Disposition Profiles of BDE 47; Developmental and Adult Exposures

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Introduction

2,2',4,4'-Tetrabromodiphenyl ether (BDE 47) is a polybrominateddiphenyl ether (PBDE) congener which is part of a class of brominated flame retardants (BFRs) commonly used in a variety of highly flammable consumer goods. Concern for the effects of PBDEs has increased significantly in recent years as their presence has been detected in environmental samples and in human tissues at steadily increasing concentrations[1-2]. Despite its small contribution to the PBDE global production and usage, BDE 47 is the major congener found in environmental samples and human tissue. Limited toxicology studies suggest that PBDEs are developmental neurotoxicants, reproductive toxicants, and endocrine disruptors[1-4]. Very little research is available with respect to the individual congeners; however, Erikkson[3] and Branchi[4] have demonstrated developmental neurotoxicity in mice with BDEs 47 and 99.

Previous toxicokinetic data has shown that BDE 47 is well absorbed, distributes to tissues based on lipophilicity, and has a low rate of metabolism[5-6]. It has also been shown in these studies to be rapidly excreted as parent compound in mice but not in rats, demonstrating a clear species-difference in toxicokinetic parameters[6]. Because developing populations appear to be a more sensitive population, it is important to understand the toxicokinetics of BDE 47 and other PBDEs of toxicological interest. Alterations in disposition may play a direct role in toxicity and aid in determination of potential target tissues. It is currently assumed that nursing infants and young children have the highest rates of exposure to these chemicals, furthering the need to understand toxicokinetic parameters in this population as part of the effort to accurately characterize the human health risk.

This study was designed to investigate the disposition and excretion patterns of BDE 47 in developing mice pups. Using the dosing paradigm from the developmental neurotoxicity study available for BDE 47[3], ten day old mice were given a single, oral dose of BDE 47. Tissues disposition was monitored one, two, and five days following exposure and compared to adult tissue concentrations. Limited excretion data was collected; results and preliminary analyses are presented. All developmental exposure data is then compared with disposition and excretion trends from adult exposures[5].

Materials and Methods

Gravid C57BL/6J mice were obtained from Charles River Laboratories. Animals were maintained on a 12-hour light/dark cycle at ambient temperature (22°C) and relative humidity (55±5%), and were provided with Purina 5008 Rodent Chow (Ralston Purina Co., St. Louis, MO) and tap water ad libitum. Pups were born in-house and liters were culled to eight at birth. On post natal day 10 (PND 10), all pups were administered a single dose of [^{14}C]BDE 47 (1.0 mg/kg, ~0.1µCi) in corn oil by oral gavage (10 ml/kg). Individual pups were randomly selected for sacrifice at 1, 2, and 5 days following exposure (n=4/time point). Liver, blood, adipose, brain, muscle (abdominal), skin (ears), lung, and kidney samples were analyzed for residual radioactivity at respective time points. Urine was collected if available at time of sacrifice. [^{14}C]BDE 47 (>97% radioactive purity) was generously provided by Great Lakes Chemical Corporation.

Results

BDE 47 was found in measurable concentrations in each tissue and time point. Wet weight tissue concentrations in the pups dosed on post natal day 10 are compared with adult tissue concentrations previously reported[5] in Figure 2. Urine was collected and pooled (n=1) for BDE 47 measurement and also compared to previously reported values (Figure 1). Tissue concentrations in pups appear to be higher than concentrations found in adults.

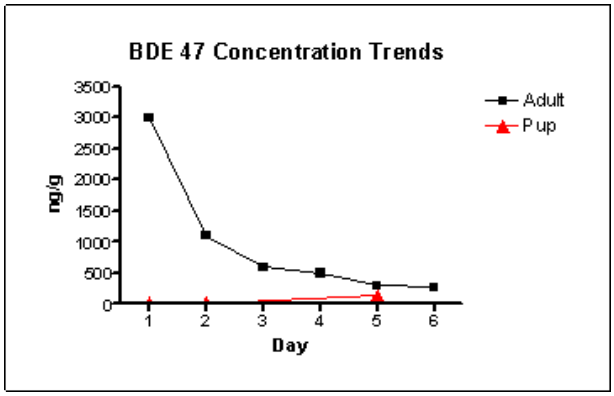

Figure 1. Concentrations of BDE 47 in urine one, two, and five days following a single, oral dose. Note: adult urine concentrations derived from a 24-hr collection.

Discussion

Currently, the available literature on the toxicokinetics of PBDEs is very limited. Due to the dominating presence of BDE 47 in environmental samples and human tissue, despite its small contribution to PBDE global production and usage, it is essential to understand the basic pharmacokinetic parameters of this chemical in sensitive populations before the human health risk can be adequately assessed. Previous studies in adult animals have shown that BDE 47 is well absorbed orally (~80%), as well as through other routes of exposure, in mice[5,6] . Tissue distribution is governed by its lipophilicity.

The preliminary analyses of this study indicate that toxicokinetic differences may exist between developing mice pups and adults. Tissue concentrations of BDE 47 are higher in pups exposed on PND 10 than adult mice (~100 days old). It is important to note that while wet weight concentrations are higher, partitioning into the tissues remains the same between pups and adults. Analyses of the urine suggest that excretion of BDE 47 is less in pups than in adult animals. Our laboratory has previously reported that BDE 47 is rapidly excreted in mice[5]. Urinary excretion significantly contributes to the biphasic elimination of the chemical in adults; the initial half life is under two days while the terminal half life is greater than 20 days. These preliminary results suggest that a reduced rate of excretion in the pups leaves more BDE 47 in the body and hence leads to higher body burdens in the developing animals.

Other studies reported in our laboratory support the role of an active transport mechanism responsible for the rapid urinary excretion of BDE 47 in mice. Several of these transporters are present in various tissues during different times in development and generally function by extruding toxins and xenobiotics out of cells. Further investigation into the specific transporter, or family of transporters involved, may play a role in explaining the toxicity resulting from exposure to PBDEs. Additionally, investigations into the mechanism of rapid excretion in mice will contribute to a more accurate extrapolation of human body burden, as well as an explanation of the range in current tissue concentrations found in the human population.

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References

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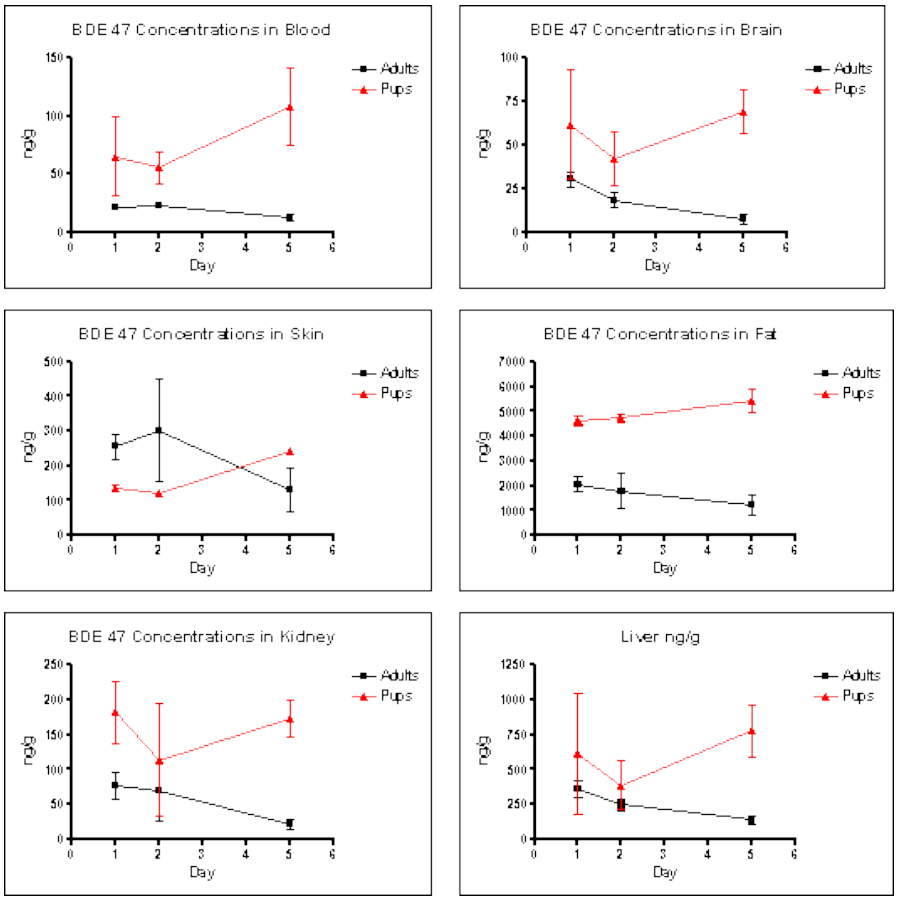

Figure 2. Wet weight tissue concentrations of BDE 47 in pups and adults one, two, and five days following a single, oral dose (1 mg/kg).