

Polybrominated Flame Retardants

Introduction

Polybrominated diphenyl ethers (PBDEs) are a class of persistent halogenated organic compounds widely used as flame retardants. Like dioxins and PCBs, PBDE molecules resemble bicycles. They consist of two phenyl rings studded with bromine atoms (the wheels) and attached by an oxygen bridge (the frame). When PBDE molecules are exposed to heat—a s in a house fire—the bromines detach and quench the flames.

PBDEs, like PCBs, exist as more than 200 potential congeners. However, only three mixtures have been available for commercial use, as identified by the average number of bromines in the dominant congener: Deca, Octa, and Penta. Deca, with ten bromine atoms, is used in hard polystyrene plastics, textiles, and electronic equipment such as televisions. It is also used in polyethylene for wires, cables, and pipes. Octa-PBDE, with eight bromine atoms, has primarily been used in the plastic housings of computer monitors and in circuit boards. With five bromine atoms, Penta-BDE has been used in flexible foam products, such as polyurethane furniture cushions, carpet padding, and mattresses. Penta has also been used in rigid foams.¹⁻⁴ These three mixtures are not strictly homogeneous and can contain PBDEs with other numbers of bromine; for example, Penta can contain some fraction of Tetra-BDE. The only mixture currently available in the United States and the European Union is Deca-BDE. The European Union banned Octa and Penta in 2004, and the sole U.S. manufacturer voluntarily stopped production in the same year.⁵

PBDEs first became commercially available as flame retardants in 1960⁴ and have been widely used throughout the world for the last 30 years. Usage has tripled during the previous two decades.⁶ In 2001, approximately 67,440 metric tons of PBDEs were manufactured, with the majority of use occurring in North America.⁷ The U.S. has been, by far, the predominant producer and user of Penta.⁸ Over time and under ordinary conditions of use, PBDEs have diffused out of the polymer matrices in which they were embedded and are now a ubiquitous contaminant of indoor and outdoor environments.^{3, 8-10} By the late 1990s, Swedish researchers had documented exponential increases in PBDE levels in breast milk samples collected from 1972 to 1997. These findings were one factor that inspired a ban on PBDE manufacture in the European Union. Between 1998 and 2002, levels in human milk in Sweden decreased significantly.^{3, 4, 8, 10}

Here in the United States, PBDE levels in Great Lakes fish rose rapidly during the 1980s and 1990s and doubled in less than three years. PBDEs have also turned up in commonly consumed fish, including salmon, mackerel, swordfish, herring, catfish, and shellfish; and they have been detected in many types of wildlife around the world, with some of the highest levels found in harbor seals in the San Francisco Bay.⁴ This discovery, together with the Swedish breast milk results, prompted researchers to measure levels of PBDEs among U.S. human residents. U.S. inhabitants have the highest documented levels of PBDEs in the world. These levels are 10- to 100-fold higher than levels observed in Europe, Asia, or New Zealand.^{7, 8, 11-13} Moreover, as seen in fish and wildlife, body burdens appear to be increasing.^{4, 10, 11, 14, 15}

Owing to their similar molecular structure and toxic profile, PBDEs are often referred to as the ‘PCBs of the future.’^{8, 16} The less-brominated forms—Penta and Octa—are the more persistent, lipophilic, and biologically active. Some of the congeners contained in Penta-DBE have been identified as estrogenic.⁴ By contrast, Deca-BDE is less well absorbed and less bioaccumulative. Its bulky size and high molecular weight restrict its toxicity and ability to biomagnify. Furthermore, Deca-BDE binds strongly to soil and sediments, limiting its bioavailability.^{2, 3, 8, 10, 17} Ominously, however, debromination of Deca can generate the lighter, more toxic forms. The degree to which Deca degrades to the less brominated congeners in the environment is a source of ongoing debate.

Despite their widespread use, very little is known about the human health effects of exposures to PBDEs. Only a few epidemiological investigations have been conducted.^{18, 19} Limited data from animal studies suggest that these compounds may exert endocrine-disrupting effects at levels close to those being documented in the current U.S. population, especially among children,²⁰ making them of particular concern for breast cancer.

Regulatory History of PBDEs

The banning of PBDEs in Sweden in the late 1990s inspired a European Union-wide ban of the Penta and Octa formulations in 2001, which became effective in 2004.^{10, 21} In 2003, California followed suit and became the first U.S. state to enact a ban of Penta and Octa, which will go into effect in 2008. Since that time, eight other states have enacted legislation to ban these two congener formulations and, in 2004, the sole American manufacturer of PBDEs voluntarily removed

Penta and Octa from the U.S. market. Subsequently, the U.S. EPA issued a regulation to ensure no new manufacture or import of Penta and Octa after January 2005. These various legislative efforts effectively ceased the introduction of new sources of Penta- and Octa-DBEs from entering the U.S. marketplace. They do not, however, eliminate exposures from products currently in use or the manufacture of new products with recycled materials containing PBDEs or from the disposal of products containing Penta and Octa.²²

There are no comprehensive bans on the use of Deca-BDE anywhere in the U.S. In April 2007, the Washington state legislature passed a bill, now signed by the governor, that bans the use of Deca from mattresses by 2008 and from televisions, computers, and furniture by 2011.²³ Maine recently introduced similar legislation and has already passed some of the strictest laws to date.²⁴ However, in both states, the bills contain a number of loopholes/exemptions for Deca, including provisions that proven safer alternatives must be available prior to phasing it out. It remains unclear if the use of Deca-BDE will actually decline in these states after 2008. As of March 2007, nine states had introduced legislation to restrict or prohibit uses of PBDEs, including Deca, for specific purposes. More states will likely follow. The National Caucus of Environmental Legislators monitors PBDE legislation. An annotated compilation of enacted laws, executive orders, and introduced bills that seek to limit the use of PBDEs can be found on its website, www.ncel.net.

PBDEs in the Environment

PBDEs are detectable in many environmental media, including air, soil, household dust, clothes

dryer lint, sewage, fish, and wildlife.^{1, 2, 10, 11, 13, 25-}

³³ In North America, Penta-BDE is the primary contaminant found,¹¹ although Deca is often dominant in house dust. A recent meta-analysis of environmental PBDE concentrations reported exponential increases over the last 30 years, with a doubling time of approximately four to six years.¹¹ This study also demonstrated especially high levels of contamination in North America compared to Europe and Japan, the other two regions of the world with available data.^{3, 11, 13, 29}

Sources of contamination have not been fully evaluated. One important non-point source of contamination is thought to be household trash, which often contains furniture, bedding, foam cushions, and electronics loaded with PBDEs. No information, however, is currently available on the degree to which incineration and landfills contribute to environmental contamination.⁸

Recent work in Great Britain along urban-rural transects suggests that cities themselves may be sources, possibly from leakage of PBDEs from indoor to outdoor air.³⁴ Because incomplete combustion may produce brominated dioxins and furans, concern has also focused on incomplete incineration and accidental fires as additional sources of exposure.^{8, 10} Sewage sludge is a well-documented source of persistent environmental contamination, especially for Deca, which binds strongly to sediment.^{11, 29} Concentrations of PBDEs in water generally haven't been assessed due to their low solubility in water.^{8, 29} Fish and marine mammals tend to have higher levels than do their terrestrial counterparts.^{11, 29}

PBDEs in People

PBDEs have been detected in human blood, breast milk, umbilical cord blood, and in adipose, brain, liver, and placental tissue.^{7, 8, 10, 12, 13, 35-40}

Over the past three decades, PBDE body burden levels have increased 100-fold, representing a doubling time of approximately five years. On average, U.S. blood levels (35ng/g lipid, which equals 35 ppb) are 17 times higher than in those seen in European populations (2 ng/g lipid or 2 ppb).¹¹ PBDE levels in the breast milk of U.S. mothers are 10–100 times those seen in the breast milk of European mothers.⁴⁰ Within the U.S., human body burdens of PBDEs vary wildly. Most PBDE researchers report levels between 4 and 400 in human blood and breast milk. However, in 2005, a team of researchers found individuals in New York City with levels as high as 9,630 ppb (in a 32-year-old man) and 4,060 ppb (in a 23-year-old woman). These levels are 4 to 9.5 times higher than any previously reported in people anywhere in the world.^{41, 42}

The exponential rise in body burden levels of PBDEs stands in stark contrast to the temporal trends of other well-known organohalogenated compounds, many of which have markedly declined over the last few decades.^{7, 15} A recent analysis comparing body burden levels of PBDEs, dioxins, furans, and PCBs measured in current and archived sera from 1973 in a U.S. population demonstrated this dramatically changing exposure profile.⁷ PCBs, dioxins, and furans all declined dramatically during the 30-year span (1973–2003) marked by the collection of the two sets of sera, presumably reflecting the banning and regulation of these compounds. In contrast, PBDEs were

virtually undetected in the 1973 samples but were the predominant compound in the current sera. On average, these levels were more than twice those of current levels of PCBs, and 100 to nearly 2,000 times those of the dioxins and dibenzofurans. These levels may decline in the U.S. population with the recent ban of Octa and Penta. Initial reports from Sweden indicate that body burden levels there may be leveling off or even declining after exponential increases observed during the 1980s and 1990s.¹¹ However, the Swedish ban on PBDEs is more comprehensive.

Routes of Exposure

Routes of human exposure to PBDEs and the relative contribution of different sources depend on the congener or congener group, the country, and the life stage of the individual.^{1, 8, 43, 44} Food is a vector for exposure but appears to play a lesser role than it does for other common persistent organic pollutants.⁴⁵⁻⁴⁷ There is now good evidence that both diet and the indoor environment (probably inadvertent dust ingestion) contribute to exposure to Penta-BDE in adults in the U.S.⁴⁷ The indoor environment – both dust ingestion and dust inhalation – may dominate for exposure to Deca-BDE in the U.S.⁴³

The Debromination Question

Some human exposure to bioactive Penta- and Octa-PBDE may come from the degradation of Deca. In contrast to industry claims, several studies now indicate that Deca can debrominate under ordinary environmental conditions, including through exposure to sunlight and via metabolism. Bacteria and fish, for example, can convert Deca into lighter brominated congeners^{10,}

^{17, 32, 48-52} and there is some evidence for metabolic debromination of Deca in mammals.⁵³ While Deca is not easily absorbed across the gut wall, its less brominated congeners are.^{10, 11} Moreover, recent studies of workers exposed to Deca indicate that some fraction of Deca is absorbed. Deca has also been detected in blood and breast milk samples from the general population.⁴

Occupational Exposures

Occupational exposures may be important for workers in computer and electronic manufacturing, recycling, and disassembly plants and in PBDE formulation facilities.^{1, 3, 8, 11, 54}

Diet

Diet is not the sole significant route of exposure to PBDEs and appears to explain only a portion of the variability in PBDE levels.^{10, 35, 38, 44, 47}

Several lines of evidence suggest a smaller role for diet than the lipophilic nature of PBDEs might suggest.^{12, 35, 37} First, research has established a link between Penta-BDE concentrations found in people with the quantities found in dust from their homes, independent of diet.⁴⁷ Second, although levels of fish contamination are orders of magnitude higher in North America than they are in Japan or Europe, analyses in U.S. populations tend not to see a large correlation between fish consumption and body burden levels of PBDEs.^{11, 14, 47} Third, PBDE levels are not positively correlated with age. Indeed, children have higher body levels than adults. Two recent studies reported that PBDE levels in U.S. children are two to five times those found in adult populations.^{36, 55} One case study of a San Francisco Bay Area

family³⁶ found blood levels of Deca comparable to levels seen in Swedish workers manufacturing and/or dismantling Deca-treated products.^{56, 57}

Total PBDE levels in the children, which ranged from 151–651 ng/g lipid, approached the 95th percentile of what has been reported in U.S. adult populations.⁷

All together, these results suggest that diet is not the sole or primary route of exposure for children and adults. Ingestion of breast milk does appear to be the primary route of exposure among breast-feeding infants.¹ PBDEs can also pass through the placenta.¹ Liver tissues from seven live-born and four stillborn U.S. infants attest to prenatal PBDE transfer from mother to offspring. The mean level was 23.1 ppb in these infants, and the median 15.2 ppb, lipid.³⁹

Household Dust Ingestion and Inhalation

Among children and adults, dust appears to be an important vector for exposure. Unlike PCBs, PBDEs are a pervasive indoor pollutant found at high levels in household and office dust.^{7, 31, 32, 47}

A recent analysis of PBDE levels in breast milk samples reported a strong correlation with household dust samples, and to a lesser degree, with dietary consumption of dairy and meat products.⁴⁷ Thus, inhalation and ingestion of dust may be a particularly significant route of human exposure, especially among young children.^{36, 58}

Allen et al.⁴³ found that inhalation of dust may be important for exposure of adults to Deca.

The degree to which leaching of PBDEs from products in the home or office—directly into the indoor environment or through direct dermal absorption from furniture/mattresses—contributes

to human exposures requires further exploration. House dust samples from the Washington DC area found no correlations between total PBDE concentration and year of house construction, type of flooring, presence of carpeting, or number of television sets or personal computers in the home.³² A new study focusing on house dust likewise found no direct connection between household products known to contain PBDEs and levels of PBDEs in dust.⁴⁷ However, when using x-ray fluorescence to screen for bromine, researchers in Boston did definitively link PBDE concentrations in dust with bromine concentrations of household furnishings, including TVs, power strips, CD players, VCRs, alarm clocks, chairs, couches, mattresses, pillows, and futons.⁴⁵

Critical Review of the Literature

In spite of the widespread usage of and documented human exposures to PBDEs, remarkably little data on the health effects of PBDEs exist. The full-bore introduction of PBDEs into electronics and furniture manufacturing in the 1970s preceded a systematic investigation of their toxicological properties. Concerns about the environmental health impacts of PBDEs were greatly heightened after documentation of an exponential rise in PBDE levels in national breast milk samples in Sweden. This report was published in 1998.⁵⁹ Thus, research on the health impacts associated with these widespread exposures is less than a decade old. To date, no breast cancer studies have been conducted in humans. However, the virtual absence of PBDEs in human sera prior to 1973 means that the oldest cohort of U.S. women exposed to PBDEs in

infancy is now only in their 30s – too young for most to develop breast cancer. For women who are old enough to be at risk for breast cancer, PBDE exposure occurred in adulthood, not during fetal, infant, or pubertal life when the mammary gland was under development and when exposures may raise the most risk for harm. Moreover, widespread human exposure to PBDEs may not yet have exceeded the latency period for carcinogenesis. Meaningful retrospective epidemiological investigations into PBDEs as a contributor to breast cancer risk are thus decades away. The suggestion that some congeners, especially Penta, act as endocrine disruptors, nevertheless, make PBDEs of particular interest with respect to breast cancer etiology.

In Vitro Studies

A number of in vitro studies have suggested potential endocrine-disrupting activity for PBDEs. PBDEs, which structurally resemble thyroid hormone, have been shown in vitro to disrupt thyroid activity by competitively binding to the T4 receptor site.^{3, 60, 61} They may also bind to the plasma carrier protein transthyretin, causing more rapid metabolism of thyroid hormone.⁶²

However, the resemblance between PBDEs and thyroid hormone is not the whole story. Additional studies have shown that PBDEs – or their hydroxylated and methoxylated metabolites – can bind with estrogen receptors in vitro,⁶³⁻⁶⁵ while one study reported anti-androgenic activity.⁶⁶ Furthermore, PBDE metabolites disrupt cytochrome P45017 (CYP17) enzyme activity in vitro.⁶⁷ Because CYP17 catalyzes key steps in sex hormone synthesis in humans, these results may

be particularly relevant to breast cancer, although such effects have yet to be evaluated in vivo.

In Vivo Studies

Carcinogenicity studies in animals have only been conducted for Deca-BDE, the least toxic mixture. Based on very limited bioassay data from chronic oral dose studies in rats, the U.S. Environmental Protection Agency classified Deca-BDE as a Class C (Possible Human Carcinogen). This classification, published in 1986, was based on no human data and limited evidence of carcinogenicity in rodents, specifically increased incidences of neoplastic liver nodules in male and female rats and increased incidences of hepatocellular adenomas in male rats.⁶⁸ All of the PBDE mixtures have been shown to disrupt thyroid balance in vivo, although Deca-BDE appears to be the least potent in this regard.³

The mechanism by which PBDEs lower thyroid levels has not been fully characterized. Furthermore, the degree to which these findings are applicable to humans, who are considered to be less sensitive to disruption of thyroid function than rodents, is not currently known.³ Finally, the relevance of these findings to breast cancer is not known. While there have been reports of an elevated incidence of thyroid diseases among breast cancer patients, a causal link has not been established; but this is an area of growing and intense interest to breast cancer researchers.⁶⁹

A handful of animal studies have examined the reproductive effects of PBDEs. Structural changes were observed in the ovaries of PBDE-treated female rats,⁷⁰ and sperm function decreased in male mice exposed to Deca.⁷¹ Furthermore, a

number of studies have reported delays in puberty onset in both male and female rats exposed to PBDEs.^{66, 72-74} Stoker and colleagues reported delayed puberty in male rats as well as suppressed growth of androgen-dependent tissues following a peri-pubertal exposure. This disruption appeared to indicate that PBDE was acting as an androgen receptor antagonist.^{66, 74}

No studies have examined the effect of PBDEs on mammary gland development.

Human Studies

To date, no epidemiologic study of breast cancer and PBDE exposures has been conducted. Two small studies from Sweden, however, suggest potential carcinogenic effects in humans. In 1998, Hardell and colleagues reported a non-significant two-fold elevated risk of non-Hodgkin's lymphoma associated with adipose levels of Tetra-BDE.⁷⁵ A later study by the same research group in Sweden reported an increased risk of testicular cancer (OR = 2.5, 95% CI = 1.02–6.0) associated with maternal, but not case, sera levels of PBDEs.⁷⁶ These latter findings are particularly intriguing with regards to breast cancer, as risk for testicular cancer is thought to be at least partially mediated by pre-/peri-natal exposures to endogenous and exogenous hormone levels. The maternal blood levels in this study, however, were collected at the time of the son's diagnosis and may not reflect the *in-utero* exposures experienced by the sons from decades prior.

Two new birth cohort studies have found associations between PBDE concentrations and health effects other than cancer. In a Danish-Finnish study, the concentration of PBDEs in

breast milk was significantly higher in boys with cryptorchidism (undescended testicles) than in controls.¹⁹ A study in Taiwan found a relationship between PBDE levels in breast milk and birth outcome: higher PBDE levels were associated with lower birth weight and shorter birth length.¹⁸

Conclusions and Future Directions

PBDE exposures to humans are pervasive and, in contrast to other PCBs and dioxins, human body burden levels are increasing, with a doubling time of about five years.¹⁶ While recent regulatory action to restrict the use of some PBDEs may stem the extraordinary increases in exposures observed over the last three decades, human exposures are likely to continue for decades to come, because PBDEs persist and bioaccumulate in the environment. Despite known widespread exposures, the health effects remain largely unknown. Retrospective epidemiology studies to illuminate breast cancer risks are unlikely to yield insights in the near future because the widespread commercialization of PBDEs occurred only within the last thirty years. However, it is feasible to investigate the developmental effects of PBDEs on the human mammary gland now. Outstanding questions include:

What are the main routes of human exposure among both adults and children?

How are the various PBDE congeners metabolized and excreted? What are their half-lives in humans? To what degree does Deca-BDE break down into more toxic congeners?

What is the environmental fate of PBDEs, in particular Deca-BDE, which is still being produced and used in the U.S.?

Do workers with high levels of occupational exposures have higher-than-expected risks of cancer?

Are body burden levels of PBDEs able to serve as early indicators of breast cancer risk? Do they affect menstrual function, onset of puberty, development of mammary glands, or timing of menopause?

Are Octa- and Penta-BDEs carcinogenic? Basic cancer bioassays are needed.

How do PBDE congeners affect endocrine pathways that may play a contributory role in breast carcinogenesis?

How do PBDEs contribute to the overall body burden of estrogenic and mitogenic synthetic chemicals, such as chlorinated persistent organic pollutants, pesticides, and pharmaceuticals, and, in so doing, are there important additive or synergistic effects?

Does thyroid hormone disruption play a role in breast cancer risk?

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Identifying Gaps in Breast Cancer Research

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