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Assessment of Human Dermal Absorption of Flame Retardant Additives in Polyethylene and Polypropylene Microplastics Using 3D Human Skin Equivalent Models.

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Abstract

To overcome ethical and technical challenges impeding the study of human dermal uptake of chemical additives present in microplastics (MPs), we employed 3D human skin equivalent (3D-HSE) models to provide first insights into the dermal bioavailability of polybrominated diphenyl ether (PBDEs) present in MPs; and evaluated different factors influencing human percutaneous absorption of PBDEs under real-life exposure scenario. PBDEs were bioavailable to varying degrees (up to 8 % of the exposure dose) and percutaneous permeation was evident, albeit at low levels (≤ 0.1 % of the exposure dose). While the polymer type influenced the release of PBDEs from the studied MPs to the skin, the polymer type was less important in driving the percutaneous absorption of PBDEs. The absorbed fraction of PBDEs was strongly correlated ($r^2 = 0.88$) with their water solubility, while the dermal permeation coefficient P_{app} of PBDEs showed strong association with their molecular weight and $logK_{OW}$. More sweaty skin resulted in higher bioavailability of PBDEs from dermal contact with MPs than dry skin. Overall, percutaneous absorption of PBDEs upon skin contact with MPs was evident, highlighting, for the first time, the potential significance of the dermal pathway as an important route of human exposure to toxic additive chemicals in MPs.

Keywords: Bioavailability; Polybrominated Diphenyl Ethers; brominated flame retardants; 3D-HSE; PBDEs; MPs.

Introduction

Microplastics (MPs), defined as plastic particles of less than 5 mm in size, are ubiquitous in the environment and consumer products which inevitably leads to human exposure to these particles confirmed by the recent detection of MPs in human stool [1], lungs [2] and blood [3]. This has raised concern due to the high concentrations of MPs detected in several environmental compartments relevant to human exposure (e.g., air, dust, food, and water), as well as the expected substantial annual increase in environmental MPs concentrations, if no action is taken [4]. While the toxicity of MPs in humans is not fully understood, a few animal studies have reported reproductive toxicity in oysters, reduced feeding in daphnia, hepatotoxicity in zebrafish, tissue accumulation and disturbance of lipid metabolism in mice exposed to MPs [5]. A number of studies have raised concern over the potential translocation of MPs to vital organs such as the liver and kidney, with *in vitro* metabolomics studies indicating oxidative stress due to MPs exposures [6].

Although human toxicological studies of MPs are still in their infancy, there is increasing concern over the role of MPs as conduits of toxic chemicals to human body fluids and subsequent absorption to the systemic circulation, due to the small particle size and corresponding large surface area of MPs [7]. A wide range of chemical additives such as plasticizers, pigments, fillers, and flame retardants are often incorporated in plastics during manufacture to impart specific desirable properties. Many of these additives, particularly in the flame retardant and plasticizer categories, such as polybrominated diphenyl ethers (PBDEs), have been found to cause adverse health effects including: endocrine disruption, reproductive toxicity, neurotoxicity, hepatotoxicity and cancer [8]. Despite the ban on commercial formulations of PBDEs in Europe and other parts of the globe and the subsequent phase-out of the production of penta-, octa- and decaBDE commercial mixtures [9], the environmental contamination of PBDEs is anticipated to last for decades owing to the global in-use and waste stocks of PBDEs as well as their well-known environmental persistence [9,10].

Brominated flame retardants e.g. PBDEs are an important class of additive chemicals used (at concentrations in the range 0.7 – 25 % w/w) in polyethylene and polypropylene plastics [8,11]. These types of MP polymers are the most commonly detected in various human exposure relevant media such as indoor dusts and particulate matters [12,13]. However, it is uncertain how external exposure to MP contributes to the human body burden of MP additives even though very high concentrations of PBDEs are still being detected in environmental samples

e.g. domestic and office indoor dust [14] and dust from the International Space Station [9], highlighting the significance of PBDEs as an important class of additive chemicals with serious implications for environmental and human health. Recently, we reported that PBDEs in MPs are dermally bioaccessible into human skin surface film liquids i.e., sweat, raising concern over potential dermal uptake of these chemicals [15]. Bioaccessibility refers to the fraction of the flame retardant chemicals released from microplastics into human sweat; thereby becoming available for absorption. However, there are no available data on the dermal *absorption* of these toxic chemicals from MPs upon contact with human skin, which is the largest body organ and its main barrier against xenobiotics [16]. Skin is in direct contact with the external environment, thus is constantly exposed to both intentional and unintentional MPs through e.g., microbeads in topically applied cosmetics, microfibers from textiles as well as atmospheric deposition from both indoor and outdoor air and skin contact with dust [6], highlighting the significance of the dermal pathway as a potential route of human exposure to MPs and associated toxic additive chemicals. More importantly, the risk arising from human exposure to MPs via any exposure pathway is not known. This knowledge gap was recently highlighted as a limitation for the accurate quantification of the risk and toxicity of MPs in two separate reports by the European Commission's Science Advice for Policy (SAPEA) and the World Health Organization (WHO) [17,18].

This research gap may be attributed *inter alia* to ethical considerations related to both *in vivo* and *in vitro* studies using human tissues, limited analytical methodologies, strict restrictions on the use of laboratory animals in toxicological studies and large variabilities associated with the allometric scaling of dermatokinetic data from animals to humans due to inter-species variability in *e.g.,* hair distribution and barrier function [19].

To overcome these challenges, 3-dimensional human skin equivalent (3D-HSE) models offer a sustainable next generation alternative to study the dermal uptake of toxic chemicals in MPs. 3D-HSE models are multi-layered, fully differentiated and commercially available dermal tissues that mimic the human skin both histologically and physiologically [20,21]. They are composed mainly of human keratinocytes and fibroblasts obtained from consenting healthy human donors and cultured at the air-liquid interphase in a viable inert support that allows the growth and differentiation of cells in a culture medium[22]. 3D-HSE models have proven suitable for testing skin permeation of topically applied substances and metabolism studies of xenobiotics [22] due to their similar physiological function and metabolic capacity to excised human skin [23–25]. These models have been approved by the Organization for Economic Co-

operation and Development (OECD) and the European Centre for the Validation of Alternatives Methods (ECVAM) for the testing of corrosion, phototoxicity and skin irritation potential of xenobiotics [21] and have been successfully applied to study the dermal uptake of various xenobiotics including brominated and organophosphate flame retardants, both applied as free chemicals in solution [21] and in matrices relevant to human exposure, such as indoor dust and furniture fabrics [26].

Against this backdrop, the present study provides first experimental insights into the dermal uptake of toxic PBDEs additives in MPs and the contribution of the dermal pathway to the human body-burden of these toxic chemicals upon skin contact with MPs of different polymer types using 3D–HSE model. The influence of different factors (e.g. the physicochemical properties of PBDEs, type of microplastic polymer and the degree of skin hydration) driving the percutaneous permeation of these toxic chemicals from MPs were examined.

2. Materials and method

2.1. Chemicals and Reagents

Solvents used *e.g.* hexane, ethyl acetate, isooctane, and nonane were of HPLC grade obtained from Fisher Scientific, Loughborough, United Kingdom. Individual and neat standards of BDEs 28, 47, 99, 100, 153, 154, 183, 209, 77, 128, $^{13}C_{12}$-BDE 100 and $^{13}C_{12}$–BDE 209 were purchased from Wellington Laboratories Inc., Ontario, Canada. Microplastics were obtained from two standard reference materials: European Reference Material for polyethylene (ERM-EC-590) and polypropylene (ERM-EC-591) certified for polybrominated diphenyl ethers (PBDEs) concentrations, purchased from the European Joint Research Centre Institute for Reference Materials and Measurements (Brussels, Belgium).

2.2. Microplastics

Microplastics of particle size <0.45 mm were produced from standard reference materials ERM-EC-590 and ERM-EC-591 (original pellet size of 3.5 – 4 mm) using a Fritsch Pulverisette 0 cryo-vibratory micro mill (Idar-Oberstein, Germany). The MP pellets were frozen (-80 °C) and were transferred to a stainless-steel grinding mortar (50 mL volume) together with a 25 mm diameter stainless steel ball and submerged in liquid nitrogen (−196 °C) to aid the pulverisation process. The sample was ground at a vibrational frequency of 30 Hz for 5 min and repeated 3 times resulting in plastic particles that passed through a 0.45 mm mesh

aluminium sieve [15]. Both ERM-EC-590 and ERM-EC-591 contained certified concentrations of polybrominated diphenyl ethers.

2.3. 3D-Human Skin Equivalent Model Tissue

Three-dimensional human skin equivalent (3D-HSE) EPISKIN™ RHE/FT/L/13 (1.07 cm^2) models were obtained from SkinEthic Laboratories, Lyon, France. The skin tissue constructs were shipped on the 13th day of culture required for acceptable tissue differentiation (www.episkin.com). The kit includes a proprietary Dulbecco's Modified Eagle's Medium (DMEM) i.e., the maintenance medium, which allows acceptable differentiated morphology of the tissue for 5 days upon receipt by end users. Following receipt in the laboratory, the EPISKIN™ tissues were equilibrated overnight with the EPISKIN™ maintenance medium at 5% CO_2 and 37 °C before use in the dermal absorption experiments. The study protocol received ethical approval (Ref. ERN_12–1502) from the University of Birmingham's Medical, Engineering and Mathematics Ethical Review Committee.

2.4. Skin Surface Film Liquid (SSFL)

The degree of skin hydration has been shown to play a role in the dermal permeability of chemicals [27]. To check the influence of skin hydration on the dermal uptake of PBDEs from microplastics, we employed 50 µL and 10 µL of a physiologically based skin surface film liquid (i.e. a mixture of sweat: sebum) to represent sweaty skin and dry skin exposure scenarios. The physiologically based SSFL was prepared as reported in a US patent (US20080311613A1) [28] using a combination of more than 25 organic and inorganic components [15]. The SSFL comprising 1:1 sweat: sebum was prepared and the pH of the mixture was adjusted to the physiological pH of 5.3 ± 0.1 as described previously [15].

2.5. Dermal uptake assay

Dermal uptake experiments were carried out in a static diffusion cell configuration (Fig. 1) with the EPISKIN™ tissue mounted on a permeation device with the stratum corneum facing up. The permeation device was designed specifically for this model (SkinEthic Laboratories, Lyon, France). Prior to commencement of the exposure to microplastics, the skin tissues were equilibrated with the receptor fluid (2 mL of DMEM-based culture medium containing 5 % bovine serum albumin (BSA)) for 30 mins in 5% CO_2 at 37 °C in an incubator. This was followed by moistening the skin with SSFL (50 µL or 10 µL for wet and dry skin scenarios, respectively), and the MPs (0.0496 – 0.0503 mg) were evenly applied onto the surface of the

skin in the donor compartment (see Table S1 for the average dose of PBDEs in the MPs). The permeation experiment was carried out in 5 % CO_2 at 37 °C in an incubator to mimic normal human body temperature. The receptor fluids were collected from the receptor compartment and immediately replaced with fresh 2 mL aliquots of receptor fluid at fixed time points over 24 hours of exposure (supplementary Table S3). At the end of the 24 hours of exposure, the surface of the skin was gently and thoroughly wiped to remove all MP particles and washed with cotton buds impregnated in 1:1 ethyl acetate: hexane solution (2 mL x 5 times). After this, the skin tissues were carefully removed from the permeation device. The receptor and donor compartments were separately washed with 2 mL x 5 times 1:1 ethyl acetate: hexane mixture. Each exposure experiment was simultaneously carried out in triplicate and all samples were stored at 4 ± 3°C until analysis.

Each of the dermal uptake experiments generated five types of samples, namely: (a) receptor fluids, (b) skin wash and MPs, (c) skin tissue, (d) donor compartment wash, and (e) receptor compartment wash. For simplicity, concentrations of target PBDEs in samples of (a) + (e) are presented as "absorbed", while those in samples (b) + (d) are presented as "unabsorbed". Concentrations of PBDEs in samples (c) are presented as "accumulated within the skin tissue".

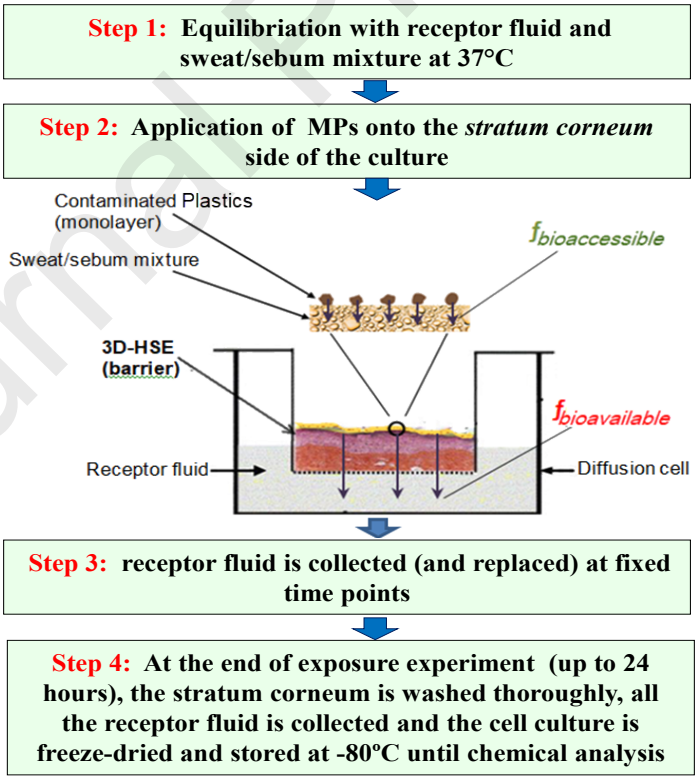

Figure 1: General outline of *in vitro* exposure experiments using 3D-HSE.

2.6. Extraction of PBDEs in Samples and Chemical Analysis.

The MPs and skin wash, skin tissue, donor and receptor compartment washes were extracted following a previously reported method [15,29]. Receptor fluids were spiked with 60 ng of mixture of internal standard ($^{13}C_{12}$ – BDE 100, BDE 128, and $^{13}C_{12}$- BDE 209), followed by the addition of 10 mL of dichloromethane (DCM). The mixture was vortexed for 3 mins and ultrasonicated at 40 °C for 5 mins, followed by centrifugation at 3900 rpm for 10 mins. The organic layer was transferred into a fresh test tube. The procedure was repeated twice with the addition of fresh 10 mL DCM. The combined organic layer was concentrated to approximately 1 mL and 2 mL of hexane added to precipitate any dissolved plastic. The mixture was reduced to 1 mL before 2 mL hexane was added, followed by 2 mL concentrated sulfuric acid. The mixture was vortex mixed for 2 mins and allowed to stand for at least 1 hour before centrifugation at 3900 rpm for 5 mins. The supernatant was transferred into a separate test tube. The sulfuric acid phase was further washed twice with 2 mL hexane. The combined hexane phase was concentrated into incipient dryness and reconstituted with 150 µL of 1:1 hexane: isooctane containing 250 pg of BDE-77 as recovery determination standard.

PBDEs were quantified using a Trace 1310 Gas Chromatograph coupled with an ISQ™ single quadrupole mass spectrometer (Thermo Scientific, Austin, Tx. USA) using an instrumental method reported previously [15] [30] and presented in supplementary material S1. The method's limit of detection (LOD) and limit of quantification (LOQ) ranged from 0.09 – 0.37 ng g^{-1} and 0.27 – 1.15 ng g^{-1}, respectively (Supplementary Table S5).

2.7. Data analysis & Estimation of Dermal uptake parameters

The steady-state conditions employed in this study were obtained following the method described by Niedorf et al. [31]. The steady-state parameters were estimated by a linear regression coefficient [($R^2 > 0.9$; $p \leq 0.01$, Table 3 and Supplementary Figure S1)], with the slopes representing the steady-state fluxes (J_{ss}).

The quantitative description of the permeation of PBDEs through the skin barrier was derived from Fick's first law of diffusion as follows:

$$J_{ss} = \frac{\Delta m}{\Delta t.A} = \frac{D.K.\Delta C}{dx} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

Where: J_{ss} is the steady-state flux (ng cm^{-2} hr^{-1}), Δm is the permeated dose (ng); Δt is the time interval (hr); D is the diffusion coefficient; K is the partition coefficient; ΔC is the concentration

difference across the permeation membrane (ng cm^{-2}) and dx is the thickness of the permeation membrane (cm). Since the donor dose greatly exceeded the concentrations in the receptor compartment ($C_D \gg C_A$) i.e. infinite dose set-ups, ΔC was replaced by the known donor concentration, C_D , and we assumed the permeated mass per time to be constant [21]. In each of the permeation experiments, the cumulative dose of the permeated PBDE in the receptor fluid per unit area of the exposed surface area of the skin (ng cm^{-2}) was plotted against the corresponding time points (hr) in which the receptor fluid were collected. The slope of this plot was used to calculate the J_{ss} for each studied PBDE in the linear part of the curve according to the method described by Niedorf et al. [31].

The independent resistance against the permeation of PBDEs i.e. the apparent permeability coefficient P_{app} (cm hr^{-1}) was calculated as:

$$P_{app} = \frac{D\,.\,K}{dx} = \frac{J_{ss}}{C_D} \quad \text{………………………………} \quad (2)$$

The lag time (T_{lag}) i.e. the time taken for PBDEs from the start of exposure until reaching the receptor fluid with non-detectable flux was estimated [27] as shown in equation 3:

$$T_{lag} = -\frac{b_o}{J_{ss}} \quad \text{………………………………….} \quad (3)$$

Where b_o is the y-axis intercept and J_{ss} is the slope (i.e. steady-state flux) of the linear regression line.

2.8 Quality Assurance/ Quality Control

Several quality control and quality assurance procedures were undertaken to ensure the suitability and validity of the workflow in this study. A procedural blank consisting of skin tissue exposed to SSFL without MPs was performed with each batch of samples. No PBDE was detected above the LOQ in any of the blanks (n = 4). The recoveries of internal standards and recovery determination standards were generally greater than 85 % indicating the efficiency of the analytical procedure. The uniform distribution of MP on the surface of the skin were monitored using the PerkinElmer™ Spotlight 400 microscopic FT-IR imaging system (Supplementary Figure S1). Furthermore, the mass balance of all PBDEs in the ERM-EC-590 and ERM-EC-591 following the dermal permeation experiments across all compartments showed recoveries in the range 100 ± 35 % (Table 1), indicating acceptable accuracy and within and between-day reproducibility of the method. Skin tissues used as negative controls exposed

to decabromodiphenyl ethane accompanied each batch of analyses. No dermal permeation (i.e., 0 %) was observed in the negative control throughout the 24 hours of the exposure experiment.

2.9. Statistical analysis

Statistical analysis was performed with XLSTAT version 2021.3.1 and Microsoft Office Excel 2016. The data were normally distributed confirmed by a Shapiro Wilk Test. The differences in skin permeation in each of the matrices were evaluated by using a Paired Student's t-test between two datasets, while the differences among several datasets were evaluated with a Mann Whitney U test. A $p < 0.05$ was considered statistically significant. The results of the experiments are presented as the arithmetic means of triplicate measurements ± standard deviations.

3.0. Results & Discussion.

The stratum corneum, the outermost layer, provides the main permeation barrier in the skin. We hypothesise that *inter alia* the diffusion of highly lipophilic chemicals e.g. PBDEs from hydrophobic matrices such as microplastics would significantly influence their skin permeability propagated by their distinct physicochemical properties.

3.1. Skin permeation of PBDEs from polyethylene microplastics

Mass balance calculations showed that we could account for between 72 and 109 % of the applied dose of PBDEs with excellent reproducibility (≤ 15%) observed between replicate experiments. Most of the recovered PBDEs were present in the skin wash, exceeding 87 % of the applied dose on average (Table 1), which is generally consistent with the infinite dosing approach adopted in this experiment.

The concentrations and fractions of PBDEs (expressed as % of the exposure dose) permeated through skin and measured in the receptor fluid (*i.e., absorbed fraction*), the fraction of target analytes that accumulated within the skin tissue, and the unabsorbed fraction of the PBDE congeners (*i.e., fractions in skin wash and donor compartment wash*) upon contact of polyethylene MPs (PE-MPs) with the 3D-HSE for 24 hours are presented in Table 1.

Except for BDE 28 and BDE 154, the remaining target PBDE congeners (BDEs 47, 99, 100, 153, 183, and 209) were released from the PE-MPs and were taken up by the skin tissue at varying degrees ranging from 0.8 – 7.7 % of the applied dose. Percutaneous penetration of

PBDEs into the receptor fluid following 24 hr exposure to PE-MPs was generally low, ranging from 1.50 – 11.49 ng (representing 0.02 – 0.12 % of the applied dose) and increased in the order: BDE 47 < BDE 100 <153 ≤ BDE 183 < BDE 99 (Table 1), with BDE 28, BDE 154, and BDE 209 undetectable in the receptor fluid. The mass of PBDE accumulated within the skin tissue ranged from 51 – 887 ng (corresponding to 0.8 – 7.7 % of the applied dose) and increased in the order BDE 153 < BDE 183 < BDE 100 < BDE 209 < BDE 99 < BDE 47.

Generally, the penetration of PBDEs into the skin from PE-MPs seems to have been influenced by the degree of bromination for the tetra – to hexaBDE congeners, while the applied dose and the matrix were more influential drivers for the accumulation of the higher brominated congeners (BDE 183 and BDE 209) within the skin tissue. Relative to the applied dose, BDE 153 presented the highest percentage (0.12 % of the exposed dose) of PBDEs in the receptor fluid, albeit at no statistically significant difference ($p = 0.11$). BDE 99 presented the highest average cumulative absorbed mass of 11.49 ng in the receptor fluid after 24 hours exposure.

Whilst the degree of bromination and molecular weight of PBDEs have been reported as the main drivers of their dermal bioavailability in previous *in vitro* dermal uptake studies [32], the exposure dose appears to be a major factor in real life exposure to PBDEs in hydrophobic matrices such as microplastics. As shown in Table S1, the exposure doses were markedly different for each of the PBDE congeners in the tested MPs. The non-detection of BDE 28 and BDE 154 in the receptor fluid is likely due to their low dose (86.7 ng cm^{-2} and 1282 ng cm^{-2}) in the MPs compared to the other congeners. However, though BDE 209 had the highest average applied dose of 32435 ng cm^{-2} in the MPs, it did not permeate into the receptor fluid, likely due to its large molecular weight and high log K_{ow}, which limits its permeation through the skin and its diffusion through the aqueous-rich cellular layer of the epidermis beneath the stratum corneum [32].

3.2. Skin permeation of PBDEs from polypropylene microplastics

Similar to the trend observed in PE-MPs, we were able to account for 68-116% of the dose of PBDEs applied following the exposure of the EPISKIN™ tissue to polypropylene microplastics (PP-MPs), with excellent reproducibility (generally < 15%). All target PBDE congeners except BDE 28 and BDE 154 leached out from the MPs and were taken up by the skin at a fraction ranging from 0.9 to 5.5 % of the exposure dose. The absorbed mass of PBDEs into the receptor fluid ranged from 1.0 – 10.87 ng (corresponding to 0.01 – 0.14 % of the exposure dose), and increased in the order BDE 47< BDE 183 < BDE 153 < BDE 100 < BDE

99, whereas the mass of PBDE accumulated within the skin tissue following 24 hr exposure to PP MPs ranged from 30 – 1910 ng and increased in the order BDE 153 < BDE 183 < BDE 100 < 47 < BDE 99 < BDE 209.

Although BDE 209 accumulated within the skin tissue (up to 4.7 % of the exposure dose), it was not detected in the receptor fluid. The high accumulated mass of BDE 209 in the skin compared to the lower brominated congeners could be due in part to the much higher exposure dose of BDE 209, which was an order of magnitude more than those of BDE 153 to BDE 183 in the applied MPs. However, the non-detection of BDE 209 in the receptor fluid can also be linked to its large molecular weight and high log K_{ow} probably limiting its permeation through the skin and diffusion through the hydrophilic cellular layer of the epidermis to reach the receptor fluid [32].

Whilst uptake of PBDEs from PP-MPs into skin was evident, the absorption of PBDEs into the receptor fluid after 24 hours exposure was low, ranging from <LOQ (for BDE 28, 154, and 209) – 0.14% (for BDE 153) of the applied dose. BDE 28 and 154 were neither detected in the skin tissue nor in the receptor fluid, most likely due to their relatively low exposure dose (Supplementary Table 1) as well as the influence of the highly hydrophobic PP which is characterised with lower bioaccessibility of PBDEs compared to PE [15] . Interestingly, while BDE 99 presented the highest cumulative absorbed mass (10.87 ng) in the receptor fluid after 24 h exposure; when the data are presented as fractions of the applied dose, BDE 153 showed the highest % absorbed fraction, albeit at no statistical difference from the other congeners (Table 1).

The main barrier for percutaneous penetration is generally considered to be the stratum corneum [35]. However, for highly lipophilic PBDEs, the hydrophilic viable epidermis and dermis may provide a significant permeability barrier and act as a sink for the temporary deposition of these compounds and subsequent availability for systemic absorption [33,36]. This may, at least partially, account for the mass of PBDEs accumulated within the skin tissue in our experiments. Also of importance in the context of our exposure experiments, is the role of the highly hydrophobic PE and PP polymer matrices which could limit the availability of hydrophobic PBDEs for absorption by the skin tissue.

The results of the current study are consistent with previous dermal bioavailability studies of PBDEs wherein lower brominated PBDE congeners are generally more bioavailable compared to more highly brominated congeners [27,32]. However, while dermal bioavailability of

PBDEs is largely driven by the exposure dose (especially for lower brominated congeners), the % absorbed fractions of PBDEs in PE and PP MPs are generally lower than their corresponding values in dust and fabrics exposed to human *ex vivo skin* [27] and in neat PBDE standard solution exposed to Episkin™ [32]. The observed differences could be due in part to the more hydrophobic nature of MPs compared to dust and fabrics, resulting in a more prolonged time for PBDEs to become bioaccessible for systemic absorption [15].

Table 1. Concentrations in ng and fractions (*expressed as % of the exposure dose*) of PBDEs in different compartments of the EPISKIN™ 3D-HSE model following 24 hours exposure to polyethylene (ERM-EC-590) and polypropylene (ERM-EC-591) microplastics.

	BDE 28	BDE 47	BDE 99	BDE 100	BDE 153	BDE 154	BDE 183	BDE 209
Polyethylene (PE)								
Absorbed dose[a]	ND	1.50 ± 0.14 (0.01)	11.49 ± 0.25 (0.08)	2.29 ± 0.07 (0.07)	2.82 ± 0.17 (0.12)	ND	3.07 ± 0.37 (0.05)	ND
Skin tissue[b]	ND	887± 126 (7.7)	806 ± 137 (5.4)	215 ± 123 (6.9)	51 ± 15(2.2)	ND	53 ± 38 (0.8)	551 ± 213 (1.7)
Unabsorbed[b]	87 ± 10 (96)	11873 ± 1056 (77)	17838 ± 1264 (89)	3863± 522 (92)	2391 ± 132 (76)	1878 ± 141 (109)	6300 ± 599 (72)	38660 ± 2695 (89)
Mass balance	87 ± 10 (96)	12762 ± 1187 (85)	18655 ± 1401 (94)	4080 ± 647 (99)	2444 ± 146 (78)	1878 ± 140 (109)	6356 ± 636 (73)	39211 ± 2908 (91)
Polypropylene (PP)								
Absorbed dose[a]	ND	1.0 ± 0.11 (0.01)	10.87 ± 1.05 (0.07)	3.79 ± 0.87 (0.11)	3.11 ± 0.35 (0.14)	ND	2.35 ± 0.22 (0.05)	ND
Skin tissue[b]	ND	650 ± 76 (5.1)	918 ± 98 (5.5)	187 ± 19 (5.4)	30 ± 3.4 (1.3)	ND	43 ± 20 (0.9)	1910 ± 300(4.7)
Unabsorbed[b]	126 ± 5 (86)	10390 ± 254 (72)	15605 ± 638 (83)	3290 ± 125 (85)	1654 ± 303 (88)	1499 ± 258 (117)	2680 ± 325 (64)	32752 ± 2643 (72)
Mass balance	126 ± 5 (86)	11041 ± 330 (77)	16534 ± 736 (89)	3481±145 (91)	1687± 307 (89)	1500 ± 258 (117)	2725 ± 345 (65)	34662 ± 2943 (76)

[a]absorbed mass (ng), [b]Concentration ng g^{-1}

Table 2. Kinetics data for dermal uptake of PBDEs from PE and PP microplastics using 3D – HSE model

	BDE 47	BDE 99	BDE 100	BDE 153	BDE 154	BDE 183	BDE 209
Polyethylene (PE)							
Flux (ng cm^2 h^{-1})	0.16	0.20	0.09	0.18	ND	0.11	ND
P_{app} (cm h^{-1})	1.36×10^{-5}	1.32×10^{-5}	2.68×10^{-5}	7.58×10^{-5}	ND	1.67×10^{-5}	ND
T_{lag} (h)	0.27	0.72	0.76	1.26	ND	2.58	ND
Polypropylene (PP)							
Flux (ng cm^2 h^{-1})	0.03	0.18	0.14	0.27	ND	0.14	ND
P_{app} (cm h^{-1})	2.91×10^{-6}	1.10×10^{-5}	4.09×10^{-5}	1.20×10^{-4}	ND	3.17×10^{-5}	ND
T_{lag} (h)	0.90	5.37	4.39	2.88	ND	3.39	ND

ND: Not detected

3.3. Dermal absorption kinetics

3.3.1. Dermal flux, permeability coefficient and lag time

The fraction of chemicals absorbed by the skin has been reported to depend on experimental conditions such as the exposure matrix and skin loading, hence reliance on only the permeated fraction of the chemical in the receptor fluid (expressed as percent of the exposure dose) can be largely misleading [36,37]. As such, the dermal flux and permeability coefficient (P_{app}) are more important parameters [36,37].

It was not possible to estimate P_{app}, flux and lag time (T_{lag}) for BDE 28, 154, and BDE 209 in experiments with PE and PP-MPs, due to their low percutaneous permeation and failure to reach steady state at the end of the 24 hours exposure experiment.

The dermal flux of the studied PBDEs ranged between 0.09 – 0.20 ng cm^{-2} and 0.08 – 0.274 ng cm^{-2} for PE-MPs and PP-MPs, respectively. Whilst dermal flux generally decreased (with the exception of a few outliers e.g. BDE 47 and 100 in PE; BDE 47 and 153 in PP MPs) with increasing degree of bromination from penta to octaBDEs (Table 2), the influence of exposure dose was evident by the strong positive correlation (R^2 = 0.9913 in PE-MPs and R^2 = 0.6945 in PP-MPs) of dermal flux of target PBDEs (ng/cm^2/hour) and exposure dose (ng/cm^2) in both matrices (Fig. 2). The results confirm dermal flux of target PBDEs in hydrophobic MPs is dependent on the exposure dose [18].

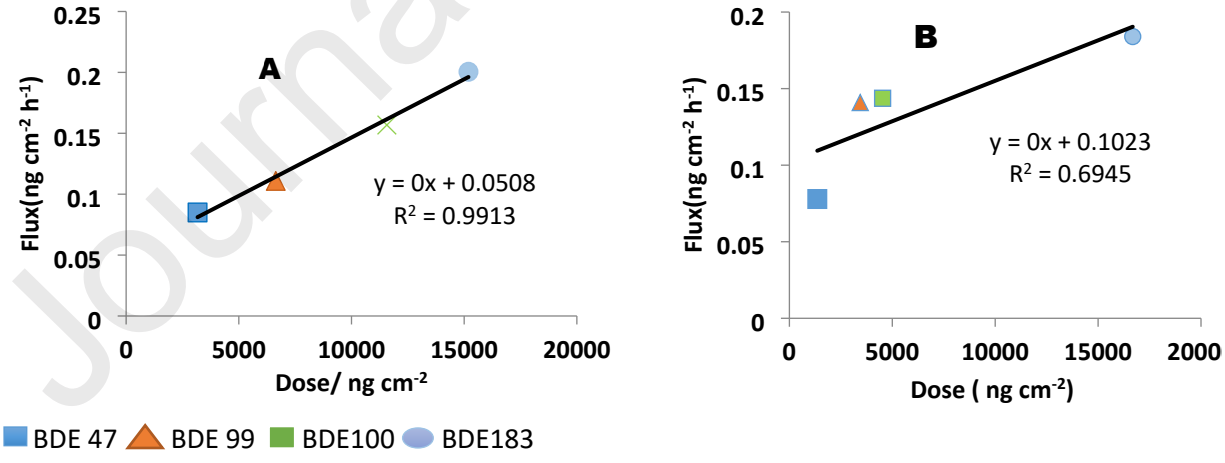

Fig. 2. Plot of steady state flux (ng/cm^2/hour) vs exposure dose (ng/cm^2) of BDEs 47, 99, 100 and 183 in (a) PE-MPs, and (b) PP-MPs.

The estimated P_{app} values ranged from 1.32 x 10^{-5} to 7.58 x 10^{-5} cm h^{-1} and 1.10 x 10^{-5} to 1.20 x 10^{-4} ng cm h^{-1} for the studied PBDEs in PE and PP MPs, respectively. There was no statistically significant difference (p = 0.649) between the P_{app} values of PBDEs in both matrices, even though the bioaccessibility of PBDEs from both matrices is different [15]. Not much is known about percutaneous permeation and dermal uptake of chemicals from MPs, however our research group have previously reported the dermal uptake of PBDEs and other chemicals from different matrices relevant to human exposure, such as indoor dust, furniture fabrics and neat PBDE standards. While it is unusual to compare absolute numbers such as P_{app} derived from different experimental setups, the rank order of our P_{app} is generally similar to those previously reported for PBDEs in different matrices exposed to both human *ex vivo* skin and 3D-HSE models [27,32]. The P_{app} values obtained in the current study did not statistically differ from P_{app}values of three commonly reported PBDE congeners (BDE 47, 99, and 153) in dust (p = 0.1438), furniture fabrics (p= 0.134) and neat chemical standards (p = 0.098). A similar lack of statistically significant difference was observed between the P_{app} values of PBDEs in PP-MPs in the current study and those reported in dust (p = 0.1728), fabrics (p= 0.168), and neat standards (p = 0.1168) [27,32]. The observed slight variations in values of P_{app} obtained in the present study and those previously reported, albeit statistically indistinguishable, are most likely driven by the bioaccessibility of PBDEs from the different exposure matrices [27,32].

Estimated T_{lag} values (Table 2) increased with increasing degree of bromination of PBDE congeners and ranged between 0.27 – 2.58 hours from BDE 47 to BDE 183 in PE-MPs. However, such a relationship was not observed for PBDEs in PP-MPs, where longer T_{lag} values for BDE 99 (5.37 h) and BDE 100 were observed compared to BDE 153 and 183, even though BDE 47 quickly permeated through the skin tissues with a T_{lag} of 0.90 h (Table 2). There is no clear explanation for this observation, apart from possible variation in the diffusion dynamics of PBDEs from PP compared to PE-MPs. Generally, PBDEs showed significantly longer T_{lag} values (p = 0.009) in PP than PE-MPs, highlighting the importance of the exposure matrix in dermal permeability of PBDEs.

It has been hypothesized that highly lipophilic compounds like PBDEs can be temporarily retained in the skin and may not reach the receptor fluid during the duration of the exposure experiment [36], with PBDEs thus retained within the skin forming a sink from which they could permeate gradually into the receptor fluid *i.e.* reach the blood stream [21]. Specifically,

since dermal absorption is a dynamic process, certain chemicals retained in the stratum corneum will continuously transfer into the viable layers of the skin such that in the absence of loss by either metabolism or desquamation, the accumulated chemical in the skin would ultimately become available for systemic absorption. Moreover, the exposure dose is a relevant factor in the dermal uptake of PBDEs from microplastics, such that the low-dosed congeners e.g. BDE 28 and 154 were not dermally bioavailable under the experimental set-up. However, the remaining target congeners with higher doses were bioavailable. Results from previous dermal absorption studies of PBDEs as pure standard solutions of the same concentration for all congeners directly exposed to 3D-HSE and human *ex vivo* skin [20, 35] were also in agreement with this hypothesis. Hence, we believe that if the exposure dose is the same for all congeners in the microplastics, we may observe similar behaviour for closely related PBDEs e.g. BDE 153 and BDE 154, at least in the same microplastics polymer.

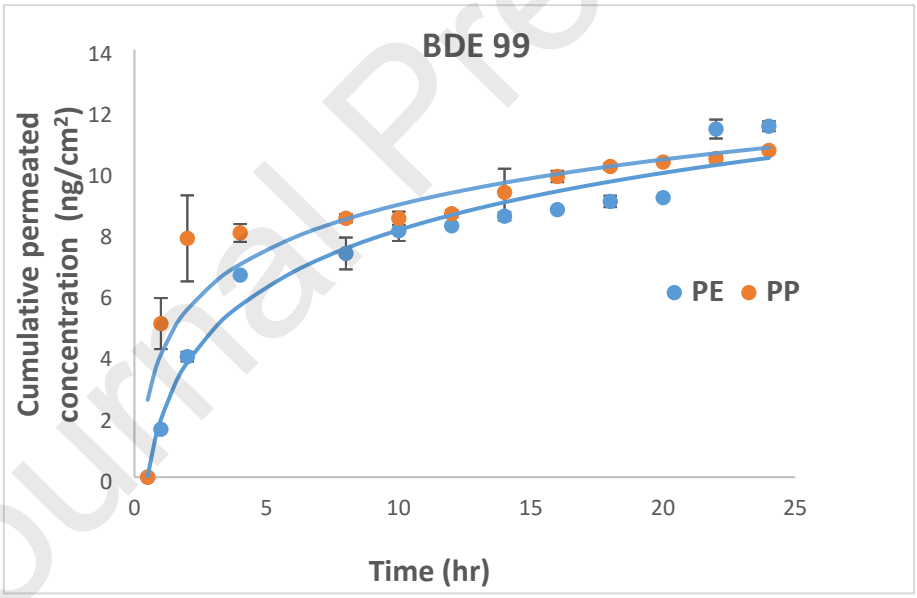

Fig 3. Cumulative permeated dose of BDE 99 following 24 hr exposure of Episkin™ to PE and PP-MPs.

3.4. Factors influencing the dermal uptake of PBDEs in microplastics

3.4.1. Microplastic polymer type

The present study highlights for the first time that external exposure to MPs through skin contact contributes to human body burdens of PBDEs. While the absorbed fraction of PBDEs

i.e. amount in the receptor fluid were generally similar (i.e. ≤ 0.1 % of exposure dose; $p = 0.7386$) for both MP types, the fractions of PBDEs accumulated in the skin were relatively (but not significantly; $p = 0.8549$) higher for PE-MPs (ND – 7.7 % of applied dose) than PP-MPs (ND – 5.5 % of the applied dose). The pattern of dermal uptake was similar in both matrices with the lower brominated pentaBDE possessing higher percutaneous permeation (Fig. 3 and Supplementary Fig. 2). The slight variations in the uptake of PBDEs from the two matrices are likely associated with the more hydrophobic characteristics of PP polymers. It was generally observed that while the polymer type influenced the release of PBDEs from MPs onto the skin [30], they were a less important driver for the percutaneous permeation of PBDEs through the skin into the receptor fluid.

3.4.2. Skin hydration

Though the polymer type did not significantly influence the dermal uptake of PBDEs in MPs, the degree of hydration significantly influenced the diffusion of these chemicals onto the skin and their subsequent permeation through the stratum corneum unto the receptor fluids. We applied 50 µL and 10 µL of skin surface film liquids (SSFL) to mimic wet and dry skin exposure conditions, respectively. While all target PBDEs (except BDE 28 and 154) were bioavailable to certain degrees in both polymer types, only BDE 47 and 99 were bioavailable under the dry skin scenario. Comparatively, the bioavailable fraction of BDE 47 and 99 in PE-MPs were not significantly different ($p = 0.3026$) for both exposure scenarios, which implies that for these congeners, skin hydration exerts a strong influence on the bioaccessibility of the chemicals from the matrix onto the skin, but is less influential in their subsequent penetration through the stratum corneum. The cumulative concentrations of BDE 99 in the receptor fluid were much higher under the wet skin compared to the dry skin scenario, however, BDE 47 displayed a rather unusual phenomenon where the absorbed concentration was higher under the dry skin compared to the wet skin scenario (Figure 4 and supplementary Figure 3) in both MP types. The cause of this observation requires further exploration.

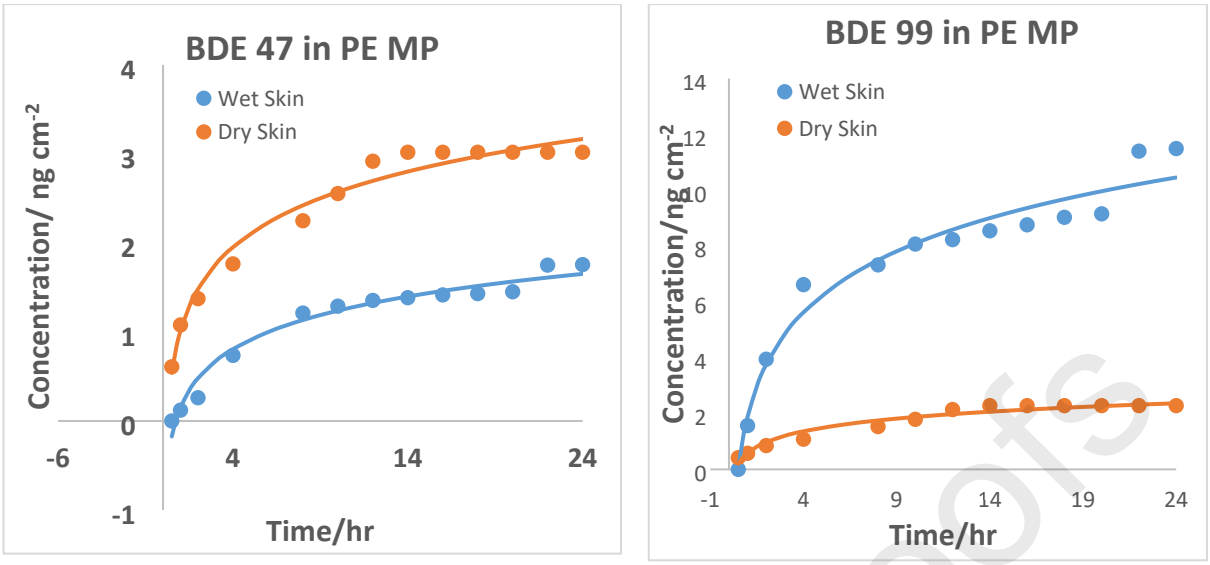

Fig 4. Influence of skin hydration on the dermal uptake of BDE 47 and BDE 99 in PE and PP MPs.

3.4.3. Physicochemical properties

Increasing the degree of bromination results in substantial variation in the physicochemical properties of PBDEs *e.g.* molecular weight, water solubility, vapor pressure, and the octanol-water coefficient (K_{OW}) etc presented in supplementary material Table S4. We examined the influence of these variables on the experimentally derived kinetic parameters for the dermally bioavailable PBDE congeners (BDE 47, 99, 100, 153, and 183), following exposure to both PE and PP-MPs using a Paired Student's t-test between two datasets and Mann Whitney U test for several datasets. Our results revealed significant association of P_{app} with the molecular weight ($r^2 = 0.31$, $p = 0.0001$ and $r^2 = 0.46$, $p = 0.0001$, for PE and PP-MPs, respectively) and $LogK_{OW}$ of target PBDEs ($r^2 = 0.38$, $p = 0.000006$ *and* $r^2 = 0.52$, $p = 0.000008$ for PE and PP-MPs, respectively).

We observed a strong negative association (r^2 = -0.98 and -0.90 for PE and PP-MPs) between the fraction of PBDEs accumulated within the skin tissue and their $logK_{OW}$. Interestingly, the absorbed fraction of PBDEs (i.e. fraction in the receptor fluid) following skin exposure to PP-MPs showed a strong positive correlation (r^2 = 0.88) with the water solubility of PBDEs, but a moderate negative association (r^2 = -0.37) following exposure of PE-MPs. For both exposed matrices, a moderate negative association (r^2 = -0.35 & -0.52) was observed between the fraction of PBDEs in the receptor fluid and their vapor pressure. Our results revealed in part that whilst the lipid-rich stratum corneum provided an active site for the deposition of these

lipophilic compounds, the water-rich dermis may represent a barrier for the diffusion of lipophilic PBDEs. However, it is important to state that while we have studied all the available PBDE congeners with certified concentrations in the standard reference materials applied in this study, the observed significant association pertains to a relatively small number of PBDE congeners. More studies are required in the future to investigate more congeners/chemicals.

4.0. Conclusion

This study provides first insight into the dermal bioavailability of PBDEs upon skin contact with different types of MPs containing flame retardant additives. Whilst as much as 8 % of the exposure dose can be taken up by the skin for some PBDEs, values of the absorbed fraction i.e. the fraction of PBDEs available for circulation through the bloodstream, did not exceed 0.14 % of the dose of PBDE originally present in the MPs. We found that while exposure to polyethylene MPs could lead to the accumulation of higher doses of PBDEs within the skin tissues compared to exposure to polypropylene MPs, there was no statistically significant difference in the amount of the chemical that reaches systemic circulation, upon exposure to either type of MPs. We observed that a more hydrated (i.e. sweaty) skin resulted in increased risk of dermal uptake of PBDEs (especially the highly brominated congeners) present in MPs compared to a dry skin. The influence of various physicochemical properties of PBDEs on their dermal uptake and subsequent absorption into the bloodstream were evident. Overall, we experimentally confirm for the first time that human exposure via skin contact with MPs containing PBDEs (as flame-retardant additives) contributes to the body burdens of these toxic chemicals. These results provide important experimental evidence for regulators and policy makers to legislate for microplastics and safeguard public health against such exposure, which contributes to the human body-burdens of toxic additive chemicals linked with causing cancer, and disruption of the endocrine system.

Authors declaration: Authors declare that they do not have any known competing interest.

Supporting Information.

Supplementary data associated with this article can be found in the online version at: xxxx.

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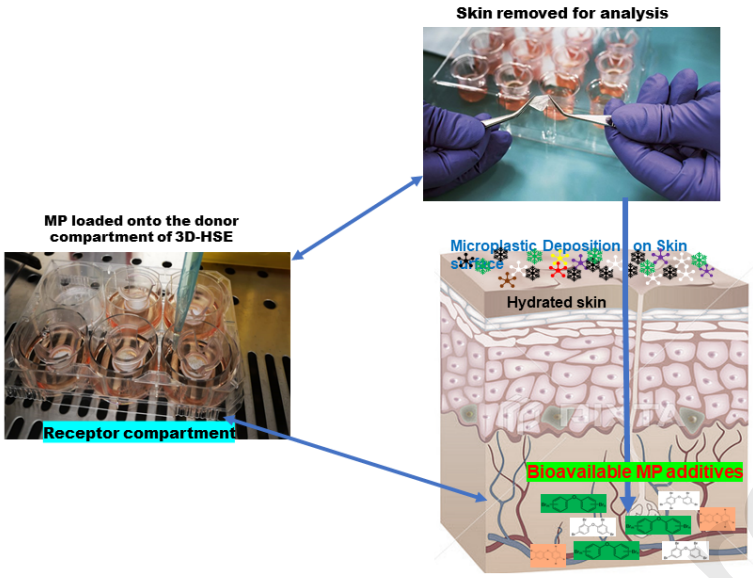

Highlights

First experimental evidence of dermal bioavailability of toxic chemical additives from microplastics.

BDE 47, 99, 100, 153 and 183 crossed skin barrier to reach the bloodstream.

Dermal uptake of PBDEs not significantly influenced by polymer type.

A sweaty skin enhances dermal bioavailability of some PBDEs.

Exposure via skin contact with MPs containing PBDEs contributes to their body burdens.

CRediT Author Statement

Ovokeroye Akpojevwe Abafe: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Validation; Visualization; Roles/Writing - original draft; and Writing - review & editing

Stuart Harrad: Conceptualization; Funding acquisition; Project administration; Writing - review & editing.

Mohamed Abdallah: Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Visualization; Writing - review & editing

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: