TBBPA-DHEE levels were not quantified because of low recovery but TBBPA-DBPE was found to be taken up and eliminated rapidly [72].

In rats, TBBPA-DBPE was absorbed poorly, but the small amounts that were taken up accumulated in the liver were metabolized slowly and eliminated via feces [94].

8 Bis(2-ethylhexyl) Tetrabromophthalate and 2-Ethylhexyltetrabromobenzoate

8.1 Background

Bis(2-ethylhexyl) tetrabromophthalate (TBPH) is used as a plasticizer in polyvinylchloride (PVC) plastic and neoprene rubber [86] as well as in wire and cable insulation, film and sheeting, carpet backing, coated fabrics, wall coverings, and adhesives (http://www.chemtura.com, accessed March 2010). TBPH is also used, together with 2-ethylhexyltetrabromobenzoate (TBB), in the additive flame retardant product Firemaster 550, produced since 2003 by Chemtura as a replacement for PentaBDE in polyurethane foam applications [22]. The approximate ratio of TBB to TBPH in Firemaster 550 is 4:1 by mass [22]. Davis and Stapleton [95] also report that TBB and TBPH are found in the fire retardant BZ-54, and TBPH is present in a mixture called DP-45, both produced by Chemtura. US production volumes of TBPH were 450–4,500 metric tons/year from 1990 to 2006 [85, 96]. No production information after 2006 is available for TBPH. There is no production information available for TBB. In laboratory photodegradation experiments, TBB and TBPH have both been shown to undergo sequential reductive debromination, possibly down to nonbrominated degradation products [95]. For TBPH, this could lead to the formation of bis(2-ethylhexyl)-phthalate (DEHP), a plasticizer which is currently restricted or banned for specific uses in many countries.

8.2 Abiotic Samples

TBPH was recently found in dust samples from 19 homes in Boston, Massachusetts, USA, at concentrations ranging from 1.5 to 10,630 ng/g dw [22]. The highest geometric mean concentrations were found in researcher-collected dust from the main living area (234 ng/g dw), followed by the bedroom (105 ng/g dw) and vacuum cleaner dust (65.8 ng/g dw). In the same study, Stapleton et al. [22] found TBB concentrations ranging from <6.6 to 15,030 ng/g dw, with highest geometric mean concentrations in dust from the main living area (322 ng/g dw), followed by the home vacuum cleaner bag (91.1 ng/g dw) and the bedroom (90.4 ng/g dw). These concentrations were similar or somewhat lower than that found for HBCD in the same samples. The ratio of TBB/TBPH in dust ranged from 0.05 to 50, indicating different sources or fate in indoor environments.

Stapleton et al. [22] also found TBPH, but not TBB in the standard reference material dust (NIST SRM 2585).

In an additional 50 house dust samples collected from vacuum cleaner bags from homes in Boston, TBPH was found in 60% and TBB in 44% of the samples [23]. Geometric mean TBPH and TBB concentrations were 650 ng/g dw (range <300–47,110 ng/g dw) and 840 ng/g dw (range <450–75,000 ng/g dw), respectively.

In a screening study of foam from 26 pieces of furniture bought in the USA between 2003 and 2009, TBB and TBPH were both detected in one sample at 4.2% by weight [23].

TBPH and TBB have been detected in sewage sludge from two wastewater treatment plants in San Francisco, California, US [97–99]. Concentrations for TBB ranged from 40 to 1,412 ng/g dw and for TBPH, 57–515 ng/g dw and were in the same range as or higher than concentrations of HBCD and BDE-209.

8.3 Biota

A commercial dietary cod liver oil supplement using Norwegian cod liver oil, was analyzed for a large number of organohalogen compounds [100]. Among these, TBB and TBPH were identified. However, they were also detected in the blank samples after clean up using gel permeation chromatography (GPC), and the authors concluded that the clean up step contaminated the cod liver oil extract. They compared the cod liver oil extract and blank with the Firemaster 550 technical product and concluded that this was the source of both chemicals, but could not explain how the contamination occurred.

Blubber samples from stranded Indo-Pacific humpback dolphins (*Sousa chinensis*) and finless porpoises (*Neophocaena phocaenoides*) were analyzed for TBB and TBPH [101]. Samples were collected from Hong Kong, south China during 2002–2008. Mean TBB concentrations were 5.6 ng/g lw in the porpoises but below the detection limit (<0.04 ng/g lw) in the dolphins. Mean TBPH concentrations were 342 ng/g lw in the porpoises and 0.51 ng/g lw in the dolphins, with TBB: TBPH ratios ranging from 0.0003 to 3. These concentrations were much lower than those found for PBDEs in the same samples. However, TBPH concentrations in the porpoises were higher than HBCD concentrations [101].

9 1,2-Dibromo-4-(1,2-dibromoethyl)cyclohexane

9.1 Background

Commercial 1,2-dibromo-4-(1,2-dibromoethyl)cyclohexane (TBECH) is marketed by Albemarle as Saytex BCL-462 and contains equal amounts of the two diastereomers, α- and β-TBECH [36, 102]. It is an additive flame retardant used

in expandable polystyrene beads for house insulation, extruded polystyrene, for adhesives in fabric, electrical cable coatings, high impact plastic in appliances, and some construction materials [86] (http://www.albemarle.com, accessed March 2010). U.S. production volumes were 4.5–230 metric tons/year from 1986 to 2002 [96]. No production information is available after this time point. TBECH undergoes some thermal rearrangement to γ– and δ-TBECH at temperatures above 120°C, which could be expected to occur at the high temperatures used to incorporate it into products [103]. Muir and Howard [104] reviewed screening and categorization studies of chemicals in commerce with high predicted bioconcentration potential, low biodegradation rates, and long range atmospheric transport potential. TBECH was one of the 30 chemicals included in their list.

9.2 Sediment

In a screening of a broad range of chemicals, TBECH was identified in one sediment sample collected in 1996 from the dry channel near a discharge pipe of the Frutarom VCM/PVC plant near Haifa, Israel [105]. No quantitative data were given however.

9.3 Biota

In two laboratory studies, zebrafish were fed a diet containing 11 BFRs including TBECH for 42 days [71, 72]. In the study of maternal transfer from female fish to eggs, TBECH was found in both, indicating that TBECH is absorbed and can be transferred to the eggs [71]. The second study on male fish showed a high uptake efficiency from the gut (>60%), but rapid elimination, with a half-life of less than 2 days [72]. However, after the 2-week elimination period, the fish still had detectable levels of TBECH as well as HBCD and several PBDEs, indicating that TBECH has bioaccumulation potential.

ΣTBECH (sum of α- and β-TBECH isomers) was analyzed in herring gull eggs collected from seven colonies on the Great Lakes between 1982 and 2006 [36]. TBECH was found in eggs from all seven colonies with mean ΣTBECH for 2006 ranging from 0.11 to 0.54 ng/g ww. The highest concentration was found in eggs from Channel-Shelter Island, Lake Huron. ΣTBECH was also found in eggs from all years studied at each site, but no temporal trends were discernible. However, the isomer pattern did differ between sites and years, with the β-TBECH isomer being predominant [36].

In support of the predictions of Muir and Howard [104], Tomy et al. [103] identified and quantified TBECH in Canadian Arctic beluga (*Delphinapterus leucas*). Beluga blubber samples from males were obtained from four Arctic sites in 2003, 2005, and 2006 and analyzed on a diastereomer basis. Only the β-TBECH isomer was found, at concentrations of 1.1–9.3 ng/g lw. These concentrations were in the same range as of HBCD, but about ten times lower than that of PBDEs.

10 2,4,6-Tribromophenol

10.1 Background

The commercial 2,4,6-tribromophenol (TBP) product is produced by Chemtura under the trade name PH-73FF and by ICL Industrial Products under the trade name FR-613. It is used as a reactive flame retardant, an antifungal agent (e.g., wood treatment), and as a chemical intermediate (http://www.chemtura.com, http://www.icl-group.com, accessed March 2010). U.S. production was 4,500 to <23,000 metric tons in 2006 and it is considered a high production volume chemical (HPV) in the EU [8]. Japanese production in 2001 was 3,600 metric tons [49]. In China, TBP is produced by Weidong International Group, Ltd. (Weifang, Shandong, http://www.oceanchemical.en.ecplaza.net, accessed March 2010). 2,4,6-TBP is also produced naturally by marine algae [106–108] and polychaetes [109]. It may also be formed metabolically from some PBDEs [110] and is a by-product in commercial BTBPE productions [111]. Thus there are multiple sources of TBP that may explain its presence in various environmental compartments. On reading the literature, its presence in the marine environment, i.e., water [112], sediments [113], invertebrates [114], and fish [115, 116] seems to be the result of its presence as a natural product. Its presence on vegetation collected near sawmills is probably related to its use as a fungicide on wood products [117]. TBP has also been found in marine birds and polar bears [116] at low concentrations, with possible origins speculated to be from metabolism of hydroxy-PBDEs and methoxy-PBDEs. These compounds in turn may be present largely as a result of natural production from marine organisms [118–120].

10.2 Abiotic Samples

Perhaps the best evidence of TBP presence due to its use as a flame retardant or as a by-product in other BFRs is from the indoor environment. Takigami et al. [121] found that indoor air concentrations inside two Japanese homes were much higher (range 220–690 pg/m^3) than air concentrations outside the homes (49 and 73 pg/m^3). The authors also found high bromine contents in various electronic equipment as well as some textiles in the homes indicating that TBP and other BFRs were released from flame-retarded materials in the homes. TBP air concentrations were higher than those of HBCD, TBBPA, BDE-209, and ΣPBDEs. Dust samples from the two homes had TBP concentrations of 15 and 30 ng/g, which were lower than concentrations for HBCD, TBBPA, BDE-209, and ΣPBDEs.

In a study of BFRs, TBP was found in air samples from 18 houses and 14 offices in Tokyo, Japan in 2002 [69]. TBP air concentrations ranged from not detectable level to 6,800 pg/m^3. For outdoor air, TBP concentrations were below the detection limit.

Indoor air (passive sampling) and dust were sampled in 2006 for BFRs from various rooms of a Japanese hotel in Osaka [50]. Unfortunately, data are only given for the sum of four tribromophenols, including TBP, and these ranged from 1.6 to 380 ng/g in dust and 12 and 70 ng/g in air sample (no air volumes were reported).

House dust from 19 houses and 14 offices collected from Japan in 2005 were analyzed for TBP [111]. TBP was a major phenolic component with higher concentrations in offices (median 90 ng/g, range 27–620 ng/g) than in houses (median 34 ng/g, range 16–130 ng/g).

TBP has been found in sewage sludge in a study of 22 wastewater treatment plants in Sweden [122]. Concentrations ranged from not detectable level to 0.9 ng/g ww, which were lower than those of PBDEs and TBBPA. TBP was also found in 16% of leachate samples from 38 municipal solid waste landfill sites in Japan, with a mean concentration of 21 ng/L (range <3–430 ng/L) [123].

10.3 Biota

Nyholm et al. [71, 72] conducted two studies where zebrafish were fed a mixture of BFRs, including TBP for 42 days. In the study of maternal transfer, TBP was found in both the female fish and the eggs [71]. In the second study, TBP was found to have a relatively high uptake rate (45%) but was eliminated rapidly in the male fish [72].

10.4 Humans

TBP was identified but not quantified in human plasma samples from Sweden [124]. Thomsen et al. [125] included TBP in a study of BFRs in plasma from three different occupational groups from Norway. Mean TBP concentrations were 24 ng/g lw (range 4.7–81 ng/g lw) in electronics dismantlers, 31 ng/g lw (range 8.7–65 ng/g lw) in circuit board producers, and 11 ng/g lw (range 0.17–28 ng/g lw) in laboratory personnel (nonexposed). No statistically significant difference was found between the three groups and diet was indicated to be the main exposure route for TBP. The TBP concentrations were higher than tri-heptaBDE and TBBPA concentrations.

Thomsen et al. [126] also studied temporal and age trends of BFRs in human plasma from Norway, including TBP. The mean TBP concentration in plasma samples from 1999 was 0.3 ng/g lw and no temporal trends were seen from 1977 to 1999, unlike the tri-hexaBDEs which increased with time. There was also no clear age trend, unlike the mean for tri-hexaBDE concentration where the highest concentrations were found in the 0–4 year-old group. For TBP, highest concentrations were found in the 25–59 year-old women (26 ng/g lw) and in the 4–14 year-old group (14 ng/g lw).

In a study of BFRs in Canadian Inuit from Nunavik, Quebec, plasma samples were found to contain a geometric mean TBP concentration of 58 ng/L or approximately 9.4 ng/g lw [127]. These concentrations were somewhat higher than those of BDE-47 and -153 and in the same range as those found in Norway. TBP concentrations were not explained by dietary intake measures (marine based diet, western diet) and were not correlated to PBDE concentrations, ruling out their presence as metabolites of these. The authors concluded that, at present, there is no clear explanation for TBP exposure routes in this population.

In the US (Indiana), Qiu et al. [110] found mean TBP concentrations of 5.6 ng/g lw in fetal plasma and 0.8 ng/g lw in maternal plasma. TBP concentrations were lower than the sum of the concentrations of tri-hexaBDEs.

In the only study of human breast milk, Ohta et al. [128] found TBP to be present but only as a minor portion of the total tribromophenol content.

11 2,4,6-Tribromophenyl Allyl Ether and 2,3-Dibromopropyl-2,4,6-tribromophenyl Ether

11.1 Background

2,4,6-Tribromophenyl allyl ether (ATE) is marketed by Chemtura as PHE-65 and recommended as a reactive [90, 129] and an additive FR for expanded polystyrene and foamed polystyrene (http://www.chemtura.com, accessed March 2010). It may also be used as a synergist for aromatic bromine containing FRs in applications where maximum process temperatures do not exceed 150°C. ATE can also be formed from anaerobic degradation of 2,3-dibromopropyl-2,4,6-tribromophenyl ether (DPTE, CAS 35109-60-5) and is probably also formed metabolically [130]. ATE is listed as an LPV chemical in the EU [8]. The US production volume of ATE in 2006 was <227 metric tons [85].

In a screening exercise, ATE was one of 120 chemicals identified to be structurally similar to known Arctic contaminants and/or have partitioning properties that suggest that they are potential Arctic contaminants [131]. ATE was defined as a multihopper compound with partitioning properties that make it exceptionally susceptible to becoming an Arctic contaminant [90].

2,3-Dibromopropyl-2,4,6-tribromophenyl ether (DPTE) was manufactured by Chemische Fabrik Kalk in Germany under the trade name Bromkal 73-5PE until the mid-1980s but seems to no longer be a commercial product [132].

11.2 Sewage Sludge

ATE was detected in 15 of 18 municipal sewage sludge samples in Germany from ten different plants (<5–91 ng/g dw) (Weisser, 1992 cited in [90]. DPTE

was also detected in 12 of the samples (<25–600 ng/g dw). The mean ATE/DPTE ratio was 0.17.

11.3 Biota

DPTE has been detected in fish from the north Pacific and the south Atlantic as summarized in Vetter et al. [132]. ATE was screened for but not detected in Great Lakes herring gull eggs [36].

ATE was detected in blubber (5.4–9.1 ng/g ww) and brain (3.1–10 ng/g ww) samples of harp seals (*Phoca groenlandica*) from the Barents and Greenland Seas [130]. DPTE was the predominant organobromine compound in these samples (blubber 322–470 ng/g ww, brain 130–340 ng/g ww). 2-Bromoallyl-2,4,6-tribromophenyl ether (BATE) was also present in the samples at about the same concentrations as ATE. The ATE/DPTE and BATE/DPTE ratios were 0.018 and 0.015 respectively in blubber and 0.030 and 0.019 respectively in brain. The general co-occurrence of ATE and BATE indicates that the source for ATE in these samples was from the biotransformation of DPTE. In brain, as opposed to blubber extracts, PBDEs were virtually absent, indicating that ATE, DPTE, and BATE penetrate the blood–brain barrier to a much higher degree [130].

12 Hexachlorocyclopentadienyldibromocyclooctane

12.1 Background

There is very little information on this chemical in the open literature. No information has been found on producers or production volumes. Hexachlorocyclopentadienyldibromocyclooctane (HCDBCO) is marketed by Wellington Laboratories as a reference standard. It has been reported to be used as a flame retardant in "styrenic polymers" [76]. Structurally it belongs to a group of halogenated norbornane flame retardants, which is a subgroup of alicyclic halogenated flame retardants. HCDBCO is unusual as it contains both chlorine and bromine atoms. According to Riddell et al. [133] it was first described as a BFR agent in a US patent in 1975. HCDBCO exists as a pair of enantiomers. No information is available on production volumes in the US or in the EU.

12.2 Indoor Air and Dust

The only environmental findings of HCDBCO seem to be from the indoor environment, i.e., in residential indoor air and dust collected during 2002–2003 in Ottawa,

Canada. In 44 out of 55 indoor air samples, the HCDBCO levels were above the detection limits [134]. The median HCDBCO air concentration (66 pg/m^3) was higher than that found for the major PBDEs (BDE-47 (66 pg/m^3), and BDE-99 (15 pg/m^3)), and the maximum HCDBCO concentration (3,000 pg/m^3), was almost twice the maximum BDE-47 concentration. The median HCDBCO concentration in dust was 2.0 ng/g and this was lower than the median concentrations of major PBDEs (BDE-99 (430 ng/g) and BDE-209 (630 ng/g)). The maximum measured HCDBCO concentration in dust (93,000 ng/g) was however higher than both BDE-99 (60,000 ng/g) and BDE-209 (10,000 ng/g) concentrations [134]. Air and dust levels did not correlate.

12.3 Fish and Mammals

There are a few reports where HCDBCO was analyzed for in environmental samples but not detected. All 50 blubber samples from marine mammals (Hong Kong, China) had concentrations below the detection limit (0.04 ng/g lw), [101]. Likewise, HCDBCO levels in all 22 fish samples from Great Lakes were below the limit of quantitation (0.39 ng/g, probably fw) [135].

13 *Tris*(2,3-dibromopropyl) Isocyanurate

13.1 Background

Structurally *tris*(2,3-dibromopropyl) isocyanurate (TBC) belongs to the group of heterocyclic flame retardants with a triazine ring. It is used as an additive flame retardant in a variety of polymeric materials, e.g., glass fiber reinforced plastics and polyurethane and is also used widely in polyolefin, PVC, polyphenyl alkenes, ABS, unsaturated polyester, synthetic rubber, and fiber (reference to a document in Chinese in [136]). It is added at about 5–10% w/w. The production in China began in the mid-1980s, and was ~500 metric tons/year in 1996 [136]. It is marketed by a number of Chinese companies under several trade names. It is considered an LPV chemical in the EU [8].

13.2 Environmental Levels

TBC has been detected in the vicinity of a manufacturing plant in southern China. Ruan et al. [136] sampled river water and surface sediment upstream and downstream (several sites) from the factory, and soil and earthworms upwind and

downwind (predominant wind direction) at several sites. The concentrations ranged from 2.3 to 160 ng/L in river water, 85–6,000 ng/g dw in surface sediment, 20–670 ng/g dw in soil, and 9.8–79 ng/g dw in earthworms, with a trend of decreasing concentrations with distance from the factory. It was assumed that soil concentrations could be the result of dust deposition and river water irrigation. TBC concentrations in common carp sampled 6 km downstream from the outlet were 12–650 ng/g dw. The distribution was uneven in carp tissues and organs, indicating accumulation in the fat-rich organs such as brain and adipose [136].

14 Tetrabromophthalic Anhydride

14.1 Background

Tetrabromophthalic anhydride (TBPA) is used as a reactive BFR in unsaturated or saturated polyesters, polyols, esters, and imides (http://www.albemarle.com, accessed March 2010), and is marketed as PHT4 by Chemtura and Saytex RB-49 by Albemarle. Its derivatives have been used as FRs in applications as diverse as rigid polyurethane polyols, wire coatings, and wool (http://www.chemtura.com, accessed March 2010). The US production volume in 2006 was 4,500 to <23,000 tons [85]. In Europe TBPA is registered as an LPV chemical [8].

14.2 Environmental Levels

TBPA was detected in cod liver oil samples, most probably because of blank problems (GPC) and thermal degradation of TBB and TBPH in the GC–MS system [100]. It was not detected in Dutch sediments and suspended particulate matter [29]. TBPA is on the list of chemicals predicted to become Arctic contaminants because of its structural similarity to known Arctic contaminants [131].

15 1,2,5,6-Tetrabromocyclooctane

15.1 Background

1,2,5,6-Tetrabromocyclooctane (TBCO) is an additive flame retardant marketed by Albemarle Corporation under the trade name Saytex BCL-48 [36]. No information is available on production volumes in the US or in the EU. TBCO can exist as two diastereomers that can easily interconvert thermally [137]. TBCO meets the EU criteria as a potential aquatic hazardous substance and a very persistent and

bioaccumulative substance [129], and is on the Canadian nondomestic substances list with as much as 10 metric tons/year being currently imported into Canada [137].

15.2 Birds

TBCO was detected in herring gull eggs from the Great Lakes, in North America, but was not quantifiable [36].

16 Octabromo-1,3,3-trimethyl-1-phenylindane

16.1 Background

There is no information on octabromo-1,3,3-trimethyl-1-phenylindane (OBIND) production volumes. It has previously been manufactured by Dead Sea Bromine Group (now ICL Industrial Products) as FR-1808.

16.2 Environmental Levels

OBIND was found to be present as a contaminant in the feed additive choline chloride at 0.140–0.700 ng/g [138]. OBIND was occasionally detected in dust samples from Czech households but no concentration data were reported [25]. Leonards et al. [51] found maximum OBIND concentrations of 1 ng/g dw in sediments from two locations in the Western Scheldt.

OBIND was screened for and detected in herring gull eggs from the Great Lakes, North America, but was not quantifiable [36].

17 Other

Lopez et al. [29] quantified pentabromocyclohexane, 2,3,5,6-tetrabromo-*p*-xylene, and tetrabromo-*o*-chlorotoluene in sediments and suspended particulate material from several sites in the Western Scheldt of the Netherlands.

18 Conclusions

The database on the environmental occurrence of emerging BFRs is small. The best studied emerging BFRs are BTBPE and DBDPE, with some data for HBBz, PBEB, PBT, TBBPA derivatives, TBB, TBPH, TBECH, and TBP, and much less available

for ATE, TBPA, TBCO, TBC, HCDBCO, and OBIND. There are many other BFRs on the market but we found no environmental data on these. For those that have been studied, the findings show that they are present in many environmental compartments including biota. Indoor air concentrations are generally higher than outdoor air concentrations, and where measured, they are even higher in occupational settings. Many are found in indoor air and dust, indicating possible human exposure from this pathway, but there are little human data available for evaluating the extent of exposure to most of these BFRs. The presence of several of these compounds in fish, birds, and mammals indicates that they are bioavailable, can be absorbed, and accumulated and in some cases, bioaccumulation and biomagnification may occur. Their presence in outdoor air and in the Arctic indicates that several are capable of long range atmospheric transport. Higher concentrations are seen in samples near BFR production facilities or manufacturing facilities using BFRs, making these point sources to the environment. Many of the emerging BFRs are showing similar environmental behavior as older BFRs, such as the PBDEs, that have recently been banned or restricted. As many of these emerging BFRs are being used as replacements for PBDEs, and the use of flame retardants is increasing because of more stringent fire regulations, there is a risk that the emerging BFRs will also become environmental problems. More data are therefore needed in order to determine if any of these emerging BFRs poses a threat to the environment or to human health.

References

1. Alaee M, Arias P, Sjodin A, Bergman A (2003) An overview of commercially used brominated flame retardants, their applications, their use patterns in different countries/regions and possible modes of release. Environ Int 29:683–689
2. Hess G (2009) Industry to phase out decaBDE. Chem Eng News. http://pubs.acs.org/cen/news/87/i51/8751notw12.html. Accessed March 2010
3. Albemarle (2009) Albemarle announces phase-out of Decabrom. Press release 17 December 2009. http://www.albemarle.com/News_and_events/index.asp?news=text&releaseID=1367378. Accessed March 2010
4. Chemtura (2009) Chemtura corporation announces phase-out of DecaBDE. Press release 17 December 2009. http://phx.corporate-ir.net/phoenix.zhtml?c=68079&p=irol-newsArticle&ID=1367410&highlight=. Accessed March 2010
5. de Wit CA, Herzke D, Vorkamp K (2010) Brominated flame retardants in the Arctic environment – trends and new candidates. Sci Total Environ 408:2885–2918
6. Hoh E, Zhu LY, Hites RA (2005) Novel flame retardants, 1,2-bis(2,4,6-tribromophenoxy) ethane and 2, 3, 4, 5, 6-pentabromoethylbenzene, in United States' environmental samples. Environ Sci Technol 39:2472–2477
7. Shi T, Chen SJ, Luo XJ et al (2009) Occurrence of brominated flame retardants other than polybrominated diphenyl ethers in environmental and biota samples from southern China. Chemosphere 74:910–916
8. ESIS (2010) European chemical substance information system. European Commission Joint Research Centre European Chemicals Bureau. http://ecb.jrc.ec.europa.eu/esis/
9. Verreault J, Gebbink WA, Gauthier LT, Gabrielsen GW, Letcher RJ (2007) Brominated flame retardants in glaucous gulls from the Norwegian Arctic: more than just an issue of polybrominated diphenyl ethers. Environ Sci Technol 41:4925–4931

10. Zweidinger RA, Cooper SD, Pellizzari ED (1979) Identification and quantitation of brominated fire retardants. In: Van Hall CE (ed) Measurement of organic pollutants in water and wastewater. ASTM STP 686. American Society for Testing and Materials, p 365
11. Zweidinger RA, Cooper SD, Erickson MD, Michael LC, Pellizzari ED (1979) Sampling and analysis for semivolatile brominated organics in ambient air. ACS Symp Ser 94:217–231
12. DeCarlo VJ (1979) Studies on brominated chemicals in the environment. Ann N Y Acad Sci 320:678–681
13. Hoh E, Hites RA (2005) Brominated flame retardants in the atmosphere of the east-central United States. Environ Sci Technol 39:7794–7802
14. Venier M, Hites RA (2008) Flame retardants in the atmosphere near the Great Lakes. Environ Sci Technol 42:4745–4751
15. Sjödin A, Carlsson H, Thuresson K, Sjölin S, Bergman Å, Östman C (2001) Flame retardants in indoor air at an electronics recycling plant and at other work environments. Environ Sci Technol 35:448–454
16. Chen LG, Mai BX, Bi XH et al (2006) Concentration levels, compositional profiles, and gas-particle partitioning of polybrominated diphenyl ethers in the atmosphere of an urban city in South China. Environ Sci Technol 40:1190–1196
17. Zhu LY, Hites RA (2006) Brominated flame retardants in tree bark from North America. Environ Sci Technol 40:3711–3716
18. Qiu XH, Hites RA (2008) Dechlorane plus and other flame retardants in tree bark from the northeastern United States. Environ Sci Technol 42:31–36
19. Pettersson-Julander A, van Bavel B, Engwall M, Westberg H (2004) Personal air sampling and analysis of polybrominated diphenyl ethers and other bromine containing compounds at an electronic recycling facility in Sweden. J Environ Monit 6:874–880
20. Julander A, Westberg H, Engwall M, van Bavel B (2005) Distribution of brominated flame retardants in different dust fractions in air from an electronics recycling facility. Sci Total Environ 350:151–160
21. Karlsson M, Julander A, van Bavel B, Hardell L (2007) Levels of brominated flame retardants in blood in relation to levels in household air and dust. Environ Int 33:62–69
22. Stapleton HM, Allen JG, Kelly SM et al (2008) Alternate and new brominated flame retardants detected in US house dust. Environ Sci Technol 42:6910–6916
23. Stapleton HM, Klosterhaus S, Eagle S, Fuh J, Meeker JD, Blum A, Webster TF (2009) Detection of organophosphate flame retardants in furniture foam and US house dust. Environ Sci Technol 43:7490–7495
24. Harrad S, Ibarra C, Abdallah MAE, Boon R, Neels H, Covaci A (2008) Concentrations of brominated flame retardants in dust from United Kingdom cars, homes, and offices: causes of variability and implications for human exposure. Environ Int 34:1170–1175
25. Kalachová K, Pulkrabová J, Hrádková P, Poustka J, Hajšlová J (2009) Polybrominated diphenyl ethers (PBDEs) in dust samples from Czech households. Organohalogen Compd 71:2320–2324
26. Chen SJ, Ma YJ, Wang J, Chen D, Luo XJ, Mai BX (2009) Brominated flame retardants in children's toys: concentration, composition, and children's exposure and risk assessment. Environ Sci Technol 43:4200–4206
27. Law K, Halldorson T, Danell R et al (2006) Bioaccumulation and trophic transfer of some brominated flame retardants in a Lake Winnipeg (Canada) food web. Environ Toxicol Chem 25:2177–2186
28. Qiu X, Marvin CH, Hites RA (2007) Dechlorane plus and other flame retardants in a sediment core from Lake Ontario. Environ Sci Technol 41:6014–6019
29. Lopez P, Leonards P, Brandsma S, De Boer J (2008) New brominated flame retardants in Dutch sediments and suspended particulate matter. Organohalogen Compd 70:224–227
30. Law K, Halldorson T, Danell R et al (2007) Bioaccumulation and trophic transfer of some brominated flame retardants in a Lake Winnipeg (Canada) food web. [Erratum to document cited in CA145:277560]. Environ Toxicol Chem 26:190–190

31. Tomy GT, Palace VP, Pleskach K et al (2007) Dietary exposure of juvenile rainbow trout (*Oncorhynchus mykiss*) to 1, 2-bis(2, 4, 6-tribromo- phenoxy)ethane: bioaccumulation parameters, biochemical effects, and metabolism. Environ Sci Technol 41:4913–4918
32. Ismail N, Gewurtz SB, Pleskach K, Whittle DM, Helm PA, Marvin CH, Tomy GT (2009) Brominated and chlorinated flame retardants in Lake Ontario, Canada, lake trout (*Salvelinus Namaycush*) between 1979 and 2004 and possible influences of food-web changes. Environ Toxicol Chem 28:910–920
33. Munschy C, Heas-Moisan K, Loizeau V, Tixier C, Tronczynski J, Alaee M, Pacepavicius G (2007) Identification of past and novel brominated flame retardants in common sole (*Solea solea L.*) from coastal areas in France. Organohalogen Compd 69:2681–2685
34. Park J-S, Holden A, Chu V et al (2009) Exposure of California peregrine falcon (*Falco Peregrinus*) to brominated flame retardants (PBDEs and new alternative BFRs) and PCBs: different profiles of PBDEs, prey, and isotope patterns between coastal and big city nesting birds. Organohalogen Compd 71:820–823
35. Gauthier LT, Hebert CE, Weseloh DVC, Letcher RJ (2007) Current-use flame retardants in the eggs of herring gulls (*Larus argentatus*) from the Laurentian Great Lakes. Environ Sci Technol 41:4561–4567
36. Gauthier LT, Potter D, Hebert CE, Letcher RJ (2009) Temporal trends and spatial distribution of non-polybrominated diphenyl ether flame retardants in the eggs of colonial populations of Great Lakes herring gulls. Environ Sci Technol 43:312–317
37. Karlsson M, Ericson I, van Bavel B, Jensen JK, Dam M (2006) Levels of brominated flame retardants in Northern Fulmar (*Fulmarus glacialis*) eggs from the Faroe Islands. Sci Total Environ 367:840–846
38. Tomy GT, Ismail N, Pleskach K et al (2007) Temporal and spatial trends of brominated and chlorinated flame retardants in beluga (*Delphinapterus leucas*) from the Canadian Arctic. In: Fourth international workshop on brominated flame retardants (BFR 2007), Toronto, Canada, 6-9 June, Extended abstract
39. Muir D, Kwan M, Evans M (2007) Temporal trends of persistent organic pollutants and metals in ringed seals from the Canadian Arctic. In: Smith S, Stow J (eds) Synopsis of research conducted under the 2006–2007 Northern Contaminants Program, Indian Affairs and Northern Development, Ottawa, ON, Canada
40. Sjödin A, Patterson DG, Bergman Å (2003) A review on human exposure to brominated flame retardants – particularly polybrominated diphenyl ethers. Environ Int 29:829–839
41. Zhu L, Ma B, Hites RA (2009) Brominated flame retardants in serum from the general population in northern China. Environ Sci Technol 43:6963–6968
42. Hakk H, Larsen G, Bowers J (2004) Metabolism, tissue disposition, and excretion of 1,2-bis(2,4,6-tribromophenoxy)ethane (BTBPE) in male Sprague-Dawley rats. Chemosphere 54:1367–1374
43. Nomeir AA, Markham PM, Ghanayem BI, Chadwick M (1993) Disposition of the flame-retardant 1,2-bis(2,4,6-tribromophenoxy)ethane in rats following administration in the diet. Drug Metab Dispos 21:209–214
44. UBA (2001) Erarbeitung von Bewertungsgrundlagen zur Substitution umweltrelevanter Flammschutzmittel. Umweltbundesamt, Germany. http://www.umweltbundesamt.org/fpdf-l/1988.pdf. Accessed October 2005
45. Arias PA (2001) Brominated flame retardants – an overview. In: The second international workshop on brominated flame retardants (BFR 2001), Stockholm, Sweden, 14–16 May 2001, Extended abstract
46. Kierkegaard A, Björklund J, Friden U (2004) Identification of the flame retardant decabromodiphenyl ethane in the environment. Environ Sci Technol 38:3247–3253
47. Albemarle (2007) Albemarle to expand production of popular Saytex 8010 flame retardant. Newsletter September 17, 2007. http://www.albemarle.com/Products_and_services/Polymer_additives/?news=text&releaseID=1052248. Accessed September 2009

48. Zhang XL, Luo XJ, Chen SJ, Wu JP, Mai BX (2009) Spatial distribution and vertical profile of polybrominated diphenyl ethers, tetrabromobisphenol A, and decabromodiphenylethane in river sediment from an industrialized region of south China. Environ Pollut 157: 1917–1923
49. Watanabe I, Sakai SI (2003) Environmental release and behavior of brominated flame retardants. Environ Int 29:665–682
50. Takigami H, Suzuki G, Hirai Y, Ishikawa Y, Sunami M, Sakai S (2009) Flame retardants in indoor dust and air of a hotel in Japan. Environ Int 35:688–693
51. Leonards P, Lopez P, De Boer J (2008) Analysis and occurrence of new brominated flame retardants in the environment. Organohalogen Compd 70:926–929
52. Eljarrat E, Labandeira A, Martinez A, Fabrellas B, Barceló D (2005) Occurrence of the "new" brominated flame retardant, decabromodiphenyl ethane, in sewage sludge from Spain. Organohalogen Compd 67:459–461
53. de la Torre A, Concejero MA, Sanz P, Martinez MA (2007) Optimisation of a MS/MS method for DBDPE: applications to Spanish sewage sludges. Organohalogen Compd 69:2702–2705
54. Konstantinov A, Arsenault G, Chittim B et al (2006) Characterization of mass-labeled [$^{13}C_{14}$]-decabromodiphenylethane and its use as a surrogate standard in the analysis of sewage sludge samples. Chemosphere 64:245–249
55. Ricklund N, Kierkegaard A, McLachlan MS (2008) An international survey of decabromodiphenyl ethane (deBDethane) and decabromodiphenyl ether (decaBDE) in sewage sludge samples. Chemosphere 73:1799–1804
56. Law RJ, Allchin CR, De Boer J et al (2006) Levels and trends of brominated flame retardants in the European environment. Chemosphere 64:187–208
57. Ricklund N, Kierkegaard A, McLachlan MS, Wahlberg C (2009) Mass balance of decabromodiphenyl ethane and decabromodiphenyl ether in a WWTP. Chemosphere 74:389–394
58. de la Torre A, Sanz P, Martinez MA (2008) Presence of PBDEs and DBDPE in leachate and compost from different Spanish landfills. Organohalogen Compd 70:1958–1960
59. Ricklund N, Kierkegaard A, McLachlan MS (2010) Levels and potential sources of decabromodiphenyl ethane (DBDPE) and decabromodiphenyl ether (DecaBDE) in lake and marine sediments in Sweden. Environ Sci Technol 44:1987–1991
60. Ismail N, Pleskach K, Marvin C, Whittle M, Keir M, Helm P, Tomy GT (2006) Temporal trends of flame retardants in Lake Ontario lake trout (1979–2004). Organohalogen Compd 68:1808–1811
61. Gao F, Luo XJ, Yang ZF, Wang XM, Mai BX (2009) Brominated flame retardants, polychlorinated biphenyls, and organochlorine pesticides in bird eggs from the Yellow River delta, north China. Environ Sci Technol 43:6956–6962
62. Luo XJ, Zhang XL, Liu J et al (2009) Persistent halogenated compounds in waterbirds from an e-waste recycling region in south China. Environ Sci Technol 43:306–311
63. Hu GC, Luo XJ, Dai JY et al (2008) Brominated flame retardants, polychlorinated biphenyls, and organochlorine pesticides in captive giant panda (*Ailuropoda melanoleuca*) and red panda (*Ailurus fulgens*) from China. Environ Sci Technol 42:4704–4709
64. Yamaguchi Y, Kawano M, Tatsukawa R, Moriwaki S (1988) Hexabromobenzene and its debrominated compounds in human adipose tissues of Japan. Chemosphere 17:703–707
65. Watanabe I, Kashimoto T, Tatsukawa R (1986) Hexabromobenzene and its debrominated compounds in river and estuary sediments in Japan. Bull Environ Contam Toxicol 36:778–784
66. Buser H-R (1986) Polybrominated dibenzofurans and dibenzo-*p*-dioxins: thermal reaction products of polybrominated diphenyl ether flame retardants. Environ Sci Technol 20:404–408
67. Gouteux B, Alaee M, Mabury SA, Pacepavicius G, Muir DCG (2008) Polymeric brominated flame retardants: are they a relevant source of emerging brominated aromatic compounds in the environment? Environ Sci Technol 42:9039–9044

68. Sawal G, Feibicke M, Meinecke S, Warmbrunn-Suckrow E, Lepom P (2008) Identification of a novel brominated flame retardant in dust. Organohalogen Compd 70:2029–2032
69. Saito I, Onuki A, Seto H (2007) Indoor organophosphate and polybrominated flame retardants in Tokyo. Indoor Air 17:28–36
70. Sinkkonen S, Paasivirta J, Lahtiperä M, Vattulainen A (2004) Screening of halogenated aromatic compounds in some raw material lots for an aluminium recycling plant. Environ Int 30:363–366
71. Nyholm JR, Norman A, Norrgren L, Haglund P, Andersson PL (2008) Maternal transfer of brominated flame retardants in zebrafish (*Danio rerio*). Chemosphere 73:203–208
72. Nyholm JR, Norman A, Norrgren L, Haglund P, Andersson PL (2009) Uptake and biotransformation of structurally diverse brominated flame retardants in zebrafish (*Danio rerio*) after dietary exposure. Environ Toxicol Chem 28:1035–1042
73. Letcher RJ (2007) Temporal and spatial trends of organic and metal contaminants in Canadian polar bears: 2006–2007 project summary report. In: Smith S, Stow J (eds) Synopsis of research conducted under the 2006–2007 Northern Contaminants Program, Indian Affairs and Northern Development, Ottawa, ON, Canada
74. Smeds A, Saukko P (2003) Brominated flame retardants and phenolic endocrine disrupters in Finnish human adipose tissue. Chemosphere 53:1123–1130
75. Shen H, Main KM, Andersson AM et al (2008) Concentrations of persistent organochlorine compounds in human milk and placenta are higher in Denmark than in Finland. Hum Reprod 23:201–210
76. WHO (1997) Environmental health criteria 192. Flame retardants: a general introduction. World Health Organization, Geneva, Switzerland. http://www.inchem.org/documents/ehc/ehc/ehc192.htm
77. OSPAR (2001) OSPAR list of chemicals for priority action (Update 2007). http://www.ospar.org/content/content.asp?menu=00120000000074_000000_000000. Accessed March 2010
78. Lee RGM, Thomas GO, Jones KC (2002) Atmospheric concentrations of PBDEs in western Europe. Organohalogen Compd 58:193–196
79. Niimi AJ, Oliver BG (1988) Influence of molecular weight and molecular volume on dietary absorption efficiency of chemicals by fishes. Can J Fish Aquat Sci 45:222–227
80. Mattsson PE, Norström Å, Rappe C (1975) Identification of the flame retardant pentabromotoluene in sewage sludge. J Chromatogr 111:209–213
81. Jakab E, MdA U, Bhaskar T, Sakata Y (2003) Thermal decomposition of flame-retarded high-impact polystyrene. J Anal Appl Pyrolysis 68–69:83–99
82. Lopez P, Brandsma SA, Leonards PEG, De Boer J (2009) Methods for the determination of phenolic brominated flame retardants, and by-products, formulation intermediates and decomposition products of brominated flame retardants in water. J Chromatogr A 1216:334–345
83. Schwarzbauer J, Ricking M, Franke S, Francke W (2001) Organic compounds as contaminants of the Elbe River and its tributaries. Part 5. Halogenated organic contaminants in sediments of the Havel and Spree Rivers (Germany). Environ Sci Technol 35:4015–4025
84. Zitko V, Carson WG (1977) Uptake and excretion of chlorinated diphenyl ethers and brominated toluenes by fish. Chemosphere 6:293–301
85. US EPA (2006) Non-confidential 2006 IUR records by chemical. Inventory update reporting (IUR), US Environmental Protection Agency. http://www.epa.gov/oppt/iur/tools/data/index.html
86. Andersson PL, Öberg K, Örn U (2006) Chemical characterization of brominated flame retardants and identification of structurally representative compounds. Environ Toxicol Chem 25:1275–1282
87. WHO (1995) Environmental health criteria 172. Tetrabromobisphenol A and derivatives. World Health Organization, Geneva, Switzerland. http://www.inchem.org/documents/ehc/ehc/ehc172.htm

88. Rahm S, Green N, Norrgran J, Bergman Å (2005) Hydrolysis of environmental contaminants as an experimental tool for indication of their persistency. Environ Sci Technol 39:3128–3133
89. Jonsson S, Hörsing M (2009) Investigation of sorption phenomena by solid phase extraction and liquid chromatography for the determination of some ether derivatives of tetrabromobisphenol A. J Phys Org Chem 22:1120–1126
90. Harju M, Heimstad ES, Herzke D et al (2009) Emerging "new" brominated flame retardants in flame retarded products and the environment. SFT report 2462, Norwegian Pollution Control Authority, Oslo, Norway, p 113
91. Breivik K, Wania F, Muir DCG, Alaee M, Backus S, Pacepavicius G (2006) Empirical and modeling evidence of the long-range atmospheric transport of decabromodiphenyl ether. Environ Sci Technol 40:4612–4618
92. Karlsson M (2006) Levels of brominated flame retardants in humans and their environment – occupational and home exposure. PhD Thesis, Örebro University, Örebro, Sweden. ISBN:91-7668-499-7
93. Köppen R, Becker R, Jung C, Piechotta C, Nehls I (2006) Investigation of extraction procedures and HPLC-DAD/MS for the determination of the brominated flame retardant tetrabromobisphenol A bis(2,3-dibromopropylether) in environmental samples. Anal Bioanal Chem 384:1485–1492
94. Knudsen GA, Jacobs LM, Kuester RK, Sipes IG (2007) Absorption, distribution, metabolism and excretion of intravenously and orally administered tetrabromobisphenol A [2,3-dibromopropyl ether] in male Fischer-344 rats. Toxicology 237:158–167
95. Davis EF, Stapleton HM (2009) Photodegradation pathways of nonabrominated diphenyl ethers, 2-ethylhexyltetrabromobenzoate and di(2-ethylhexyl)tetrabromophthalate: identifying potential markers of photodegradation. Environ Sci Technol 43:5739–5746
96. US EPA (2010) Non-confidential production volume information submitted by companies under the 1986, 1990, 1994, 1998, and 2002 IUR. Inventory update reporting (IUR), US Environmental Protection Agency. http://www.epa.gov/oppt/iur/tools/data/2002-vol.html
97. Betts K (2008) New flame retardants detected in indoor and outdoor environments. Environ Sci Technol 42:6778
98. Klosterhaus S, Konstantinov A, Stapleton HM (2008) Characterization of the brominated chemicals in PentaBDE replacement mixture and their detection in biosolids collected from two San Francisco Bay Area wastewater treatment plants. http://www.sfei.org/rmp/posters/08BFR_Poster_klosterhaus_shrunk.pdf. Accessed March 2010
99. Klosterhaus S, Stapleton HM, La Guardia M, Davis E, Eagle S, Blum A (2010) Recent studies on the identification and occurrence of PentaBDE replacement chemicals in indoor and outdoor environments. In: Fifth international symposium on brominated flame retardants (BFR 2010), Kyoto, Japan, 7–9 April 2010, Extended abstract
100. Hoh E, Lehotay SJ, Mastovska K, Ngo HL, Vetter W, Pangallo KC, Reddy CM (2009) Capabilities of direct sample introduction-comprehensive two-dimensional gas chromatography-time-of-flight mass spectrometry to analyze organic chemicals of interest in fish oils. Environ Sci Technol 43:3240–3247
101. Lam JCW, Lau RKF, Murphy MB, Lam PKS (2009) Temporal trends of hexabromocyclododecanes (HBCDs) and polybrominated diphenyl ethers (PBDEs) and detection of two novel flame retardants in marine mammals from Hong Kong, south China. Environ Sci Technol 43:6949
102. Arsenault G, Lough A, Marvin C et al (2008) Structure characterization and thermal stabilities of the isomers of the brominated flame retardant 1,2-dibromo-4-(1,2-dibromoethyl)cyclohexane. Chemosphere 72:1163–1170
103. Tomy GT, Pleskach K, Arsenault G et al (2008) Identification of the novel cycloaliphatic brominated flame retardant 1,2-dihromo-4-(1,2-dibromoethyl)cyclo-hexane in Canadian arctic beluga (*Delphinapterus leucas*). Environ Sci Technol 42:543–549

104. Muir DCG, Howard PH (2006) Are there other persistent organic pollutants? A challenge for environmental chemists. Environ Sci Technol 40:7157–7166
105. Santillo D, Labounskaia I, Stringer R, Johnston P (1997) Report on the analysis of industrial wastewaters from the Frutarom VCM/PVC plant, near Haifa, Israel, and adjacent shoreline sediments for organic contaminants. Greenpeace Research Laboratories Technical Note 03/97 1-25
106. Whitfield FB, Drew M, Helidoniotis F, Svoronos D (1999) Distribution of bromophenols in species of marine polychaetes and bryozoans from eastern Australia and the role of such animals in the flavor of edible ocean fish and prawns (shrimp). J Agric Food Chem 47:4756–4762
107. Flodin C, Whitfield FB (2000) Brominated anisoles and cresols in the red alga *Polysiphonia sphaerocarpa*. Phytochemistry 53:77–80
108. Chung HY, Ma WCJ, Ang PO Jr, Kim JS, Chen F (2003) Seasonal variations of bromophenols in brown algae (*Padina arborescens*, *Sargassum siliquastrum*, and *Lobophora variegata*) collected in Hong Kong. J Agric Food Chem 51:2619–2624
109. Fielman KT, Woodin SA, Lincoln DE (2001) Polychaete indicator species as a source of natural halogenated organic compounds in marine sediments. Environ Toxicol Chem 20:738–747
110. Qiu X, Bigsby RM, Hites RA (2009) Hydroxylated metabolites of polybrominated diphenyl ethers in human blood samples from the United States. Environ Health Perspect 117:93–98
111. Suzuki G, Takigami H, Watanabe M, Takahashi S, Nose K, Asari M, Sakai S (2008) Identification of brominated and chlorinated phenols as potential thyroid-disrupting compounds in indoor dusts. Environ Sci Technol 42:1794–1800
112. Vetter W, Haase-Aschoff P, Rosenfelder N, Komarova T, Mueller JF (2009) Determination of halogenated natural products in passive samplers deployed along the Great Barrier Reef, Queensland/Australia. Environ Sci Technol 43:6131–6137
113. Sim WJ, Lee IS, Lee SH, Oh JE, Lee TS (2007) Distribution of chlorinated and brominated phenols in marine, riverine, and estuarine sediments in southeastern Korea. Organohalogen Compd 69:1697–1700
114. Löfstrand K, Malmvärn A, Haglund P, Bignert A, Bergman Å, Asplund L (2007) PBDD, MeO-PBDE, OH-PBDE and brominated phenols in blue mussels from the Swedish coast line. Organohalogen Compd 69:287–290
115. Chung HY, Ma WCJ, Kim JS (2003) Seasonal distribution of bromophenols in selected Hong Kong seafood. J Agric Food Chem 51:6752–6760
116. Wan Y, Wiseman S, Chang H et al (2009) Origin of hydroxylated brominated diphenyl ethers: natural compounds or man-made flame retardants? Environ Sci Technol 43:7536–7542
117. Mardones C, Palma J, Sepulveda C, Berg A, von Baer D (2003) Determination of tribromophenol and pentachlorophenol and its metabolite pentachloroanisole in *Asparagus officinalis* by gas chromatography/mass spectrometry. J Sep Sci 26:923–926
118. Unson MD, Holland ND, Faulkner DJ (1994) A brominated secondary metabolite synthesized by the cyanobacterial symbiont of a marine sponge and accumulation of the crystalline metabolite in the sponge tissue. Mar Biol 119:1–11
119. Teuten EL, Xu L, Reddy CM (2005) Two abundant bioaccumulated halogenated compounds are natural products. Science 307:917–920
120. Malmvärn A, Marsh G, Kautsky L, Athanasiadou M, Bergman Å, Asplund L (2005) Hydroxylated and methoxylated brominated diphenyl ethers in the red algae *Ceramium tenuicorne* and blue mussels from the Baltic Sea. Environ Sci Technol 39:2990–2997
121. Takigami H, Suzuki G, Hirai Y, Sakai S (2009) Brominated flame retardants and other polyhalogenated compounds in indoor air and dust from two houses in Japan. Chemosphere 76:270–277
122. Öberg K, Warman K, Öberg T (2002) Distribution and levels of brominated flame retardants in sewage sludge. Chemosphere 48:805–809

123. Kurata Y, Ono Y, Ono Y (2008) Occurrence of phenols in leachates from municipal solid waste landfill sites in Japan. J Mater Cycles Waste Manage 10:144–152
124. Hovander L, Malmberg T, Athanasiadou M, Athanassiadis I, Rahm S, Bergman A, Wehler EK (2002) Identification of hydroxylated PCB metabolites and other phenolic halogenated pollutants in human blood plasma. Arch Environ Contam Toxicol 42:105–117
125. Thomsen C, Lundanes E, Becher G (2001) Brominated flame retardants in plasma samples from three different occupational groups in Norway. J Environ Monit 3:366–370
126. Thomsen C, Lundanes E, Becher G (2002) Brominated flame retardants in archived serum samples from Norway: a study on temporal trends and the role of age. Environ Sci Technol 36:1414–1418
127. Dallaire R, Ayotte P, Pereg D, Dery S, Dumas P, Langlois E, Dewailly E (2009) Determinants of plasma concentrations of perfluorooctanesulfonate and brominated organic compounds in Nunavik inuit adults (Canada). Environ Sci Technol 43:5130–5136
128. Ohta S, Okumura T, Nishimura H et al (2010) Levels of PBDEs, TBBPA, TBPs, PCDDs/DFs, PXDDs/DFs and PBDDs/DFs in human milk of nursing women and dairy milk products in Japan. Organohalogen Compd 66:2857–2862
129. Fisk PR, Girling AE, Wildey RJ (2003) Prioritisation of flame retardants for environmental risk assessment. UK Environment Science Agency. http://www.ec.europa.eu/environment/waste/stakeholders/industry_assoc/ebfrip/annex2.pdf. Accessed 2010-03-10
130. von der Recke R, Vetter W (2007) Synthesis and characterization of 2, 3-dibromopropyl-2,4,6-tribromophenyl ether (DPTE) and structurally related compounds evidenced in seal blubber and brain. Environ Sci Technol 41:1590–1595
131. Brown TN, Wania F (2008) Screening chemicals for the potential to be persistent organic pollutants: a case study of Arctic contaminants. Environ Sci Technol 42:5202–5209
132. Vetter W, von der Recke R, Ostrowicz P, Rosenfelder N (2010) Liquid chromatographic enantioseparation of the brominated flame retardant 2,3-dibromopropyl-2, 4, 6-tribromophenyl ether (DPTE) and enantiomer fractions in seal blubber. Chemosphere 78:134–138
133. Riddell N, Arsenault G, Lough A, McAlees A, Mccrindle R, Meissner J, Robertson V (2008) The three-dimensional structural characterization of hexachlorocyclopentenyldibromocyclooctane (HCDBCO). Chemosphere 73:479–483
134. Zhu J, Hou Y, Feng Y-L, Shoeib M, Harner T (2008) Identification and determination of hexachlorocyclopentadienyl-dibromocyclooctane (HCDBCO) in residential indoor air and dust: a previously unreported halogenated flame retardant in the environment. Environ Sci Technol 42:386–391
135. Zhou SN, Reiner EJ, Marvin C et al (2010) Liquid chromatography–atmospheric pressure photoionization tandem mass spectrometry for analysis of 36 halogenated flame retardants in fish. J Chromatogr A 1217:633–641
136. Ruan T, Wang YW, Wang C et al (2009) Identification and evaluation of a novel heterocyclic brominated flame retardant tris(2,3-dibromopropyl) isocyanurate in environmental matrices near a manufacturing plant in southern China. Environ Sci Technol 43:3080–3086
137. Riddell N, Arsenault G, Klein J et al (2009) Structural characterization and thermal stabilities of the isomers of the brominated flame retardant 1,2,5,6-tetrabromocyclooctane (TBCO). Chemosphere 74:1538–1543
138. Traag W, Kotz A, van der Weg G, Malisch R, Hoogenboom R (2009) Bioassay directed detection of brominated dioxins in the feed additive cholin chloride. Organohalogen Compd 71:2210–2213
139. Kuramochi H, Maeda K, Kawamoto K (2004) Measurements of water solubilities and 1-octanol/water partition coefficients and estimations of Henry's law constants for brominated benzenes. J Chem Eng Data 49:720–724
140. Tittlemier SA, Halldorson T, Stern GA, Tomy GT (2002) Vapor pressures, aqueous solubilities, and Henry's law constants of some brominated flame retardants. Environ Toxicol Chem 21:1804–1810

Index

E. Eljarrat and D. Barceló (eds.), *Brominated Flame Retardants*,
Hdb Env Chem (2011) 16: 287–290, DOI 10.1007/698_2010,