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ORIGINAL ARTICLE

Dermal bioaccessibility of flame retardants from indoor dust and the influence of topically applied cosmetics

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Despite extensive literature on their potential adverse health effects, there is a lack of information on human dermal exposure to organic flame retardant chemicals (FRs). This study applies an *in vitro* physiologically based extraction test to provide new insights into the dermal bioaccessibility of various FRs from indoor dust to synthetic sweat/sebum mixture (SSSM). The bioaccessible fractions of α-, β- and γ-hexabromocyclododecane (HBCD) and tetrabromobisphenol A (TBBPA) to 1:1 (sweat/sebum) mixture were 41%, 47%, 50% and 40%, respectively. For Tris-2-chloroethyl phosphate (TCEP), tris (1-chloro-2-propyl) phosphate (TCIPP) and tris-1,3-dichloropropyl phosphate (TDCIPP), bioaccessible fractions were 10%, 17% and 19%. Composition of the SSSM and compound-specific physicochemical properties were the major factors influencing the bioaccessibility of target FRs. Except for TBBPA, the presence of cosmetics (moisturising cream, sunscreen lotion, body spray and shower gel) had a significant effect ($P < 0.05$) on the bioaccessibility of the studied FRs. The presence of cosmetics decreased the bioaccessibility of HBCDs from indoor dust, whereas shower gel and sunscreen lotion enhanced the bioaccessibility of target PFRs. Our bioaccessibility data were applied to estimate the internal exposure of UK adults and toddlers to the target FRs via dermal contact with dust. Our worst-case scenario exposure estimates fell far below available health-based limit values for TCEP, TCIPP and TDCIPP. However, future research may erode the margin of safety for these chemicals.

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Keywords: BFRs; bioaccessibility; cosmetics; dermal exposure; indoor dust; PFRs

INTRODUCTION

Organic flame retardants (FRs) like polybrominated diphenyl ethers (PBDEs), hexabromocyclododecane (HBCD), tetrabromobisphenol-A (TBBPA), novel brominated flame retardants (NBFRs), and organophosphate flame retardants (PFRs) have found widespread application in a plethora of consumer items.[1,2] However, concerns exist over possible adverse health impacts following numerous reports of exposure to BFRs through inhalation, dermal contact and ingestion of both diet and settled dust.[3,4] In a recent review[5] we highlighted the potential importance of dermal uptake of FRs as an exposure pathway. The lack of experimental information on human dermal uptake of these chemicals from contact with organic films present on indoor surfaces as well as contact with dust particles and source materials may be attributed to ethical issues associated with both *in vivo* and *in vitro* studies using human tissues. In addition, uncertainties arise from interspecies variation and allometric scaling of dermatokinetic data from animals to humans.[5] These challenges further support the need for alternative *in vitro* methods to study dermal availability of FRs in indoor dust to humans.

Survey of existing literature reveals various modelling approaches for dermal risk assessment including quantitative structure activity relationship (QSAR)-based methods[6,7] and pharmacokinetic (PK) modelling methods.[8] However, such approaches have some limitations; for example, QSAR-based approaches report uncertainties associated with the relationship between K_m (the partition coefficient between the exposure vehicle and *stratum corneum* (SC)) of the studied molecule and its K_{OW}, where the extent to which K_{OW} is good predictor for K_m is questionable, especially when the exposure vehicle is not water. Moreover, the thickness of the SC varies between species and estimated values of the compound diffusivity through the skin based on extrapolation from other studies on different compounds can be misleading.[9]

On the other hand, PK modelling studies of FRs report uncertainties associated with the fraction of FR available for absorption following exposure via different pathways (that is, ingestion, inhalation or dermal contact) in addition to the lack of reliable information on the elimination half-lives of different FRs from various tissues.[10,11] Moreover, the influence of physiological fluids (e.g., sweat, gastrointestinal fluid, etc) on the bioavailable fraction of FRs is often neglected.

Physiologically based *in vitro* bioaccessibility tests have emerged as an alternative method to study the availability for dermal uptake of several xenobiotics including heavy metals[12–16] and pesticides.[17] Such bioaccessibility tests have been incorporated in regulatory frameworks such as the European standard for the release of nickel in artificial sweat (BS EN 1811, 2011). Bioaccessibility may be defined as "the fraction of the total dose of a specific chemical/contaminant present in a matrix that becomes liberated into the body fluids and hence, is available for absorption".[18] In other words, a combination of data on bioaccessibility and subsequent dermal uptake is required to

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determine the ability of a chemical (e.g., an FR) present in a matrix (e.g., dust) to be released from that matrix and be subsequently absorbed by an organ of the human body like the skin.[17] Bioaccessibility data from *in vitro* studies are conservative, because not all the mass of a given chemical released into the body fluid (that is, the bioaccessible fraction) will likely be absorbed through the biological membrane (e.g., skin) to reach the systemic circulation (that is, bioavailable).[19] The outermost surface of the human skin, the SC, is covered with a skin surface film liquid (SSFL) mixture that consists of varying proportions of sweat and sebum.[20,21] Sweat is aqueous in nature and secreted to regulate body temperature. It consists mainly of electrolytes, organic acids, amino acids, vitamins and other nitrogenous substances. Sebum is a clear, oily substance secreted by sebaceous glands and forms a 0.5 to $>4.0\,\mu$m thick layer to protect the skin from drying out. It mainly consists of squalene, wax esters and triglycerides, as well as free fatty acids, with a small amount of cholesterol and cholesterol esters.[22]

Cosmetics (e.g., sunscreen creams) may contain certain ingredients (e.g., surfactants) that can remain on the skin and become incorporated within the SSFL. This in turn may alter the lipid domain of the skin by interacting with the proteins in the barrier, or hydration, thereby increasing partitioning of chemicals to the SC.[23] Previous studies have shown certain sunscreen lotions to act as inadvertent penetration enhancers for potentially harmful chemicals.[24,25] Therefore, it is important to investigate the effect of topically applied cosmetics on the dermal bioaccessibility of FRs in indoor dust.

Against this background, we investigate, for the first time, the dermal bioaccessibility of selected organic FRs present in house dust, including TBBPA, *α*-, *β*- and γ-HBCD, Tris-2-chloroethyl phosphate (TCEP), tris (1-chloro-2-propyl) phosphate (TCIPP) and tris-1,3-dichloropropyl phosphate (TDCIPP). We quantify the bioaccessible fraction of these FRs from dust to varying physiologically relevant mixtures of synthetic sweat and sebum, and examine the impact on bioaccessibility of various topically applied cosmetic products.

MATERIALS AND METHODS

Characterisation of the Studied House Dust

SRM 2585 (organics in house dust, particle size $<100\,\mu$m and total moisture content $=2.11\pm0.06\%$) was purchased from NIST (Gaithersburg, MD, USA). Aliquots ($n=5$, ~0.1 g each) of SRM2585 were analysed for target FRs using previously reported methods by our research group.[26,27] Results compared well with the indicative and reported levels of target FRs in this SRM (Supplementary Tables S1–S5).

Preparation of Synthetic Sweat and Sebum Mixture

Physiologically simulated artificial sweat and sebum mixture (SSSM) was prepared according to a previously reported method and US patent using over 25 different chemical components[22,28] (see Supplementary Table S6 for details). The pH was adjusted to that of normal human skin (5.3 ± 0.1) and preserved at 8 °C. Synthetic sweat and sebum were prepared separately, and then mixed in different physiologically relevant proportions using Tween-80 to mimic the naturally secreted surface active agents in the SSSM.[22,28]

Dermal Bioaccessibility in *In Vitro* Test Protocol

Briefly, ~60 mg of NIST SRM2585 dust and (when tested) 6 mg of cosmetics (moisturising cream, sun screen lotion, shower gel and body spray were each examined separately) were accurately weighed and transferred into a clean dry test tube. In the absence of definitive data on the dust to sweat ratio on human skin (which is greatly influenced by variations of sweat secretion and dust loadings), we adopted a previously reported method[17] to mimic "wet skin conditions" using 1:100 w/v dust to sweat ratio (that is, 6 ml of the SSSM were applied for each 60 mg of dust). The mixture was then gently agitated on a heated magnetic-stirrer plate maintained at physiological skin temperature (32 °C). After 1 h, phase separation was achieved by centrifugation at 3000 r.p.m. for 15 min. The dust (solid residue) and SSSM (supernatant) samples were analysed separately.

Chemical Analysis

Determination of HBCDs and TBBPA. Dust/SSSM/cosmetic samples were spiked with 30 μl of ^{13}C-isotopically labelled *α*-HBCD, *β*-HBCD, *γ*-HBCD and TBBPA (1 ng/μl) before extraction with 3 ml of hexane/ethyl acetate (1:1 v/v) using a QuEChERS-based method. Sample tubes were vortexed on a multi-positional mixer for 5 min, followed by ultrasonication for 5 min and centrifugation at 3000 r.p.m. for 5 min. The extraction cycle was repeated twice before the pooled supernatant was collected in a clean tube and evaporated to ~1 ml under a stream of N_2. The crude extract was washed with ~2 ml of 95% H_2SO_4 to remove lipids. The organic layer and washings were combined and evaporated to incipient dryness under N_2. Target analytes were reconstituted in 150 μl of methanol containing 50 pg/μl of d_{18}-*α*-HBCD used as recovery determination standard (RDS) before LC-MS/MS analysis using previously reported methods.[29]

Determination of PFRs. Dust/SSSM/cosmetic samples were spiked with 30 μl of d_{15}-triphenyl phosphate (d_{15}-TPHP, 10 ng/μl) used as internal (surrogate) standard before extraction with hexane/ethyl acetate (1:1 v/v, 3 ml) using the same procedure applied for HBCDs. The crude extract (~1 ml) was cleaned up by loading onto a Florisil SPE cartridge (preconditioned with 6 ml of hexane). Fractionation was achieved by eluting with 8 ml of hexane (F1, discarded) followed by 10 ml of ethyl acetate (F2). F2 was evaporated to incipient dryness under N_2. Target PFRs were reconstituted in 100 μl of isooctane containing ^{13}C-BDE-100 used as RDS before GC/MS analysis according to a previously reported method.[30]

Quality Assurance and Quality Control

All experiments were conducted in triplicate. Good IS recoveries were obtained for all samples (Supplementary Table S7). One procedural blank was run every six samples. This consisted of anhydrous sodium sulphate (~0.1 g) exposed to the same experimental protocol as a dust sample. None of the target compounds were detected in procedural blanks. Identification and quantification of target analytes were performed according to the retention times and peak areas of the corresponding calibration standards injected before and after each sample batch. Whereas the overall method performance for dust analysis was evaluated via replicate analysis ($n=5$) of SRM 2585, method performance for the analysis of SSSM/cosmetic samples was checked by a matrix spike exercise at three concentration levels. The results obtained (Supplementary Table S8) indicated good accuracy and precision of the applied analytical method.

Assessment of Dermal Bioaccessibility

In this study, bioaccessibility is expressed as $f_{\text{bioaccessible}}$, calculated (Eq. (1)) as the percentage of each target FR detected in the dust that was found in the supernatant at the end of each bioaccessibility experiments (all experiments were carried out in triplicate, hence average values were used) (Supplementary Tables S2 and S5):

$$f_{\text{bioaccessibile}}(\%) = \frac{\text{Average mass of FR in supernatant}}{\text{Average mass of FR in dust}} \times 100 \qquad (1)$$

Statistical Analysis and Data Processing

Statistical analysis of data was conducted using Microsoft Excel 2010 and SPSS 22 for Windows. Means of various data sets were estimated and compared using ANOVA and Tukey's honestly significant difference *post hoc* test. The *P*-values of <0.05 were considered significant.

RESULTS AND DISCUSSION

Dermal Bioaccessibility of FRs in Indoor Dust

The process of human dermal uptake of chemicals from house dust to the general circulation is limited by two main factors. These are the bioaccessibility and the penetration rate. In the human skin, the SC (outermost dead corneous layer) presents the major limiting factor for penetration of chemicals, and passive diffusion is the main transport mechanism for organic chemicals.

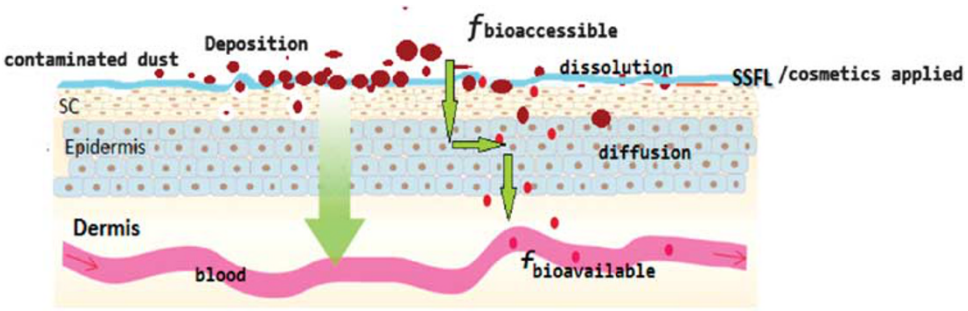

Figure 1. Schematic illustration depicting the structure of the skin and the absorption process for FRs in indoor dust in the presence of sweat/sebum mixture and topically applied cosmetics.

Table 1. Effect of the composition of synthetic sweat and sebum mixture (SSSM) on the bioaccessibility ($f_{bioaccessible}$) of target FRs from indoor dust.

	$f_{bioaccessible}$ (%) for different SSSM compositions						
Compound	*100% Sweat*	*99:1 Sweat/sebum*	*95:5 Sweat/sebum*	*9:1 Sweat/sebum*	*8:2 Sweat/sebum*	*1:1 Sweat/sebum*	*100% Sebum*
α-HBCD	2.3 ± 0.2	2.4 ± 0.2	12.0 ± 6.0	20.0 ± 2.8	36.1 ± 2.7	40.9 ± 2.9	50.5 ± 7.0
β-HBCD	1.6 ± 0.6	3.6 ± 0.7	10.1 ± 1.3	14.5 ± 5.7	29.7 ± 0.6	46.9 ± 3.4	60.4 ± 10.1
γ-HBCD	1.4 ± 0.1	4.1 ± 1.8	11.4 ± 2.2	19.0 ± 5.4	23.2 ± 6.5	49.6 ± 5.8	67.2 ± 3.37
Σ-HBCD	1.8 ± 0.2	3.3 ± 0.89	11.47 ± 4.1	18.7 ± 4.0	30.0 ± 4.2	45.2 ± 4.1	58.5 ± 5.7
TBBPA	3.5 ± 0.5	4.8 ± 1.9	9.6 ± 4.2	25.2 ± 7.1	32.4 ± 5.4	39.5 ± 4.3	55.7 ± 8.5
TCEP	16.0 ± 1.22	15.8 ± 0.8	14.8 ± 0.9	12.2 ± 1.0	11.2 ± 1.4	10.4 ± 1.8	22.3 ± 2.3
TCIPP	12.4 ± 4.4	15.4 ± 2.8	20.6 ± 3.2	8.4 ± 2.2	11.9 ± 1.9	17.4 ± 2.7	26.9 ± 6.4
TDCIPP	11.9 ± 3.6	12.0 ± 0.5	13.0 ± 0.4	10.5 ± 0.4	12.4 ± 0.3	18.6 ± 0.8	28.1 ± 0.6

Experiments were performed in triplicate, and results are presented as average ± SD.

Therefore, the penetration rate across the SC is mainly controlled by compound-specific physicochemical properties. However, for chemicals bound to particulate matter as in indoor dust, the chemical's release from particles into the body fluids on the skin surface can be more important.[17,31,32] The hydrolipidic SSFL and other ingredients of topically applied cosmetics may enhance or reduce the chemical release ($f_{bioaccessible}$) from particles adhered to the skin. 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 ($f_{bioavailable}$) (Figure 1). Our results show that none of the target FRs were 100% bioaccessible from indoor dust particles into any of the studied SSSM combinations (Table 1). This indicates that assumption of 100% absorption of intake via the dermal route could lead to a substantial overestimation of human exposure to FRs via indoor dust.

Dermal bioaccessibility of HBCDs and TBBPA. In general, $f_{bioaccessible}$ of HBCDs and TBBPA increased with increasing sebum content of the SSFL (Table 1). At 100% sweat, the $f_{bioaccessible}$ of *γ*-HBCD (1.4 ± 0.1%) was less than that of *β*-HBCD (1.6 ± 0.6%) and *α*-HBCD (2.3 ± 0.2%). However, the reverse trend was observed at 100% sebum, where the $f_{bioaccessible}$ was highest for *γ*-HBCD (67.2 ± 3.37%), followed by *β*-HBCD (60.4 ± 10.1%) and *α*-HBCD (50.5 ± 7.0%). This behaviour is consistent with the lower water solubility of the *γ*-isomer (2 *μ*g/l) compared with that of *β*-HBCD (15 *μ*g/l) and *α*-HBCD (49 *μ*g/l).[19]

We recorded $f_{bioaccessible}$ values for TBBPA of 3.5 ± 0.5% and 55.7 ± 8.5% in 100% sweat and 100% sebum, respectively. Compared with HBCDs, the higher $f_{bioaccessible}$ value for TBBPA in 100% sweat is likely attributable to the higher water solubility of TBBPA (1.26×10^3 *μ*g/l).

Compared with the aqueous-based sweat, the substantially higher bioaccessibility of the studied BFRs in sebum can be attributed to the enhanced solubility of these lipophilic chemicals in the oily sebum.

Dermal bioaccessibility of PFRs. In general, PFRs were more bioaccessible in sebum than sweat. In 100% sweat, $f_{bioaccessible}$ values for the studied PFRs were 16.0 ± 1.2% (TCEP), 12.4 ± 4.4% (TCIPP) and 11.9 ± 3.6% (TDCIPP), whereas in 100% sebum, the corresponding values were 22.3 ± 2.3% (TCEP), 26.9 ± 6.4% (TCIPP) and 28.1 ± 0.6% (TDCIPP). This concurs with the physicochemical properties of our target PFRs (Supplementary Table S9). In particular, the water solubility of TCEP, TCIPP and TDCIPP was reported as 7×10^3, 1.6×10^3 and 1.5 mg/l, respectively.[2] Compared with the studied BFRs, PFRs show higher bioaccessibility in sweat and lower bioaccessibility in sebum (Table 1) that can be attributed to the differences in log K_{ow} and water solubility among these two classes of FRs (Supplementary Table S9). Overall, at the most realistic SSFL composition (1:1 sweat/sebum) studied here, BFRs showed higher dermal bioaccessibility than PFRs that may be attributed to increased partitioning of the more lipophilic BFRs from dust to the oily sebum.

Effect of cosmetics on the dermal bioaccessibility of FRs in indoor dust. To investigate the influence of commonly applied cosmetics on the dermal bioaccessibility of FRs in indoor dust, we determined $f_{bioaccessible}$ values of target FRs from reference dust into 1:1 sweat/sebum mixture in the presence of (separately) moisturising cream, sunscreen lotion, body spray and shower gel. Results for each target compound were compared with a control group comprising reference dust exposed only to 1:1 sweat/sebum mixture without any surfactant or cosmetics. Except for TBBPA, statistically significant differences ($P < 0.05$; ANOVA) were observed between $f_{bioaccessible}$ values of target FRs in the presence of various cosmetics compared with the control group (Figure 2).

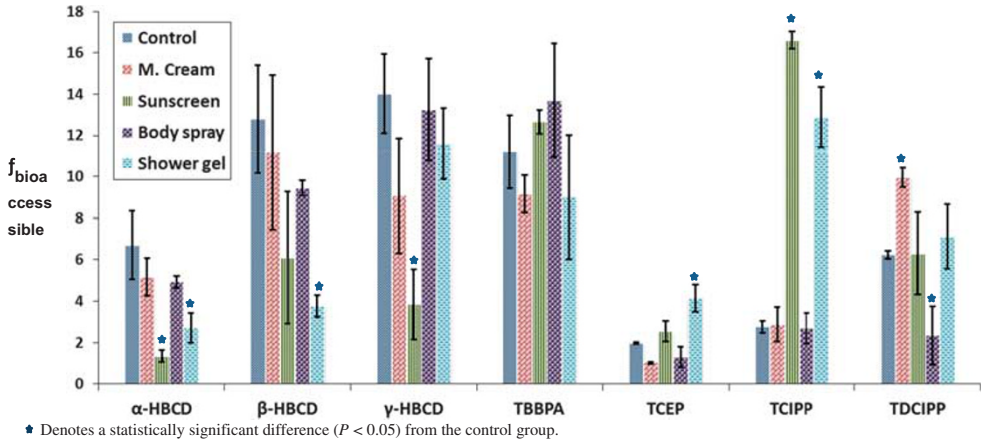

Figure 2. Effect of applied cosmetics on the bioaccessibility ($f_{bioaccessible}$ %) of target FRs from indoor dust.

Table 2. Parameters used in dermal exposure assessment of target FRs in indoor dust.[35]

Parameter	*Adult*	*Toddler*
Age	> 18 Years	2–3 Years
Body weight	70 kg	15 kg
Body surface area	1.94 m^2	0.6 m^2
Skin surface exposed	4615 cm^2 (head, forearms, hands and feet)	2564 cm^2 (head, extremeties including hands and feet)
Dust adhered to skin	0.01 mg/cm^2	0.04 mg/cm^2
Indoor exposure fraction[26]		
House	63.8%	86.1%
Office	22.3%	—
Car	4.1%	4.1%

Interestingly, the presence of cosmetics seems to decrease the bioaccessibility of HBCDs from indoor dust (Figure 2). This is in agreement with the reported slight decrease in dermal bioaccessibility of PCBs from house dust in the presence of skin cream[17] that was attributed to possible retention of the lipophilic chemicals by skin cream lipids. Our results also show that whereas shower gel and sunscreen lotion enhanced the bioaccessibility of target PFRs, body spray significantly decreased the $f_{bioaccessible}$ value of TDCIPP from indoor dust (Figure 2).

To summarise, our results agree with previous reports that cosmetics contain various ingredients that can alter the composition of the SSFL and affect the availability of dust-bound FRs for dermal uptake. However, it is also evident that the nature and magnitude of this effect is substance specific and highly dependent on the composition of the cosmetic preparation. The effect of surfactants—that are common ingredients of most cosmetics—on the dermal absorption of various chemicals has been previously highlighted.[24,25] In addition, we hypothesise that the lipid content, ionic strength and skin contact period of these cosmetics can also influence the bioaccessibility of FRs from indoor dust. Detailed studies are required to test this hypothesis and fully investigate the factors affecting the bioaccessibility of FRs and ultimately their dermal uptake in the presence of various cosmetic preparations.

Comparison of digestive and dermal bioaccessibility. Despite the vast differences between the digestive and dermal body fluids in terms of both composition and function, it is instructive to compare our results with previously reported bioaccessibilities of target FRs via the oral route. This can shed some light on the relative importance of dermal uptake *versus* ingestion as pathways of human exposure to FRs in indoor dust.

Abdallah et al.[19] reported on the gut bioaccessibility of HBCDs and TBBPA from indoor dust using a colon-enhanced–physiologically based extraction test (CE-PBET). On average, $f_{bioaccessible}$ values of 92%, 80%, 72% and 94% were reported for *α*-, *β*-, *γ*-HBCDs and TBBPA, respectively. These are almost twice the dermal $f_{bioaccessible}$ values for the same BFRs in our study (Table 1). The gut bioaccessibility of PFRs following ingestion of indoor dust was also studied using a modified version of the CE-PBET mentioned above.[33] Mean $f_{bioaccessible}$ values for TCEP, TCIPP and TDCIPP from 17 house dust samples were 80%, 82% and 85%, respectively, that are substantially higher than the corresponding dermal $f_{bioaccessible}$ values for the same PFRs (Table 1).

The substantially higher gut bioaccessibility of FRs may be attributed to several factors. These include the strong acidic medium in the stomach (pH = 1), the bile salts and digestive enzymes in the small intestine, the presence of carbohydrates to simulate the fed status, coupled with the long contaminant residence time in the models used (~13–21.5 h)[19,33] compared with the 1 h dermal exposure period used in this study. More research is required to fully understand the influence of prolonged dermal exposure times on the bioaccessibility of FRs from indoor dust and examine the kinetics of the release of various FRs from indoor dust to the sweat/sebum mixture.

Assessment of Human Dermal Exposure to FRs in Indoor Dust

The results of dermal bioaccessibility experiments obtained in this study (Table 1) were used to gain some insight into the internal dose of the target FRs arising from dermal exposure to contaminated indoor dust. Results revealed that $f_{bioaccessible}$ values for the studied FRs in indoor dust were significantly influenced by the presence of various cosmetic preparations. However, incorporation of our data into risk assessment models is hampered by the current lack of reliable information on the exact amount of cosmetics remaining on the skin after application and on the skin residence time of such formulations. Therefore, exposure assessment estimations were performed without such data.

Human dermal exposure to our target FRs was estimated using the general equation:

$$DED = \frac{C \times BSA \times DAS \times F_A \times IEF}{BW \times 1000} \ldots \quad (2)$$

where *DED* = daily exposure dose (ng/kg bw/day), *C* = FR concentration in dust (ng/g), *BSA* = body surface area exposed (cm^2),

DAS = dust adhered to skin (mg/cm^2), F_A = fraction absorbed by the skin (unitless), *IEF* = indoor exposure fraction (hours spent over a day in an indoor environment) (unitless), BW = body weight (kg).

We estimated the dermal exposure of two age groups (adults and toddlers) using three exposure scenarios. We used data previously reported by our research group on the minimum, median and maximum concentrations (Supplementary Table S10) of target FRs in indoor dust from several UK microenvironments[26,34] to estimate low, average and high exposure, respectively. The parameter F_A in Eq. (2) was replaced by the experimental values of $f_{bioaccessible}$ obtained in this study for each target FR at the most physiologically abundant sweat/sebum mixture (1:1) (Table 1). Values for other parameters in Eq. (2) were obtained from the USEPA exposure factors handbook[35] and summarised in Table 2.

Table 3. Assessment of human dermal exposure (ng/kg bw/day) to FRs present in indoor dust upon contact with a skin surface film composed of 1:1 sweat/sebum.

FR/scenario	*UK adult*			*UK toddler*		
	Low	*Average*	*High*	*Low*	*Average*	*High*
α-HBCD	0.1	1.0	14.1	0.1	1.1	16.9
β-HBCD	< 0.1	0.3	6.7	< 0.1	0.4	7.9
γ-HBCD	0.2	3.0	25.8	0.2	3.3	29.7
TBBPA	< 0.1	0.1	0.7	< 0.1	0.1	0.9
TCEP	< 0.1	0.1	3.7	< 0.1	0.5	17.4
TCIPP	0.3	0.5	6.4	3.9	4.7	46.8
TDCIPP	< 0.1	0.1	2.2	< 0.1	0.9	19.2

Our dermal exposure estimates (Table 3) highlight the potential importance of the dermal route as a pathway of human exposure to FRs in indoor dust. The average scenario estimate of dermal exposure of UK adults and toddlers to the target BFRs ranged from 99–110% to 44–59% respectively, of their estimated exposure via dust ingestion[26] (Figure 3). For PFRs, the estimated average dermal exposure corresponded to 26–42% and 28–45% of previously reported exposure via dust ingestion.[34] However, it should be noted that our dermal exposure estimates assume a fixed body area undergoing constant exposure to FRs in indoor dust for a constant period daily at a fixed absorbed fraction derived from 1 h dermal contact time with indoor dust. Such rigid assumptions are likely unrealistic and introduce uncertainty to our estimates of dermal exposure. A further significant caveat is that our estimates account only for bioaccessibility—that is, the efficiency of release of FRs from dust into sweat/sebum. Although this is important, reliable data are not yet available on the subsequent dermal transfer of the studied FRs from sweat/sebum across the epidermis to the systemic circulation. Such transfer will very likely be < 100%, and thus the true influence of dermal exposure to dust will likely be appreciably lower than the values shown in Table 3. While noting this caveat, we also note that our

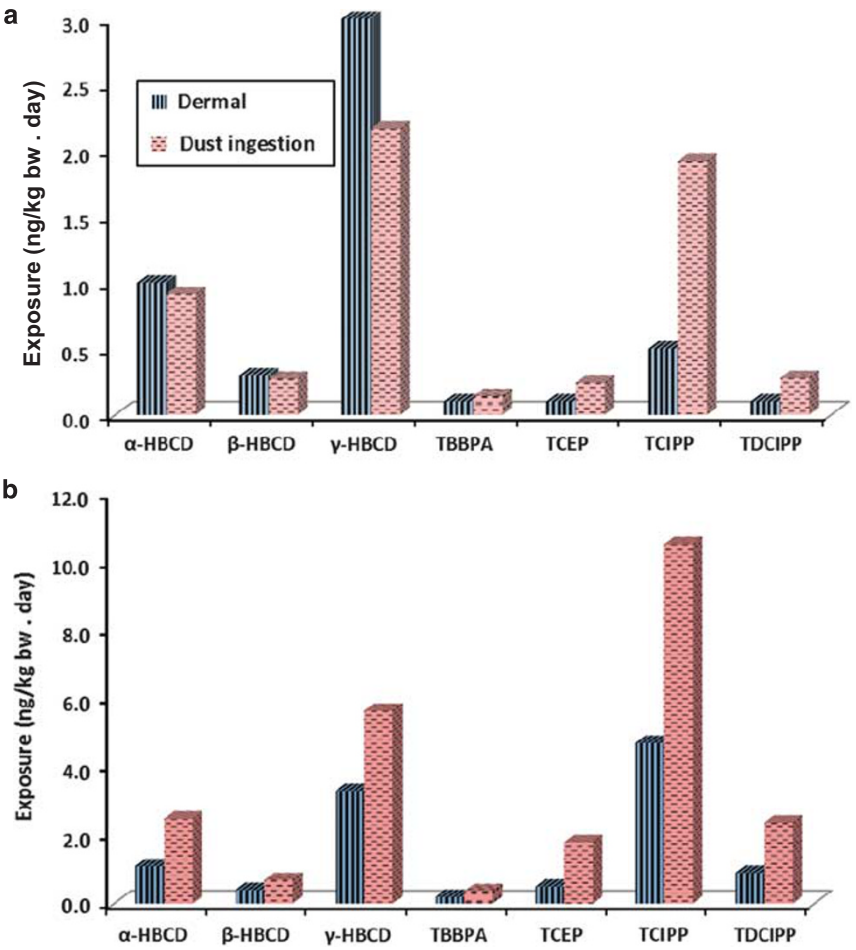

Figure 3. Comparison for (a) UK adults and (b) toddlers of exposure (ng/kg bw day) to FRs in indoor dust via dermal contact (this study, average exposure scenario) and dust ingestion.[26,34]

estimates of exposure via dust ingestion assume 100% efficiency of transfer from dust into gut fluids and thence across the gastrointestinal tract.

In a risk assessment context, an extensive survey of the available literature revealed a no significant risk level (NSRL) of 5.4 μg/day for TDCIPP listed as a carcinogen under the State of California safe drinking water and toxic enforcement act of 1986, PROPOSITION 65.[36] No other health-based limit values (HBLVs) of legislative standing for our target FRs were found in the literature. However, based on a chronic no observed adverse effect level (NOAEL) divided by an uncertainty factor of 1000, HBLVs of 22,000 and 80,000 ng/kg bw/day were derived for TCEP and TCIPP respectively.[37] Our worst-case scenario exposure estimates for dermal exposure of adults and toddlers fall far below these HBLV values even under our high-end dermal exposure scenario. However, as noted by Ali et al.,[37] the HBLV values cited here were based on relatively old toxicological studies and it is possible that future research may erode the margin of safety.

In conclusion, not withstanding the various caveats noted above, the results of this *in vitro* bioaccessibility study provide some important first insights into human dermal exposure to various FRs present in indoor dust. The composition (that is, sweat/sebum ratio) of skin fluids, as well as the presence/absence of commonly used skin cosmetics, is demonstrated to exert a substantial influence on the efficiency with which our target FRs are released from dust and rendered available for dermal uptake.

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Supplementary Information accompanies the paper on the Journal of Exposure Science and Environmental Epidemiology website (http://www.nature.com/jes)