Effect of Bromine Substitution on Human Dermal Absorption of Polybrominated Diphenyl Ethers

Mohamed A. Abdallah, Gopal Pawar, Stuart Harrad

School of Geography, Earth & Environmental Sciences, University of Birmingham, Birmingham, B15 2TT, UK

Introduction

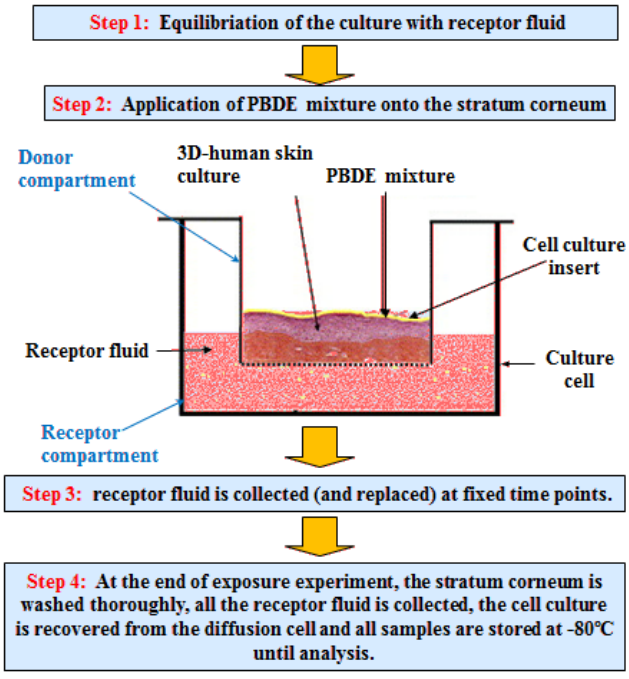
Current understanding is that non-occupational human exposure to POPs occurs mainly via a combination of diet, ingestion of indoor dust, dermal contact with dust/consumer products, and inhalation of indoor air. [1] While ingestion of indoor dust is considered the major exposure pathway for many individuals, especially for young children and toddlers [2], dermal exposure (via contact with indoor dust and flame retarded products) was predicted as the 2nd most important contributor to PBDE body burdens of adult Americans [3]. The significance of the dermal route as pathway of human exposure to PBDEs was further highlighted by Watkins *et al.* who reported a significant correlation between PBDE levels on hand wipes (assumed to result from contact with contaminated dust or flame-retarded products) and PBDE concentrations in serum from American adults.[4] However, very little is known about the fraction of PBDEs that becomes bioavailable to humans following dermal contact. This represents a research gap, which hinders accurate risk assessment of these hazardous chemicals. Furthermore, while it is known that lower brominated PBDEs display greater toxicological effects than higher brominated congeners, there exist no experimental data on how the degree of bromination affects the human dermal bioavailability of PBDEs.

To address this dearth of information, the objectives of this paper are to: (a) assess percutaneous penetration of target PBDEs in humans using an EPISKIN™ 3D-HSE model [5]; (b) evaluate the influence of bromine substitution on the dermal bioavailability of PBDEs; and (c) provide the first insights into the dermal bioavailability of several PBDEs.

Materials and Methods

All experiments were performed in a fashion that complied with the principles of good laboratory practice and the OECD guidelines for *in vitro* dermal absorption testing[5]. EPISKIN™ RHE/L/13 human skin equivalent kits were purchased from SkinEthic Laboratories (Lyon, France). Two different concentration levels of (I) 5 ng/µL and (II) 10 ng/µL of each of the target PBDEs were prepared in acetone. Based on the exposed surface area, a net dose of 500 ng/cm^2 and 1000 ng/cm^2 was applied (infinite dose scenario) to each of the investigated skin tissues according to a standard protocol (Figure 1). The generated samples were extracted using a previously reported QuEChERs based method [6] and analysed by GC-NCI/MS[7].

Figure 1: Standard experimental protocol applied to study the percutaneous permeation of PBDEs



Results and Discussion

Percutaneous penetration

The studied PBDE congeners displayed wide variability in their ability to penetrate the skin under the applied experimental conditions (Table 1). Results revealed that the degree of dermal penetration was inversely proportional to the degree of PBDE bromination. Maximum penetration was observed for BDE-1 with ~30% of the applied dose detected in the receptor fluid after 24 h of exposure, while the more environmentally-abundant BDE-47 and BDE-99 showed an average absorption of ~ 3% and 2%, respectively. Interestingly, BDE-209 was not detected in the receptor fluid after 24 h indicating low dermal bioavailability of this congener in humans.

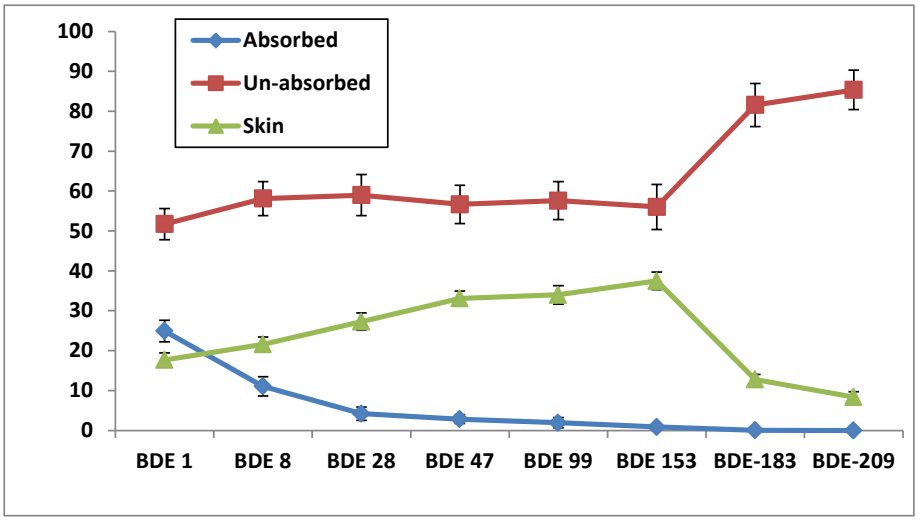
All target PBDEs accumulated in the skin tissue to varying degrees. While the proportion of the applied PBDE dose accumulated in the skin increased with increasing bromine substitution from BDE-1 (~18%) to BDE-153 (~37%), this proportion dropped steeply from BDE-183 (~13%) through to BDE-209 (8%) (Figure 2). This can be attributed to the physicochemical parameters of the studied PBDEs.

Table 1: Cumulative levels (expressed as average percentage ± standard deviation of applied dose) of target PBDEs in the receptor fluid following exposure of EPISKIN™ to 500 ng/cm^2 of target PBDEs.

Time (hours)	BDE-1	BDE-8	BDE-28	BDE-47	BDE-99	BDE-153	BDE-183	BDE-209
0.25	ND*	ND	ND	ND	ND	ND	ND	ND
0.50	0.29 ± 0.07	0.10 ± 0.04	0.07 ± 0.03	0.04 ± 0.01	ND	ND	ND	ND
1.00	1.05 ± 0.26	0.41 ± 0.05	0.20 ± 0.02	0.13 ± 0.02	0.08 ± 0.01	0.03 ± 0.01	ND	ND
2.00	1.98 ± 0.57	0.82 ± 0.07	0.31 ± 0.09	0.21 ± 0.09	0.07 ± 0.04	0.04 ± 0.01	ND	ND
6.00	5.06 ± 1.08	1.88 ± 0.65	0.46 ± 0.31	0.48 ± 0.32	0.43 ± 0.15	0.13 ± 0.05	ND	ND
10.00	10.18 ± 1.89	4.34 ± 1.72	1.59 ± 1.56	0.97 ± 0.82	0.57 ± 0.77	0.33 ± 0.03	ND	ND
12.00	14.21 ± 2.07	6.75 ± 2.24	2.19 ± 1.36	1.56 ± 0.89	0.86 ± 0.84	0.46 ± 0.02	0.03 ± 0.01	ND
18.00	20.43 ± 2.51	8.68 ± 2.17	2.77 ± 1.43	2.23 ± 0.88	1.29 ± 1.07	0.68 ± 0.04	0.04 ± 0.01	ND
24.00	24.92 ± 2.71	11.08 ± 2.43	4.23 ± 1.68	2.85 ± 1.09	1.96 ± 1.26	0.89 ± 0.11	0.05 ± 0.01	ND

* Not detected (less than 0.02% of applied dose for all congeners, or 0.05% for BDE-209).

Figure 2: Percent of applied dose (500 ng/cm^2) of target PBDEs absorbed, un-absorbed and accumulated in the skin tissue following 24 h exposure.



Dermal flux (J_{ss}) and permeation coefficients (P_{app})

Steady state flux ***(J_{ss})*** and skin permeation coefficient ***(P_{app})*** values were derived for the studied PBDEs (Table 2). It was not possible to estimate either property for BDE-183 and BDE-209 due to their low percutaneous penetration and failure to reach steady state within our 24 h exposure period. Results show a decreased flux across the skin and higher resistance to percutaneous penetration with increasing bromine substitution from mono- to hexa-PBDEs. a significantly positive correlation ($P < 0.05$) was observed between $\boldsymbol{P_{app}}$ values of the studied mono- through hexa-BDEs and the water solubility and vapour pressure of these congeners, while a significant negative correlation ($P < 0.05$) was observed between $\boldsymbol{P_{app}}$ and log K_{OW}, as well as the molecular weight of the studied PBDEs.

Implications for human exposure

Our results indicate that following exposure of a unit area of human skin to a mixture of PBDEs with varying degrees of bromination, lower brominated congeners achieve comparatively rapid penetration to the systemic circulation. In contrast, higher brominated congeners penetrate more slowly through the skin layers to the blood. However, these higher PBDEs will achieve higher levels of accumulation within the skin layers. This is likely due to the time required for the more lipophilic, higher molecular weight PBDEs to penetrate from the *stratum corneum* through the aqueous-based viable epidermis prior to reaching the blood stream[8].

We therefore argue that for the purposes of risk assessment, the total mass of a chemical that becomes systemically available over time following exposure should be considered. Indications from our study are that this value is better expressed by the mass of target compound that has entered the skin, rather than by that which has traversed the skin. Moreover, for higher molecular weight PBDEs such as BDE-209, metabolism of this skin depot may result in exposure to more toxic lower molecular weight PBDEs that were not present in the matrix to which the external skin barrier was exposed.

Table 2: Steady state flux, permeation coefficient and lag time values estimated from exposure of EPISKIN™ to 500 ng/cm^2 of target PBDEs for 24 h.

	Flux (ng/cm^2.h)	Permeation coefficient (cm/h)	Lag time (h)
BDE 1	**5.45**	**1.09×10^{-2}**	**0.25**
BDE 8	**2.42**	**4.84×10^{-3}**	**0.42**
BDE 28	**0.88**	**1.76×10^{-3}**	**0.82**
BDE 47	**0.63**	**1.26×10^{-3}**	**0.90**
BDE 99	**0.40**	**8.00×10^{-4}**	**1.10**
BDE 153	**0.20**	**4.00×10^{-4}**	**1.26**

Acknowledgement

The research leading to these results has received funding from the European Union Seventh Framework Programme FP7/2007-2013 under grant agreements 327232 (ADAPT project) and 316665 (A-TEAM project). Further support was provided by Restek Corporation.

References

1. D. Trudel, M. Scheringer, N. von Goetz, K. Hungerbuehler, *Environ Sci Technol* **45**, 2391 (2011).
2. S. Harrad, E. Goosey, J. Desborough *et al.*, *Environ Sci Technol* **44**, 4198 (2010).
3. M. Lorber, *J Expo Sci Env Epid* **18**, 2 (2008).
4. D. J. Watkins, M. D. McClean, A. J. Fraser *et al.*, *Environ Health Persp* **119**, 1247 (2011).
5. OECD, *Organisation for Economic Cooperation and Development TG 428*, (2004).
6. M. A.-E. Abdallah, J. Zhang, G. Pawar *et al.*, *Anal Bioanal Chem* **407**, 1871 (2015).
7. L. Roosens, M. A. Abdallah, S. Harrad, H. Neels, A. Covaci, *Environ Sci Technol* **43**, 3535 (2009).
8. USEPA, *http://www.epa.gov/oppt/exposure/presentations/efast/usepa_1992d_dermalea.pdf*, (1992).