INTRODUCTION

Polybrominated diphenyl ethers (PBDE) are found in the fire retardants used in plastic cases, such as televisions, computers, and electronic equipment, as well as in carpets, clothing, and car components (Sjödin et al., 2001; de Wit, 2002; Betts, 2006). PBDEs can be found in food, household dust, and sewage sludge because they can persist in the environment with higher lipophilicity (Hites, 2004; Schecter et al., 2004; Akutsu et al., 2003). Commercial PBDE products consist mainly of penta-, octa- and deca-bromodiphenyl ether (BDE) products (BSEF, 2007). Deca-BDE is currently the largest product on the market, comprising more than 80% of the total production of PBDE; penta-BDE and octa-BDE products constitute approximately 10% of the total PBDE production (de Wit, 2002). 2,2′,3,3′,4,4′,5,5′,6,6′-decaBDE (BDE-209) is still used in the production of polystyrene plastic products such as televisions, computers, and electronic equipment (Hardy, 2002). However, there is no data on

Original Article

Evaluation of liver and thyroid toxicity in Sprague-Dawley rats after exposure to polybrominated diphenyl ether BDE-209

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ABSTRACT — Our goal in the present study was to evaluate whether decabromodiphenyl ether (BDE-209), which is the most abundant polybrominated diphenyl ether (PBDE) found in human samples, affects against target organs. Sprague-Dawley male rats were exposed to vehicle or BDE-209 (100, 300, or 600 mg/kg body weight, daily) from postnatal day (PND) 10 to PND 42. There was no significant difference in body and male reproductive organ weight changes compared with controls. However, liver, thyroid and adrenal gland weights were significantly increased in the high-dose of BDE-209 group. BDE-209 significantly induced the expression of cytochrome P450 (CYP1A2, CYP3A1, and CYP2B1) enzymes in the liver. Furthermore, constitutive androstane receptor (CAR) and pregnane xenobiotic receptor (PXR) expression levels were also increased in a dose-dependent manner. Total serum triiodothyronine (T3) concentration was significantly reduced in a dose-dependent manner, whereas the level of thyroid-stimulating hormone was significantly increased with BDE-209 treatment. In the histological findings, multiple areas of degenerated follicular epithelium and slight attenuation of the follicular epithelium were observed in the thyroid glands by high doses (300 and 600 mg/kg) of BDE-209 treatment. The presence of hepatocytic fatty degeneration and inflammatory foci were also observed in the 300 and 600 mg/kg of BDE-209 group. These findings demonstrate that BDE-209 induces hyperthyroidism and hepatotoxicity. In the future, further research is needed to determine the relationship between target organ toxicity and blood concentrations of BDE-209.

Key words: Polybrominated diphenyl ether, Hepatotoxicity, Thyroid hormone, CAR, PXR

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the effects of neonatal exposure to PBDE on target organ toxicity.

PBDEs are structurally similar to thyroid hormones and can affect thyroid hormone homeostasis, which may result in developmental neurotoxicity, including low intelligence and learning disabilities (Zhou et al., 2002; Branchi et al., 2003; McDonald, 2002). In addition, they can influence both the male and female reproductive systems (Kuriyama et al., 2005; Talsness et al., 2005; Lilenthal et al., 2006; Tseng et al., 2006). Bahn et al. (1980) reported that some workers in the manufacture of BDE-209 who have induced hypothyroidism have higher levels of BDE-209 in their blood serum than control group. A recent study detected BDE-209 in the milk of 13% of Indonesian women at concentrations of 3.6 ng/g lipid wt. (Sudaryanto et al., 2008). Compared with the other PBDE congeners such as BDE-47 and BDE-99, BDE-209 was detected only at low frequency in human samples because environmental exposure appears to be the main pathway. The detection levels of BDE-209 in biological samples are currently an important issue because this congener is used worldwide, but the possible adverse effects of BDE-209 are unclear.

Therefore, this study examined the effects of BDE-209 on the target organ toxicity in animals. For this study, male Sprague-Dawley rats were exposed to BDE-209 at 100, 300 or 600 mg/kg for 30 days.

MATERIALS AND METHODS

Animals and housing

Sprague-Dawley male and female rats weighing 250 ± 15 g were obtained from Charles River Laboratory Animal Resources (Seoul, Korea). All animals were maintained in a specific pathogen free (SPF)-conditioned room with a 12 hr light/dark cycle. The ambient air temperature and relative humidity was set to 23 ± 2°C and 55%, respectively. Before the experiments, all animals were checked for any overt signs of illness and only healthy animals were selected. Tap water and rodent chow were given ad libitum. Two females were placed with one male for 3 hr on 7 consecutive days. Daily vaginal smears were examined for the presence of sperm. The day of sperm detection was considered day 0 of gestation (GD 0). The pregnant females were each housed in a cage with stainless steel covers and wood shavings. The rat pups were then weighed and allocated randomly to the experimental groups (6 animals/group). Weight-matched groups of neonatal rats received a daily oral gavage of vehicle or BDE-209 (CAS#1163-19-5, 98% pure) at 100, 300 or 600 mg/kg body weight from postnatal days (PND) 10 to PND 42. The BDE-209 was prepared by mixing in corn oil and Tween-80 (Sigma-Aldrich, St. Louis, MO, USA). The volume of each dose was adjusted to 5 ml/kg b.w. based on the daily body weight. The control rats received the vehicle only. The dose levels of BDE-209 used in this study were based on a previous study, which reported spontaneous behavior in Sprague-Dawley rats after neonatal exposure to BDE-209 (Viberg et al., 2007). The animals were treated humanely, and care was taken to ease suffering. The experimental protocol (PNU-2008-0042) was approved by the committee of Pusan National University in accordance with the Korea Food and Drug Administration Animal Protection.

Clinical signs and body weight changes

Throughout the study period, all animals were observed at least once daily for any clinical signs of toxicity related to the chemical treatment. On working days, all cages were checked in the morning and afternoon for any dead or moribund animals. All females were observed daily for any clinical signs of toxicity. Food consumption was measured at three-day intervals beginning on PND 6. The body weights were recorded every day.

Organ weights

At PND 42, all animals were sacrificed. Blood was obtained and then centrifuged at 1,500 xg for 15 min. The serum samples were collected and stored frozen at -80°C until needed for hormone analysis. The body and organ weights (liver, kidneys, testes, epididymis, prostate, thyroid and adrenal glands) were measured.

Protein extract preparation and Western blot analysis

The livers were thawed and homogenized in lysis buffer containing 50 mM Tris-HCl (pH 7.5), 150 mM NaCl, 1 mM EDTA, 2.5 mM EGTA, 10% glycerol, 1 mM dithiothreitol, 100 mM phenylmethylsulfonyl fluoride, 10 μg/ml aprotinin, and 10 μg/ml leupeptin. After incubation for 60 min at 4°C, the homogenate was centrifuged at 16,000 xg for 20 min at 4°C, and the supernatant was collected to determine the protein concentration. The protein concentration in the cell extract was determined in triplicate using a BioRad (Hercules, CA, USA) protein assay kit. Equal amounts of total protein were resolved on 10% SDS-polyacrylamide gels and transferred to PVDF membranes. The membranes were blocked with 5% non-fat dried milk in PBST containing 0.1% Tween-20 for 30 min, and then incubated with primary antibodies against CYP1A2 (1:200), CYP3A1 (1:200), CYP2B1 (1:200), constitutive androstane receptor (CAR, 1:200),...
pregnane X receptor (PXR, 1:200) or β-actin (1:500) for 1 hr at room temperature. The blots were washed three times for 15 min with PBS containing 0.1% Tween-20 and incubated for 1 hr with horseradish peroxidase-conjugated anti-rabbit (1:1,000) or anti-mouse immunoglobulin G (1:1,000). The membranes were washed again 4 times. The blots were developed using an enhanced chemiluminescence (ECL) system (Amersham Corp., Cardiff, UK). An image analyzer was used to determine the relative band intensities.

RNA isolation and reverse transcription PCR
Total RNA was isolated from the left testes of all animals using Trizol (Invitrogen, Carlsbad, CA, USA) according to the manufacturer’s instructions. Total RNA was checked for its integrity and DNA contamination using a UV spectrophotometer and 1.5% agarose gel electrophoresis. Total RNA extracted from the testes was used to synthesize cDNA using a SuperScript™ kit (Invitrogen). The RT-PCR reactions were performed using a RT-PCR system (Applied Biosystems, Foster City, CA, USA) according to the manufacturer’s instructions. The lists of primers and PCR conditions for SR-B1, StAR, P450scc, CYP17, CYP19, and β-actin were indicated in Table 1. Approximately 2 μl of cDNA per sample was used for amplification. The RT reaction was carried out at 50°C for 1 hr and terminated by heating at 94°C for 2 min. The cDNA fragments were generated by initial denaturation at 94°C for 5 min. The PCR products were separated by electrophoresis on a 2% agarose gel and detected under UV light.

Thyroid hormone concentration
The thyroid hormone (T3, T4 and TSH) concentrations in serum samples were measured using a competitive radioimmunoassay (RIA) kit (Diagnostic Products Corp., Los Angeles, CA, USA) according to the manufacturer’s instructions.

Histological evaluations
After sacrifice, the liver, right thyroid glands, and testes were fixed overnight in 10% neutral buffered formalin and dehydrated with 70% ethanol. Each tissue was embedded in paraffin and 5-μm sections were cut and mounted on slides. The slide sections were stained with hematoxylin and eosin (H&E). The histopathological findings were investigated under optical microscopy observation. Photomicrographs of 10 fields per thyroid were taken at 400 × magnification using a Zeiss Axiphot light microscope (Zeiss, Oberkochen, Germany) fitted with a Sony 3CCD camera (AVT Horn, Aalen, Germany).

Data analysis
All values are expressed as mean ± S.E. (n = 6 animals). Data for the mean initial or necropsy body weights, organ weights, and serum hormone levels were analyzed statistically for the homogeneity of variance using Bartlett’s test. Nonparametric analysis of variance was

<table>
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<tr>
<th>Gene</th>
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<th>Primers R</th>
<th>PCR conditions</th>
<th>Product size</th>
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<td>CCATTCAATGACACCGGTTCTCTCTGT</td>
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<td>StAR</td>
<td>CATCAGAAGCAGGAGGAAAGG</td>
<td>TCGAGATTTGACTCTTTGAGG</td>
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<tr>
<td>P450scc</td>
<td>CGTCTGAGGTCGTCGAAAGG</td>
<td>TCTGTGAGAAGGTCGAT</td>
<td>94°C 5 min, 25 cycles (94°C 30 sec, 55°C)</td>
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</tr>
<tr>
<td>Cyp17</td>
<td>GAACAGGAGAGGGGTG</td>
<td>CATCCAGGATACCACTACCACT</td>
<td>95°C 12 min, 24 cycles (94°C 30 sec, 45°C)</td>
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<td>Cyp19</td>
<td>ATAGGTCGATGACTGACGAG</td>
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<td>95°C 12 min, 30 cycles (94°C 30 sec, 55°C)</td>
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<td>β-actin</td>
<td>TGGGAGAAGGATTTGGCAACCAC</td>
<td>AGCTAGGGCAACCATAGC</td>
<td>95°C 12 min, 20 cycles (94°C 30 sec, 45°C)</td>
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Vol. 35 No. 4
applied when the samples were found to be homogeneous. A p value < 0.05 was considered significant.

RESULTS

Clinical signs and body weight changes
During the study period, there were no clinical signs of toxicity in any treatment group. Likewise, significant differences in body weight change were not observed between control and treatment groups (data not shown).

Organ weights
There were no significance differences in absolute or relative kidney, testes, prostate glands and epididymis weights between the BDE-209 and control groups. However, absolute liver, thyroid, and adrenal glands weights were increased in a dose-dependent manner and significant differences in liver, thyroid and adrenal glands weights were observed in the high-dose (600 mg/kg) BDE-209 group (Table 2). Similarly, high-dose of BDE-209 (600 mg/kg) significantly increased the relative liver, thyroid, and adrenal glands weight (Table 3).

CYP family and nuclear receptors expression in the liver
To investigate the possible involvement of several metabolizing enzymes, we examined the expression levels of CYP family enzymes. Because BDE-209 significantly increased the liver weight, we decided to investigate the expression of CYP1A2, CYP2B1 and CYP3A1 in the liver after BDE-209 treatment. As shown in Fig. 1, CYP1A2 and CYP3A1 expression levels were increased by BDE-209 treatment in a dose-dependent manner. CYP2B1 expression was weakly induced in liver of BDE-209-treated rats. Likewise, expression levels of the nuclear receptors, CAR and PXR, were also up-regulated in a dose-dependent manner. Previous results demonstrated that induction of CAR and PXR expression may correlate with the bromine content in BDE congeners (Sanders et al., 2005).

Steroidogenesis-related gene expression in the testis
The expression levels of the steroidogenesis-related genes, including SR-B1, PBR, StAR, P450sc, CYP17, and CYP19, were examined in the testis. Similar to organ weight, there were no significant effects on the mRNA levels of StAR, PBR, SR-B1, P450sc and CYP17. However, CYP19 mRNA was slightly increased in the BDE-209 treatment groups (Fig. 2).

Hormone concentration
The serum T3 level was decreased significantly by up to 45% in the 300 and 600 mg/kg BDE-209 groups (Fig. 3a). In contrast, high doses of DBE-209 significantly increased the serum TSH levels in male rats at PND 42 (Fig. 3b). There were no significant differences in the serum T4 levels between BDE-209 groups and control (Fig. 3c).

Histological findings
Histology of the testes showed apparently normal spermatogenesis in both BDE-209 and control rats. The seminiferous tubules in the control rats were filled with spermagonia, spermatocytes, and spermatids, and lumen development was also observed (Fig. 4). Lumen formation and interstitial cells or Sertoli cells were clearly detected in high-dose of BDE-209-treated rats. In contrast, histology of the thyroid glands showed that only a few slightly acini with colloid in the 600 mg/kg BDE-209 treatment groups compared to the controls. The normal cuboidal epithelium had dose-dependently transformed into squamous epithelium, the most notable change found in the group treated with 300 and 600 mg/kg of BDE-209. There were multiple areas of degenerated follicular epithelium in the high doses (300 and 600 mg/kg) BDE-209 group and slight attenuation of the follicular epithelium (Fig. 4). In addition, treatment-related histological lesions were seen in the liver. The presence of hepatocytic fatty degeneration and vascular degeneration were observed in high doses (300 and 600 mg/kg) BDE-209 exposure groups compared with control (Fig. 5). Furthermore, inflammatory foci and necrosis were also found in the 300 and 600 mg/kg BDE-209 groups (Fig. 5). In contrast, the histopathological study of testes did not reveal morphological alterations due to treatment with BDE-209 (Fig. 6).

DISCUSSION
This study examined the effects of neonatal exposure to BDE-209 on target organ toxicity in Sprague-Dawley rats. Overall, BDE-209 did not affect the body weight gains or reproductive organ weight, in all treatment groups, but high-dose of BDE-209 significantly increased the liver, thyroid or adrenal gland weights. These results are similar to a previous study in which developmental exposure to BDE-2 09 had no maternal or fetal toxicity in male mice offspring (Tseng et al., 2008). Recently, a few studies have been conducted on the influence of metabolism and disposition of BDE congeners in rodents (Chen et al., 2006; Sanders et al., 2005). However, the mecha-
nisms of target organ toxicity of PBDE congeners are not fully characterized. Based on these results, we examined the thyroid hormone synthesis and liver and reproductive organ damages after exposure to BDE-209 to identify BDE-induced target organs toxicities.

Generally, the primary toxic response occurs in the liver of animals exposed to various chemicals. Little or no liver toxicity occurred at the doses comparable to human exposure levels, but more severe liver toxicity occurred at the high exposure levels of PBDE congeners (approximately 500 mg/kg/day). PBDE-induced toxicities were characterized by increases in liver enzyme levels, liver

| Table 2. Comparisons of the absolute organ weights in the Sprague-Dawley rats treated with BDE-209 a |
| Groups | Control b | BDE-209 100 mg/kg | BDE-209 300 mg/kg | BDE-209 600 mg/kg |
| Initial B.W. (g) | 115.53 ± 3.60 c | 114.97 ± 3.57 | 117.38 ± 2.95 | 114.81 ± 6.32 |
| Final B.W. (g) | 209.07 ± 13.52 | 215.42 ± 11.05 | 223.20 ± 7.67 | 211.39 ± 13.35 |
| Liver (g) | 8.02 ± 1.23 | 8.06 ± 0.29 | 8.68 ± 0.32 * | 8.98 ± 1.24 * |
| Kidney (g) | 0.95 ± 0.17 | 0.95 ± 0.05 | 0.99 ± 0.07 | 0.98 ± 0.11 |
| Testis (g) | 0.93 ± 0.06 | 1.03 ± 0.06 | 1.00 ± 0.09 | 0.94 ± 0.05 |
| Epididymis (g) | 299.4 ± 30.8 | 284.9 ± 24.1 | 290.1 ± 14.5 | 291.8 ± 38.6 |
| Seminal vesicles (g) | 0.39 ± 0.08 | 0.31 ± 0.09 | 0.28 ± 0.04 | 0.27 ± 0.05 |
| Ventral prostate (g) | 0.17 ± 0.08 | 0.18 ± 0.05 | 0.16 ± 0.04 * | 0.18 ± 0.05 |
| Thyroid glands (mg) | 8.65 ± 1.72 | 10.84 ± 4.12 | 11.63 ± 2.94 | 13.78 ± 2.93 * |
| Adrenal glands (mg) | 37.11 ± 8.43 | 36.65 ± 4.32 | 38.72 ± 3.06 | 42.48 ± 4.31 * |

* Male rats were administered with BDE-209 (100, 300 or 600 mg/kg/day) by oral gavage for 30 days.
* Control received corn oil containing 0.25% DMSO.
* Data are presented as mean ± S.E. (n = 6).
* Significantly different from vehicle control (*p < 0.05).

| Table 3. Comparisons of the relative organ weights in the Sprague-Dawley rats treated with BDE-209 a |
| Groups | Control b | BDE-209 100 mg/kg | BDE-209 300 mg/kg | BDE-209 600 mg/kg |
| Liver (g) | 37.02 ± 7.13 | 37.48 ± 2.44 | 40.51 ± 1.95 * | 42.85 ± 4.84 * |
| Kidney (g) | 4.46 ± 0.97 | 4.15 ± 0.12 | 4.42 ± 0.28 | 4.63 ± 0.31 |
| Testis (g) | 4.50 ± 0.37 | 4.77 ± 0.33 | 4.48 ± 0.34 | 4.47 ± 0.26 |
| Epididymis (g) | 1.43 ± 0.16 | 1.32 ± 0.08 | 1.30 ± 0.05 | 1.38 ± 0.16 |
| Seminal vesicles (g) | 0.18 ± 0.04 | 0.14 ± 0.07 | 0.13 ± 0.05 | 0.13 ± 0.07 |
| Ventral prostate (g) | 0.08 ± 0.02 | 0.08 ± 0.03 | 0.07 ± 0.02 | 0.08 ± 0.02 |
| Thyroid glands (mg) | 0.040 ± 0.012 | 0.051 ± 0.01 | 0.052 ± 0.013 | 0.056 ± 0.012 * |
| Adrenal glands (mg) | 0.168 ± 0.044 | 0.174 ± 0.012 | 0.173 ± 0.017 | 0.2021 ± 0.020 * |

* Male rats were administered with BDE-209 (100, 300 or 600 mg/kg/day) by oral gavage for 30 days.
* Control received corn oil containing 0.25% DMSO.
* Data are presented as mean ± S.E. (n = 6).
* Significantly different from vehicle control (*p < 0.05).
Effect of BDE-209 on the expression levels of CYPs, CAR and PXR. Sprague-Dawley rats were treated with BDE-209 (100, 300, or 600 mg/kg) by oral intubation for 30 days. Protein was isolated from the liver of Sprague-Dawley rats. Expression levels of CYP1A1, CYP3A1, CYP2B1, CAR, and PXR were detected by Western blot analysis using their respective antibodies. A representative blot from three separate experiments is shown.

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The expression levels of steroidogenesis-related genes in the testis. The rats were treated with BDE-209 (100, 300, or 600 mg/kg) by oral intubation for 30 days. The RNA was also isolated from the testes of Sprague-Dawley rats. The RT-PCR products representing the CYP17, SR-B1, StAR, P450scc, and CYP19 transcripts were separated on agarose gels. Photo is representative of three separate blots.

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Fig. 3. Effects of BDE-209 on serum thyroid hormone levels. Sprague-Dawley rats were treated with BDE-209 (100, 300, or 600 mg/kg) by oral intubation for 30 days. Serum was isolated from the blood of Sprague-Dawley rats. The serum T3 (a), T4 (b) and TSH (c) levels were measured using a RIA. The data are reported as the mean ± S.E. of 6 animals/group. The asterisk indicates a significant difference from the control (p < 0.05).

Fig. 4. Histological changes in the thyroid glands after BDE-209 exposure. Sprague-Dawley rats were treated with BDE-209 (100, 300, or 600 mg/kg) by oral intubation for 30 days. Thyroid gland taken from rats in the control group had normal architecture. (a) control, the acinar epithelium was cuboidal in shape with larger follicles and the density of colloid was uniform. (b) BDE-209 100 mg/kg, no significant differences in histopathological changes were observed. (c) Thyroid gland from male rats treated with 300 mg/kg BDE-209 showed slightly enlarged colloid in a few acini, which were encircled by a layer of squamous epithelium. (d) Thyroid gland from male rats treated with 600 mg/kg BDE-209 shown slightly enlarged with colloid in a few acini, which were encircled by a layer of squamous epithelium.
er weights, and toxic liver and thyroid lesions (rats), and decreases in serum thyroid hormone levels (Sanders et al., 2005; Kim et al., 2009). PBDE-induced liver toxicity and alterations in liver enzyme levels, and, thus, metabolic activation is a likely mechanism for this toxicity. Dunnick and Nyska (2009) demonstrated that increases in liver weights and induction of liver cytochrome P450 (1A1, 1A2, 2B) and UDPGT levels were observed in both rats and mice after BDE-exposure. In addition, hepatocyte hypertrophy and vacuolization increased in incidence and severity with treatment, and occurred at levels of 50 mg/kg and above in rats. These results suggest that liver is a target organ for carcinogenesis processes after long-term administration of PBDE congeners. BDE-209 induced significant hepatocellular adenomas and carcinomas in male mice, but not rats (NTP, 1986). These data was similar to our data that increased liver weight and severe morphological changes were observed in the liver after high dose of BDE-209 exposure.

The present results are in line with other studies showing that CYP2B gene expression is inducible and might be involved in the metabolism of BDE-209 (Meerts et

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**Fig. 5.** Histological change in rat liver after BDE-209 exposure. Sprague-Dawley rats were treated with BDE-209 (100, 300, or 600 mg/kg) by oral intubation for 30 days. The photomicrographs were taken at a × 400 magnification after H&E staining. (a, b) control group; (c, d) BDE-209 300 mg/kg; (e, f) BDE-209 600 mg/kg. Note the presence of hepatocytic fatty degeneration (yellow arrows) and inflammatory foci or hepatocytic necrosis (white arrows) were observed in 300 or 600 mg/kg BDE-209.
These results are similar to our study in which BDE-209 significantly induced CYP1A2 and CYP3A1 expression in the liver. PBDE congeners appear to share an AhR-independent mechanism of action with non-coplanar PCBs. PBDEs and PCB153 upregulated CYP2B and CYP3A gene expression in livers of treated rats and thus apparent CAR and PXR agonists. The genes regulated by CAR and PXR mainly comprise those encoding certain drug-metabolizing enzymes most notably CYP3A enzymes.

PBDE can alter thyroid hormone levels in rodents, but the response appears to occur at doses higher than environmental exposure to humans (McDonald, 2002). BDE treatment-related thyroid lesions occurred particularly at the lower dose compared with that of induced liver toxicity. Therefore, our study demonstrated that the most sensitive parameter for PBDE toxicity was the increase in thyroid gland weights that occurred at 100 mg/kg or above in rats. Norris et al. (1975) first reported the induction of thyroid hyperplasia by PBDE compounds in adult rats exposed to octa-BDE and BDE-209 mixtures. Abdelouahab et al. (2009) also observed a significant decrease in total T4 and T3 in exposed lambs. Our finding indicates that BDE-209 exposure can affect thyroid hormone synthesis and metabolism. PBDE exposure reduced serum T4 levels in rats, and these decreases in T4 levels were consistent with the observed induction of UDPGT activity, suggesting that increased glucuronidation of T4 may be one factor contributing to a reduction in T4 serum activity, suggesting that increased glucuronidation of T4 may be one factor contributing to a reduction in T4 serum activity. Because of their structural similarity to thyroid hormones, PBDEs may act as endocrine disrupters via interference with the thyroid receptors (Meerts et al., 2000). There are several reports on the decreased circulating concentrations of thyroid hormones after developmental exposure to PBDE mixtures and single congeners in mice and rats (Zhou et al., 2002; Kurita et al., 2005). It is unclear why the decreased thyroid hormones are directly associated with PBDE exposure. However, it was suggested that brominated flame retardants and their metabolites compete with T4 to bind to the tran-
sthyretin transport protein in vitro (Meerts et al., 2000). These results are not similar to our data, in which the serum T3 levels were significantly lower only in the 300 and 600 mg/kg BDE-209 groups. This indicates that some PBDE congeners and metabolites can affect the activity of CYP19 (aromatase) a key enzyme in estrogen biosynthesis.

This study also provides some important information for human risk assessment of the most environmentally relevant BDE-209. Further study is needed to determine the relationship between the maternal and fetal blood concentrations of BDE-209 for a proper human risk assessment and to examine the biomarkers involved in normal brain development at the environmentally relevant doses of PBDE 209.

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Target organ toxicity of PBDE in rats


