Tissue distribtuion and elimination of BDE 47 in mice following a single oral dose

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Introduction

2,2',4,4'-Tetrabromodiphenyl ether (BDE 47) is a polybrominated diphenyl 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]. 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 BDE 47 is a developmental neurotoxicant and an endocrine disruptor[1]; however, several data gaps exist and must be investigated in order to evaluate the human health risk of BDE 47.

One of the major gaps in PBDE knowledge is a lack of basic toxicokinetic data. Orn and Wehler[3] have previously reported limited toxicokinetic properties of BDE 47 in male C57 mice following a single oral dose (30 umol/kg). Our laboratory has also recently reported the effects of dose and route of exposure on the toxicokinetics of BDE 47 in mice[2]. This congener is well absorbed, not readily metabolized, and distributes as expected based on its lipophilic nature; adipose, liver, and skin were major tissues of disposition following an acute exposure. BDE 47 is readily excreted in the urine and feces: the dose being eliminated in the urine is excreted as parent compound, although this process appears to be saturable[2].

This study investigated basic toxicokinetic properties of BDE 47 in female C57BL/6J mice. Here we report the effect of time on the absorption, distribution, and excretion following a single, oral dose of ^{14}C-labeled BDE 47. Animals were administered 1.0mg BDE 47/kg bw, a dose chosen based on previous studies[2]. Distribution and elimination were monitored at several time points ranging from 1 hour to 21 days following exposure. Data from these basic toxicokinetic studies will be applied to studies investigating the toxicokinetics of BDE 47 in a developmental model as well as in the development of a physiologically-based pharmacokinetic (PBPK) model.

Materials and Methods

10-week old female C57BL/6J mice from Charles River Laboratories were pre-adapted in Nalge metabolism cages (3/cage) one week prior to dosing and provided food and water ad libitum. Mice were administered a single dose of [^{14}C]BDE 47 (1.0 mg/kg, ~1µCi) in corn oil by oral gavage (10 ml/kg) and individually housed following exposure. Excreta (collected daily), liver, blood, adipose, brain, muscle (abdominal), skin (ears), lung, and kidney samples were analyzed for residual radioactivity at respective time points (1,3, and 8 hours or 1, 2, 3, 7, 10, 14, and 21 days following exposure). Further analysis by HPLC was conducted for determination of parent compound in urine (data not shown). [^{14}C]BDE 47 (>97% pure) was generously provided by Great Lakes Chemical Corporation.

Results

Twenty-one days following exposure, most of the administered dose (>80%) had been eliminated via the excreta: 39% in the urine and 43% in the feces (**Figure 1**). Tissue distribution was primarily dictated by BDE 47's lipophilicity (log K_{OW} = 6.7) as it tends to distribute into lipid-rich tissues; adipose, skin, liver, and muscle had the highest concentrations (**Figure 2**). Highly perfused tissues had peak BDE 47 concentrations at three hours; these include the kidney, liver, blood, and lung. Peak tissue concentrations in brain and muscle appear to be at eight hours, whereas skin and fat tissue concentrations peaked between one and two days. Tissue distribution profiles are the same when compared as % dose or wet weight tissue concentrations (data not shown). The whole animal half life of BDE 47 was calculated as approximately two days.

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 before the human health risk can be adequately assessed. Previous studies have shown that BDE 47 is well absorbed orally (~80%), as well as through other routes of exposure in mice.[2,3] Tissue distribution is governed by its lipophilicity.

Other studies in our laboratory in combination with this kinetic study have shown that up to 40% of the dose was excreted in the urine as unmetabolized parent compound[2]; a surprising result for this high molecular weight compound. This data is consistent with the other available toxicokinetic study[3]. Because the chemical is not bound and not metabolized[2], we hypothesize that BDE 47 may be a substrate for active transport. Previous studies have shown that there is a dose-dependent effect on urinary excretion, suggesting a saturation of the process by which BDE 47 is eliminated into the urine[2]. The potential role of active transport is of particular interest because of stark species differences in excretion patterns of BDE 47; mice readily excrete BDE 47 via urine and feces whereas rats do not excrete BDE 47 in the urine and have limited excretion in the feces.

BDE 47 is rapidly excreted by mice. Preliminary calculations estimate the whole body half life of BDE 47 in mice to be approximately two days, which is much shorter than the predicted half life in

rats. Estimations from data presented by Orn and Klasson-Wehler[3] suggest that the half life of BDE 47 in rats is greater than 14 days. This is in agreement with the half life predicted by von Meyerinck et al[4], who reported a half life of 19-30 days for BDE 47 in rats following a single, oral dose (300 mg/kg). 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.

Acknowledgements

Partial funding provided by the NHEERL-DESE Training in Environmental Sciences Research, EPA CT 826513. This abstract does not necessarily reflect EPA policy.

References

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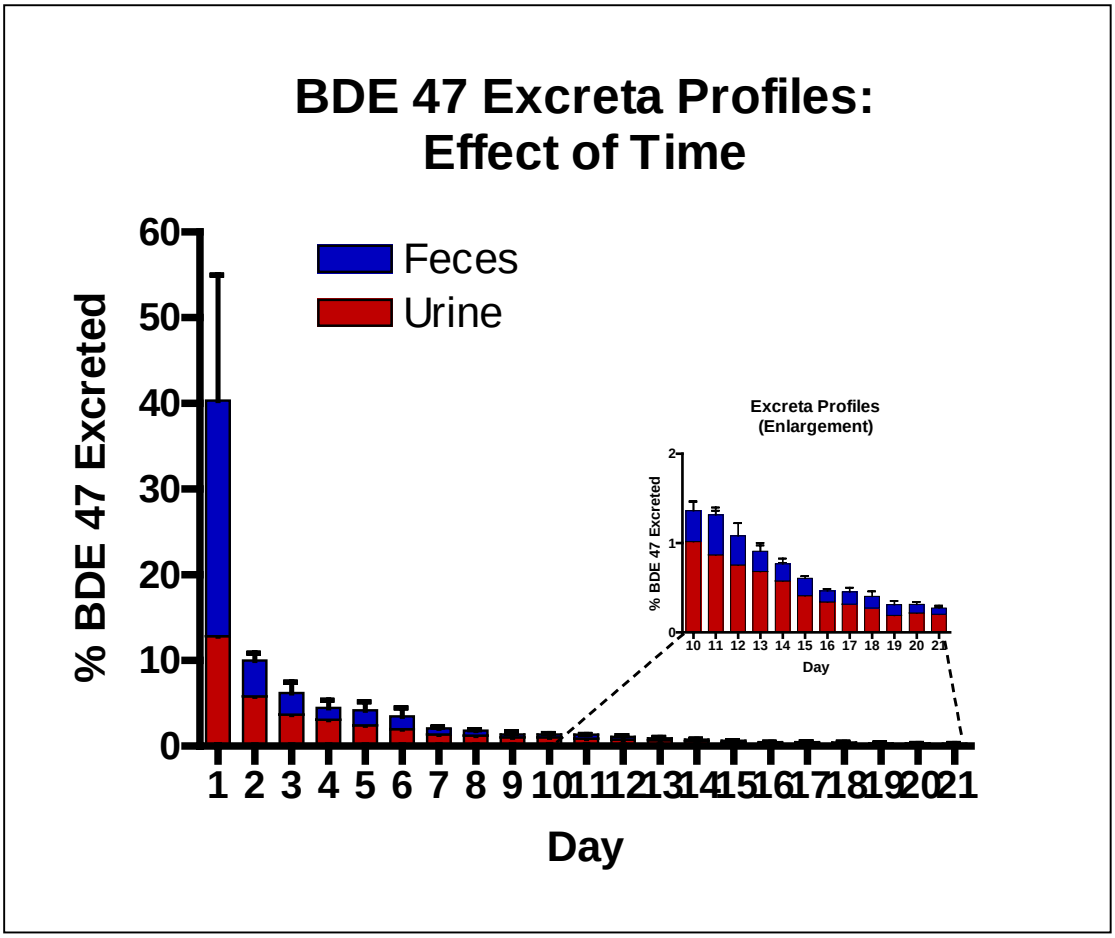

Figure 1. Percent of the dose (BDE 47 derived radioactivity) excreted in the urine and feces following a single, oral dose of BDE 47 (1mg/kg) in female C57BL/6N mice.

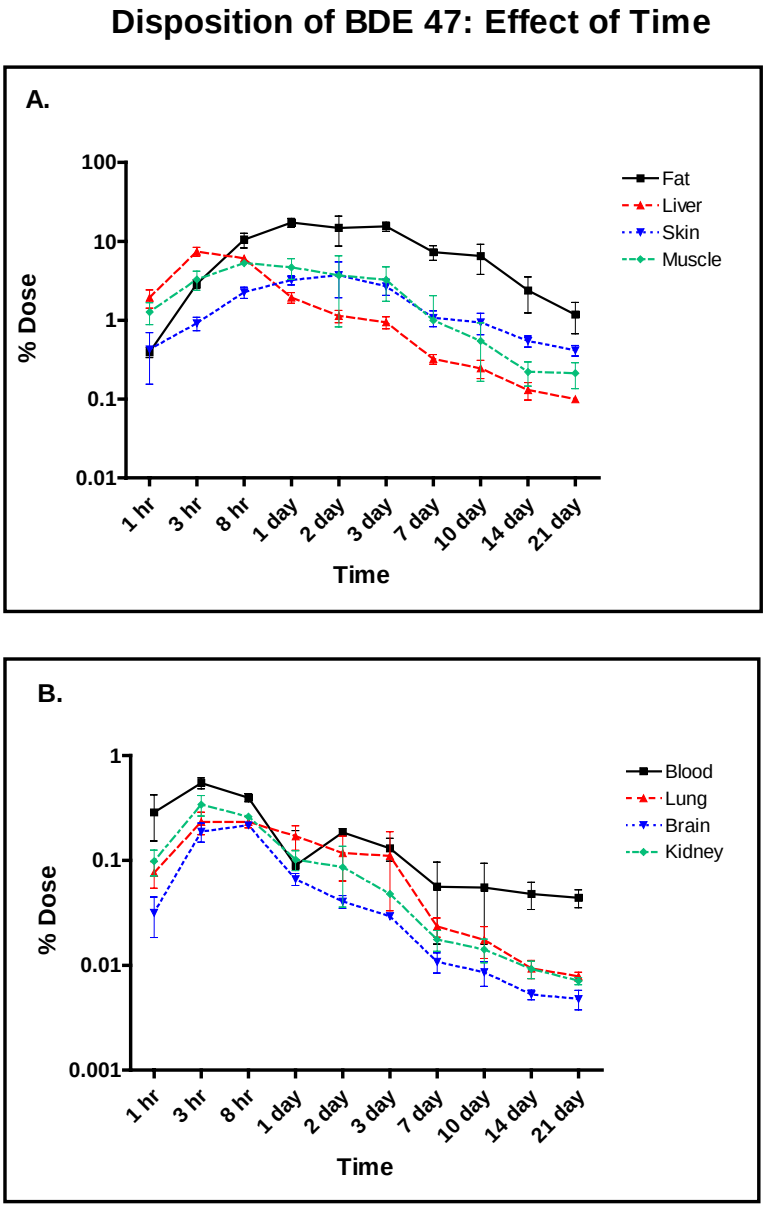

Figure 2. Effect of time on the disposition of BDE 47 in female, C57BL/6 mice following a single, oral exposure (1mg/kg). Data represent mean (n=4) ± SD (%dose).