




Brominated Flame Retardants

Rising Levels of Concern

SARAH JANSSEN, M.D., PHD, M.P.H.
JUNE 2005

Health Care Without Harm

Brominated Flame Retardants: Rising Levels of Concern

SARAH JANSSEN, M.D., PHD, M.P.H.

JUNE 2005

Health Care Without Harm
1901 North Moore St., Suite 509
Arlington, VA 22209
Phone: 703.243.0056
Fax: 703.243.4008
www.noharm.org
info@hcwh.org

ABOUT THE AUTHOR

Sarah Janssen, M.D, PhD, M.P.H. is an Occupational and Environmental Medicine Fellow at the University of California at San Francisco. She can be contacted by e-mail at sjanssen69@yahoo.com or at Campus Box 0843, San Francisco, CA 94143-0843

ACKNOWLEDGEMENTS

Thanks to the many people who helped draft, review, and edit this document: Tracey Easthope, MPH, The Ecology Center, Michigan; Larissa Lubomudrov Sano Ph.D. Candidate, Cooperative Institute for Limnology and Ecosystems Research, University of Michigan; Stacy Malkan, Media Director, Health Care Without Harm; Mark Miller, M.D., MPH, Assistant Clinical Professor of Pediatrics, Director Pediatric Environmental Health Specialty Unit, University of California at San Francisco; Mark Rossi, PhD, Clean Production Action; Karolina Ruzickova, Health Care Without Harm Europe, Czech Republic; Ted Schettler, M.D., MPH, Science and Environmental Health Network; Kathleen Schuler, MPH, Institute for Agriculture and Trade Policy; Julie Silas, San Francisco Bay Area Physicians for Social Responsibility; Lara Sutherland, Health Care Without Harm; Laurie Valeriano, Washington State Toxics Coalition; and David Wallinga, MD, MPH, Institute for Agriculture and Trade Policy.

PREFACE

Flame retardants are all around us in health care settings. Intravenous pumps, hospital beds, waiting room chairs, and hospital privacy curtains all share the common need to be fire resistant. To meet fire safety standards, fire resistant chemicals, known as "flame retardants", are added by manufacturers of health care products to slow or prevent fires. Unfortunately many of these flame retardants do not remain fixed in the product. Instead they slowly leak from the products into our air, dust, water, and environment and eventually they enter our food and bodies. A subset of these flame retardants, called "brominated flame retardants" (BFRs), are now the subject of intense scrutiny. Evidence shows they are likely to persist in our environment, bioaccumulate in the food chain and in our bodies, and cause adverse effects in our children. The breast milk of American women contains the highest levels of BFRs in human breast milk found anywhere in the world.

Concerned that health care may be an inadvertent source of hazardous flame retardants, contaminating the environment, people, and the food web, Health Care Without Harm has prepared this report to summarize the latest scientific research on halogenated brominated flame retardants, including their toxicity, persistence, and presence in humans and wildlife. The purpose of the report is to alert health care practitioners to the potential hazard and to spur the development and use of safer alternatives. The report was prepared using scientific reports, government documents and industry information obtained through internet-based searches.

Health Care Without Harm (HCWH), the sponsor of this assessment, is a campaign for environmentally responsible health care. Made up of 430 organizations in 52 countries, HCWH's mission is to transform the health care industry worldwide, without compromising patient safety or care, so that it is ecologically sustainable and no longer a source of harm to public health or the environment. The campaign's goals include the advocacy of policies, practices and laws that eliminate the incineration of medical waste, minimize the amount and toxicity of all waste generated, and promote the use of safer materials and treatment practices.

HCWH is a main sponsor of CleanMed, the largest health care conference for environmentally preferable products and green buildings (see www.cleanmed.org). At CleanMed 2004, Group Purchasing Organizations representing more than 70% of health care buying power in the United States made several commitments to support environmentally preferable products. Among those was a commitment to seek disclosure from their suppliers about the content of brominated flame retardants in products and to move toward BFR-free products as safe, effective alternatives become available.

HCWH will continue to monitor emerging science on brominated flame retardants and the development of alternatives, and provide updated information on our website at www.noharm.org.

Anna Gilmore Hall, R.N., CAE
Executive Director
Health Care Without Harm

CONTENTS

EXECUTIVE SUMMARY

Synthetic polymers have largely replaced the use of wood, glass, and metal materials in our homes, offices, automobiles, public transit, and other public areas. These synthetic materials are often petroleum-based plastics that easily ignite, spread flames quickly, and release toxicants when burned.

Fire is a significant cause of property damage and of death. In the United States, fire kills more than 3,000 people per year, injures more than 20,000 people, and results in property damages exceeding an estimated $11 billion *(1)*. In Canada, between 1986 and 1995 there was an average of 67,000 fires annually with 3,700 injuries, 465 deaths, and losses of over $1.125 billion Canadian dollars *(2)*.

Fire safety standards for electrical appliances, textiles, upholstery, and many other materials and products help to minimize these losses. To meet fire safety standards, products made of synthetic materials are modified with flame retardants, chemicals that inhibit the ignition and spread of flames.

Over 175 different flame retardants are on the market today and fall into four major chemical groups: inorganic, organophosphorous, halogenated organic, and nitrogen-based compounds *(2)*. Halogenated organic flame retardants are further classified as containing either chlorine or bromine (brominated flame retardants or BFRs). Chlorine and bromine are the only halogens used as flame retardants in synthetic materials, especially plastics, with bromine being a more effective retardant, costing less, and having wider applications than chlorine *(3)*.

Whereas flame resistant products save lives and prevent property damage, there are increasing concerns about the environmental and health effects of flame retardants such as BFRs. Concerns with brominated flame retardants emerged in the 1970s when polybrominated biphenyls (PBBs) were discovered in feed for dairy cattle, livestock, and poultry in Michigan *(1)*.

Widespread PBB contamination of milk, meat, and eggs in the region resulted in the exposure of over 9 million humans to the toxicant. The U.S. government acted quickly, suspending the use of PBB flame retardants in 1979. Growing evidence suggests that BFRs are similar to PBBs and another class of banned persistent, bioaccumulative toxicants—polychlorinated biphenyls (PCBs).

There are three classes of BFRs currently produced in high volumes: polybrominated diphenyl ethers (PBDEs), tetrabromobisphenol A (TBBPA), and hexabromocyclododecane (HBCD). The PBDEs that have been commonly used in products are Deca-, Octa-, and Penta-BDE. The concentration of BFRs in products ranges from 5-30%. The total world demand for the highest production volume BFRs in 2001 was estimated by the bromine industry at 203,740 metric tons with TBBPA and Deca-BDE being the most widely used BFRs *(6)*. Deca-BDE is used in virtually every type of plastic polymer that requires a flame retardant. Table ES-1 shows the typical use of each of the major BFRs.

In the health care setting, BFRs are as pervasive as they are in our homes and offices. Patients' rooms, mattresses, foam pads and other bedding materials may contain BFRs. Other furniture and textiles in patient rooms may be treated with BFRs, including furniture cushions, lamp shades, cubicle curtains, privacy curtains, drapery, and window blinds. Electronic equipment such as televisions, pulse oximeters, monitors, ventilators, or IV pumps likely have BFRs in the plastic housing. At the nursing stations, BFRs may be in computers, printers, fax and copy machines, and assorted office furniture. In the cafeteria and other eating areas, BFRs may be in microwave ovens, refrigerators, and other appliances. In nearly every area of the hospital—from shipping and receiving to the operating rooms—foam packaging is found that can contain BFRs.

Table ES-1. Examples of major BFR products by chemical.

Chemical Name	Typical Products
Pentabromodiphenyl ether (Penta-BDE, PBDE, or Penta)	Polyurethane foams: mattresses, seat cushions, other upholstered furniture and foam packaging. Also: carpet padding, imitation wood, paints, sound insulation panels, small electronic parts, fabric coatings, epoxy resins, conveyor belts
Octabromodiphenyl ether (Octa-BDE, OBDE, or Octa)	Acrylonitrile -butadiene - styrene (ABS) plastic: housings for fax machines, computers and other electronics. Also: automobile trim, telephone handsets, kitchen appliance casings, small electronics parts, audio/video equipment, remote control products
Decabromodiphenyl ether (Deca-BDE, DBDE or Deca)	High-impact polystyrene (HIPS) plastic: housings for televisions, computers, stereos and other small electronics. Also: mobile phones
	Various plastics: polycarbonates, polyester resins, polyamides, polyvinyl chloride, polypropylenes, terephthalates (PBT and PET), and rubber. Also: upholstery textiles (sofas, office chairs, backcoating), paints, rubber cables, lighting (panels, lamp sockets), smoke detectors, electrical equipment (connectors, wires, cables, fuses, housings, boxes, switches), stadium seats
Tetrabromobisphenol A (TBBPA)	Reactive flame retardant: epoxy and polycarbonate resins. Also: printed circuit boards in electronics (96%), office equipment housings
	Additive flame retardant: various plastics, paper and textiles. Also: housings of computers, monitors, TV, office equipment, adhesive coatings in paper and textiles
Hexabromocyclododecane (HBCD)	Various plastics: Polystyrene (EPS, XPS), HIPS, polypropylene. Also: textiles and carpet backing, television and computer housings, textiles in automobiles, building materials (insulation panels, construction blocks, thermal insulation, roofs), upholstered foam, latex binders

Sources: (1, 4-6)

ENVIRONMENTAL FATE AND TRANSPORT

Brominated flame retardants are not only found in numerous household, health care, and consumer products, but they are now ubiquitous in our environment. In the past decade, scientists have detected BFRs in both human and wildlife tissues, as well as in house dust, sediments, sewage sludge, air, soil, and water samples in the United States, Canada, northern Europe, Taiwan, and Japan *(1, 4, 7-10)*. PBDEs and HBCD have been found in air samples of remote regions such as the Arctic and in marine mammals from the deep seas, indicating long range transport of BFRs *(4, 9)*.

The entire life cycle of BFRs likely contributes to their distribution in the environment. Industrial facilities that produce BFRs, as well as manufacturing facilities that incorporate BFRs into consumer products, release these chemicals during polymer formulation, processing, or manufacturing practices. Disintegration of foam products, volatilization (especially under conditions of high temperature), and leaching from products during laundering or use, results in the release of BFRs from products in homes and businesses. Finally, disposal of products, including combustion and recycling of waste products, as well as leaching from landfills, is the final route of entry for BFRs into the environment *(7, 9)*.

Many BFRs are highly lipophilic (fat-soluble) rather than water soluble. BFRs also have a high affinity for binding to particles, which is reflected in low measurements in water samples and higher measurements in sediment, sewage sludge, and particulate samples such as dust particles *(1)*. Transportation as particle

bound contaminants on airborne dust may explain the wide distribution of BFRs to remote areas.

BREAKDOWN IN THE ENVIRONMENT

BFRs are generally very stable and resistant to degradation. The tendency of an environmental contaminant to resist physical, biological, and chemical degradation is called "persistence." The persistence of a substance in a given medium is scientifically defined by its overall half-life in a medium such as soil, water, or sediment *(11)*.

Although new production of Penta- BDE and Octa-BDE is being phased out voluntarily in the United States and the substances have been banned in the European Union, a large number of products containing these flame retardants are still in use. This means their release into the environment will continue throughout product lifecycles, potentially for several more decades. In addition, the increasing use of Deca-BDE makes it important to understand its degradation in relation to the occurrence of lower brominated PBDEs in environmental samples. Several studies have shown the lower brominated congeners are the most toxic and are accumulating at the highest rates and levels in wildlife and human tissue samples *(1)*.

Studies have shown the higher brominated PBDEs, such as deca-BDE, undergo degradation that removes bromine atoms resulting in the formation of the more persistent and toxic lower brominated compounds *(1)*. Several studies have found deca-BDE breaks down to lower brominated congeners (nona- to hexa- BDEs) in sand, sediment, and soils under laboratory conditions of both artificial and natural sunlight *(1, 12)*. The breakdown of deca-BDE occurs much more quickly in UV light (half-life < 30 min) compared to natural sunlight where the estimated half-life was 53 hours on sediment and 150-200 hours on soil *(12)*. The degradation products can be more toxic than the original compounds and include lower brominated PBDEs, brominated bisphenols, and polybrominated dibenzodioxins (PBDDs)/polybrominated dibenzofurans (PBDFs).

EXPOSURES

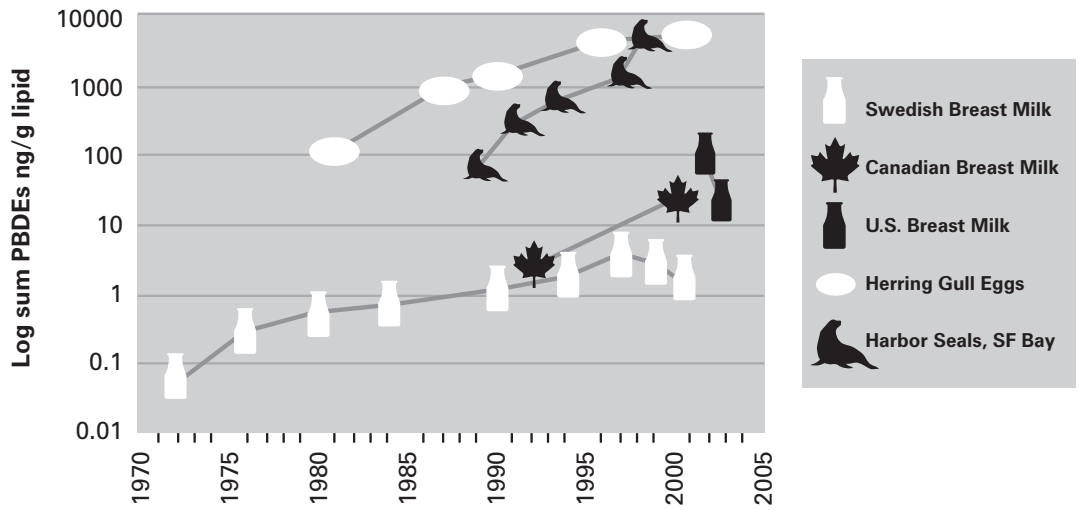
Given the ubiquity and persistence of BFRs in our environment, it is not surprising that these chemicals find their way into tissues of both wildlife and humans. Similar to PCBs, concentrations of BFRs increase up each step of the food chain indicating these chemicals are readily absorbed by the body where they accumulate in fatty tissues *(1)*. The lower brominated compounds accumulate in the highest concentrations, indicating that these compounds are either preferentially absorbed or metabolic breakdown of higher brominated compounds occurs *(1)*.

In the past, higher brominated BDEs such as deca-BDE were thought to be too large for absorption and therefore not bioavailable to organisms *(7, 13)*. Industry has used this argument to suggest that the use and accumulation of deca-BDE in the environment is not harmful. However, recent evidence has proven otherwise. Deca-BDE was detected in Swedish peregrine falcon eggs (<20-430 ng/g lipid weight) and freshwater fish (median 48 ng/g lipid weight), indicating deca-BDE is bioavailable *(14, 15)*. There is also evidence for the metabolism of Octa-BDE and Deca-BDE formulations to penta-octa BDE congeners in fish *(1, 16, 17)*. These studies indicate higher brominated PBDEs are absorbed and metabolized to lower brominated PBDEs, which are highly bioaccumulative and toxic.

As in wildlife tissues, scientists have measured substantial and rapidly increasing levels of BFRs in human tissues including blood, fat tissue, and breast milk. PBDEs are in human fatty tissue, blood, and breast milk of individuals with no known exposure sources *(1, 7, 18)*. The median body burden of PBDEs in the United States is 35 ng/g lipid weight (ng/g = parts per billion = ppb). In Sweden, the median concentration is nearly 20 times lower at 2 ng/g lipid weight *(18)*. Human tissue samples from the United States have some of the highest levels of PBDEs in the world. Concentrations of total PBDEs as high as 500 ng/g lipid weight have been measured in blood and over 700 ng/g lipid weight have been observed in breast milk *(19, 20)*. Figure ES-1 illustrates how levels of PBDEs in the breast milk of American women are beginning to approach the levels found in wildlife.

Several studies have demonstrated that PBDEs can accumulate in the human fetus. A recent study in Indiana found individual fetal cord blood concentrations did not differ from maternal concentrations, ranging from 15 - 580 ng/g lipid weight in mothers and from 14 - 460 ng/g lipid weight in fetal serum *(21)*. Fetal cord blood levels are similar to levels found in breast milk and are up to 100-fold higher than levels found in a similar Swedish study. These

Figure ES-1: Selected Human and Wildlife levels of PBDEs



Source: from Clean Production Action, Hites 2004 *(18)*; Lunder, 2003 *(20)*.

studies indicate that PBDEs can enter the fetus through the placenta *(21)*. If PBDEs are transferred as efficiently through breast milk as they are through the placenta, both fetuses and infants are being exposed to potentially high levels of harmful chemicals at critical developmental stages.

The reasons for higher concentrations of PBDEs in United States wildlife and humans are unexplained. Yet, it is plausible that future researchers will find that the decision of Sweden to take early action and ban the use of PBDEs in the early 1990s has contributed to that nation's declining levels of PBDEs, while the failure of the U.S. to take action explains the much higher, and increasing, levels of PBDEs in the breast milk of American women.

TOXICITY

The most up-to-date and thorough reviews of the toxicology of BFRs including PBDEs, TBBPA, and HBCD can be found in recent articles *(1, 7, 22)*. In general, HBCD, TBBPA, and PBDEs are absorbed from the gastrointestinal tract and accumulate in fatty tissues. None of the BFRs discussed in this report appear to cause immediate symptoms from acute toxicity at average doses. Rather, like PCBs, health effects from chronic exposure, particularly in developing infants and wildlife, are of more concern.

Overall, the available literature on BFR toxicology is incomplete. Based on the available data, however, we know that BFRs are associated with several health effects in animal studies, including neurobehavioral toxicity, thyroid hormone disruption, and (for some PBDE congeners) possibly cancer. Additionally, there are data gaps but some evidence that BFRs can cause developmental effects, endocrine disruption, immunotoxicity, reproductive, and long term effects, including second generation effects. Some evidence is available for estrogenic activity of PBDEs and TBBPA, but more studies are needed to determine if low-dose exposures have estrogenic activity in humans or other species *(1, 7, 22)*.

Most of the toxicity data available on BFRs involve the effects noted in animal studies. However, tissue levels of PBDEs measured in humans are troubling because they are rapidly approaching levels associated with adverse effects in rodent studies, indicating there is a dwindling margin of safety. In the US, 5% of women have concentrations of total PBDEs greater than 300 ng/g lipid weight and levels of some individual congeners (such as the penta-BDE congeners BDE-47 and BDE-99) exceed 100 ng/g lipid weight *(23-25)*. Levels that cause adverse neurodevelopmental effects in animal studies are less than 10 times this amount, indicating an uncomfortably small margin of safety for the children of the most highly exposed women *(24)*. Animal studies have shown uptake of PBDEs from breast milk and human studies have confirmed that PBDEs are transferred across the placenta *(21)*.

ALTERNATIVES TO HALOGENATED FLAME RETARDANTS

Changes to both product design and materials used can decrease the amount of flame retardants needed. Furniture, plastic, and electronics products can be manufactured to meet fire standards without the use of chemical flame retardants. Electronics products can be redesigned to contain lower temperature generating components or redesigned to separate heat-generating components from highly flammable components. An example of a design change to eliminate the need for flame retardants is construction of television sets with greater spacing or metallic barriers between components. In addition, lower voltage components can be used.

Another method to reduce flammability is to replace highly flammable plastics that release toxicants when burned with materials that are more inherently flame resistant. Materials that don't require the addition of chemicals for flame resistance include metal, leather, glass, preceramic polymers, aramide blends (Kevlar), and natural fibers such as jute, hemp, and wool. Three plastics—polysulfone, polyaryletherketone, and polyethersulfone—are self-extinguishing and can be used without the addition of flame retardants *(5)*.

Finally, when chemical-free alternative materials or designs are not feasible, non-halogenated flame retardants can be used to meet fire safety standards. The Danish EPA's assessment of alternatives indicates that, for a large proportion of applications, non-brominated alternatives are already commercially available *(5)*. A report commissioned by the German government determined that the flame retardants aluminum trihydroxide, ammonium polyphosphates, and red phosphorus are less problematic in the environment *(26)*. Information about the safety of other alternatives is growing and in the future it will be possible to make more specific recommendations.

PHASE-OUT OF HALOGENATED FLAME RETARDANTS

The European Union began substituting for BFRs in the 1990s. Now PBDE levels in breast milk are beginning to decrease in Europe. The European Union has enacted a ban on Penta- and Octa-BDEs and has banned Deca-BDE in electronics beginning in 2006.

States in the U.S. are acting to phase-out the use of the PBDEs as well. California, Hawaii, New York, Michigan, and Maine have already passed legislation to ban certain PBDEs, with similar initiatives underway in Maryland, Massachusetts, Illinois, Minnesota, Oregon and Washington (27-31). The United States government has yet to ban brominated flame retardants.

Along with legislative initiatives, manufacturers and retailers are taking voluntary actions to eliminate BFRs. Some computer and electronics manufacturers like Apple, Ericsson, IBM, Intel, Motorola, Panasonic, Phillips, and Sony are using alternatives to halogenated flame retardants. For example, Motorola now uses a halogen-free laminate that is cost effective, while meeting fire safety standards. Toshiba has replaced BFR-containing plastic casings in electronic parts with inherently flame-resistant polyphenylene sulfide. IKEA furniture, Crate and Barrel, and Eddie Bauer are now using PBDE-free polyurethane foam.

BFRs are an example of the failure of chemical regulation to prevent hazardous chemicals from entering the marketplace, and thus the environment, the food web, and ultimately the next generation of children. Federal regulation of industrial chemicals should be guided by the Toxic Substances Control Act (TSCA) of 1976. Yet, the vast majority of chemicals, more than 95% by volume, continue to be used without adequate baseline safety testing. Only 12 chemicals have been fully tested for health impacts, including neurotoxicity. Even new chemicals are not subjected to comprehensive safety testing. Since TSCA impos-

es a nearly impossible burden of proof before the federal government can take action to restrict the marketing of a chemical, only a handful of chemicals have ever been restricted under the law.

Clearly, the discovery of brominated flame retardants in fetuses and the breast milk of lactating women represent a dramatic example of a failed system of chemicals regulation. Responsible members of the health care sector are again placed in the position of researching and evaluating the potential hazards, seeking disclosure of product content to determine where BFRs are entering the sector, and then finding and evaluating the safety and efficacy of alternatives. This is neither efficient nor core to the mission of health care, but a burden on the sector imposed by a broader failure at the federal level.

The widespread distribution of BFRs, the emerging evidence of threats to humans and wildlife at levels close to those in the environment, and the likelihood that levels will increase as products containing them enter the environment, all suggest that BFRs should be phased out as soon as practical by manufacturers, users (including hospitals), and the government.

INTRODUCTION

Synthetic polymers have largely replaced the use of wood, glass, and metal materials in our homes, offices, automobiles, public transit, and other public areas. These synthetic materials are often petroleum-based plastics that easily ignite, spread flames quickly, and release toxicants when burned.

Fire is a significant cause of property damage and of death. In the United States, fire kills more than 3,000 people per year, injures more than 20,000 people, and results in property damages exceeding an estimated $11 billion *(1)*. In Canada, between 1986 and 1995 there was an average of 67,000 fires annually with 3,700 injuries, 465 deaths, and losses of over $1.125 billion Canadian dollars *(2)*.

Fire safety standards for electrical appliances, textiles, upholstery, and many other materials and products help to minimize these losses. To meet fire safety standards, products made of synthetic materials are modified with flame retardants, chemicals that inhibit the ignition and spread of flames. (It is important to note, the term 'flame retardant' is not equivalent to 'fire-proof,' meaning that a flame-retardant product is still flammable.)

Over 175 different flame retardants are on the market today and fall into four major chemical groups: inorganic, organophosphorous, halogenated organic, and nitrogen-based compounds *(2)*. Halogenated organic flame retardants are further classified as containing either chlorine or bromine (brominated flame retardants or BFRs). Chlorine and bromine are the only halogens used as flame retardants in synthetic materials, especially plastics. Flourine and iodine are considered unsuitable for flame retardant applications. Bromine is a more effective retardant, costs less, and has wider applications than chlorine and therefore, is used more readily in products *(3)*.

Brominated flame retardants (BFRs) have been commercially available since the 1960s. With the growth in popularity of personal computers and other electronics in the 1980s, the demand for BFRs grew substantially. Over ninety percent of printed circuit boards contain BFRs (33). The European Flame Retardant Association (http://www.cefic-efra.com/) reports that BFRs comprise nearly 20% by weight of the world use of flame retardants but in terms of dollars spent, BFRs comprise nearly 40% of the world market *(34)*.

While flame resistant products save lives and prevent property damage, there are increasing concerns about the environmental and health effects of flame retardants such as BFRs. BFRs accumulate in the environment, including remote areas such as the Arctic and deep seas. Scientists have measured exponential increases in the levels of some BFRs in wildlife and humans. Growing evidence suggests that BFRs are similar to other persistent, bioaccumulative toxicants such as polychlorinated biphenyls (PCBs), chemicals known to cause human health problems.

This report will present a scientifically-based review of the use, environmental fate, wildlife and human exposures, and toxicity of BFRs and other halogenated flame retardants and will briefly discuss alternatives for fire safety and international and national efforts to phase-out BFR use.

OVERVIEW OF BROMINATED FLAME RETARDANTS

Brominated flame retardants (BFRs) are a diverse group of organic compounds that share the element bromine in their structure. Bromine is an element found in seawater, salt lakes, inland seas, and the earth's crust. Bromine is most prevalent in combination with other inorganic and organic elements (in this form it is referred to as a "bromide"). Although bromine has many industrial applications, including use in water purification, agricultural pesticides, car batteries, pharmaceuticals, solvents, and photography,

the largest use of bromine is in flame retardant production. The global demand for bromine use in flame retardants has increased significantly, up from 8% in 1975 to 38% in the year 2000 *(1)*.

Although BFRs are a highly diverse group of compounds, the flame retardancy mechanism is basically the same for each member of the group *(35)*. The retardant releases hydrogen bromide gas, which then acts as a free radical scavenger to interfere with the chemical reaction that normally spreads flames.

More than 75 different types of BFRs are grouped roughly by the nature of the core structure of the molecule. Some of these chemical classes include brominated bisphenols, diphenyl ethers, cyclododecanes, biphenyls, phenols, phenoxyethanes, and phthalic acid derivatives. The use of individual flame retardants in products is dependent on the type of polymer, performance, durability, and aesthetics of the end product. Manufacturers introduce new BFR compounds continually, particularly as some compounds are banned from the marketplace.

Example of BFRs Already Banned

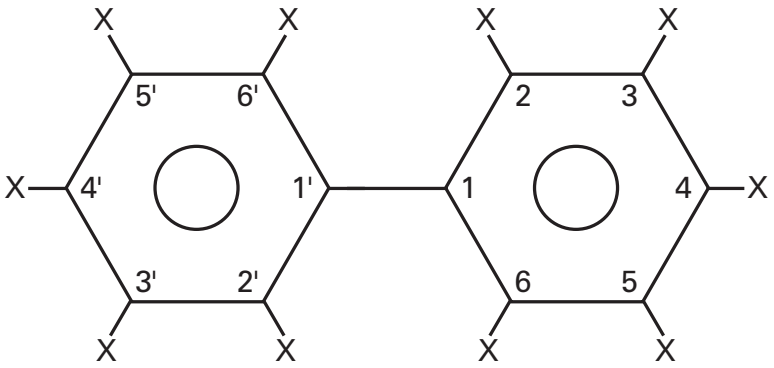
An example of a class of BFRs no longer in use is polybrominated biphenyls (PBBs). Polybrominated biphenyls have the same chemical structure as PCBs, except bromine replaces chlorine atoms (see Figure 1).

Although the United States banned production of PCBs in 1977, they were used heavily for nearly fifty years. They are very stable chemically, which made them useful in industry, primarily as cooling liquids in transformers. However, that same stability made them undesirable in the environment, where they linger and accumulate up the food chain, stored in animal fat, e.g., beef, dairy, pork, fish, and breast milk. Although the cancer-causing potential of PCBs sparked early efforts to ban their use, evidence of persistent and pervasive adverse neurodevelopmental effects of human prenatal PCB exposure has emerged as a more widespread concern at exposure levels typical of the general population. PCB developmental neurotoxicity is now recognized as a more sensitive endpoint than cancer *(36, 37)*.

North America suspended the production of the flame retardant class PBBs in 1979 and the last European manufacturer terminated production in 2000. The ban was spurred by the accidental mixing of a commercial flame retardant containing PBBs with feed for dairy cattle, livestock, and poultry in Michigan *(1)*. Widespread PBB contamination of milk, meat, and eggs in the region resulted in the exposure of over 9 million humans to the toxicant.

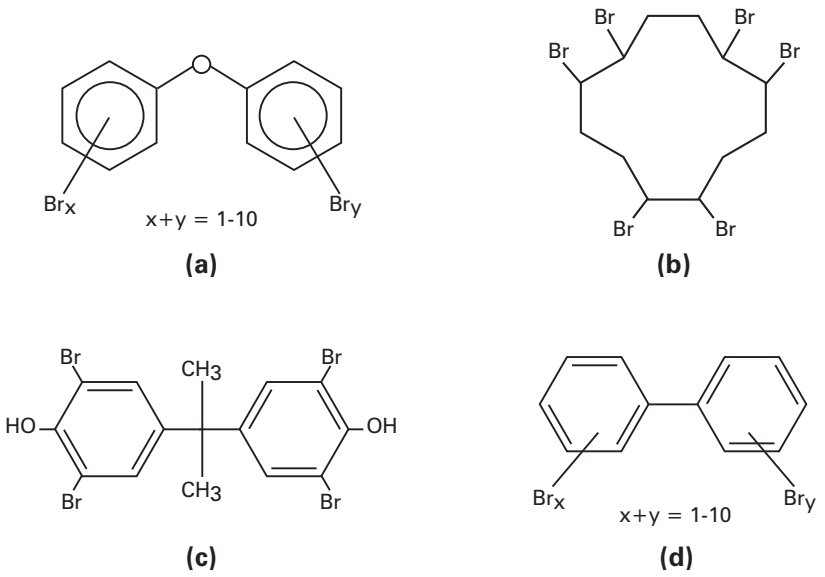
Although results of studies of the impacts of PBB exposure were inconsistent, abdominal pain, fatigue, weight loss, immune suppression, and effects on liver function were reported in a variety of investigations *(38)*. One study found an increased incidence of digestive tract cancer and lymphoma in the highest exposed groups *(39)*. Scientists found PBBs to be very persistent in tissues and detected them in the blood and fat of exposed individuals many years after exposures had occurred and production of the chemical had ceased. The median half-life of PBBs in women is reported to be 29 years *(40)*.

Figure 1. Chemical structure of a PCB.



The x's represent chlorine atoms and the ring numbering system is shown.

Figure 2. Chemical structures of (a) PBDEs; (b) HBCD; (c) TBBPA and (d) PBBs



Because PCBs, and PBBs, share many structural similarities, it is not surprising that people exposed to PBBs had health effects similar to those in people exposed to PCBs. As seen in the figures, PCBs and PBBs are also structurally similar to other widely used BFRs, particularly polybrominated diphenyls (PBDEs) and tetrabromobisphenyl A (TBBPA) (see Figure 2).

PBDEs, for example, consist of a large group of compounds that differ in the degree of bromination of the diphenyl ether core structure. There are ten possible positions for bromine atoms on the PBDE molecule. The number of bromine atoms is denoted in chemical nomenclature as mono (one) to deca (ten). PBDEs are named according to the numbering system used for PCBs shown in Figure 1. The total number of possible congeners or configurations of bromine atoms on the molecule is 209 and the number of isomers for mono-, di-, tri-, tetra-, penta-, hexa-, hepta-, octa-, nona- and deca- bromodiphenyl ethers are 3, 12, 24, 42, 46, 42, 24, 12, 3 and 1, respectively *(35)*.

Three major PBDEs are in use in North America: Decabromodiphenyl ether (Deca-BDE); Octabromodiphenyl ether (Octa-BDE); and Pentabromodiphenyl ether (Penta-BDE).

Commercial formulations of PBDEs do not consist of a single compound but rather a mixture named for the predominant congener in the group. For example, commercial Penta-BDE contains a mixture of 40% tetra-, 50-60% penta-, and 6% hexa- BDEs.[1] Appendix 1 lists the common PBDE congener formulations. The distinctions among different formulations are important because individual congeners have different exposure and toxicity profiles.

Europe recently banned the use of both Penta-BDE and Octa-BDE due to concerns about toxicity. The major United States manufacturer, however, voluntarily agreed to end production of both Penta-BDE and Octa-BDE beginning in 2005. Until the voluntary agreement was reached, Penta-BDE was still widely used in the United States. In addition, the states of California, Hawaii, Maine, Michigan, and New York passed legislation requiring manufacturers to eliminate the use of Penta-BDE and Octa-BDE *(27-31, 41)*.

As a result of bans on Penta-BDE and Octa-BDE formulations in Europe and some parts of North America, other BFRs such as HBCD and Deca-BDE are expected to increase in North America. Some parts of Europe and North America are calling for a ban of Deca-BDE and the European Union has moved forward with further testing of Deca-BDE.

[1] In this document, the commercial BFR mixture is capitalized, and the individual congeners are in lower case.

A separate Europe-wide ban under the Restriction on Hazardous Substances (RoHS), which has a specific focus on electronics, is slated to eliminate all PBDEs, including Deca, in electronics by 2006, although the industry has sought a four-year exemption. A few states in the United States are considering phase outs of Deca-BDE, including Maine, Washington, New York, Illinois, and Michigan.

WIDESPREAD USE OF BFRS

Market Demand

There are three classes of BFRs currently produced in high volumes: polybrominated diphenyl ethers (PBDEs); tetrabromobisphenol A (TBBPA); and hexabromocyclododecane (HBCD). The total world demand for the highest production volume BFRs in 2001 was estimated by the bromine industry at 203,740 metric tons (6). Table 1 shows BFR market demand by region, according to the bromine industry.

Regional differences in the types and amounts of BFR use are a result of legislation banning production of some PBDEs in European countries and the nature of products being manufactured in these regions. In 2001, Asia accounted for 50% of worldwide BFR use, the Americas less than 30%, and Europe, 15%. The Americas are the primary users of Deca-BDE and Penta-BDE, whereas in Asia, TBBPA use predominates. HBCD is used most extensively in Europe, replacing PBDEs for the non-foam applications.

BFRs in Products

BFRs are incorporated into products in one of two manners. They are either chemically bound to the product matrix as "reactive" mixtures, or they are dissolved in the polymer materials as "additives."

Additive flame retardants are relatively unattached to the polymer matrix and may readily migrate from products to the surrounding environment during manufacture, normal use, and disposal. Reactive BFRs are bound to the polymer matrix and as such are less mobile. However, the potential remains for loss of reactive BFRs to the environment through abrasion during use, as well as during manufacturing and disposal of products. PBDEs and HBCD are used as additive flame retardants. TBBPA is used primarily as a reactive flame retardant with some additive use (~10%). Notably, although only 10% of TBBPA is used as an additive flame retardant, because of the large volume of TBBPA produced each year, the amount of TBBPA used as an additive is still greater by volume than Penta-BDE.

BFRs perform well in many products, preserving the durability and performance of the material while providing flame retardancy at a reasonable cost. These characteristics have resulted in their widespread use in hundreds of consumer products, including many plastics, foams, and textiles. (See Figure 3.)

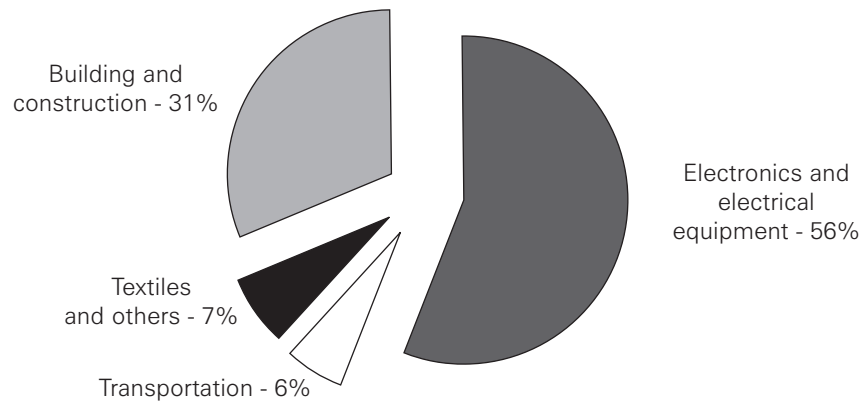
The concentration of BFRs in products ranges from 5-30%. For example, fire-retardant polyurethane foams typically contain 10-30% Penta-BDE by weight. TBBPA and Deca-BDE predominate in the marketplace in a wide variety of products, especially electronics and plastics. Although some use of Penta-BDE in circuit boards occurred until the mid-1990s, over 96% of printed circuit boards today contain TBBPA. (Many electronics produced before the market switch, however, remain in service and their future disposal may be an avenue for release of Penta-BDE into the environment *(8)*.) Deca-BDE is used in virtually every type of plastic polymer. Table 2 shows the typical use of each of the major BFRs.

Table 1. Brominated Flame Retardants Total Market Demand

	Europe	Americas	Asia	Other	Total MT (%)
TBBPA	11,600	18,000	89,400	600	119,600 (59%)
Deca-BDE	7,600	24,500	23,000	1,050	56,150 (28%)
HBCD	9,500	2,800	3,900	500	16,700 (8%)
Penta-BDE	150	7,100	150	100	7,500 (4%)
Octa-BDE	610	1,500	1,500	180	3,790 (2%)
Total	**29,460** (14.5%)	**53,900** (26.5%)	**117,950** (57.9%)	**2,430** (1.2%)	**203,740** (100%)

Estimates by Region in 2001, (metric tons) (6)

Figure 3. Brominated Flame Retardants in consumer and commercial products.



Source: BSEF, 2001 (6).

Table 2. Examples of major BFR products by chemical.

Chemical Name	Typical Products
Pentabromodiphenyl ether (Penta-BDE, PBDE, or Penta)	Polyurethane foams: mattresses, seat cushions, other upholstered furniture and foam packaging. Also: carpet padding, imitation wood, paints, sound insulation panels, small electronic parts, fabric coatings, epoxy resins, conveyor belts
Octabromodiphenyl ether (Octa-BDE, OBDE, or Octa)	Acrylonitrile -butadiene - styrene (ABS) plastic: housings for fax machines, computers and other electronics. Also: automobile trim, telephone handsets, kitchen appliance casings, small electronics parts, audio/video equipment, remote control products
Decabromodiphenyl ether (Deca-BDE, DBDE or Deca)	High-impact polystyrene (HIPS) plastic: housings for televisions, computers, stereos and other small electronics. Also: mobile phones
	Various plastics: polycarbonates, polyester resins, polyamides, polyvinyl chloride, polypropylenes, terephthalates (PBT and PET), and rubber. Also: upholstery textiles (sofas, office chairs, backcoating), paints, rubber cables, lighting (panels, lamp sockets), smoke detectors, electrical equipment (connectors, wires, cables, fuses, housings, boxes, switches), stadium seats
Tetrabromobisphenol A (TBBPA)	Reactive flame retardant: epoxy and polycarbonate resins. Also: printed circuit boards in electronics (96%), office equipment housings
	Additive flame retardant: various plastics, paper and textiles. Also: housings of computers, monitors, TV, office equipment, adhesive coatings in paper and textiles
Hexabromocyclododecane (HBCD)	Various plastics: Polystyrene (EPS, XPS), HIPS, polypropylene. Also: textiles and carpet backing, television and computer housings, textiles in automobiles, building materials (insulation panels, construction blocks, thermal insulation, roofs), upholstered foam, latex binders

Sources: (1, 4-6)

BFRs in Health Care Products

In the health care setting, brominated flame retardants are as pervasive as they are in our homes and offices. Patients' rooms, mattresses, foam pads and other bedding materials may contain BFRs. Other furniture and textiles in patient rooms may be treated with BFRs, including furniture cushions, lamp shades, cubicle curtains, privacy curtains, drapery, and window blinds. Electronic equipment such as televisions, pulse oximeters, monitors, ventilators, or IV pumps likely have BFRs in the plastic housing. At the nursing stations, BFRs may be in computers, printers, fax and copy machines, and assorted office furniture. In the cafeteria and other eating areas, BFRs may be in microwave ovens, refrigerators, and other appliances. In nearly every area of the hospital - from shipping and receiving to the operating rooms - foam packaging is found that can contain BFRs. Finally, the infrastructure of the building itself contains BFRs in the walls, roofing materials, floor tiles, carpeting, wiring, electrical switches, sockets, and insulation.

ENVIRONMENTAL FATE AND TRANSPORT

Brominated flame retardants are not only found in numerous household, health care, and consumer products, but they are now ubiquitous in our environment. In the past decade, scientists have detected BFRs in both human and wildlife tissues, as well as in house dust, sediments, sewage sludge, air, soil, and water samples in the United States, Canada, northern Europe, Taiwan, and Japan *(1, 4, 7-10)*.

The entire life cycle of BFRs likely contributes to their distribution in the environment. Industrial facilities that produce BFRs, as well as manufacturing facilities that incorporate BFRs into consumer products, release these chemicals during polymer formulation, processing, or manufacturing practices. Disintegration of foam products, volatilization (especially under conditions of high temperature), and leaching from products during laundering or use, results in the release of BFRs from products in use in homes and businesses. Finally, disposal of products, including combustion and recycling of waste products, as well as leaching from landfills, is the final route of entry for BFRs into the environment *(7, 9)*.

BFR levels in the environment are highest near industrial sources such as facilities involved in the production of flame retardants, manufacturing facilities that incorporate BFRs into their products, and in electronics recycling facilities *(7-9, 42)*. However, scientists have found PBDEs and HBCD in air samples of remote areas such as the Arctic and in marine mammals from the deep seas, which indicates long range transport of BFRs *(4, 9)*.

Many BFRs are highly lipophilic (fat-soluble) rather than water soluble. BFRs also have a high affinity for binding to particles, which is reflected in low measurements in water samples and higher measurements in sediment, sewage sludge, and particulate samples such as dust particles *(1)*. Transportation as particle bound contaminants on airborne dust may explain the wide distribution of BFRs to remote areas.

Although the United States is a major producer and consumer of BFRs, few data are available on the sources and levels of BFRs in the environment of North America. More studies have been done in Europe and Asia *(1, 4, 7, 8)*. The majority of BFRs that have been tested for and found in environmental samples are associated with the PBDE family. Information on environmental levels of TBBPA and HBCD is limited, especially in the United States and Canada.

Most of the research on PBDEs is congener-specific. Researchers have found that the environmental fate and transport of PBDEs depends on the number of bromine atoms. Lower brominated congeners have higher vapor pressures than the higher brominated congeners, therefore there is a predominance of lower brominated congeners such tetra-BDE (BDE-47) and penta-BDE (BDE-99) in air samples *(1)*. Researchers have found higher brominated BDEs such as deca-BDE (BDE-209) predominately in the particulate phase in sediments, sewage sludge, and indoor dust. Some congeners such as hexa-BDE (BDE-153) can exist in both phases *(4)*.

Representative measurements of BFRs in various media are shown in Table 3. Data on Octa-BDE are not available. Levels are measured from samples taken from more than one area and are reported as a range of values rather than as averages. Where possible, measurements from the United States or Canada are included.

Table 3. Representative measurements of BFRs in environmental media.

	Penta-BDE	Deca-BDE	HBCD	TBBPA
Air (ng/m³)	0.005-0.052 (U.S.) 0.010 - 2.1 (N. Canada)	<0.0001-0.0003 (U.S.)	1070 (Industrial facility, Sweden) 0.005-0.006 (background air, Sweden)	1800 (production facility, Japan)
Water (ng/L)	7.6 - 74 (Canadian freshwater)	n/a.	3 -9 (landfill leachate, Sweden) 31 (laundry facility effluent)	n/a
Sewage Sludge (ng/g dry weight)	1100-2290 (U.S.)	85-4890 (U.S.)	4-650 (Sweden) (average = 45)	3-76 (Sweden)
Soil (µg/kg dry weight)	76 (production facility, U.S.)	19-36 (production facility, U.S.)	140-1300 (Industrial facility, Sweden)	0.5-140 (Japan)
Sediment (µg/kg dry weight)	n.d. - 52 (U.S.) 132 (production facility, U.S.)	5000 (point source, U.S.)	n.d.-7600 (Sweden)	2-150 (Japan)

Sources: (1, 4, 7-9, 43-45).

Levels of PBDEs in air samples are similar in Sweden, Britain, Japan, the United States and Canada, with the consistent pattern of low levels in rural or remote areas and higher levels in industrial or urban areas *(7, 8)*. Levels of PBDE congeners in sewage sludge are 10 to 100-fold higher in North America than in Europe *(44)*.

TBBPA and its metabolites are in air, sewage sludge, and sediments from Sweden and Japan, but generally are not in water samples *(1, 7)*. HBCD is in air, soil, sewage sludge, sediments, and water samples from Sweden *(7, 9)*. Researchers measured HBCD levels in water from landfill leachate at 3-9 ng/L, while water from a public laundry facility had 31 ng/L, indicating a greater release of HBCD from the laundering of textiles *(9)*.

Sewage sludge is spread as a fertilizer on agricultural fields in the United States, potentially causing wide distribution and accumulation of BFRs in the environment and food supply. The presence of PBDEs, TBBPA, and HBCD in sewage sludge indicates the chemicals are entering municipal sewage treatment systems, either from households and businesses, traffic, and/or environment releases. There are no published data on PBDE concentrations in sewage treatment plant effluents in North America. However, studies in Germany and the Netherlands have observed PBDEs in sewage treatment effluent and suspended particles, indicating that PBDE burdens are likely a function of the sewage treatment plant's efficiency in removing suspended particles from its effluent *(8)*.

BREAKDOWN IN THE ENVIRONMENT

The same physicochemical properties of BFRs that make them useful as flame retardants, namely high absorption/adsorption quality and chemical stability, make them undesirable in the environment. BFRs are generally very stable and resistant to degradation. The tendency of an environmental contaminant to resist physical, biological, and chemical degradation is called "persistence." The persistence of a substance in a given medium is scientifically defined by its overall half-life in a medium such as soil, water, or sediment *(11)*.

PBDEs

Although new production of Penta- BDE and Octa-BDE is being phased out voluntarily in the United States and the substances have been banned in the European Union, a large number of products containing these flame retardants are still in use. This means their release into the environment will continue throughout product lifecycles, potentially for several more decades. In addition, the increasing use of Deca-BDE makes it important to understand its degradation in relation to the occurrence of lower brominated PBDEs in environmental samples. Several studies have shown that the lower brominated congeners are the most toxic and are accumulating at the highest rates and levels in wildlife and human tissue samples *(1)*.

PBDEs are persistent in the environment because of their resistance to degradation by acids, bases, reducing or oxidizing compounds *(35)*. Whereas the lower brominated congeners are more resistant to degradation, the higher brominated congeners are not as stable. Studies have shown the higher brominated PBDEs, such as deca-BDE, undergo degradation that removes bromine atoms resulting in the formation of the more persistent and toxic lower brominated compounds *(1)*. Several studies have found that deca-BDE breaks down to lower brominated congeners (nona- to hexa- BDEs) in sand, sediment, and soils in laboratory conditions of both artificial and natural sunlight *(1, 12)*. The breakdown of deca-BDE occurs much more quickly in UV light (half-life < 30 min) compared to natural sunlight where the estimated half-life was 53 hours on sediment and 150-200 hours on soil *(12)*.

There is limited evidence that PBDEs undergo bacterial degradation *(13, 46)*. A recent laboratory study of sewage sludge in Sweden showed bacteria are able to degrade deca-BDE to octa- and nona-brominated congeners under anaerobic conditions *(46)*. Similar metabolism may occur in sewage treatment facilities or in anaerobic soil and sediments.

PBDEs with less than four bromine atoms have been detected in the environment, possibly as a result of degradation of higher-brominated compounds *(13, 47)*. Continued release and accumulation of higher brominated congeners that break down slowly may result in a continuous release of lower brominated congeners into the environment *(12, 16)*. PBDE manufacturers dispute this theory, attributing the rise in environmental PBDE levels to historic activities such as the offshore oil industry *(35)*.

TBBPA

UV light and bacteria degrade TBBPA. When exposed to UV light, the main breakdown product is 2,4,6-tribromophenol. Researchers have also found a number of other decomposition products, including bromobisphenols, bromobenzenes, and bisphenol A *(7, 48)*. Depending on the season, photolytic degradation of TBBPA has a half-life of 7-81 days in water *(1)*. Bacteria degrade TBBPA in soils and sediments under both aerobic and anaerobic conditions with a half-life of approximately 2 months *(1)*.

HBCD

HBCD has a half-life of 3 days in air and 2-25 days in water *(1)*. HBCD has low solubility in water and is therefore expected to accumulate in sediments *(26)*. HBCD can exist as three different isomers (α, β, and γ) and and is usually present in sediments as γ-HBCD. But in sewage sludge, all three isomers were found in equal ratios *(1)*. HBCD has been found in sediments that are several decades old, indicating HBCD is persistent *(9)*. Commercial ratios of HBCD isomers are very different from ratios in environmental media, suggesting environmental transformation of the product occurs.

Formation of Dioxin-like Compounds

There are data to indicate that some BFRs (PBDEs and TBBPA) are converted to the dioxin-like compounds polybrominated dibenzodioxins (PBDDs) and polybrominated dibenzofurans (PBDFs) during accidental fires and incineration, during the recycling of materials containing BFRs, and during environmental degradation *(13, 35, 49, 50)*. They also may form during the use of some consumer products at elevated temperatures (e.g., hair dryers and television sets) resulting in indoor air contamination *(35)*. In experimental tests simulating fire conditions, burning of television sets and electronics casing, scientists found total PBDD/PBDF concentrations in combustion residues ranged from 1 - 9000 μg/g. PBDD/PBDF concentrations in smoke samples ranged between 0.8 - 1700 $\mu g/m^3$ with PBDD concentrations less than 3% of total *(50)*.

Finally, PBDDs and PBDFs have been observed to form during photolytic degradation of lower brominated PBDEs *(35)*. Analysis of sewage sludge in Germany indicated that the concentrations of PBDEs were correlated with PBDF concentrations, suggesting environmental conversion of PBDEs to PBDFs. PBDF concentrations in United States sewage sludge samples are not known.

In conclusion, BFRs breakdown in the environment as a result of exposure to sunlight, heat, and possible bacteria degradation. The degradation products can be more toxic than the original compounds and include lower brominated PBDEs, brominated bisphenols, and PBDDs /PBDFs.

EXPOSURES

Given the ubiquity and persistence of BFRs in our environment, it is not surprising that these chemicals find their way into tissues of both wildlife and humans. Similar to PCBs, concentrations of BFRs increase up each step of the food chain indicating these chemicals are readily absorbed by the body where they accumulate in fatty tissues *(1)*. The lower brominated compounds accumulate in the highest concentrations, indicating that these compounds are either preferentially absorbed or metabolic breakdown of higher brominated compounds occurs *(1)*.

Wildlife Studies

PBDEs

Many reports focus on and confirm the global presence of PBDEs in wildlife, including birds, reindeer, moose, freshwater and ocean fish, shrimp, crabs, porpoises, seals, and whales. The highest concentrations are most consistently found in wildlife of aquatic and marine ecosystems. A sampling of PBDE levels found in wildlife is shown in Table 4. The table is based on a review by R. Hites (2004) and displays average levels of the sum of PBDE congeners tetra-BDE (BDE-47), penta-BDE (BDE-99 and BDE-100), and hexa-BDE (BDE-153 and BDE-154) in birds and aquatic species. Although many other studies have looked at concentrations of other congeners, including deca-BDE (BDE-209), reporting has not been consistent and those values are not reported here. For more information, the reader is referred to recent reviews of PBDE levels in wildlife *(1, 7, 18, 51)*.

Researchers have measured some of the highest levels of PBDEs in the United States. Carp composite samples collected from a rural location in Virginia found total PBDEs up to 47,900 ng/g lipid weight *(52)*. In general, fish from the United States average a ten-fold higher concentration of PBDEs (1050 ng/g lipid) than European fish (average 120 ng/g lipid) *(18)*.

Further analysis reveals a rapid acceleration of North American wildlife PBDE levels over the past two decades. Total PBDE levels in harbor seal blubber from the San Francisco Bay are among the highest reported in the world (average 4950 ng/g lipid weight) and have increased 100-fold over the past decade *(53)*. Herring gull eggs from the Great Lakes have total PBDE concentrations over 6000 ng/g lipid weight and levels have doubled approximately every 3 years *(18)*. Levels of PBDEs in ringed seals from the Canadian arctic, while relatively low at 4 ng/g lipid weight, have increased 10-fold in the past 19 years *(54)*. Overall the exponential increases in wildlife tissue levels of PBDEs indicate doubling on average every 4-6 years *(18)*. At these doubling rates, it is estimated the wildlife levels of PBDEs will soon surpass those of PCBs in wildlife *(54, 55)*.

In the past, higher brominated BDEs such as deca-BDE were thought to be too large for absorption and therefore not bioavailable to organisms *(7, 13)*. Industry has used this argument to suggest that the use and accumulation of deca-BDE in the environment is not harmful. However, recent evidence has proven otherwise. Deca-BDE was detected in Swedish peregrine falcon eggs (<20-430 ng/g lipid weight) and freshwater fish (median 48 ng/g lipid weight), indicating deca-BDE is bioavailable *(14, 15)*. There is also evidence for the metabolism of Octa-BDE and Deca-BDE formulations to penta-octa BDE congeners in fish *(1, 16, 17)*. These studies indicate higher brominated PBDEs are absorbed and metabolized to lower brominated PBDEs, which are highly bioaccumulative and toxic.

TBBPA

There have been very few studies investigating the presence of TBBPA in wildlife. It has a relatively short half-life in air, water, and sediment *(1)*. In fish and oysters, TBBPA has a short half life of <1 or <5 days, respectively, indicating there is little potential for bioaccumulation *(1)*. Studies in rodents have shown most of the compound is excreted within 72 hours of treatment, although there is some evidence for retention of small amounts in fatty tissues and muscle *(1)*. Repeated exposures to TBBPA, however, may result in relatively constant tissue levels despite rapid elimination.

HBCD

HBCD is usually present in sediments as γ-HBCD (>90%), but in sewage sludge, the three isomers (α, β, and γ) are found in nearly equal proportions *(1)*. In wildlife samples, however, the γ-isomer predomi-

Table 4. Levels of PBDEs in wildlife of North America.
(Values displayed are average sums of tetra (BDE-47), penta (BDE-99 and BDE-100), hexa (BDE-153 and -154.)

Wildlife sampled	Concentration ng/g lipid wt	Source	Location	Year
Herring gulls	124	Eggs	Great Lakes	1981
Herring gulls	831	Eggs	Great Lakes	1987
Herring gulls	1270	Eggs	Great Lakes	1990
Herring gulls	4280	Eggs	Great Lakes	1996
Herring gulls	6600	Eggs	Great Lakes	1999
English sole	34	Whole fish	British Columbia	1992
English sole	92	Whole fish	British Columbia	2000
Freshwater fish, 2 species	150-300	Whole fish	Lake of the Ozarks, MO	1999
Freshwater fish, 2 species	2400	Whole fish	Indiana, near PBDE facility	1999
Salmonids	1970	Whole fish	Lake Michigan	1996
Lake trout	2970	Whole fish	Lake Michigan	1996
Freshwater fish, 3 species	7200	Whole fish	Virginia	1998
Porpoise	470	Blubber	Rural British Columbia	1991-92
Porpoise	2121	Blubber	Urban, British Columbia	1993
Ringed seal	0.42	Blubber	Canadian arctic	1981
Ringed seal	1.63	Blubber	Canadian arctic	1991
Ringed seal	2.44	Blubber	Canadian arctic	1996
Ringed seal	4.3	Blubber	Canadian arctic	2000
Ringed seal	87.7	Blubber	San Francisco Bay	1989
Ringed seal	348	Blubber	San Francisco Bay	1991
Ringed seal	658	Blubber	San Francisco Bay	1993
Ringed seal	1940	Blubber	San Francisco Bay	1997
Ringed seal	4950	Blubber	San Francisco Bay	1998

nates over the other forms, indicating that there is either selective uptake or metabolism of HBCD isomers. In studies of northern Europe wildlife, HBCD shows up in fish, birds, and mammals *(9, 14)*. In Sweden, researchers observed concentrations of up to 8,000 ng/g lipid weight in fish and up to 520 ng/g lipid weight in peregrine falcons *(7, 14)*. A recent study of fish in Lake Ontario found the highest levels of HBCD in lake trout ranging from 0.4 to 3.8 ng/g (wet wt) for the α-isomer and 0.1 to 0.7 ng/g (wet wt) for the γ-isomer *(56)*.

There is also good evidence that HBCD has a high bioaccumulation potential. Biomagnification factors in Lake Ontario biota ranged from 0.4 to 10.8 for the α-isomer and 0.2 to 10 for the γ-isomer (56). In some instances, these biomagnification factors were slightly higher than for the organochlorines, p-p' DDE and PCBs.

PBBs

Although production of PBBs ceased in North America in 1979 and in Europe in 2000, due to their former use, PBBs are presently detectable in several species of freshwater fish, birds, and bottlenose dolphins *(14, 57)*.

Human exposures

Routes of Exposure
As in wildlife tissues, scientists have measured substantial and rapidly increasing levels of BFRs in human tissues including blood, fat tissue, and breast milk. Sources of human exposure remain poorly characterized, although likely routes of exposure are by inhalation of contaminated particles or ingestion of contaminated food. BFRs can evaporate from consumer products and are deposited on dust particles that are ingested or inhaled *(10, 23)*. Researchers have documented occupational exposure in the electronics and computer industries with high levels of BFRs in the blood of workers *(7)*. Absorption of BFRs through skin contact with products such as electronics and textiles is not likely to contribute substantially to elevated BFR levels *(38)*.

Diet
Clearly, one route of exposure in humans is through diet, especially by eating contaminated fish and fatty foods, including meat, eggs, dairy products, and fats and oils. Freshwater fish have some of the highest recorded levels of PBDEs in the world. There have been a handful of studies of dietary exposure to PBDEs in Europe and Canada [reviewed in *(58)*], the U.S. *(59)* and a small study of HBCD exposure in foodstuffs in Sweden *(9)*. There are no dietary studies of TBBPA.

In general PBDE and HBCD concentrations are highest in fish and shellfish, with lesser but significant amounts in meat, dairy products, eggs, fats and oils. In the U.S. study, fish bought in a supermarket in Dallas had levels of PBDEs ranging from 8.5 - 3078 pg/g wet weight (median 1725) *(59)*. Although the penta-BDE congener, BDE-47, predominated in the food samples, deca-BDE was also found in many of the foods samples, including fish and soy milk. The PBDE levels measured in this study are 9-20 times higher than those reported for food from Japan or Sweden. The detected levels of HBCD in a small Swedish sample were highest in fish and ranged from 6.7-51 ng/g lipid weight, a concentration somewhat higher than levels of PBDEs measured in fish *(9)*. Estimates of average intake of total PBDEs ranged from 41 - 97 ng/day, a level which is higher than estimates of daily intake of PCDDs (2 ng/d) and lower than PCBs (285 ng/d).

The congener pattern for most food samples is similar to the congener profiles found in human and wildlife samples, with a predominance of tetra-BDE and penta-BDE. The influence of diet on body burdens of tetra-BDE was compared in individuals with high fish intake or no fish intake *(7)*. The high fish intake group had median tetra-BDE blood serum concentrations of 2.1 ng/g lipid weight, whereas the no fish intake group had median concentrations of 0.40 ng/g lipid weight. This study indicates that fish are a significant dietary source of PBDEs and contribute to elevated body burdens of lower brominated congeners.

Dust and Indoor Air
In addition to ingestion of contaminated foods, another potential route of human exposure to BFRs is common dust particles. Numerous studies have demonstrated BFRs in indoor dust particles, where environmental degradation and dispersal are minimal *(10, 42, 43, 60-62)*. As most of the products containing BFRs are found in homes and offices, it is not surprising that the indoor environment has been found to have 1.5 to 50 times greater levels of BFRs compared to the outdoor environment *(42, 60)*. A recent exploratory study from the United States Environmental Protection Agency (EPA) and the National Institutes of Standards and Technology (NIST) surveyed a small sample of homes in Washington, D.C. and Charleston, S.C. and found high concentrations of PBDEs in household dust, ranging from 700 to 30,100 ng/g (mean 5,900 ng/g) (*10)*. Researchers analyzed both dust from floors and clothes dryer lint for 22 variants of commercial PBDEs and found PBDEs in every sample. Similar to other studies of household dust, deca-BDE (BDE-209) was found in the highest concentration with a mean level of 2090 ng/g (range 162 - 8750 ng/g) and represented up to 88% of the total dust in some samples. Furthermore, when the results of this study are compared to studies of indoor dust in the European Union, concentrations of PBDEs are nearly ten times higher in the U.S.*(10)*. These differences between the U.S. and EU are similar to the differences observed for contamination of fish and human tissues.

Indoor dust samples also contain PBBs, HBCD, and TBBPA *(1, 62)*. The PBB and TBBPA concentrations were on average 1-3 orders of magnitude (10 to 1000 times) lower than the concentrations of PBDEs.

Although the sources of dust were not identified in these studies, they may include a multitude of indoor materials including treated carpet fibers, furniture, wiring, computers and other electronics. Considering that humans spend over 80% of their time indoors,

an accumulation of BFRs indoors likely represents an important exposure route through inhalation and/or ingestion *(42, 60)*.

Occupational Exposures
Occupational studies indicate that much higher levels of BFRs are released into the air during disposal of electronics and that these exposures result in high blood levels in the workers. Air samples from an electronics dismantling plant found deca-BDE (BDE-209) and TBBPA were the predominant congeners at 36,000 pg/m3 and 30,000 pg/m3, respectively *(63)*. The study identified the plastic shredder as a possible point source where concentrations of PBDEs were found to be 4-10 times higher than air samples at other sites in the dismantling plant. Follow up studies found serum concentrations of deca-BDE (BDE-209) significantly higher in electronics dismantling workers than in those not occupationally exposed to PBDEs *(38)*.

Biomonitoring PBDEs in Humans
PBDEs are in human fatty tissue, blood, and breast milk of individuals with no known exposure sources *(1, 7, 18)*. The median body burden of PBDEs in the United States is 35 ng/g lipid weight (ng/g = parts per billion = ppb). In Sweden, the median concentration is nearly 20 times lower at 2 ng/g lipid weight *(18)*. Human tissue samples from the United States have some of the highest levels of PBDEs in the world. Concentrations of total PBDEs as high as 500 ng/g lipid weight have been measured in blood and over 700 ng/g lipid weight have been observed in breast milk (19, 20). Although human PBDE levels have been increasing dramatically, they are still lower than concentrations found in fish and marine mammals.

There have been few studies investigating higher brominated BDE (hepta-deca) levels outside of occupational exposures. In the United States, deca-BDE (BDE-209) was in the blood and breast milk of non-occupationally exposed individuals *(23, 63)*. In Sweden, levels of deca-BDE are five times higher in computer technicians than in computer clerks or hospital workers *(64)*. The half-life of deca-BDE (BDE-209) was recently reported to be 6.8 days, indicating that deca-BDE exposures and tissue uptake must be occurring regularly to sustain detectable levels *(38)*.

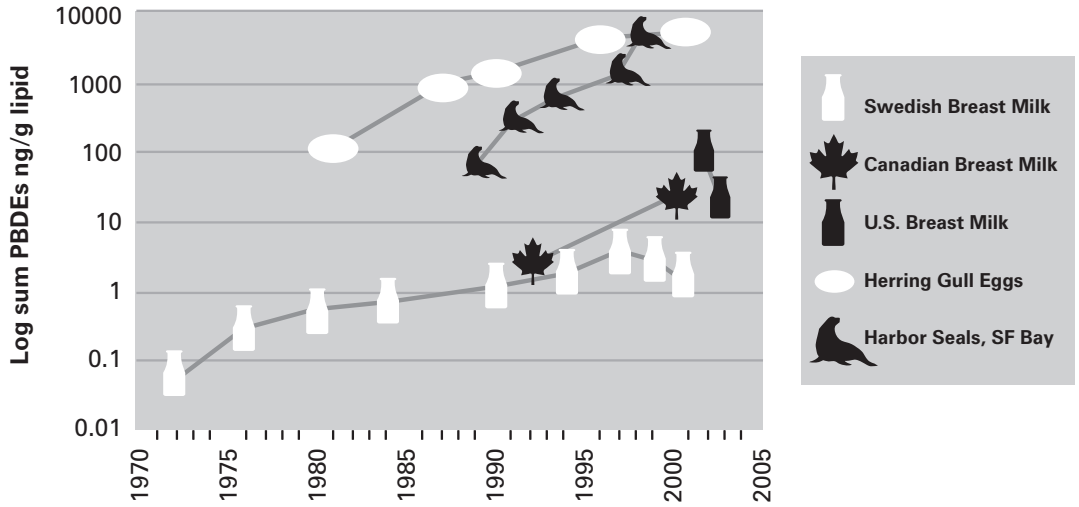
The presence of PBDEs in human milk was first documented in Sweden in 1999 and subsequent measures have revealed a rapid increase with a doubling every 5 years *(2)*. By 1998-2000, the levels in breast milk in Sweden had stabilized, after the country banned both the production and use of Penta-BDE in the early 1990s. In contrast, in North America, the levels of PBDEs in breast milk have not only continued to increase but have surpassed the highest levels measured in European studies, and yet the United States government has not acted to ban PBDEs. In Sweden, the median sum PBDE level is 3.2 ng/g lipid, in Japan the median is 1.4 ng/g lipid, in Canada the median is 25 ng/g lipid, whereas in the United States the median level is 41 ng/g lipid *(1)*. A graph comparing human and wildlife levels of PBDEs is shown in Figure 4.

Concentrations of BFRs in breast milk vary widely in the United States. In two recent studies, concentrations of PBDEs in American women ranged from 9.5 to 1,078 ng/g lipid weight (median 58 ng/g) and from 6.2- 419 ng/g lipid weight (median 34 ng/g) in breast milk *(20, 23)*. Researchers recently measured deca-BDE (BDE-209) in 30% of breast milk samples in Texas at concentrations up to 8 ng/g lipid weight *(23)*. This was the first study to document deca-BDE in breast milk.

Fetal Exposure
Several studies have demonstrated that PBDEs can accumulate in the human fetus. A recent study in Indiana found individual fetal cord blood concentrations did not differ from maternal concentrations, ranging from 15 - 580 ng/g lipid weight in mothers and from 14 - 460 ng/g lipid weight in fetal serum *(21)*. Fetal cord blood levels are similar to levels found in breast milk and are up to 100-fold higher than levels found in a similar Swedish study. These studies indicate that PBDEs can enter the fetus through the placenta *(21)*. If PBDEs are transferred as efficiently through breast milk as they are through the placenta, both fetuses and infants are being exposed to potentially high levels of harmful chemicals at critical developmental stages.

The reasons for higher concentrations of PBDEs in United States wildlife and humans are unexplained. The United States has been a major producer and consumer of Penta-BDE formulations, while some European manufacturers ceased production and use of the Penta-BDE formulation in the early 1990s. It is likely that the predominance of penta-BDE (BDE-47) in tissue samples is a result of its greater persistence and/or as a result of debromination of higher brominated PBDEs. Given the lag time from current-year usage to the time a bioaccumulative pollutant makes its way up the food chain, tissue concentra-

Figure 4: Selected Human and Wildlife levels of PBDEs



Source: from Clean Production Action, Hites 2004 *(18)*; Lunder, 2003 *(20)*.

tions of BFRs are likely to continue to rise over the next several years.

As in wildlife, there are few studies of TBBPA exposure in humans. Studies have measured TBBPA in human breast milk in Europe at levels of 1-11 ng/g lipid weight *(26)*. Human TBBPA serum levels in 8/10 computer technicians ranged from 1-3.4 pmol/g lipid weight (1). In occupationally exposed workers, researchers estimated TBBPA to have a half-life of 2.2 days, indicating rapid turnover *(38)*. Despite relatively rapid metabolism of the compound, it can be expected that continuous exposure will maintain constant serum levels

There are also few reports of HBCD exposure in humans. Studies have detected HBCD in workplace air samples at levels up to 1400 ng/g dust *(1)*. Levels in breast milk in Canada range from 0-126 ng/g lipid weight with a median of 1.3 ng/g lipid weight *(1)*. These concentrations are low, but are important because HBCD is highly bioaccumulative and persistent.

Toxicity

The most up-to-date and thorough reviews of the toxicology of BFRs including PBDEs, TBBPA and HBCD can be found in recent articles *(1, 7, 22, 32)*. In general, HBCD, TBBPA, and PBDEs are absorbed from the gastrointestinal tract and accumulate in fatty tissues. None of the BFRs discussed in this report appear to cause immediate symptoms from acute toxicity at average doses. Rather, like PCBs, health effects from chronic exposure, particularly in developing infants and wildlife, are of more concern.

Overall, the available literature on BFR toxicology is incomplete. Based on the available data, however, we know that BFRs are associated with several health effects in animal studies, including neurobehavioral toxicity, thyroid hormone disruption, and (for some PBDE congeners) possibly cancer. Additionally, there are data gaps but some evidence that BFRs can cause developmental effects, endocrine disruption, immunotoxicity, reproductive, and long term effects, including second generation effects. Some evidence is available for estrogenic activity of PBDE and TBBPA, but more studies are needed to determine if low-dose exposures have estrogenic activity in humans or other species *(1, 7, 22, 32)*.

The lower brominated penta-BDE congeners have been shown to cause toxicity at lower doses than the higher brominated octa-BDE or deca-BDE congeners *(22)*. There are no data on the relative toxicity of the different HBCD isomers or TBBPA derivatives *(1)*. Furthermore, there are no data on the toxicity of exposure to mixtures of BFRs.

Most of the toxicity data available on BFRs involve the effects noted in animal studies. However, tissue levels of PBDEs measured in humans are troubling because they are rapidly approaching levels associated with adverse effects in rodent studies, indicating there is a dwindling margin of safety. In the US, 5% of women have concentrations of total PBDEs greater than 300 ng/g lipid weight and levels of some individual congeners (such as penta-BDE congeners BDE-47 and BDE-99) exceed 100 ng/g lipid weight *(23-25)*. Levels that cause adverse neurodevelopmental effects in animal studies are less than 10 times this amount, indicating an uncomfortably small margin of safety for the children of the most highly exposed women *(24)*. Animal studies have shown uptake of PBDEs from breast milk and, as this paper identified earlier, human studies have confirmed that PBDEs are transferred across the placenta *(21)*. Historically animal testing has underestimated the effects PCBs, mercury, and lead can have on the developing human brain of children by several orders of magnitude *(72)*.

Neurodevelopment

Exposures in fetuses and newborns may be the most vulnerable time for exposure to BFRs. Studies indicate that brain development is one of the most sensitive endpoints for BFR toxicity. Possible mechanisms include thyroid hormone disruption and/or alteration of neurotransmitter systems. PBDEs and HBCD alter thyroid hormone levels in rodent studies (22). Both TBBPA and HBCD have the potential to alter concentrations of chemicals in the brain, such as dopamine and glutamate *(65)*.

Human brain development begins early in fetal development and continues throughout pregnancy, infancy, and well into adolescence. Normal levels of thyroid hormone are essential throughout the developmental process. It is well documented that small decreases in maternal and fetal thyroid hormone levels can cause neurological impairments, including a small decrease in the IQ of offspring. Even small decreases in thyroid hormone that are not clinically apparent may result in neurological impairment of offspring *(66, 67)*. The effects of maternal PCB levels on fetal brain development and subsequent function have been reported in several large epidemiologic studies *(36, 37, 68)*.

Studies indicate that PBDEs and HBCD cause neurobehavioral changes in neonatal rodents *(1)*. Other studies show mice exposed neonatally to low doses of PBDEs have decreased spontaneous activity, learning, and memory that worsen with age *(1, 69)*. There is evidence that exposure to PBDEs interferes with normal brain function by altering the cholinergic nervous system *(70, 71)*. Moreover, effects have been found at the lowest concentrations of penta-BDEs used in these studies, 0.8 mg/kg, indicating the threshold of harm may occur at very low doses *(32)*. Further studies are needed to determine if there is a no-observable adverse effect level (NOAEL) for neurodevelopmental toxicity.

Doses of PBDEs necessary to cause neurodevelopmental problems in rodent studies are within a 10-fold range of PBDE levels measured in human breast milk and fetal cord blood *(24)*. Although it is difficult to extrapolate laboratory studies to wildlife and human health outcomes, the increasing levels of PBDEs in the environment when measured against levels in rodents shown to cause neurodevelopmental toxicity are a cause for concern. The dwindling margin of safety highlights the need for precautionary measures to be put in place now, before we are able to collect evidence of harm. These trends are of particular concern since an historical review of neurodevelopmental impacts from PCBs shows that animal testing underestimated sensitivity of the developing human brain by several orders of magnitude *(72)*. Since PBDEs have a chemical structure similar to PCBs and their biological effects in animal studies are similar, one might infer that animal testing of PBDEs will also underestimate the sensitivity of the developing human brain to PBDEs. For that reason, current human exposure levels are of particular concern, with little or no margin of safety.

Whereas the majority of studies looking at neurodevelopmental effects have been done on penta-BDE congeners, similar irreversible changes in brain function also have been observed in mice given a single dose of higher brominated congeners (hexa-BDE 153 and deca-BDE 209) as neonates *(70, 73)*. These studies provide more evidence that the higher brominated PBDEs are bioavailable and capable of causing toxicity.

Mice exposed to a sub-toxic dose of PCB with a low dose of penta-BDE (BDE-99) were found to perform even worse on tests of learning and memory than

mice exposed to a 10 times higher dose of PCB alone *(74, 75)*. The results from this study imply that there is at least an additive interaction of PBDEs and PCBs in causing neurobehavioral toxicity

HBCD has the potential to cause neurobehavioral alterations as well. In addition to the possible effects on circulating thyroid hormone levels (as discussed below), HBCD has effects on spontaneous behavior, learning and memory, and causes changes in the number of nicotinic receptors at relatively low concentrations *(1)*. Co-exposure to PCBs resulted in an increase in response compared to either exposure alone *(1)*.

A single study of TBBPA did not find any neurobehavioral effects in neonatally exposed mice *(69)*. Although TBBPA appears to be rapidly eliminated, additional neurotoxicity studies on TBBPA and its derivatives are warranted.

Endocrine disruption: Thyroid Function

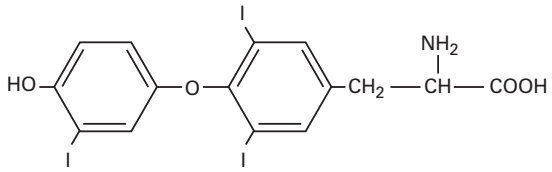
One of the most sensitive end points of PBDE and TBBPA toxicity observed in animal bioassays appear to be effects on thyroid function. PBDEs and TBBPA bear a strong structural similarity to thyroid hormone and have been extensively studied for effects on thyroid function. The structure of thyroid hormone is shown below.

There are several ways that BFRs can interfere with thyroid hormone activity and/or function. Studies illustrate that PBDEs, TBBPA, and PCBs lower thyroid hormone levels-to varying degrees and with varying consistency. PCBs also interfere with thyroid hormone activated gene transcription *(76)*. A recent laboratory study has shown that HBCD, but not TBBPA or deca-BDE can stimulate genes normally triggered by thyroid hormone *(77)*. BFRs also can bind to the thyroid hormone receptor with varying affinities (as noted below). Moreover, BFRs can bind to thyroid transport proteins with varying affinities (as noted below), where the relevance to humans is uncertain. Lastly, some human studies of occupational exposure indicate that workers show hypothyroidism.

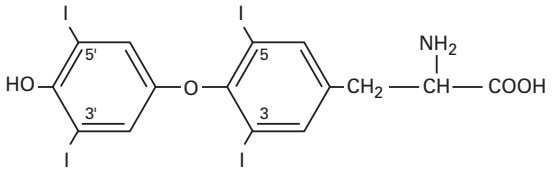
In animal studies, all of the commercial PBDE products (Penta-, Octa- and Deca-BDE) disrupt thyroid hormone balance, although the potency of Deca-BDE appears much lower than the rest *(32)*. Numerous studies have shown in mice and rats that exposure to Penta-BDE (tetra-penta BDE congeners) results in a decrease in serum thyroid levels, a condition known as hypothyroidism *(22)*. This reduction in thyroid hormone levels was observed in both adults and pups exposed in utero. Likewise, PCBs and hydroxylated PCBs have been found to reduce thyroid hormone levels in animal experiments *(78)*. Preliminary experiments have found that PCBs can act additively with PBDEs to reduce thyroid hormone levels *(32)*.

In laboratory models, PBDEs, hydroxylated metabolites of the lower brominated PBDEs, and TBBPA can bind to the thyroid hormone receptor and to the

Figure 5. Structure of the thyroid hormones, T3 is the active form of the hormone.



T3
triiodothyronine



T4
tetraiodothyronine
(thyroxine)

transport protein, transthyretin *(7, 22, 78)*. Transthyretin is responsible for binding and transporting thyroid hormone in the blood and interference with its function can result in lower thyroid hormone levels. It should be noted that there is some uncertainty about the human relevance of transthyretin, since the primary thyroid transport protein in humans is thyroid binding globulin (TBG). TBG is believed to facilitate transfer of maternal thyroid hormone to the fetus, but this has not been verified. Although the affinities of PBDEs for TBG have not been studied, the affinities of various hydroxy-PCBs for TBG are generally low *(32)*.

An increase in thyroid cell numbers or hyperplasia, a potentially pre-cancerous condition, also has been observed in studies of mice and rats exposed to PBDEs *(79)*.

Studies of the capacity of TBBPA to bind to isolated molecules of human transthyretin show that TBBPA binds with the strongest affinity of all brominated and chlorinated substances tested so far. It is up to 10 times more potent than thyroid hormone *(78)*. However, when TBBPA was administered to pregnant rats through their diet, there were no effects on thyroid hormone levels in either the dams or fetuses *(1)*. Thyroid stimulating hormone increased significantly in fetal plasma by 196% but no effect was seen in dams. The discrepancy between test tube and whole animal studies may be due to the fact that TBBPA was poorly absorbed from the gastrointestinal tract and/or there was fast metabolism or elimination of TBBPA preventing it from binding to transthyretin.

One animal study found decreased thyroid hormone levels after high dose exposure to HBCD *(22)*. Other than the previously mentioned study showing HBCD can stimulate thyroid responsive genes in a test tube (77), there are no other studies of HBCD effects on thyroid function.

There have been very few studies of thyroid hormone levels in humans exposed to PBDEs. One study found workers exposed to PBDEs and PBBs during manufacturing were found to have a statistically significant increase in hypothyroidism *(22)*. However, it cannot be determined if this was the result of exposure to PBDE, PBB, or the combination of both. PBBs also have been associated with decreased thyroid hormone levels in animal studies *(22)*.

Carcinogenicity

There is general agreement within the scientific community that there are insufficient data to evaluate the carcinogenicity of BFRs. Only one form of PBDEs, deca-BDE, has been tested for carcinogenicity in animals *(22)*. It caused statistically significant increases in hepatocellular (liver) carcinomas and marginal increases in thyroid follicular cell carcinomas in mice. In rats, scientists found dose-related increases in non-cancerous liver and pancreatic adenomas. Because of these studies, the International Agency for Research on Cancer (IARC) has classified deca-BDE as having limited evidence for a carcinogenic effect in animals, but stopped short of classifying the substance as carcinogenic in humans *(80)*.

It is worrisome, however, that deca-BDE, considered to be poorly absorbed and of relatively low toxicity amongst the PBDEs, showed evidence of carcinogenicity in rodent studies. The entire group of chemicals may pose a cancer concern. Since the highest environmental and tissue levels of PBDEs are Penta-BDE congeners, it is critical these PBDEs be tested for their potential to cause cancer.

A 1998 Swedish human study described a dose-dependent trend toward increasing fat tissue levels of tetra-BDE (BDE-47) associated with non-Hodgkin's lymphoma *(81)*. Scientists measured an average level of 13 ng/g in fat from the non-Hodgkin's patients compared to 5 ng/g in fat samples from patients without cancer. These differences, however, were not statistically significant in this small study.

HBCD was tested for carcinogenicity in mice and found to be associated with increased incidence of liver tumors, but there were inconsistencies in the study and bears repeating *(22)*. TBBPA has not been tested for carcinogenicity in whole animal studies.

Both HBCD and lower brominated PBDEs are capable of inducing genetic recombination in mammalian cell lines, a possible indicator of carcinogenicity, similar to other environmental contaminants such as DDT and PCB *(7)*. Conversely, TBBPA did not induce genetic recombination in two cellular assays using mammalian cells *(22)*.

Other Endocrine Disrupting Concerns

Man-made chemicals that interfere with the normal action of hormones are known as endocrine disruptors. In addition to interfering with thyroid hormone function, some studies have examined the capacity of

BFRs to interfere with estrogen hormone action. Depending on the PBDE congener being studied, some PBDEs have estrogenic activity whereas others are anti-estrogenic.

Laboratory experiments have shown that hydroxylated PBDEs with 2-4 bromines bind to the estrogen receptor and cause expression of genes normally regulated by estrogen, albeit at concentrations at least 50,000 fold higher *(79, 82)*. This is similar to the strength of the known environmental estrogen, bisphenol A *(82)*. Conversely, some forms of hexa-BDE and hepta-BDEs have been shown to bind to the estrogen receptor and inhibit expression of estrogen regulated genes *(79)*.

There have been conflicting results on the ability of TBBPA to simulate estrogen gene regulation. One group examined the estrogenic potential of TBBPA in cultured cells and found that TBBPA had no estrogenic effect, but the lower brominated forms of bisphenol A did *(82)*. In contrast, another cell culture study found TBBPA was able to stimulate expression of genes normally regulated by estrogen *(83)*. Tests in fish and chickens found TBBPA does not have estrogen-like effects *(79)*.

Other laboratory studies indicate that hydroxylated PBDE and TBBPA metabolites may indirectly interfere with estrogen action by inhibiting estrogen metabolizing enzymes. If this inhibition occurs in the whole animal, it could result in elevated levels of estrogen *(1)*.

Reproduction
There is little information available on the reproductive effects of BFRs. Studies using a commercial mixture of Penta-BDE found a delay in male and female reproductive development at high doses *(1)*. Recent reports demonstrated one-time, low dose penta-BDE (BDE-99) exposure in utero resulted in decreased sperm counts *(84)*. Although the rats in this study remained fertile, the observed decrease in sperm counts is concerning because the exposure dose was very small and similar to levels of current human exposure. Chronic HBCD exposure was found to inhibit egg production in the ovary of female rats but did not have any effect on male reproductive function *(7, 22)*.

Immune suppression
There is limited information suggesting that BFRs can cause a suppression of the immune system, leading to increased susceptibility to infections. In standardized tests of immune response, Penta-BDEs resulted in immune suppression in mice with cellular changes in organs critical to immune function, such as the spleen and thymus *(22)*. The immunosuppressive effects of PBDEs have been reported to exceed the effects of PCBs in laboratory animals *(22)*.

Investigations of the impacts of TBBPA on the immune system are limited to *in vitro* studies of immune cells and HBCD has not been tested for immunotoxic effects at all. *In vitro* studies have shown TBBPA to be a potent inhibitor of T-cell activation *(1)*, and if found to have a similar effect in whole animals, could result in an impaired defense in fighting infections.

Teratogenicity
Few studies have examined the ability of BFRs to cause birth defects. In rodent experiments, fetal damage was observed after exposure to Deca-BDE and Octa-BDE, when no maternal effects were seen. Exposure to developing rat fetuses to relatively high doses of Deca-BDE resulted in a delayed hardening of bones, bent limb bones, and weight decreases *(22)*.

Two reproductive/developmental studies in rats treated with HBCD or TBBPA revealed essentially no developmental effects *(1, 22)*. However more studies will be necessary to confirm these findings.

Dioxin-like effects
Dioxin-like activity, as displayed by the prototypical dioxin, TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin), leads to a wide variety of toxic endpoints including mortality, carcinogenicity, teratogenicity, and immunotoxicity. These effects all mediate through a cellular protein known as the Ah (aromatic hydrocarbon) receptor. Many structurally similar chemicals have been found to bind to this receptor with very different affinities. As some PCBs bind to the Ah receptor, researchers have studied BFRs for Ah-binding and dioxin-like activity.

The most abundant congeners of PBDEs found in the environment, tetra-BDE, penta-BDE, and deca-BDE (BDEs 47, 99, and 209 respectively), have very weak affinity for the Ah receptors and likely do not exhibit dioxin-like toxicity. Scientists have found that some PBDEs, such as hexa and hepta-BDEs bind to the Ah or dioxin receptor with potencies comparable to some PCBs *(82)*. Overall,PBDEs are weak Ah receptor agonists and bind 2-5 orders of magnitude less strongly than TCDD. Some activate the genes normally activated by TCDD while others

bind to the receptor and prevent TCDD from binding *(85)*. BDE-119 binds to the Ah receptor with a relatively high affinity. However, this is not an environmentally relevant PBDE congener. TBBPA and HBCD have not been shown to bind to the Ah receptor in cellular assays *(86)*.

ALTERNATIVES TO HALOGENATED FLAME RETARDANTS

To meet fire safety standards, large volumes of chemical flame retardants are added to most of the plastic and synthetic materials in our homes, offices, and transportation vehicles. Because these synthetic materials are used in a wide variety of applications, flame retardants also end up in materials that don't require their use, such as the foam soles of athletic shoes and the plastics used in joysticks for video games. An over-reliance on chemical additives has overshadowed the ability to design products that continue to meet fire safety standards without chemical additives. Changes to both product design and materials used can decrease the amount of flame retardants needed. Furthermore, there are safer, more sustainable alternatives to using halogenated flame retardants when a chemical flame retardant is necessary *(87)*.

Furniture, plastic, and electronics products can be manufactured to meet fire standards without the use of chemical flame retardants. Electronics products can be redesigned to contain lower temperature generating components or redesigned to separate heat-generating components from highly flammable components. An example of a design change to eliminate the need for flame retardants is construction of television sets with greater spacing or metallic barriers between components. In addition, lower voltage components can be used.

Another method to reduce flammability is to replace highly flammable plastics that release toxicants when burned with materials that are more inherently flame resistant. Materials that don't require the addition of chemicals for flame resistance include metal, leather, glass, pre-ceramic polymers, aramide blends (Kevlar), and natural fibers such as jute, hemp, and wool. Three plastics; polysulfone, polyaryletherketone, and polyethersulfone, are self-extinguishing and can be used without the addition of flame retardants (5). Finally, when chemical-free alternative materials or designs are not feasible, non-halogenated flame retardants can be used to meet fire safety standards. The Danish EPA's assessment of alternatives indicates that, for a large proportion of applications, non-brominated alternatives are already commercially available *(5)*. For example, a report commissioned by the German government determined that the flame retardants aluminum trihydroxide, ammonium polyphosphates, and red phosphorus are less problematic in the environment *(26)*. Information about the safety of other alternatives is growing and in the future it will be possible to make more specific recommendations. However, it is not clear that safer alternatives are currently available for every application.

PHASE-OUT OF HALOGENATED FLAME RETARDANTS

The widespread distribution of halogenated flame retardants, the emerging evidence of health threats to humans and wildlife at levels close to those found in the environment, and the likelihood that levels will increase as products containing them enter the environment, all suggest that halogenated flame retardants should be phased out as soon as practical. Table 5 summarizes the accumulating evidence on the persistence, bioaccumulative capacity, long range transport, and toxicity of BFRs. The combination of hazards posed by these chemicals—many of which are triggers for international phase-out under the Stockholm Convention on POPs (Persistent Organic Pollutants) or action by the State of Washington and the U.S. EPA—highlight the need for immediate action.

Efforts to redesign products and to develop safe alternatives are urgently needed for those uses for which alternatives are not yet available. For most uses, however, alternatives for fire retardancy are within reach. The European Union began substituting for BFRs in the 1990s and PBDE levels in breast milk have plateaued and are beginning to decrease. Phase-outs have included voluntary actions by manufacturers and retailers, as well as legislated mandates by regulatory authorities.

Some computer and electronics manufacturers like Apple, Ericsson, IBM, Intel, Motorola, Panasonic, Phillips, and Sony are using alternatives to halogenated flame retardants. For example, Motorola now uses a halogen-free laminate that is cost effective, while meeting fire safety standards. Toshiba has replaced BFR-containing plastic casings in electronic parts with inherently flame-resistant polyphenylene sulfide. IKEA furniture, Crate and Barrel, and Eddie Bauer

Table 5: Persistence, Bioaccumulation, and Toxicity of BFRs

BFR	Persistence	Bioaccumulation	Long-Range Transport	Toxicity
Deca-BDE	Half life > 8 months (32 weeks) in freshwater sediment (88) Note that in the presence of light –photolytic degradation—deca degrades faster: Sediment half life 53 h Soil half-life 150-200h (12) Deca-BDE breaks down into lower brominated compounds, including octa- and penta-BDE, which are persistent and bioaccumulative. (12)	Log Kow* > 6 (88) Log Kow* 10 (as cited in (7) and also in (88). Incomplete data on bioconcentration and bioaccumulation (p.91): evidence that deca-BDE does not bioconcentrate in fish, but it may bioconcentrate in other organisms, such as predatory birds. Deca-BDE breaks down into lower brominated compounds, including octa- and penta-BDE, which are persistent and bioaccumulative. (12)	Detection of the substance in moss remote regions of Norway and birds in polar regions.	Evidence of neurodevelopmental damage in mice (73) Evidence of liver and thyroid tumors in rodent students (IARC Group 2) (80)
Octa-BDE	Incomplete data but some evidence that it will degrade under certain conditions to lower brominated PBDEs, "not possible to estimate the rate or extent of these reactions" (89), (88)	Log Kow* 8.4 - 8.9 (as cited in (7) Log Kow* 10.33 (89).	No data available	Limited toxicity data - animal studies (89) Increased liver and thyroid weight. Also decreases in thyroid hormone levels
Penta-BDE	Half-life air, 12.6 days (94)	Log Kow* 6.5-7.0 (as cited in (7) Log Kow* ~7.66 (89) Bioconcentration factor water-blue mussels 1,400,000 (BDE-99) (as cited in (7)	Detected in fish and birds in remote regions of Norway and polar regions (as cited (7) Detected in remote air samples of Baltic Sea (90)	Evidence of neurodevelopmental toxicity in rodent studies (71), (91) Decreases thyroid hormone levels (as cited in (22)
HBCD	Half-life air, 3 days Half-life water, 2-25 days (as cited by (1)	Log Kow* 5.8 (as cited in (7) Bioconcentration factor water-fathead minnow 18100 (log BCF 4.26) (as cited in (7)	Detected in air and sediments in remote regions of Sweden (9)	Evidence of neurodevelopmental toxicity in rodent studies (as cited by (1) Interference with brain neurotransmitters in test tube studies (65) Limited evidence of interference with thyroid hormone in test tube and rodent studies (22), (77)
TBBPA	Half-life water, 6.6-80.7 days (dependent on season) as cited in (1)	Log Kow* 4.5 (as cited in (7) Short half-life in fish (<1 day) and oysters (< 5 days) suggests does not bioaccumulate. However, 3-6% of dose is retained in fatty tissue, suggesting potential bioaccumulation with repeated exposures (as cited by (1)	No data available	In test tube studies, toxic to liver cells and immune (T-cells). May also interfere with thyroid hormone action (as cited (1) Inhibition of brain neurotransmitters in vitro (65)
Examples of PBT Criteria				
US EPA, Waste Minimization Prioritization Program	Regional half life > 580 hrs (high); 140-580 hrs (medium); and< 140 days (low)	Bioaccumulation factor / Bioconcentration factor > 1000 (high); 250-1000 (medium); and < 250 (low)		Potential to cause cancer, non-cancer and ecological effects
Stockholm Convention Screening Criteria	Half life in: water > 2 months; soil > 6 months, or sediment > 6 months	Evidence of a bioconcentration factor or bioaccumulation factor > 5,000; or in the absence of such data, a log Kow* > 5.	Measured levels of the chemical in locations distant from the source of its release that are of potential concern	Toxicity or ecotoxicity data that indicate the potential for damage to human health or to the environment

*Octanol-water partition coefficient

are requesting PBDE-free polyurethane foam from their manufacturer, Hickory Springs. Great Lakes Chemical, the predominant United States manufacturer of Penta- and Octa-BDE, voluntarily agreed to end new production beginning in 2005. Other global manufacturers continue to produce and use these chemicals, as well as export their products to the United States, although laws passed in several states in the United States prevent the import of articles containing Penta and Octa-BDE *(27-31)*.

The European Union has enacted a ban on Penta- and Octa-BDEs and is considering a ban on Deca-BDEs as well. States in the U.S. are acting to phase-out the use of the PBDEs as well. California, Hawaii, Maine, and Michigan have already passed legislation to ban certain PBDEs, with similar initiatives underway in Maryland, Massachusetts, Illinois, Minnesota, Oregon, and Washington *(27-31)*. The United States government has yet to ban brominated flame retardants.

REGULATIONS INADEQUATE

Some brominated flame retardants have the characteristics of persistent organic pollutants (POPs) and share qualities with PCBs including chemical structure, neurotoxicity, interference with thyroid hormone levels, and immune suppression. The disposal of these compounds through combustion also results in the formation of brominated dioxins and furans that are persistent, bioaccumulative toxicants.

Although the discovery of BFRs in our environment occurred by chance, the emergence of these problems was predictable given the chemical structures, and the widespread and uncontrolled use of these halogenated organic chemicals in commerce *(92)*.

In July, 2002, Health Care Without Harm released its report, "Aggregate Exposures to Phthalates in Humans." (Available on-line: http://www.noharm.org/pvcDehp/issue). That report concluded that U.S. chemicals policy was inadequate and allows vulnerable groups of people, including developing fetuses, infants, and children, to be exposed to potentially hazardous levels of phthalates. Brominated flame retardants offer another example of the failure of chemical regulation to prevent hazardous materials from entering the marketplace, and thus the environment, the food web, and ultimately the next generation of children.

Federal regulation of industrial chemicals is guided by the Toxic Substances Control Act (TSCA). The Act, enacted in 1976 after six years of wrangling, created a testing regime for new chemicals but 'grandfathered' existing chemicals that were already in commerce. The vast majority of chemicals (more than 95% by volume) continue to be used without adequate baseline safety testing. Only 12 chemicals have been fully tested for health impacts, including neurotoxicity. Even new chemicals are not subjected to comprehensive safety testing. TSCA also imposes a nearly impossible burden of proof before the federal government can take action to restrict the marketing of a chemical. Only a handful of chemicals have ever been restricted under TSCA.

Inadequate chemical regulation extends to the difficulty of consumers to obtain information on the content of products. Manufacturers are not required by federal law to label products to indicate the presence of BFRs, and this information is generally extremely difficult to obtain.

Clearly, the discovery of brominated flame retardants in the breast milk of lactating women represents a dramatic example of a failed system of chemicals regulation. Responsible members of the health care sector are again placed in the position of researching and evaluating the potential hazards, seeking disclosure of product content to determine where BFRs are entering the sector, and then finding and evaluating the safety and efficacy of alternatives. This is neither efficient nor core to the mission of health care, but a burden on the sector imposed by a broader failure at the federal level.

The widespread distribution of BFRs, the emerging evidence of threats to humans and wildlife health at levels close to those found in the environment, and the likelihood that levels will increase as products containing them enter the environment, all suggest that BFRs should be phased out as soon as practical by manufacturers, users (including hospitals), and the government.

APPENDIX 1:

Table A-1. Names and Congeners of selected PBDEs discussed in report.

Congener number (IUPAC)	PBDE Congener
BDE-47	2, 2', 4, 4'- Tetra-BDE
BDE-99	2, 2', 4, 4', 5- Penta-BDE
BDE-100	2, 2', 4, 4', 6- Penta-BDE
BDE-119	2, 3', 4, 4', 6- Penta-BDE
BDE-153	2, 2', 4, 4', 5, 5'-Hexa-BDE
BDE-154	2, 2', 4, 4', 5, 6'-Hexa-BDE
BDE-181	2, 2', 3, 4, 4', 5, 6-Hepta-BDE
BDE-183	2, 2', 3, 4, 4', 5', 6-Hepta-BDE
BDE-190	2, 3, 3', 4, 4', 5, 6-Hepta-BDE
BDE-209	2, 2', 3, 3', 4, 4', 5, 5', 6, 6'-Deca-BDE

Commercial Penta-BDE contains a mixture of 40 % tetra-, 50-60% penta-, and 6% hexa- BDEs. The predominant penta-BDE congener from commercial mixtures is 2,2',4,4',5-pentaBDE (BDE-99) with some 2,2',4,4',6-pentaBDE (BDE-100). The most common tetra-BDE congener is 2,2',4,4'-tetra-BDE (BDE-47) whereas hexa-BDEs consist predominantly of congeners BDE -153 and -154. BDE-47 and BDE-99 account for approximately 75% of the total mass of Penta-BDE with roughly twice as much BDE-99 as BDE-47.

Deca-BDE contains 97-98% 2,2',3,3',4,4',5,5',6,6' deca-BDE, also known as BDE-209. Deca-BDE has small amounts (<3%) of nona-brominated diphenyl ethers (nona-BDE) as impurities.

Octa-BDE is a commercial mixture of 30-40% octa-BDE, 30-45% hepta-BDE, and approximately 10% nona-BDE and hexa-BDE. The major congener in commercially produced Octa-BDE is 2,2',3,4,4',5',6-heptaBDE (BDE-183) (4). It isn't clear whether or not the Octa-BDE mixtures contain any penta-BDE (1).

Other BFRs also consist of mixtures. HBCD is commercially available in a purity of 96% and consists of 3 isomeric forms: α, β and γ-HBCD. Technical HBCD consists primarily of γ-HBCD, however the isomeric profile depends on the product application.

Commerical TBBPA includes tetrabromobisphenol A as well as its dimethylether, dibromopropylether, bis(allylether), bis(2-hydroxyethyl oxide), carbonates and epoxy oligomer derivatives (93).

REFERENCES

1. Birnbaum LS, Staskal DF. Brominated flame retardants: cause for concern? Environ Health Perspect 112:9-17(2004).
2. Alaee M, Wenning RJ. The significance of brominated flame retardants in the environment: current understanding, issues and challenges. Chemosphere 46:579-582(2002).
3. Troitzsch JH. An Overview of Flame Retardants. Chemistry Today 16(1998).
4. Alaee M, Arias P, Sjodin A, Bergman A. 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(2003).
5. Lassen C, Lokke S. Brominated Flame Retardants: Substance Flow Analysis and Assessment of Alternatives No. 494. Copenhagen: Danish Environmental Protection Agency, Report #494, ISBN 87-7909-415-5 (1999).
6. Bromine Science and Environmental Forum (BSEF), Brominated Flame Retardants in consumer and commercial products, www.bsef.com, accessed in 2004, published 2001.
7. deWit CA. An overview of brominated flame retardants in the environment. Chemosphere 46:583-624(2002).
8. Hale R, Alaee M, Manchester-Neesvig J, Stapleton HM, Ikonomou MG. Polybrominated diphenyl ether flame retardants in the North American environment. Environ Int 29:771-779(2003).
9. Remberger M, Sternbeck J, Palm A, Kaj L, Stromberg K, Brorstrom-Lunden E. The environmental occurrence of hexabromocyclododedecane in Sweden. Chemosphere 54:9-21(2004).
10. Stapleton HM, Dodder NG, Offenberg JH, Schantz MM, Wise SA. Polybrominated Diphenyl Ethers in House Dust and Clothes Dryer Lint. Environ Sci Technol 39:925-931(2005).
11. Community Right-to-Know Toxic Chemical Reporting. In: Federal Register, vol 64, 1999;58666-58753.
12. Soederstroem G, Sellstroem U, de Wit CA, Tysklind M. Photolytic debromination of decabromodiphenyl ether (BDE 209). Environ Sci Technol 38:127-132(2004).
13. Darnerud PO, Eriksen GS, Johannesson T, Larsen PB, Viluksela M. Polybrominated diphenyl ethers: occurrence, dietary exposure, and toxicology. Environ Health Perspect 109:49-68(2001).
14. Lindberg P, Sellstrom U, Haggberg L, de Wit CA. Higher Brominated Diphenyl Ethers and Hexabromocyclododecane Found in Eggs of Peregrine Falcons (Falco peregrinus) Breeding in Sweden. Environ Sci Technol 38:93-96(2004).
15. Burreau S, Zebuhr Y, Broman D, Ishaq R. Biomagnification of polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) studied in pike (Esox lucius), perch (Perca fluviatilis) and roach (Rutilus rutilus) from the Baltic Sea. Chemosphere 55:1043-1052(2004).
16. Stapleton HM, Letcher RJ, Baker JE. Debromination of Polybrominated Diphenyl Ether Congeners BDE 99 and BDE 183 in the Intestinal Tract of the Common Carp (Cyprinus carpio). Environ Sci Technol 38:1054-1061(2004).
17. Stapleton HM, Alaee M, Letcher RJ, Baker JE. Debromination of the Flame Retardant Decabromodiphenyl Ether by Juvenile Carp (Cyprinus carpio) following Dietary Exposure. Environ Sci Technol 38:112 - 119(2004).
18. Hites RA. Polybrominated Diphenyl Ethers in the Environment and in People: A Meta-Analysis of Concentrations. Environ Sci Technol 38:945-956(2004).

19. Petreas M, She J, Brown R, Winkler J, Windham G, Rogers E, Zhao G, Bhatia R, Charles MJ. High Body Burdens of 2,2'4,4'-Tetrabromodiphenyl Ether (BDE-47) in California Women. Environ Health Perspect 111:1175-1179(2003).
20. Lunder S, Sharp R. Mother's Milk: Record levels of toxic fire retardants found in American mother's breast milk. Washington, D.C.: Environmental Working Group, 2003. (Available on-line: www.ewg.org/reports/mothersmilk/es.php)
21. Mazdai A, Dodder NG, Abernathy MP, Hites RA, Bigsby RM. Polybrominated Diphenyl Ethers in Maternal and Fetal Blood Samples. Environ Health Perspect 111:1249-1252(2003).
22. Darnerud PO. Toxic effects of brominated flame retardants in man and wildlife. Environ Int 29:841-853(2003).
23. Schecter A, Pavuk M, Papke O, Ryan JJ, Birnbaum LS, Rosen R. Polybrominated Diphenyl Ethers (PBDEs) in U.S. Mother's Milk. Environ Health Perspect 111:1723-1729(2003).
24. Gill U, Chu I, Ryan JJ, Feeley M. Polybrominated diphenyl ethers: human tissue levels and toxicology. Rev Environ Contam Toxico 183:55-97(2004).
25. McDonald TA. Distribution of PBDE Levels Among U.S. Women: Estimates of Daily Intake and Risk of Developmental Effects. p. 443-446. In: 3rd International Workshop on Brominated Flame Retardants, Toronto, Ontario, Canada, June 6-9, 2004.
26. Leisewitz A, Kruse H, Schramm E. Substituting environmentally relevant flame retardants: Assessment fundamentals UBA-FB 0001.71/1. Berlin, Germany: Federal Ministry of the Environment, Nature Conservation, and Nuclear Safety, 2001.
27. Polybrominated diphenyl ethers, California State Legislature, AB 302, 2003. (available on-line at: info.sen.ca.gov/cgi-bin/postquery?bill_number=ab_302&sess=PREV&house=B&site=sen)
28. An Act To Reduce Contamination of Breast Milk and the Environment from the Release of Brominated Chemicals in Consumer Products. Maine State Legislature, LD 1790, 2003, 121st Session,.(available on-line at: janus.state.me.us/legis/ros/lom/lom121st/14pub601-650/pub601-650-33.htm)
29. An Act To Protect Public Health and the Environment through the Collection and Recycling of Electronic Waste. Maine State Legislature, LD 743, 2003, 121st Session. (Available on-line at: www.mainelegislature.org/legis/bills_121st/LD.asp?LD=743)
30. Mary Beth Doyle PBDE Act. Michigan State Legislature, Senate Bill 1458, Public Act 526, 2004. (available on-line at: www.michiganvotes.org/2004-SB-1458)
31. Locke, Gary, Governor of Washington. Executive Order, Persistent Toxic Chemicals, 2004. (available on-line: www.digitalarchives.wa.gov/governorlocke/eo/eo_04-01.htm)
32. McDonald TA. A perspective on the potential health risks of PBDEs. Chemosphere 46:745-755(2002).
33. Bromine Science and Environmental Forum (BSEF). An Introduction to Brominated Flame Retardants. Brussels, Belgium, 2000. Available at: www.bsef.com
34. European Flame Retardants Association (EFRA). European Chemical Industry Council, 2001. accessed 2004 at: www.cefic-efra.com
35. Rahman F, Langford KH, Scrimshaw MD, Lester JN. Polybrominated diphenyl ether (PBDE) flame retardants. The Science of The Total Environment. 275:1-17(2001).
36. Jacobson JL, Jacobson SW. Intellectual Impairment in Children Exposed to Polychlorinated Biphenyls in Utero. N Engl J Med 335:783-789(1996).
37. Patandin S, Lanting CI, Mulder PG, Boersma ER, Sauer PJ, Weisglas-Kuperus N. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. J Pediatr 134:33-41(1999).
38. Sjödin A, Patterson DG, Bergman A. A review on human exposure to brominated flame retardants - particularly polybrominated diphenyl ethers. Environ Int 29:829-839(2003).
39. Hoque A, Sigurdson AJ, Burau KD, Humphrey HE, Hess KR, Sweeney AM. Cancer among a Michigan cohort exposed to polybrominated biphenyls in 1973. Epidemiology 9:373-378(1998).

40. Sjödin A, Patterson DG, Bergman A. Brominated Flame Retardants in Serum from U.S. Blood Donors. Environ Sci Technol 35:3830-3833(2001).

41. Deegan D. Brominated Flame Retardants To Be Voluntarily Phased Out. In: Environmental News, publication of the Environmental Protection Agency. Washington D.C. November 3, 2003.

42. Butt CM, Diamond ML, Truong J, Ikonomou MG, ter Schure A. Spatial Distribution of Polybrominated Diphenyl Ethers in Southern Ontario As Measured in Indoor and Outdoor Window Organic Films. Environ Sci Technol 38:724-731(2004).

43. Santillo D, Johnston P, Brigden K. The presence of brominated flame retardants and organotin compounds in dusts collected from Parliament buildings from eight countries. technical report. Exeter, UK: Greenpeace Research Laboratories, Dept. of Biological Sciences, University of Exeter, 2001.

44. Hale R, La Guardia M, Harvey E, Gaylor M, Matteson-Mainor T, Duff W. Flame retardants: Persistent pollutants in land-applied sludges. Nature 412:140-141(2001a).

45. Strandberg B, Dodder NG, Basu I, Hites RA. Concentrations and Spatial Variations of Polybrominated Diphenyl Ethers and Other Organohalogen Compounds in Great Lakes Air. Environ Sci Technol 35:1078-1083(2001).

46. Gerecke AC, Hartmann PC, Heeb NV, Kohler H-PE, Giger W, Schmid P, Zennegg M, Kohler M. Anaerobic Degradation of Decabromodiphenyl Ether. Environ Sci Technol 39:1078-83(2005).

47. Lacorte S, Guillamon M, Martinez E, Viana P, Barcelo D. Occurrence and specific congener profile of 40 polybrominated diphenyl ethers in river and coastal sediments from Portugal. Environ Sci Technol 37:892-898(2003).

48. Voordeckers JW, Fennell DE, Jones K, Haggblom MM. Anaerobic biotransformation of tetrabromobisphenol A, tetrachlorobisphenol A, and bisphenol A in estuarine sediments. Environ Sci Technol 36:696-701(2002).

49. Ebert J, Bahadir M. Formation of PBDD/F from flame-retarded plastic materials under thermal stress. Environ Int 29:711-716(2003).

50. Weber R, Kuch B. Relevance of BFRs and thermal conditions on the formation pathways of brominated and brominated-chlorinated dibenzodioxins and dibenzofurans. Environ Int 29:699-710(2003).

51. Law RJ, Alaee M, Allchin CR, Boon JP, Lebeuf M, Lepom P, Stern GA. Levels and trends of polybrominated diphenylethers and other brominated flame retardants in wildlife. Environ Int 29:757-770(2003).

52. Hale RC, La Guardia MJ, Harvey EP, Mainor TM, Duff WH, Gaylor MO. Polybrominated diphenyl ether flame retardants in Virginia freshwater fishes (USA). Environ Sci Technol 35:4585-4591(2001).

53. She J, Petreas M, Winkler J, Visita P, McKinney M, Kopec D. PBDEs in the San Francisco Bay Area: measurements in harbor seal blubber and human breast adipose tissue. Chemosphere 46:697-707(2002).

54. Ikonomou MG, Rayne S, Addison RF. Exponential Increases of the Brominated Flame Retardants, Polybrominated Diphenyl Ethers, in the Canadian Arctic from 1981 to 2000. Environ Sci Technol 36:1886-1892(2002).

55. Norstrom RJ, Simon M, Moisey J, Wakeford B, Weseloh DV. Geographical distribution (2000) and temporal trends (1981-2000) of brominated diphenyl ethers in Great Lakes herring gull eggs. Environ Sci Technol 36:4783-4789(2002).

56. Tomy GT, Palace VP, Halldorson T, Braekevelt E, Danell R, Wautier K, Evans B, Brinkworth L, Fisk AT. Bioaccumulation, Biotransformation, and Biochemical Effects of Brominated Diphenyl Ethers in Juvenile Lake Trout (Salvelinus namaycush). Environ Sci Technol 38:1496-1504(2004).

57. Luross J, Alaee M, Sergaent D, Cannon C, Whittle M, Solomon K, Muir D. Spatial distribution of polybrominated diphenyl ethers and polybrominated biphenyls in lake trout from the Laurentian Great Lakes. Chemosphere 46:665-672(2002).

58. Bocio A, Llobet JM, Domingo JL, Corbella J, Teixido A, Casas C. Polybrominated diphenyl ethers (PBDEs) in foodstuffs: human exposure through the diet. J Agric Food Chem 51:3191-3195(2003).

59. Schecter A, Päpke O, Tung K-C, Staskal D, Birnbaum L. Polybrominated Diphenyl Ethers Contamination of United States Food. Environ Sci Technol 38:5306-5311(2004).

60. Wilford BH, Harner T, Zhu J, Shoeib M, Jones KC. 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(2004).

61. Rudel RA, Camann JD, Spengler JD, Korn LR, Brody JG. Phthalates, Alkylphenols, Pesticides, Polybrominated Diphenyl Ethers, and Other Endocrine-Disrupting Compounds in Indoor Air and Dust. Environ Sci Technol 37:4543-4553(2003).

62. McPherson A, Thorpe B, Blake A. Brominated Flame Retardants in Dust on Computers: The case for safer chemicals and better computer design: Clean Production Action, Computer Take Back Campaign, 2004. (Available on-line at: www.cleanproduction.org)

63. Sjödin A, Carlsson H, Thuresson K, Sjolin S, Bergman A, Ostman C. Flame retardants in indoor air at an electronics recycling plant and at other work environments. Environ Sci Technol 35:448-454(2001).

64. Jakobsson E, Thuresson K, Rylander L, Sjodin A, Hagmar L, Bergman A. Exposure to polybrominated diphenyl ethers and tetrabromobisphenol A among computer technicians. Chemosphere 46:709-716(2002).

65. Mariussen E, Fonnum F. The effect of brominated flame retardants on neurotransmitter uptake into rat brain synaptosomes and vesicle. Neurochem Int 43:533-542(2003).

66. Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clin Endocrinol (Oxf). 59:282-288(2003).

67. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 341:549-555(1999).

68. Schantz SL, Widholm JJ, Rice DC. Effects of PCB exposure on neuropsychological function in children. Environ Health Perspect 111:357-376(2003).

69. Eriksson P, Jakobsson E, Fredriksson A. Brominated Flame Retardants: A Novel Class of Developmental Neurotoxicants in Our Environment? Environ Health Perspect 109:903-908(2001).

70. Viberg H, Fredriksson A, Eriksson P. Neonatal exposure to polybrominated diphenyl ether (PBDE 153) disrupts spontaneous behaviour, impairs learning and memory, and decreases hippocampal cholinergic receptors in adult mice. Toxicol Appl Pharmacol 192:95-106(2003).

71. Viberg H, Fredriksson A, Eriksson P. Neonatal exposure to the brominated flame retardant 2,2',4,4',5-pentabromodiphenyl ether causes altered susceptibility in the cholinergic transmitter system in the adult mouse.`. Toxicol Sci 67:104-107(2002).

72. Rice DC. Neurotoxicity produced by developmental exposure to PCBs. Mental Retardation and Developmental Disabilities Research Reviews 3:223-229(1997).

73. Viberg H, Fredriksson A, Jakobsson E, Orn U, Eriksson P. Neurobehavioral derangements in adult mice receiving decabrominated diphenyl ether (PBDE 209) during a defined period of neonatal brain development. Toxicol Sci 76:112-120(2003).

74. Raloff J. New PCBs? Throughout life, our bodies accumulate flame retardants, and scientists are staring to worry. Science News 164:266-268(2003).

75. Eriksson P, Fischer C, Karlsson H, Fredriksson A. Interaction between a brominated flame-retardant (PBDE 99) and an ortho-substituted PCB (PCB 52). The Toxicologist 72:323(2003).

76. Zoeller TR, Dowling AL, Herzig CT, Iannacone EA, Gauger KJ, Bansal R. Thyroid hormone, brain development, and the environment. Environ Health Perspect 110:355-361(2002).

77. Yamada-Okabe T, Sakai H, Kashima Y, Yamada-Okabe H. 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(2005).

78. Meerts I, van Zanden J, Luijks E, Leeuwen-Bol I, Marsh G, Jakobsson E, Bergman A, Brouwer A. Potent Competitive Interactions of Some Brominated Flame Retardants and Related Compounds with Human Transthyretin in vitro. Toxicol Sci 56:95-104(2000).

79. Legler J, Brouwer A. Are brominated flame retardants endocrine disruptors? Environ Int 29:879-885(2003).

80. IARC. Monographs: Some Flame Retardants and Textile Chemicals, and Exposure in the Textile Manufacturing Industry. Decabromodiphenyl Oxide p. 73-84. Lyon, France: (International Agency for Research on Cancer), 1990.

81. Lindstrom G, Hardell L, van Bavel B, Wingfors H, Sundelin E, Liljegren G, Lindholm P. Current level of 2,2'4,4'-tetrabrominated diphenyl ether in human adipose tissue in Sweden - a risk factor for non-Hodgkin's lymphoma? Organohalogen Compounds 35:431-434(1998).

82. Meerts I, Letcher RJ, Hoving S, Marsh G, Bergman A, Lemmen J, van der Burg B, Brouwer A. In Vitro Estrogenicity of Polybrominated Diphenyl Ethers, Hydroxylated PBDEs, and Polybrominated Bisphenol A Compounds. Environ Health Perspect 109:399-407(2001).

83. Kitamura S, Jinno N, Ohta S, Kuroki H, Fujimoto N. Thyroid hormonal activity of the flame retardants tetrabromobisphenol A and tetrachlorobisphenol A. Biochem Biophys Res Commun 293:554-559(2002).

84. Kuriyama SN, Talsness CE, Grote K, Chahoud I. Developmental Exposure to Low Dose PBDE 99: 1- Effects on Male Fertility and Neurobehavior in Rat Offspring. Environ Health Perspect 113:149-154 (2005).

85. Chen G, Bunce N. Polybrominated diphenyl ethers as Ah receptor agonists and antagonists. Toxicol Sci 76:310-320(2003).

86. Behnisch PA, Hosoe K, Sakai S. Brominated dioxin-like compounds: in vitro assessment in comparison to classical dioxin-like compounds and other polyaromatic compounds. Environ Int 29:861-877(2003).

87. Albinson B. Alternative ways to achieve fire safety.: Swedish Rescue Services Agency, 2002.

88. European Union. European Union Risk Assessment Report bis(pentabromophenyl) ether [Decabromophenylether] CAS: 1163-19-5; EINECS: 214-604-9: European Commission, Joint Research Centre, 2004.

89. European Union. European Union, Risk Assessement for DIPHENYL ETHER, OCTABROMO DERIVATIVE CAS No: 32536-52-0; EINECS No: 251-087-9: European Chemicals Bureau, 2003.

90. ter Schure A, Larsson P, Agrell C, Boon JP. Atmospheric Transport of Polybrominated Diphenyl Ethers and Polychlorinated Biphenyls to the Baltic Sea. Environ Sci Technol 38:1282-1287(2004).

91. Viberg H, Fredriksson A, Eriksson P. Investigations of Strain and/or Gender Differences in Developmental Neurotoxic Effects of Polybrominated Diphenyl Ethers in Mice. Toxicol Sci 81:344-353(2004).

92. Santillo D, Johnston P. Playing with fire: the global threat presented by brominated flame retardants justifies urgent substitution. Environ Int 29:725-734(2003).

93. Danish Environmental Protection Agency. Action Plan for Brominated Flame Retardants: Ministry of Environment and Energy, 2001.

94. European Union. European Union risk assessment report for diphenyl ether, Pentabromo derivative (Pentabromodipheryl ether). CAS: 32534-81-9. EINECS: 251-084-2. United Kingdon: European Chemicals Bureau, 2000.