Distribution and Potential Toxicological Effects of 2,2',4,4'-tetrabromodiphenyl Ether (BDE-47) as a Endocrine Disrupting Chemical in Human and Animals

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ABSTRACT

Polybrominated diphenyl ethers (PBDEs) are a class of "brominated" (bromine containing) man-made chemicals used as flame retardant additives in plastics, foams, and textiles. PBDEs are found in various environmental contaminants in air, soil, sediment, and water, and 209 individual forms (congeners) of PBDE exist. Among these, 2,2',4,4'-tetrabromodiphenyl ether (BDE-47) is the dominant congener found in the environment. Exposure to BDE-47 is now worldwide, and levels of BDE-47 have been detected in the blood of animals, including humans. BDE-47 can adversely affect the developmental system in both humans and animals. BDEs have structural similarities to polychlorinated biphenyls and thyroid hormones. However, recent studies have shown that BDEs may act as hormonal disrupting chemicals with detrimental effects. Therefore, a reliable assessment of BDE-47 toxicological action is required to understand the detrimental impacts of BDE-47 on human health. In this review, we overview recent studies on the distribution and potential toxicological effects of BDE-47 in humans and animals.

(Key words : tetrabromodiphenyl ether, endocrine disrupting chemicals, toxicological effect)

INTRODUCTION

Environmental chemicals are natural or synthetic chemicals with significant effects on the endocrine system. Environmental chemicals that have harmful effects on the endocrine system are called endocrine disrupting chemicals (EDCs). EDCs are present in food and consumer products and interfere with hormone biosynthesis, metabolism, or function resulting in a deviation from normal homeostatic control or reproduction (Waring and Harris, 2005). Most EDCs act as naturally occurring hormones in the body. EDCs alter normal hormone regulation through diverse mechanisms such as binding to hormone receptors, mimicking hormones, and/or blocking hormone action. Most EDCs possess estrogen-like activity and bind to estrogen receptors (ERs) and induce or modulate ER-mediated responses. EDCs may also bind to thyroid receptors and dysregulate the neuroendocrine system (Gray *et al.,* 1997; Dang *et al.,* 2007; Ozen and Darcan, 2011; Vo *et al.,* 2011).

Polybrominated diphenyl ethers (PBDEs) are a well-known class of organic brominated flame retardant chemicals used worldwide in a variety of products, including plastics and textiles, building materials, carpets, vehicles, and computers. They have been found in air, soil, sediments, humans, wildlife, and fish (Darnerud *et al*., 2001; Strandberg *et al*., 2001; Alaee *et al*., 2003; Darnerud, 2003; Siddiqi *et al*., 2003). PBDEs have been detected in the environment as well as in the tissues and milk of animals, including humans (Alaee and Wenning, 2002; Stoker *et al*., 2005) and are classified according to the average number of bromine atoms in the molecule. The family of PBDEs consists of 209 congeners such as di-, tri-, tetra-, penta-, hexa-, hepta-, octa-, nona-, and deca- bromodiphenyl ethers (Birnbaum and Staskal, 2004; Birnbaum and Cohen Hubal, 2006). One of the PBDE congeners that we focused on in this study is 2,2', 4,4'-tetrabromodiphenyl ether (BDE-47), a tetra-brominated congener. BDE-47 has been detected in tissue samples in the Pacific Northwest of the United States (McDonald, 2005; Schecter *et al.,* 2005; Schecter *et al.,* 2007), Sweden (Noren and Meironyte, 2000), India (Kumar *et al*., 2006), Australia (Toms *et al*., 2007), Taiwan (Chao *et al*., 2007), Poland (Jaraczewska *et al*., 2006; Wang *et al*., 2006), Japan (Eslami *et al*., 2006) and China (Bi *et al*., 2006; Bi *et al*., 2007). Furthermore, BDE-47 has been detected in human adipose tissue (Petreas *et al*., 2003;

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Johnson-Restrepo *et al*., 2005; Fernandez *et al*., 2007), liver (Meironyte Guvenius *et al*., 2001), human milk (Akutsu *et al*., 2003; Lind *et al*., 2003; Schecter *et al*., 2003; She *et al*., 2007), blood (Sjodin *et al*., 2001; Petreas *et al*., 2003; Bradman *et al*., 2007) and placental transport (Guvenius *et al*., 2003; Mazdai *et al*., 2003) at concentrations higher than those reported for other congeners. Thus, concentrations are increasing in the environment (Betts, 2002; Law *et al*., 2003; Birnbaum and Staskal, 2004). BDE-47 has the potential to disrupt endocrine homeostasis. Several studies have suggested that BDE-47 may disrupt thyroid hormone (TH) homeostasis (Hallgren *et al*., 2001; Richardson *et al*., 2008) and reproductive/developmental systems (Eriksson *et al*., 2001; Staskal *et al*., 2006). This raises concerns that measurable levels of BDE-47 could pose significant health risks to humans; thus, we suggest the importance of BDE-47 as an EDC in humans and animals in this review.

1. Distribution of BDE-47 in Human

BDE-47 is the major PBDE found in the environment and wildlife (Hites, 2004). BDE-47 has been found in almost all environmental samples and tissues (Staskal *et al*., 2006). Adipose tissues were taken from breast adipose samples of 23 women in San Francisco Bay, CA, USA, and BDE-47 was the highest among all congeners measured (She *et al*., 2002). In another study, tri- to hexa-BDEs were found in human samples, and BDE-47 comprised 30～50% of the total PBDE in adipose and liver tissues (Meironyte Guvenius *et al*., 2001). Milk samples from 40 first-time mothers from the Pacific Northwest of the United States and Canada were analyzed for PBDEs and BDE-47 was the dominant congener in most samples (She *et al*., 2007). Additionally, BDE-47 was at the highest level, and hexaBDE-153 and pentaBDE-99 and -100 were the next highest congeners (Schecter *et al*., 2003). BDE-47 is also found in milk samples from Japan and Sweden (Ohta *et al*., 2002; Akutsu *et al*., 2003; Lind *et al*., 2003). Taken together, these results demonstrate that humans and animals are exposed to BDE-47 and that there are differences in BDE-47 concentrations depending on ethnicity and location.

The median BDE-47 concentration in serum samples collected from 12 male blood donors in the US was 0.63 ng/g lipid weight (lw) in 1988 (Sjodin *et al*., 2001). Furthermore, the median concentration of BDE-47 in seven serum pools from the US was 34 ng/g lw in 1985～2002. Interestingly, BDE-47 concentrations in archived serum samples were arrayed by collection period; a constant increase was observed from 1985～1999 and then a small decrease in 2000～2002 (Sjodin *et al*., 2004). A study by Bradman *et al*. (2007) measured BDE-47 concentrations in 24 pregnant immigrant women and women of child-bearing age in the US and showed that BDE-47 was found at a median concentration of 11 ng/g lw. Additionally, BDE-47 was measured in a serum sample collected in 2004 from a US family. As a result, BDE-47 concentrations varied from 32 ng/g lw in the father to 60, 137, and 245 ng/g lw in the mother, child, and toddler, respectively. These results showed that the children's level was 2- to 5-fold higher than that of their parents (Fischer *et al*., 2006). Taken together, these results suggest that blood levels of PBDEs appear to depend on demographic characteristics, including age, lactation, and parity.

Maternal and cord blood samples were collected in 2000～2001 from US and Swedish mothers. In a study by Mazdai *et al*. (2003), PBDEs were measured in 12 samples collected in 2001 from the US, and concentrations of 28 and 25 ng/g lw BDE-47 were detected in maternal and fetal serum, respectively. BDE-47 concentrations in maternal and fetal serum are correlated, indicating that PBDEs cross the placenta (Mazdai *et al*., 2003). In addition, a study by Guvenius *et al.* (2003) analyzed 15 Swedish mother samples and reported different results from those of Mazdai *et al*. (2003), who found 25～32-fold lower concentrations than the median BDE-47 concentration in maternal and fetal plasma (Guvenius *et al*., 2003). Although BDE-47 can be measured in adipose tissue, liver, breast milk, serum and cord blood, there is poor understating with regard to its toxicological effects.

2. Distribution of BDE-47 in Animals

Adult male rats or mice were given a single oral dose of ^{14}C-labeled BDE-47 and ^{14}C-BDE-47 and metabolite levels in adipose tissue, liver, lung, kidney, brain, and plasma tissues were analyzed. After 5 days, 86% of the administered dose was retained in rat tissues, primarily accumulating in adipose tissue. ^{14}C-BDE-47 concentration was lower in other tissues except adipose tissue and lung because of excretion through feces and urine. However, about half of the ^{14}C-BDE-47 remained in mice after 5 days. Concentrations of ^{14}C-BDE-47 in mice were highest in adipose and liver tissues which was similar to rats. The ^{14}C-BDE- 47 concentration is 50% lower in kidney than in lung, and 10% lower in brain than in adipose tissue and liver (Orn and Klasson-Wehler, 1998). A study was conducted to characterize absorption, distribution, and ex-

cretion parameters in female mice following a single BDE-47 treatment at different doses, times, and routes of exposure. Over 80% of the administered dose was absorbed after oral or intratracheal administration, whereas ~62% was absorbed when the dose was applied dermally. The BDE-47 concentration in adipose tissue was highest after oral exposure. Levels of BDE-47 in skin, liver, muscle, and lung were intermediate, whereas those in kidney, blood, and brain were low. To conclude, almost all BDE-47 is found in lipid-rich tissue. BDE-47 is rapidly excreted in the urine and feces. BDE-47 is half of initial amount at 1.5 days after a single oral exposure in animals (Staskal *et al*., 2005). Additionally, gender and species differences are observed in BDE-47 tissue distribution and excretion. In male and female rats, adipose tissue contains 25 and 37% of the total dose in male and female rats, respectively, whereas 20 and 31% of the total dose was retained in adipose tissue of male and female mice, respectively. BDE-47 radioactivity in mice tissues was lower than that in rat tissues. However, no significant differences in the radioactivity in adipose tissue were observed between the female rats and mice or between the male rats and mice (Sanders *et al*., 2006). Staskal *et al*. (2006) examined BDE-47 distribution in postnatal day 10 (PND) and various developmental stages (PNDs 22, 28, 40 and 70) of mice identified and determined the mechanism responsible for its rapid urinary excretion. All pups were orally administered 0 or 1 mg/kg BDE-47 on PND 10. Blood, brain, adipose, liver, kidney, skin, muscle, stomach, and lung tissues were collected at sacrifice after dosing. The BDE-47 levels in each tissue in the pups were compared with results in adult mice, which were discussed above in the Staskal *et al*. (2005) study. The percent of BDE-47 dose/g brain tissue in pups was significantly higher than that in adults at PND 10. Furthermore, the dose/g adipose tissue and kidneys was greater in pups than that in adults after dosing. Based on total body level of radiolabel, retention of the administered dose was significantly higher in pups than that in adults at all time points. The second phase of the study compared the tissue deposition of BDE-47 after dosing on PND 10, 22, 28, 40, and 70. BDE-47 blood concentration decreased at all time points, but the levels in pups were significantly higher than those in adults at PND 10. Adipose tissue levels in mice at PND 10 and 22 were higher than those at PND 28, 40, and 70; thus, 59%, 41%, and 34% of the dose remained in the mice dosed on PND 22-, 28-, and 40, respectively. In addition, the BDE-47 concentrations in urine decreased significantly on PND 22 and 28 compared to those on PND 40 and 70 (Staskal *et al*., 2006).

Taken together, these results suggest that distribution and urinary excretion of BDE-47 is species and age dependent, and that it is a saturable and dose-dependent process. Developing mice pups have a reduced capacity to excrete BDE-47 during development.

3. Effect of BDE-47 on Endocrine System

PBDEs are structural similar to THs. There are substantial environmental and toxicological concerns concerning PBDEs due to their persistent and bioaccumulative properties, their structural similarity to PCBs, and their potential endocrine disrupting and developmental effects. PBDEs alter TH levels in experimental animals (Fowles *et al*., 1994; Hallgren *et al*., 2001). Among PBDEs, BDE-47 may act as an EDC in humans and animals.

The present study measured the ability of BDE-47 to change TH, vitamin A levels, and microsomal enzyme activity in orally exposed male mice. The animals were given daily oral doses of BDE-47 (18 mg/kg body weight) for 14 days Blood samples were analyzed for thyroid-stimulating hormone (TSH) and total and free thyroxine (T4), and the liver, thymus, and spleen were weighed. The activities of phase I and phase II enzymes in liver tissues were assayed. Induction of these enzymes suggests metabolic transformation of BDE-47. The liver somatic index (liver weight/body weight) increased significantly compared to that in the control, but no significant differences were found for the thymus or spleen somatic weight. BDE-47 significantly decreased plasma concentrations of free and total T4; however, TSH and vitamin A concentrations did not change significantly. Furthermore, ethoxy resorufin O-dealkylase (EROD) and methoxy resorufin O-dealkylase (MROD) increased significantly in the BDE-47-treated group. Pentoxy resorufin O-dealkylase (PROD) and the phase II enzyme uridine diphosphoglucuronosyl transferase (UDPGT) activity did not change significantly in the BDE-47-treated group (Hallgren *et al*., 2001). Another study administered various doses of 0, 3, 10, or 100 mg/kg BDE-47 to female mice of different genders for 4 days. Liver weights increased significantly in animals treated with 100 mg/kg BDE-47, and a greater decrease in serum total T4 was observed at 100 mg/kg of BDE 47 compared to that of the other doses. No increase in UDPGT mRNA expression was observed, but significant increases in hepatic Ugt1a1, Ugt1a7, and Ugt2b5 mRNA expression followed significant decreases in T4 concentrations at a BDE-47 dose of

100 mg/kg. No significant expression changes were found for Ugt1a6. The changes in UDPGT isoform expression correlated with the observed decreases in T4. However, in comparison to the observed changes in UDPGT mRNA expression, BDE-47 treatment did not change hepatic T4-UDPGT enzyme activity. The authors suggested that the T4-UDPGT enzyme activity was not sensitive to measure changes in activity of individual UDPGT isoforms (Richardson *et al*., 2008).

The effects of BDE-47 on TH levels were examined in female Sprague-Dawley rats. Rats were administered oral doses of 0, 1, 6, or 18 mg/kg-day BDE-47 for 14 days. Plasma levels of free T4 showed a decreasing trend that was significant only at 18 mg/kg-day compared with that in the control group. However, no significant differences were observed in the plasma levels of total T4 and TSH compared to those in the control. In an *ex vivo* binding study of ^{125}I-T4-derived radioactivity bound to the transporter transthyretin (TTR), a certain dose-dependency was indicated in the groups exposed to BDE-47. EROD activity increased significantly at 6 and 18 mg/kg but not in a dose-dependent manner. MROD and PROD activities showed dose-dependent increases that were statistically significant at 6 and 18 mg/kg. Treatment with BDE-47 resulted in a moderate dose-dependent induction of UDPGT activity but UDPGT activity was not correlated with the decrease in T4 levels (Hallgren and Darnerud, 2002). These results provide suggest that BDE-47 causes am imbalance in TH levels in animals.

Meerts *et al*. (2001) investigated the (anti)estrogenic effects of several PBDE congeners in breast cancer cell line (T47D) assays based on ER-dependent luciferase reporter gene expression and T47D cells stably transfected with plasmids containing an estrogen response element (ERE)-luciferase reporter gene (pERE-Luc). Eleven PBDEs showed estrogenic effects, with concentrations leading to 50% induction (EC50) varying from 2.5 to 7.3 μM. PBDEs induced luciferase in a dose-dependent manner. However, BDE-47 had very weak estrogenic activity; luciferase activity was very weak compared to all PBDEs, except BDE-15, -77, -99, -153, -166, and -190 (Meerts *et al*., 2001). A study evaluated the potential estrogenic effect of BDE-47 on the induction of calbindin-D_{9k} (CaBP-9k). CaBP-9k is a novel biomarker for detecting EDs. Uterine CaBP-9k is expressed mainly in the endometrial stroma and myometrium of the uterus in rodents and is regulated by estrogen and progesterone in the uterus (Hong *et al*., 2003; An *et al*., 2004; Hong *et al*., 2004; Hong *et al*., 2005; Dang *et al*., 2007; Choi and Jeung 2008; Vo and Jeung 2009; Vo *et al*., 2010; Vo *et al*., 2011). Immature rats (PND 16) were subcutaneously (sc) injected with BDE-47 in corn oil at doses of 0, 50, 100, or 200 mg/kg body weight for 3 days. One group of rats was treated with a high dose (200 mg/kg) of BDE-47, and the other group was sc injected with ICI 182,780, an ER antagonist, at a dose of 25 μg per rat 30 min before the BDE-47 treatment. A significant increase in uterine CaBP-9k mRNA and protein expression was observed in a dose-dependent manner following BDE-47 exposure at all doses. However, ICI 182,780 co-treatment completely reversed BDE-47-induced CaBP-9k mRNA and protein induction in the uteri of immature rats (Dang *et al*., 2007). This experiment used a high BDE-47 concentration compared to that used in other experiments. But, the findings demonstrate new insight into the estrogenic effect of BDE-47 in estrogen-responsive tissues. These results indicate the potential estrogenic effect of BDE-47.

4. Effect of BDE-47 on Neurotoxicity and Reproductive Toxicity

To assess whether PBDEs may be detrimental to neurodevelopment, Eriksson *et al*. (2001) performed a neurobehavioral study in adult male mice following neonatal exposure to BDE-47. BDE-47 was administered by gavage to male mice on PND 10 at doses of 0, 0.7, or 10.5 mg/kg BDE-47. Neonatal exposure to BDE-47 causes permanent aberrations in spontaneous behavior, which are evident in 2- and 4-month-old animals. Spontaneous motor behavior tests were used to measure locomotion (horizontal movement), rearing (vertical movement), and total activity (all types of vibration within the test cage [i.e., those caused by mouse movement, shaking/tremors, and grooming]). The spontaneous motor behavior data showed a dose-response-related disruption of habituation in mice treated with BDE-47 (Eriksson *et al*., 2001).

In vitro studies have shown that exposure to BDE-47 results in severe neurotoxic disorders. Ping He *et al*. (2008) investigated the effects of oxidative stress, DNA damage, and apoptosis induced by BDE-47 in cultured primary rat hippocampal neurons at different BDE-47 concentrations. Their results showed that BDE-47 significantly increases reactive oxygen species (ROS), percentage of apoptosis, malondialdehyde content, glutathione peroxidase level, and the lactic dehydrogenase (LDH) leakage rate at a higher DBE-47 concentration (41.2 μM), However, no significant increases were observed at lower BDE-47 concentrations (2.06 and 20.6 μM) compared with those in the control group. Dose-related reductions in the levels of glutathione, superoxide dismutase, and increased DNA damage (tested

by a comet assay) were observed when primary rat hippocampal neurons cells were exposed to varying concentrations of BDE-47 (He *et al*., 2008). The results indicate that BDE-47 is cytotoxic and genotoxic to neuronal cells.

A recent study evaluated the cytotoxic and genotoxic effects of BDE-47 in human neuroblastoma (SH-SY5Y) cells *in vitro*. Cell viability, cell proliferation (nuclear division index, NDI), LDH leakage, ROS formation, cell apoptosis, DNA breakage, and cytogenetic damage were assessed. BDE-47 exposure resulted in a significant decrease in cell viability and a significant increase in ROS formation. SH-SY5Y cells treated with BDE-47 showed a significantly increased percentage of apoptotic cells. The log-transformed olive tail moment increased significantly in cells treated with BDE-47 compared with that in the control. However, a significant increase in the percentage of DNA in the tail was only observed at 8 μg/ml BDE-47. BDE-47 caused a dose-dependent decrease in the NDI and dose-dependent increases in chromosome abnormalities as measured by total micronuclei/1,000 binucleate cells (BNCs), micronucleated binucleate cells/1,000 BNCs, and nucleoplasmic bridges/1,000 BNCs (He *et al*., 2008). These results suggest that BDE-47 could have neurotoxic effects.

Few reports are available regarding the reproductive toxicity of BDE-47. As previously mentioned, BDE-47 has estrogenic activity. Dang *et al*. (2007) measured dose and time responses to BDE-47 using an uterotrophic bioassay in immature rats. A significant increase in uterine wet weight was observed, which changed at 24 h after injection with a high dose (200 mg/kg) of BDE-47. A significant increase was seen as early as 6 h after high dose BDE-47 injection. The uterotrophic activity peaked at 12 h and continued until 24 h after the injection. Treatment with ICI 182,780 (25 μg/kg) reversed the BDE-47-induced increase in uterine wet weight in immature rats. These results suggest that BDE-47 induces uterotrophic effects through its estrogenic activity. However, data on the toxicological effects of BDE-47 on the reproductive system is very limited. Therefore, future studies should investigate BDE-47 toxicity on male and female reproductive structures.

CONCLUSION

BDE-47 is the most prominent PBDE found in the environment with significant toxicity to various human and animal tissues (Fig. 1). The BDE-47 concentration has increased markedly worldwide. Recent studies have reported associations between BDE-47 and hormones in humans and wildlife. BDE-47 adversely affects the endocrine system in humans and animals by accumulating in adipose tissues, blood, liver, and milk. Furthermore, BDE-47 has estrogenic, neurotoxic and reductive toxic effects, resulting in severe biological alterations such as changes in TH levels. Nevertheless, there is a lack of knowledge about EDCs and human health. Therefore, future research including toxicology studies about BDE are necessary.

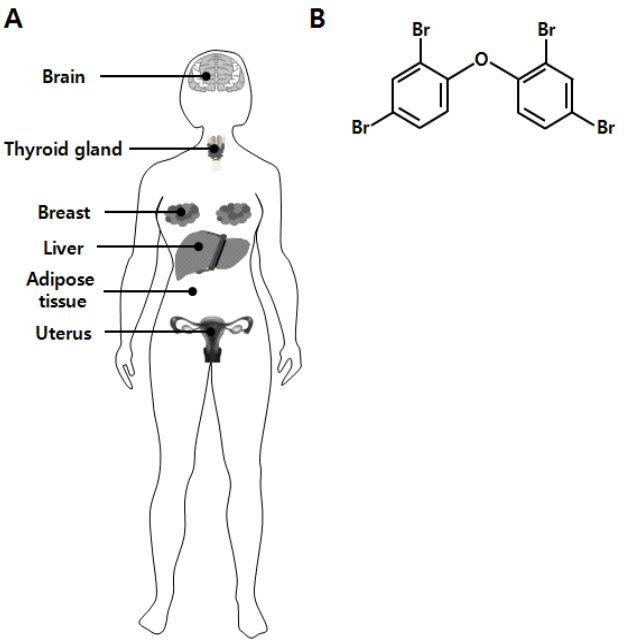

Fig. 1. Schematic diagram showing the main organs targeted by BDE-47 in body (A) and chemical structure of BDE-47 (B). This figure demonstrated that various tissues are vulnerable to BDE-47, including brain, thyroid gland, breast, liver, adipose tissue and uterus.

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