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Placental and lactational transfer of decabromodiphenyl ether and 2,2′,4,4′-tetrabromodiphenyl ether in dam-offspring pairs of Sprague-Dawley rats

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ABSTRACT

Although several studies have conducted maternal transfer of individual PBDE congener in experimental animals, there is a paucity of research on differences in maternal transfer of PBDE congeners. The purpose of the study was to investigate and compare placental and lactational transfer of BDE 47, -209 and its metabolites in rat dam-offspring pairs following repeated administration of BDE 47 and -209. ^{13}C-BDE 47, BDE 209 and its debrominated congeners were detected both in dam serum and offspring body, which indicates that PBDEs can be maternally transferred. In addition, BDE 196 and -197 appeared in offspring body earlier than in maternal serum, which suggests that debromination can be occur in offspring body. BDE 209 increased in both dam and offspring while levels of ^{13}C-BDE 47 was not increased in dam serum. 13C-BDE 47 seems to be stored in breast milk rather than in maternal serum, which can be assumed through the drastic increase of the congener in suckling pups. The magnitude of lactational transfer of the administered congeners was greater than that of placental transfer. And ^{13}C-BDE 47 was relatively more transferred to suckling pups than BDE 209 through breastfeeding.

1. Introduction

Polybrominated diphenyl ethers (PBDEs) are an important class of additive flame-retardants used in a variety of products, including textiles, furniture upholstery, and electronic appliances. Because PBDEs do not bind chemically to the product, they are emitted continuously into the environment (Frederiksen et al., 2010). Three technical mixtures have been widely used: penta-, octa- and deca-BDE formulations. Due to growing environmental and human health concerns, penta-BDEs were voluntarily phased out in 2004 due to their persistence in the environment; global regulation of both the penta- and octa-BDE formulations followed in 2009, with their inclusion in Annex A of the Stockholm Convention, which aims to protect the environment and human health (The Stockholm Convention, 2010).

PBDEs are persistent and lipophilic compounds that bioaccumulate readily in the environment. They have been shown to cause neurotoxic effects in mice (Viberg et al., 2004) and can interact with the thyroid hormone system by mimicking deiodinase enzymes, which are essential in thyroid hormone formation (Butt and Stapleton, 2013; Jin et al., 2010; Pellacani et al., 2012). Thyroid hormone is very important for brain development. Some studies have reported that pre- or postnatal exposure to PBDEs can decrease thyroid hormone levels and eventually result in neurobehavioral disorders or irreversible deficits in cognitive performance (Herbstman et al., 2015; Roze et al., 2009; Stapleton et al., 2011).

The less brominated congeners including 2,2′,4,4′-tetrabromodiphenyl ether (BDE 47) and 2,2′,4,4′,5-pentabromodiphenyl ether (BDE 99) have been investigated most widely regarding their toxicological aspects. They bioaccumulate more easily in lipid-rich tissues than do highly brominated congeners, such as 2,2′,3,3′,4,4′,5,5′,6,6′-decabromodiphenyl ether (BDE 209), which is rapidly catabolized *in vivo* (Frederiksen et al., 2010). For that reason,

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highly brominated congeners have received little attention in toxicological studies. However, there are some evidences that highly brominated congeners are degraded into less brominated congeners. Several previous studies have evaluated debromination *in vivo* in rainbow trout (Stapleton et al., 2006), carp (Stapleton et al., 2004), rats (Huwe and Smith, 2007), dairy cattle (Kierkegaard et al., 2007), and occupationally exposed workers (Thuresson et al., 2005).

BDEs 47 and 209 are the major sources of PDBE exposure in the diet and house dust (Shin et al., 2016), respectively. BDE 47 is the predominant congener, accounting for over 50% of the congeners in human and wildlife tissues (Costa et al., 2009). BDE 209 is the major component of commercial flame retardant mixtures and is found at high levels in abiotic (Eljarrat et al., 2008; Gevao et al., 2008; Lee et al., 2013a) and biotic environments (Moon et al., 2007; Yu et al., 2011). Therefore, BDEs 47 and 209 have been easily found in various human tissues. Many studies (Chen et al., 2014; Gomara et al., 2007; Kim et al., 2011; Miller et al., 2012) reporting frequent detection of these congeners in various human tissues are linked to continuing concerns that fetuses and infants are exposed to PBDEs from maternal transfer.

Interestingly, although BDE 209 was found as an overwhelming congener in environmental media, most abundant congener of PBDEs are less-brominated congeners such as BDE 47; however, there are very limited information on fate of BDE 209 after exposure and contribution to less-brominated congeners in animal (Cai et al., 2011; Koenig et al., 2012) and humans. Moreover, maternal transfer of BDEs to offspring at early life stage is less understood. In the present study, we conducted animal experiment to observe maternal transfer of BDEs 47 and 209 as predominant congeners found in environmental sources (*e.g.* dust) and foods, respectively and compare transferring patterns of each in rat dam-offspring pairs for gestation and lactation periods.

2. Methods

2.1. Experimental design

Sixteen pregnant Sprague-Dawley rats on gestation day (GD) 0 were purchased from Orient Bio (Seongnam, Korea). They were acclimatized for 1 week before the experiment and housed in individual cages under a 12/12 h light/dark cycle. Animals were allowed free access to water and food. The rats were randomly assigned to one control and three exposed groups (Fig. 1) and the number of animal per group was four. We administered both BDE 209 and BDE 47 and compare their maternal transfer to offspring body simultaneously. Considering that BDE 209 can be metabolized to BDE 47 in the body, radiolabeled BDE 47 (^{13}C-BDE 47) was used to distinguish them. The BDE 209 and ^{13}C-BDE 47 (Wellington Laboratories, Ontario, Canada) were mixed in corn oil. The final concentrations in the mixture were 2.5 μmol/mL and 6 nmol/mL for BDE 209 and ^{13}C-BDE 47, respectively. The dams in the three exposure groups were fed the mixture, with the dose calculated based on the weight of the dam before administration. The control group was fed the corn oil in the same way. The dams were serially sacrificed at GD 14, Postnatal day 0 (PND 0, i.e. birth), and PND 4, respectively. Control group was sacrificed at PND 4. Dam blood was obtained from the inferior vena cava and collected in a heparinized tube on the day of sacrifice. The collected blood was centrifuged immediately to obtain serum. The fetuses at GD 14 and the neonates at PND 0 were sampled by caesarean section. Pups at PND 4 were sacrificed in a CO_2 chamber. Fetuses/neonates/pups were freeze dried, very finely ground, and stored in an amber vial. All samples were wrapped in aluminum foil to avoid photodegradation of PBDEs and kept at −80 °C in a deep freezer until analysis. This study was approved by the Institutional Animal Care and Use Committee of Seoul National University (SNU-1403120502).

2.2. Chemical analysis

The extraction, clean up, and instrumental analysis of PBDEs have been detailed elsewhere (Lee et al., 2013a,b). Fetus/neonate/pup samples (approximately 1 g) were extracted in a Soxhlet apparatus using 200 mL 25% dichloromethane (DCM; Ultra residue analysis, J.T. Baker, Phillipsburg, NJ, USA) in hexane (Ultra residue analysis, J.T. Baker) for 16 h. Before extraction, BDE 77 (10 ng; AccuStandard, New Haven, CT, USA) was spiked into the samples as a surrogate standard. The extracts were cleaned up by passing through a multi-layer silica gel column containing anhydrous sodium sulfate (4 g), silica gel (1 g), 22% (w/w) H_2SO_4-silica gel (5 g), 44% (w/w) H_2SO_4-silica gel (5 g), silica gel (1 g), and 2% (w/w) KOH-silica gel (2 g) with 150 mL 15% DCM in hexane. The eluants were concentrated and dissolved in 100 μL nonane (Pesticide analysis grade, Sigma-Aldrich, St. Louis, MO, USA) for instrumental analysis.

Rat dam serum samples (2 mL) were fortified with 2 mL formic acid and 1 mL Milli-Q water for protein denaturation after spiking BDE 77 (AccuStandard) as surrogate standards into the samples.

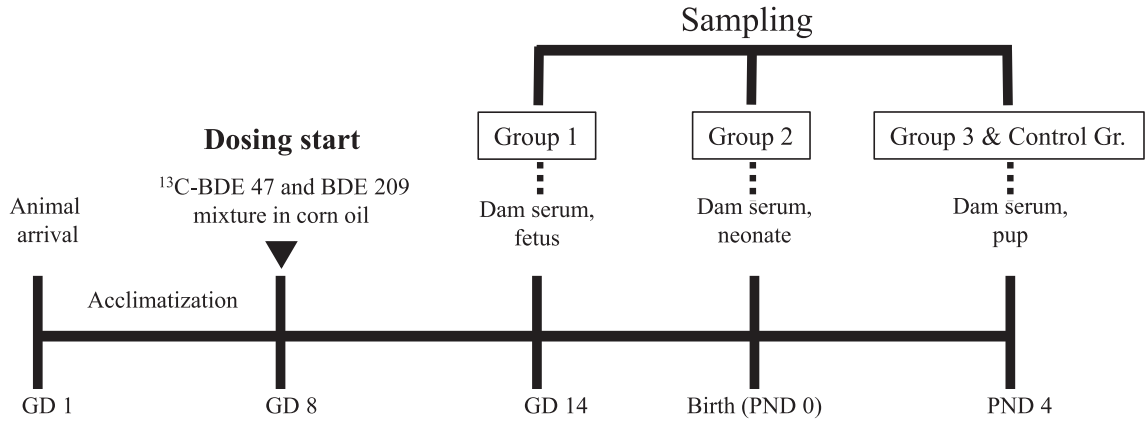

Fig. 1. The experimental design. To investigate the distributions of the dosed congeners and their debrominated congeners during the gestation and lactation periods, rat dams were administered a mixture of BDE 209 and ^{13}C-BDE 47 on a daily basis and sacrificed at gestation day (GD) 14, Postnatal day (PND) 0, or postnatal day (PND) 4. Controls were sacrificed at the end of the experiment.