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Dermal contact with furniture fabrics is a significant pathway of human exposure to brominated flame retardants

Mohamed Abou-Elwafa Abdallah[a,b,*], Stuart Harrad[a]

[a] Division of Environmental Health and Risk Management, College of Life and Environmental Sciences, University of Birmingham, Birmingham B15 2TT, United Kingdom
[b] Department of Analytical Chemistry, Faculty of Pharmacy, Assiut University, 71526 Assiut, Egypt

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ABSTRACT

Despite extensive application in consumer products and concerns over their adverse health effects, how external exposure to brominated flame retardants (BFRs) contributes to their human body burdens is not yet fully understood. While recent studies focused on inadvertent indoor dust ingestion and diet as potential major pathways of exposure, dermal uptake has been largely overlooked. We provide the first experimentally-based assessment of dermal uptake of BFRs via contact with indoor dust and flame-retarded furniture fabrics. Results reveal substantial uptake from furniture fabrics (e.g. 8.1 ng pentaBDE/kg bw/day for adults in summer), exceeding the overall adult intake of pentaBDE estimated previously via other exposure pathways. For HBCDs, despite the low absorption fraction (< 2.5%) from the studied fabrics, the estimated dermal uptake of UK adults and toddlers (101 and 76.9 ng/kg bw/day) exceed the reported average daily intakes of 7.9 and 43.0 ng/kg bw/day for these UK age groups. Conversely, uptake from dust was low (0.05 and 0.19 ng pentaBDE/kg bw/day for adults and toddlers, respectively), indicating previous pharmacokinetic approaches may have overestimated the significance of this route. Future exposure and risk assessment studies should consider dermal contact with treated products as a significant pathway of human exposure to BFRs and related chemicals.

1. Introduction

Brominated flame retardants (BFRs) are anthropogenic chemicals applied to a broad range of consumer products (e.g. foams, fabrics and plastics) to prevent or delay the onset of fire. As the majority are "*physically*" blended within rather than "*chemically*" bonded to polymeric materials, their emission from flame-retarded products to the environment is facile. The widely used BFRs (polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecanes (HBCDs)) have been detected in every studied environmental compartment and biological species (including humans) (Law et al., 2014; McGrath et al., 2017). This is of concern owing to their potential environmental and toxicological risks including: endocrine disruption, neurodevelopmental and behavioural disorders, hepatic abnormalities and cancer (Darnerud, 2008; Liu et al., 2017). Combined with their persistent and bioaccumulative characteristics, such evidence has triggered regulatory action to restrict the production and usage of PBDEs and HBCDs, culminating in their listing under the United Nations Environmental Programme (UNEP) Stockholm Convention on Persistent Organic Pollutants (POPs) (Stockholm convention on POPs, 2013). However, human exposure to PBDEs and HBCDs is likely to continue for some time, given the ubiquity of treated products remaining in use or entering the waste stream, coupled with their environmental persistence (Harrad and Diamond, 2006).

Current understanding is that human exposure to BFRs occurs mainly via a combination of diet, ingestion of indoor dust and inhalation of indoor air. However, it remains largely unknown how external exposure to these chemicals drives their human body burdens. This was demonstrated by the lack of significant associations between the concentrations of various BFRs in indoor air, dust or diet and their measured levels in human milk or serum (Roosens et al., 2009b; Toms et al., 2009; Watkins et al., 2012). Of particular importance is the lack of explanation for the occasionally-reported high concentrations of BFRs in human milk or blood in several biomonitoring studies (Roosens et al., 2009a; Toms et al., 2009; Watkins et al., 2012). Understanding the cause of such high body burdens in such individuals is crucial to implement the necessary measures to reduce human exposure to these hazardous chemicals.

While a large volume of literature in the last decade focused on indoor dust ingestion as a pathway of human exposure to BFRs, recent

* Corresponding author at: Division of Environmental Health and Risk Management, College of Life and Environmental Sciences, University of Birmingham, Birmingham B15 2TT, United Kingdom.
E-mail address: M.abdallah@bham.ac.uk (M.A.-E. Abdallah).

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studies have indicated the potential significance of the dermal pathway (Abbasi et al., 2016; Liu et al., 2017; Pawar et al., 2017). A Few studies have reported significant positive association between concentrations of BFRs measured in handwipes and those detected in human serum. However, this cannot be solely attributed to dermal exposure because ingestion via hand-to-mouth contact may be a major contributor to such associations (Hammel et al., 2017; Watkins et al., 2011). While previous pharmacokinetic (PK) modelling studies have suggested the potential significance of dermal exposure for PBDEs, these studies focused mainly on dermal uptake via contact with indoor dust and were subject to large uncertainties due to the lack of experimentally-relevant specific uptake rates for PBDEs (Lorber, 2008; Trudel et al., 2011). Blum et al. reported the dermal absorption of the flame retardant tris(2,3-dibromopropyl)phosphate (*tris-BP-banned in April 1977*) in ten children who were wearing or who had worn tris-BP-treated sleepwear (Blum et al., 1978). Imm et al. reported significant correlations ($P < 0.05$) between the lipid-adjusted serum concentrations of PBDEs in 44 adult participants and the total Br content in their sleeping pillows and vehicle seat cushions (Imm et al., 2009). The potential significance of dermal uptake of hazardous semi-volatile organic compounds (SVOCs) (e.g. Phthalates, PCBs, Chlorpyrifos and Nicotine) through contact with contaminated fabrics (e.g. clothing and bedding) was further highlighted by several authors (Beko et al., 2018; Morrison et al., 2016; Weschler and Nazaroff, 2012). Furthermore, Saini et al. reported the sorption of airborne BFRs onto clothing fabrics suggesting potential implications for human dermal exposure via contact with contaminated clothing (Saini et al., 2016). More recently, Hammel et al. reported the presence of pentaBDE in sofa foam was associated with higher levels of BDE-47 in serum of 72 American adults ($P < 0.01$), which indicate that flame-retarded items (e.g. sofas) are likely important sources of exposure to these compounds via different pathways (Hammel et al., 2017). However, there is no experimental data on the extent of human dermal uptake of PBDEs from contact with indoor dust or flame-retarded fabrics and the significance of this route as a pathway of human exposure to PBDEs. Moreover, there is no available information on human dermal exposure to HBCDs via contact with indoor dust or flame-retarded products.

Against this background, the current study provides the first experimental investigation of dermal uptake via contact with indoor dust and/or flame-retarded fabrics as a potential major contributor to human body burdens of BFRs. To address this, we applied a standard in vitro protocol (Abdallah et al., 2015b) (Fig. S1) to study human dermal uptake of tri- to hexa-BDEs (the major components of the pentaBDE commercial mixture) and HBCDs (α-, β- and γ-isomers) from indoor dust and flame-retarded fabrics, and thereby assess the significance of dermal uptake compared to other exposure pathways. Dermal uptake of BFRs from solid matrices (e.g. dust or fabrics) is a compound process involving multiple steps. Initially, the studied chemicals are released from the contact material to the physiological human skin surface film liquid (SSFL) (i.e. becomes *bioaccessible*). This is followed by penetration of the human skin barrier, formed mainly from the *stratum corneum*. Once the chemical passes through the corneous layer by passive diffusion, it follows the intracellular/intercellular routes of penetration in the epidermis and dermis layers and subsequently reaches the blood stream (i.e. becomes *bioavailable*) (Pawar et al., 2017; Williams et al., 2005). To mimic real-life conditions, we used a simulated SSFL composed of sweat/sebum (1:1) mixture (Table S1) (Stefaniak and Harvey, 2008), real indoor dust and flame-retarded furniture fabric samples (Table S3), and viable ex vivo human skin kept under physiological conditions (37 °C and 5% CO_2). In line with the reported high environmental concentrations and use of pentaBDE in North America and HBCD in Europe (Law et al., 2014), the tested samples in this study included USA dust and fabric samples that contained elevated concentrations of pentaBDE congeners, along with dust and fabric samples from the UK that were HBCD-rich (Table S3). The aims of the current study are: (a) to provide the first experimental data on the dermal bioavailability of PBDEs and HBCDs via contact with indoor dust and furniture fabrics; (b) to investigate the potential factors influencing human dermal uptake of such BFRs; and (c) to estimate human dermal uptake of PBDEs and HBCDs via contact with dust and furniture fabric samples and evaluate the significance of this exposure pathway as a contributor to human body burdens of these contaminants.

2. Materials and methods

2.1. Chemicals and standards

All solvents and reagents used for preparation, extraction, clean-up and instrumental analysis of samples were of HPLC grade and obtained from Fisher Scientific (Loughborough, UK). Standard solutions (50 µg/mL, > 99% purity) of BDE-28, BDE-47, BDE-99, BDE-100, BDE-153, BDE-154, α-HBCD, β-HBCD and γ-HBCD were purchased from Wellington Laboratories (Guelph, ON, Canada). ^{13}C-labeled BDE-47, BDE-99, BDE-153, α-HBCD, β-HBCD and γ-HBCD used as internal (surrogate) standards, in addition to ^{13}C-BDE-100 and d_{18}-α-HBCD used as recovery determination (syringe) standards were purchased from the same company. Florisil® SPE cartridges were purchased from Supelco™ (Bellefonte, Pennsylvania, USA). All culture medium components (Table S1) and simulated human skin surface film liquid (SSFL) components (Table S2) were purchased from Sigma-Aldrich UK (Gillingham, Dorset, UK).

2.2. Test matrices

The penta-BDE commercial mixture (comprising mainly BDEs# 28, 47, 99, 100, 153 and 154) was predominantly used in North America. Therefore, concentrations of tri- to hexa- BDEs in indoor dust from North America are significantly higher than those reported in Europe (Harrad et al., 2008). In contrast, HBCDs have found greater use in Europe and Asia; hence their concentrations were higher in UK indoor dust compared to North America (Law et al., 2014). Therefore, we used dust and fabric samples from the USA (NIST SRM 2585 dust and sofa fabric from California) to assess human dermal exposure to pentaBDE congeners and UK samples (house dust and armchair fabric from Birmingham) to study HBCD exposure. A full description of the dust and fabric samples applied in this study is provided in the Supporting information.

2.3. Human skin

Freshly excised, healthy human upper thigh skin was obtained via Caltag Medsystems Ltd. (Buckingham, UK) from three consented female adults (aged 33, 35 and 36 years) following plastic surgery. Selection criteria included: Caucasian, no stretchmarks, no scars, no hair and full thickness skin without adipose tissue (870 ± 180 µm). Skin was kept on ice for no longer than 4 h prior to the onset of the ex vivo skin absorption studies. Upon receipt, ex vivo skin samples were equilibrated for 1 h with 3 mL of DMEM (Dulbecco's Modified Eagle's Medium) culture medium (Table S1) at 5% CO_2 and 37 °C before use in dermal exposure experiments. The study protocol received the required ethical approval (# ERN_12-1502) from the University of Birmingham's Medical, Engineering and Mathematics Ethical Review Committee.

2.4. Skin surface film liquid (SSFL)

Physiologically-simulated skin surface film liquid (SSFL) was prepared according to a previously reported method and US patent using over 25 different chemical components (Stefaniak and Harvey, 2006; Stefaniak and Harvey, 2008) including electrolytes, amino acids, triglycerides, vitamins and squalene (Table S2). The SSFL composition (1:1 sweat/sebum) and pH (5.3 ± 0.1) were adjusted to reflect relevant human physiological conditions (Stefaniak and Harvey, 2006).