Impact of Repeated Exposure on the Toxicokinetics of BDE 47 in Mice

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Received September 1, 2005; accepted November 5, 2005

2,2′,4,4′-Tetrabromodiphenyl ether (BDE 47) is the major polybrominated diphenyl ether (PBDE) found in environmental samples and human tissue despite its small contribution to global production and usage. Currently, three toxicokinetic studies are available investigating single-dose exposures; this is the first study to investigate toxicokinetic parameters following repeated exposure to BDE 47. The disposition and excretion of BDE 47 was monitored in adult female C57BL/6 mice for 5 days following ten consecutive 1.0-mg/kg oral doses and compared with results from our previous study. Results of the present study suggest greater retention of BDE 47 and nonlinear disposition patterns following repeated exposure to this dose in mice. No target tissues of sequestration or potential toxicity were determined; however, some tissues, such as the liver, demonstrated patterns of interest following repeated exposure that were not previously observed in acute toxicokinetic studies. Repeated exposure to BDE 47 results in higher concentrations remaining in adipose tissue, which demonstrates its potential for bioaccumulation. The data also suggest that excretion of BDE 47 may be decreased following repeated exposure. These results, in combination with evidence of its persistence and toxicity, underlie the need to further understand BDE 47 toxicokinetics across species at steady-state conditions.

Key Words: BDE 47; PBDE; toxicokinetics; brominated flame retardant.

Reports of polybrominated diphenyl ethers (PBDEs) in the environment, wildlife, and people, in combination with increasing evidence of toxicity, have recently increased concern for this class of chemicals (Birnbaum and Staskal, 2004). The PBDEs constitute a large market share of brominated flame retardants (BFRs) and have been available commercially in three products known as “Deca, Octa, and Penta.” All commercial products are a mixture of brominated diphenyl ether congeners and are used in a wide variety of highly flammable consumer products. Of the 209 potential congeners, varying in number and position of bromines, 2,2′,4,4′-tetrabromodiphenyl ether (BDE 47, Fig. 1) is the dominant congener found in almost all environmental and biotic samples (Hites, 2004). However, it plays a modest role commercially, as it constitutes only 24–38% of the PentaBDE mixture (DE-71), which constitutes a minor share of the BFR market. Production of the PentaBDE mixture in the United States was voluntarily phased out at the end of 2004 (Great Lakes Chemical Corporation, 2003); production and use were banned in Europe in 2004. The PentaBDE mixture is used primarily in flexible polyurethane foam, with final applications including upholstered furniture, mattresses, bedding, and carpet underlay (BSEF, 2004).

Information on toxicity of BDE 47 is extremely limited; however, several studies have shown this compound has the potential to be a developmental, reproductive, and neurotoxicant and an endocrine disruptor. In mice, BDE 47 was shown to alter thyroid hormone activity following a 14-day exposure period (Hallgren et al., 2001). Free and total T4 were significantly decreased at 18 mg/kg/day, but accompanying induction of TSH or phase I and II hepatic enzymes was not evident. A single neurobehavioral study in mice is available for BDE 47. Male NMRI mice were administered BDE 47 (0.0, 0.7, or 10.5 mg/kg) on postnatal day 10 (PND 10) and monitored for neurodevelopmental impact at 2, 4, and 5 months of age (Eriksson et al., 2001). Spontaneous behavior was significantly affected along with decreased habituation capacity in the high-dose group, and both effects worsened with age.

A number of studies suggest that BDE 47 also has the potential to disrupt endocrine homeostasis and reproductive function during development. Specifically, BDE 47 exhibits anti-androgenic characteristics by inhibiting the binding of androgens to the androgen receptor in vitro (Stoker et al., 2005). Because of the mounting evidence for toxicity in combination...
with persistent exposure, it is important to understand the toxicokinetics of BDE 47 in potentially susceptible populations (i.e., young, developing animals) in addition to behavior in adults.

Because of its persistence, the resulting bioaccumulation and the potential for toxicity of BDE 47 underlie the need for an accurate assessment of human environmental exposure to BDE 47 and other PBDE congeners. In an effort to link daily exposure to the dose received by a target tissue of concern, it is essential to understand the toxicokinetics of these compounds. Three studies have reported on the disposition of BDE 47 following single exposures (Darnerud and Risberg, 2005; Orn and Klasson-Wehler, 1998; Staskal et al., 2005), yet there are no reports on repeated or steady-state kinetic parameters. The development of low, repeated-dose and steady-state kinetic parameters will aid in the assessment of adverse and non-adverse biological endpoints.

The present study was designed to determine if repeated exposure to BDE 47 alters distribution and excretion parameters of a subsequent, single BDE 47 exposure. Adult, female mice were dosed orally with 1.0 mg/kg of BDE 47/day consecutively for 10 days (10 mg/kg total dose). The tenth administered dose was radiolabeled for detection and analyses of the toxicokinetic parameters. Excretion was monitored daily for 5 days after the last dose, and tissues were collected on the fifth day following exposure. The disposition and excretion of BDE 47 in these mice is compared to the same parameters in mice administered a single, oral dose of 1.0 or 10.0 mg/kg (Staskal et al., 2005). This 1-mg/kg dose was chosen because it was within the range of linear kinetic behavior.

MATERIALS AND METHODS

Chemicals. Uniformly labeled $^{14}$C-2,2′,4,4′-tetrabromodiphenyl ether (BDE 47) (26.7 mCi/mmol) was a generous gift from Great Lakes Chemical Corporation with a radio-purity of $>97%$ as determined by reverse-phase high-pressure liquid chromatography (HPLC) (System Gold, Beckman Instruments, Inc., Fullerton, CA) using an Ultrasphere ODS column (5 mm, 25 × 4.6 cm) and a gradient elution of 50:50 methanol:water over 30 min to 100% methanol at a flow rate of 1.5 ml/min. A radioactive flow detector (Beckman Model 171, Beckman Instruments, Fullerton, CA), used with 1 ml/min Flo Scint III (Packard Instrument Co., Meridian, CT), was used to monitor radioactivity. Unlabeled BDE 47 was also provided by Great Lakes Chemical (>98% purity). All other chemicals used were of the highest grade commercially available.

Animals. Female C57BL/6 mice were obtained from Charles River Breeding Laboratories (Raleigh, NC). Animals were maintained in an AAALAC accredited facility on a 12-h light/dark cycle at ambient temperature (22°C) and relative humidity (55 ± 5%), and were provided with Purina 5001 Rodent Chow (Ralston Purina Co., St. Louis, MO) and tap water ad libitum. Prior to the commencement of the study, the mice (9 weeks old) were adapted (three mice/cage) for 1 week in Nalgene metabolism cages (Nalgene, Rochester, NY). At 10 weeks of age, the 10-day dosing scheme began, at which time each mouse was housed individually in metabolism cages.

Dosing. Mice $n = 10$ were administered ten consecutive doses of BDE 47 (1 mg/kg/day for 10 days, total administered dose 10 mg/kg) by oral gavage (10 ml/kg) using a curved ball-tipped animal feeding needle. The first nine doses were using unlabeled BDE 47, followed by a $^{14}$C-labeled dose on the tenth day. Unlabeled solution was prepared by dissolving BDE 47 crystals in hexane, followed by the addition of corn oil and subsequent evaporation of hexane using a speed vacuum (Speed Vac, Savant Instruments, Inc., Farmingdale, NY). For the labeled dosing solution, a stock solution of $^{14}$C-BDE 47 was made by sonicating 63.6 mg of $^{14}$C-BDE 47 (55 μCi/mg) in toluene (1 ml) until dissolved. Aliquots from this stock were used to prepare a 1-mg/kg (~5 μCi/ml) solution by direct addition of the toluene to corn oil, followed by toluene evaporation using a speed vacuum.

Sample collection and analysis. Although animals were kept in metabolism cages for the duration of the study, excreta was only collected for 5 days following the administration of radiolabeled dose (tenth dosing day). Tissues (blood, brain, adipose, liver, kidney, skin, muscle, and lung) were also collected on the fifth day following the radiolabeled dose. Radioactivity in the tissues was determined by combustion (Packard 306B Biological Oxidizer, Downers Grove, IL) of triplicate samples when available (~100 mg/sample), followed by liquid scintillation spectrometry (LSS; Beckman Scintillation Counter, Beckman Instruments, Fullerton, CA). All data are reported using wet weight values. Feces were air dried following collection, weighed, and analyzed for radioactivity by combustion and LSS. Daily urine volume was recorded; 100-μl aliquots (triplicate) were analyzed by direct addition into scintillant for radioactivity determination by LSS. Full methods for sample collection and analyses of the single-dose animals are provided in Staskal et al. (2005). All treatment, dosing methods, and sample analyses were the same for the repeated-dose and single-dose animals with the exception of the administration of nonradiolabeled BDE 47 for 9 days prior to the radiolabeled dose in the repeated-dose study.

EROD and PROD assays. Microsomal fractions were prepared from liver according to the method of DeVito et al. (1993). Protein concentrations were calculated photometrically using a Bio-Rad protein assay kit (Bio-Rad Laboratories, Hercules, CA) with bovine serum albumin as a standard. Activities of ethoxyresorufin O-deethylase (EROD), a marker of CYP1A1, and pentoxyresorufin O-deethylase (PROD), a marker for CYP2B, were determined using a spectrophotometrically based assay. All samples were run in triplicate as described by Abbott et al. (2003).

Data analysis. For calculation of percent total dose, blood, skin, muscle, and fat mass were assumed to be 8, 8, 12, and 35%, respectively (Diliberto et al., 2001). Percent dose data was normalized to recovery (>90%) for uniform comparisons with previous research, including the 1.0- and 10.0-mg/kg single-exposure data (Staskal et al., 2005). Because tissue measurements were performed by scintillation spectrometry, the authors cannot discount that the detected radioactivity may be parent or metabolite; however, previous metabolite analyses have demonstrated that >95% of BDE 47 found in tissues following a single dose is parent compound (Orn and Klasson-Wehler, 1998). An analysis of variance (ANOVA) was used to compare exposure groups followed by Bonferroni post tests. Differences between treatment groups were considered significant when $p < 0.05$. All data are presented as mean ± standard deviation.
RESULTS

Female C57BL/6 mice were administered 1 mg/kg BDE 47 consecutively for 10 days (total dose of 10 mg/kg). Tissue distribution and excretion of BDE 47 was monitored for 5 days following the single $^{14}$C-labeled dose (tenth consecutive dose). Results are compared to single 1.0-mg/kg and single 10.0-mg/kg parameters reported previously (Staskal et al., 2005). The consecutive administration of BDE 47 for 10 days did not produce any treatment-related mortality or effects on either body or organ weights.

Distribution

This overall pattern of tissue distribution of the terminal $^{14}$C-BDE 47 dose (Table 1) following preexposure to unlabeled BDE 47 for 9 days was similar to the patterns of distribution observed in single-exposure scenarios. BDE 47 distributes based on its lipophilicity; the largest percentage of $^{14}$C-BDE 47 remaining in the body 5 days after the last dose was found in adipose tissue, followed by skin and muscle (21, 2.8, and 2.7%, respectively). Less than 1% of the dose was found in all other tissues collected (liver, lung, brain, blood, and kidney). While repeated exposure to BDE 47 did not alter the overall pattern of disposition, some differences are noted when compared to the single 1.0-mg/kg exposure. The percent of dose/tissue in the fat, skin, blood, brain, and kidneys is higher in the repeatedly exposed animals as compared to the single 1.0-mg/kg exposure. Using percent dose/gram of tissue as the dose metric, there is a clear difference in the levels of BDE 47 in the tissues; repeated exposure results in levels that parallel the 10-mg/kg dose and are generally twice the levels found in the single-exposure animals. Of particular interest is the percent of the terminal BDE 47 dose remaining in the brain 5 days following repeated exposure; levels were essentially twice what were found following a single dose.

The terminal dose of BDE 47 was found in tissues 5 days following repeated exposure at concentrations ranging from ~18 to 2600 ng/g wet weight (Table 1). When compared to the single exposures, the range is higher than the 1.0-mg/kg exposure (~7–1200 ng/g). Adipose tissue was the only tissue significantly higher in the repeated-dose animals than the single 1.0-mg/kg dose when compared on a wet weight tissue concentration. Although not statistically significant due to the variability among the animals, many of the mean tissue concentrations exhibited a doubling trend when the single and repeated 1.0-mg/kg doses were compared.

The concentrations found in the repeated-dose animals were generally eight times lower than concentrations from the 10.0-mg/kg single-dose group. This is in contrast to the comparison between the single exposures; tissue concentrations between the 1.0- and 10.0-mg/kg groups are generally 10 to 16-fold different, as would be predicted by the 10-fold difference in dose level. When using percent dose/tissue and percent dose/gram, the disposition of BDE 47 following repeated exposure at concentrations ranging from 7–1200 ng/g was found in tissues 5 days following repeated exposure at concentrations ranging from ~18 to 2600 ng/g.

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Partitioning into the tissues was examined using tissue to blood ratios. Partitioning from the blood to the liver was the only ratio that was different between the repeated- and single-exposure groups (liver: blood ratios of 6.3 and >9, respectively, based on wet weight tissue concentrations). This is furthered evidenced by a slightly altered liver to fat ratio. Previous research investigating dose dependencies for BDE 47 resulted in liver to fat ratios of ~0.11. In the present study, repeated exposure to BDE 47 followed by a single labeled dose resulted in lower concentrations of the $^{14}$C-BDE 47 in the liver 5 days after repeated exposure, generating a liver to fat ratio of 0.06. This decreasing trend may suggest a number of kinetic events occurring as a result of repeated exposure.

### TABLE 1

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Single 1.0</th>
<th>Repeated</th>
<th>Single 10.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipose</td>
<td>9.64 ± 3.12</td>
<td>20.41 ± 5.94&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14.60 ± 0.69</td>
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<td></td>
<td>(1204.42 ± 390.18)</td>
<td>(2601.73 ± 771.45)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(17121.53 ± 879.81)</td>
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<td></td>
<td>[5.53 ± 1.76]</td>
<td>[13.73 ± 5.56]&lt;sup&gt;a&lt;/sup&gt;</td>
<td>[7.72 ± 0.66]</td>
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<tr>
<td>Skin</td>
<td>1.56 ± 0.76</td>
<td>2.81 ± 0.60&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.85 ± 0.37</td>
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<tr>
<td></td>
<td>(130.27 ± 63.59)</td>
<td>(238.02 ± 47.53)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(2229.29 ± 195.75)</td>
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<td></td>
<td>[0.61 ± 0.30]</td>
<td>[1.22 ± 0.23]&lt;sup&gt;a&lt;/sup&gt;</td>
<td>[0.97 ± 0.10]</td>
</tr>
<tr>
<td>Liver</td>
<td>0.76 ± 0.25</td>
<td>0.66 ± 0.12</td>
<td>0.91 ± 0.14</td>
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<td></td>
<td>(135.81 ± 30.74)</td>
<td>(164.31 ± 8.55)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(1688.29 ± 113.86)</td>
</tr>
<tr>
<td></td>
<td>[0.68 ± 0.17]</td>
<td>[0.85 ± 0.12]</td>
<td>[0.80 ± 0.07]</td>
</tr>
<tr>
<td>Muscle</td>
<td>1.37 ± 0.73</td>
<td>2.72 ± 0.91</td>
<td>2.56 ± 0.77</td>
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<td></td>
<td>(39.16 ± 20.84)</td>
<td>(110.63 ± 36.12)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>(644.13 ± 196.05)</td>
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<td>[0.18 ± 0.09]</td>
<td>[0.58 ± 0.20]&lt;sup&gt;a&lt;/sup&gt;</td>
<td>[0.28 ± 0.07]</td>
</tr>
<tr>
<td>Lung</td>
<td>0.03 ± 0.01</td>
<td>0.09 ± 0.06</td>
<td>0.07 ± 0.03</td>
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<td></td>
<td>(55.78 ± 13.86)</td>
<td>(112.26 ± 46.95)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(1044.90 ± 362.15)</td>
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<tr>
<td></td>
<td>[0.26 ± 0.06]</td>
<td>[0.59 ± 0.25]&lt;sup&gt;b&lt;/sup&gt;</td>
<td>[0.45 ± 0.15]</td>
</tr>
<tr>
<td>Brain</td>
<td>0.01 ± 0.01</td>
<td>0.04 ± 0.01&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.02 ± 0.00</td>
</tr>
<tr>
<td></td>
<td>(7.17 ± 3.08)</td>
<td>(18.07 ± 6.32)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>(109.05 ± 10.53)</td>
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<td>[0.03 ± 0.01]</td>
<td>[0.10 ± 0.04]&lt;sup&gt;a&lt;/sup&gt;</td>
<td>[0.05 ± 0.005]</td>
</tr>
<tr>
<td>Blood</td>
<td>0.10 ± 0.02</td>
<td>0.23 ± 0.12&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.15 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>(13.04 ± 3.05)</td>
<td>(26.04 ± 11.07)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(178.67 ± 22.02)</td>
</tr>
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<td></td>
<td>[0.06 ± 0.02]</td>
<td>[0.13 ± 0.06]&lt;sup&gt;a&lt;/sup&gt;</td>
<td>[0.08 ± 0.01]</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.01 ± 0.01</td>
<td>0.06 ± 0.02&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.05 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>(20.83 ± 7.24)</td>
<td>(43.04 ± 10.57)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(369.37 ± 66.51)</td>
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<tr>
<td></td>
<td>[0.10 ± 0.04]</td>
<td>[0.23 ± 0.08]&lt;sup&gt;a&lt;/sup&gt;</td>
<td>[0.16 ± 0.03]</td>
</tr>
</tbody>
</table>

<sup>a</sup>Statistically significant from single 1.0 mg/kg dose ($p < 0.05$).

<sup>b</sup>Statistically significant from single 10.0 mg/kg dose ($p < 0.05$).

Note. Tissue concentrations of BDE 47 5 days following a repeated dose paradigm (1.0 mg/kg/day, nine unlabeled-BDE 47 followed with consecutive tenth radiolabeled dose) as compared to a single oral dose with no pretreatment (1.0 or 10.0 mg/kg, Staskal et al., 2005). Data presented as mean ± standard deviation in percent dose, (ng/g wet weight), and [% dose/g tissue].
Excretion

The cumulative urinary excretion of BDE 47 following an oral dose is shown in Figure 2A. While the percent of the dose excreted on the first day was subject to a wider range of variability than in other studies, approximately 13% of the dose was excreted in the urine on the first day (after the tenth dose) in the repeated-dose animals. This is comparable to the 10.0-mg/kg single dose, in which 13% was excreted on the first day, but was lower than the percent excreted in the 1.0-mg/kg dose group (18%). By the end of the 5-day collection period, approximately 38% had been excreted in the 1.0-mg/kg single-exposure animals, but only 23% in the repeated-dose animals.

Repeated exposure to BDE 47 did not have any effect on the percent excreted in the feces (Fig. 2B). Because this was an oral dose, previous studies suggest that approximately 10% of the dose excreted on day one is unabsorbed dose (Staskal et al., 2005). On day one, the repeated-dose and single 10.0-mg/kg animals excreted 24 ± 2 and 26 ± 7%, respectively, whereas the single 1.0-mg/kg mice excreted 32 ± 13%. By day five, all groups had excreted 40–42% of the administered dose into the feces.

Hepatic Enzyme Induction

The effects of repeated low-dose BDE 47 exposure on CYP1A and CYP2B enzymatic activities were evaluated by ethoxyresorufin O-deethylase (EROD), a marker of CYP1A1, and pentoxyresorufin O-deethylase (PROD), a marker for CYP2B. Enzymatic activities were not induced by subchronic BDE 47 exposure (data not shown). This lack of induction was in agreement with our previous results (Staskal et al., 2005).

DISCUSSION

PBDE congener profiles found in wildlife and people have drawn significant interest because those found in commercial PBDE mixtures do not parallel those found in human and environmental samples. BDE 47, a tetra-substituted BDE, tends to dominate (~20–60%), despite its minor role in commercial production and usage (Hites, 2004). It is currently unclear if this is entirely due to exposure, or whether there is also a toxicokinetic component. Current data, in combination with comparisons to other persistent, bioaccumulative toxicants, suggest that the lower-substituted PBDE congeners tend to have shorter half-lives in humans than the more fully substituted PBDE congeners (with BDE 209 as the exception) (Geyer et al., 2004).

Previously, BDE 47 has been shown to have a terminal whole-body half-life of 22.9 days in mice, which is indicative of bioaccumulation (Staskal et al., 2005). Because of its potential for bioaccumulation in combination with reports of toxicity and exposure data, it is essential to understand the toxicokinetics of this congener in repeated-dose and steady-state scenarios. This study was designed to characterize the impact of repeated exposure on the disposition and excretion of BDE 47. Results from a 10-day repeated-dosing paradigm were compared to the same parameters following a single-dose exposure. The resulting body burden in the animals following 10 days of dosing is approximately 1–10 times the highest body burdens found in the U.S. population (Johnson-Restrepo et al., 2005; Schecter et al., 2003).

BDE 47 is highly lipophilic and therefore concentrates in tissues by partitioning into lipid-rich environments. No tissue-specific sequestration was noted. Adipose, muscle, skin, and liver were the major depots for BDE 47 in all scenarios tested. Partitioning into the liver appeared to decrease with repeated exposure, evidenced by a liver:blood ratio of 6.3 in contrast to ratios above 9 in the single exposures. This is further evidenced by a decreased liver:fat ratio, indicating that less BDE 47 is in the liver 5 days following a repeated-exposure scenario than would be predicted from the single-exposure data. Potential explanations could include increased metabolism of BDE 47, increased removal by active transport mechanisms with repeated exposure, or decreased metabolism or transport which would provide more time for the BDE 47 to distribute to the adipose.
The results of this study aid in understanding the potential role of active transport in the excretion of BDE 47. Previous data have demonstrated that up to \(~40\%\) of BDE 47 is rapidly excreted in the urine, in a dose-dependent fashion, 5 days following exposure (Staskal et al., 2005). It is currently unclear as to why less BDE 47 is excreted in the urine at high doses. Originally, it was hypothesized that BDE 47 was metabolized, and at high doses the metabolic capability was compromised; however, further analyses of the urine revealed >95% of the BDE 47 was parent compound. Furthermore, it appears that urinary excretion is also species dependent, as BDE 47 is not readily eliminated in rats (Orn and Klasson-Wehler, 1998).

One hypothesis for this unexpected result is a renal transport mechanism. Because most active transport proteins are subject to induction, it is therefore possible that repeated exposure to the chemical may increase the presence or activity of potential transport proteins, which would result in increased excretion of BDE 47. In contrast, it could be hypothesized that an active transport mechanism could be overwhelmed if a chemical were to selectively, competitively, or irreversibly bind to a given receptor or transport protein and interfere with renal clearance, ultimately resulting in a slower renal excretion rate. The role of active transport in the urinary excretion of BDE 47 is currently being investigated in our laboratory.

The data suggest a trend of decreasing urinary excretion following repeated exposure; however, this trend is not statistically significant due to individual variability. The increased variability in the percent dose excreted in the 10-day dosing scheme may be due to a variety of factors that include: stress induced from additional days in metabolism cages, variations in response to repeated dosing, or potentially different levels of interaction with an active transport mechanism. Future studies investigating specific levels of genetic expression may help to explain urinary excretion as well as intra- and interspecies variations. This phenomenon will also play a major role in the development of a physiologically based pharmacokinetic (PBPK) model used to extrapolate BDE 47 toxicokinetics to humans.

Induction of metabolism is another factor that might aid in the development and use of a PBPK model and has often been used as a potential indicator of toxicity. Previous studies in our laboratory (Staskal et al., 2005) have demonstrated that BDE 47 does not induce CYP1A1 at liver concentrations up to 16.6 \(\mu g/g\) wet weight; however, a two-fold induction of CYP2B was observed. CYP2B induction was not observed following a 10-mg/kg dose (1.7 \(\mu g/g\) wet weight liver concentration). Concentrations of BDE 47 in the liver following ten consecutive doses of 1 mg/kg did not induce CYP1A1 or CYP2B, suggesting that continuous low-dose exposures will probably not induce these hepatic enzymes, unless much greater tissue concentrations are reached.

While human exposure and toxicity are not well understood, more rodent data are becoming available to aid in the characterization of these parameters. Three toxicokinetic studies are currently available (Darnerud et al., 2005; Orn and Klasson-Wehler, 1998; Staskal et al., 2005); however all investigated single-dose exposure scenarios. It is important to note that the 10-day exposure paradigm used in this study most likely does not approach steady-state levels (given that the terminal half-life of BDE 47 in mice is 23 days, Staskal et al., 2005); however, it provides important data regarding repeated exposure to this dominant PBDE congener that will aid in the development of future chronic exposure studies.

The results of our study suggest greater retention of BDE 47 and nonlinear disposition patterns following repeated exposure in mice. No target tissues of sequestration or potential toxicity were identified. Repeated exposure to BDE 47 results in higher concentrations of chemical remaining in adipose tissue, which demonstrates its potential for bioaccumulation. There is also a suggestion that excretion of BDE 47 may be decreased following repeated exposure. Further studies investigating steady-state absorption, distribution, metabolism, and excretion will fill toxicokinetic data gaps and aid in assessing the risks associated with BDE 47.

ACKNOWLEDGMENTS

Frances McQuaid, Brenda Edwards, David Ross, Vicki Richardson, and Steve Godin deserve special recognition for their assistance in these studies. Partial funding provided by the NHEERL-DESE Training in Environmental Sciences Research, EPA CT 826513. The research presented in this document was funded in part by the U.S. Environmental Protection Agency.

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