Journal of Hazardous Materials Advances 23 (2026) 101277

Contents lists available at ScienceDirect

Journal of Hazardous Materials Advances

journal homepage: www.elsevier.com/locate/hazadv

Dermal uptake of hexabromocyclododecane (HBCDD) from skin contact with polystyrene microplastic particles

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ARTICLE INFO

Keywords:
Polystyrene
Microplastics
Skin
Bioavailability
HBCDD
Exposure

ABSTRACT

Despite the listing of HBCDD in Annex A of the Stockholm Convention, the environmental contamination and human health impact of HBCDD is predicted to last for decades due to HBCDD remaining in global in-use products, the waste stream and various consumer products due to uncontrolled recycling e.g., expanded and extruded polystyrene building insulation materials, toys, utensils. Recent studies from different countries have confirmed the presence of polystyrene (PS) microplastics (MPs) in air and dust from various indoor microenvironments. However, the risk arising from dermal exposure to hexabromocyclododecane (HBCDD), which was widely used as additive flame retardant in expanded and extruded PS remains unknown.

To address this gap, we experimentally determined the dermal bioavailability of HBCDDs upon skin contact with PS-MPs using a 3-dimensional human skin equivalent model. All three isomers measured, i.e., α-, β- and γ-HBCDD were dermally bioavailable. Whilst the fraction of HBCDDs that accumulated within the skin tissue after 24 h exposure ranged between 5 to ~ 8% of the dose of HBCDD in the exposed PS-MP, complete skin penetration to the bloodstream within 24 h was low for all isomers, evidenced by the dermal flux, J_{ss} and the apparent permeability coefficient, P_{app}. Observed differences among HBCDD isomers were driven mostly by their physicochemical properties e.g., Log K_{OW} and water solubility. Moreover, dermal uptake of HBCDD was greater under a sweaty skin condition. Overall, internal exposure to HBCDDs arising from skin contact with PS-MP was evident, albeit low. However, the possibility of increased risk due to prolonged exposure or higher concentrations of HBCDDs in PS-MPs is plausible and cannot be ignored.

Introduction

Microplastics (MPs) have generated significant interest across the globe as contaminants of emerging concern due to their ubiquitous detection in almost every media relevant to human exposure. Human exposure to MPs occurs through a combination of inhalation, ingestion, and dermal contact (Ageel et al., 2022). For instance, the daily inhalational intake of MPs is estimated to be 195, 326 and 622 MP/kg bw day^{-1} for adult, infant and newborns, respectively (Zuri et al., 2023), while dietary intake is estimated to be as high as 221 and 498 MP/kg bw day^{-1} for adult and newborns, respectively (Zuri et al., 2023). It has been reported that humans are dermally exposed to MPs through domestic products such as plastic items, food containers, toiletries, clothing and personal care products (Sun and Wang, 2023), which facilitates personal contact with these contaminants. Although exposure arising from inhalation and ingestion of MPs particle is being widely investigated, very little is known about dermal exposure to MPs or the risk arising from such exposure.

Whilst MPs comprise different polymers, polystyrene (PS) is one of the most commonly detected MP polymers in the environment (Singh and Kumar, 2024), due to its extensive application in the manufacture of various consumer products. The toxicity associated with PS-MPs exposure is not fully understood, although it raises concern due to recent studies reporting that exposure to PS-MPs is linked to testicular premature aging (Wu et al., 2023), stimulation of the immune system (Hwang et al., 2020; Mohamed Nor et al., 2021) and vascular calcification (Yan et al., 2023).

PS is widely used in food packaging materials, electronic appliances, and as building insulation material (Rani et al., 2013). While not much is known about the toxicological effects of human exposure to PS-MPs, there is a growing concern over the potential exposure to toxic additive chemicals used in the formulation of PS-based products. One of such

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https://doi.org/10.1016/j.hazadv.2026.101277
Received 2 December 2025; Received in revised form 1 May 2026; Accepted 2 June 2026
Available online 2 June 2026

additive chemical is 1,2,5,6,9,10-hexabromocyclododecane (HBCDD), which was extensively used and often incorporated as an additive during the production of polystyrene to impart flame retardancy in both expanded and extruded polystyrene (EPS & XPS), used primarily in building insulation (Abdallah and Harrad, 2018).

The most recent information on the global production and use of HBCDDs indicates that 90% of the 31,000 tonnes of HBCDD produced in 2011 was used in the manufacture of EPS and XPS for building insulation panels (Mao et al., 2021). As such, large quantities of HBCDD-containing building materials, recycled materials and waste stockpiles have accumulated throughout the world (Mao et al., 2021). Though HBCDDs are listed as persistent organic pollutants (POPs) under the UNEP Stockholm Convention due to their persistence, bioaccumulation, long range atmospheric transport, and toxicity, the global in-use inventory of PS due to the long service-life of up to 50 years of applications such as building insulation, as well as the extensive recycling and upcycling of PS in the context of the circular economy, have resulted in continuous human exposure to HBCDDs. HBCDDs have been detected recently in various human exposure-relevant media including freshwater fish (Pittura et al., 2022), food (Zacs et al., 2021), indoor and outdoor dust (Al-Omran et al., 2022), consumer products e.g. building and construction materials, food packaging materials, plastic toys, XPS styroboards, ice boxes, aquaculture buoys, and disposable trays (Rani et al., 2013; Mao et al., 2021; Fatunsin et al., 2020). Human exposure to HBCDDs have been linked with several toxic effects including behavioural and neurodevelopmental disorders, hepatoxicity, endocrine disruption, and probable cancer (Abdallah et al., 2015). This underscores the existing risk of HBCDDs as persistent group of toxic additive chemicals in PS-MPs, with potential toxic implications for human and environmental health.

While the contribution of MPs to the environmental contamination and human exposure to HBCDDs is not well understood, we recently highlighted that HBCDD isomers are dermally bioaccessible into human sweat upon skin contact with MPs, raising concerns over potential dermal bioavailability of this toxic group of chemicals (Abafe et al., 2023). Dermal bioaccessibility is the fraction of a chemical that is released from a solid matrix to body fluids e.g., *MPs* into human sweat and therefore becomes available for dermal absorption. Dermal bioavailability is the fraction of that chemical that penetrates the skin barrier and reaches systemic circulation (i.e., *gets absorbed*) following dermal contact. Currently, no information exists on the dermal absorption of HBCDDs upon MPs contact with human skin, which is the largest body organ (Abdallah et al., 2015).

Human skin is directly exposed to the external environment, hence, continuously in contact with MPs intentionally and unintentionally e.g., through microfibres from textiles, atmospheric deposition from both outdoor and indoor air, dust particle adherence, as well as microbeads in topically applied cosmetics (Ageel et al., 2022). This emphasises the importance of the dermal pathway as a potential route of human exposure to MPs and related toxic additive chemicals, despite the lack of data on the exact contribution of this pathway to human body burdens of toxic chemicals (SAPEA, 2019; Leslie and Depledge, 2020). Of particular importance is the lack of data on magnitude and risk of human exposure to HBCDDs via dermal contact with PS-MPs, despite the documented existence of PS-MPs in indoor air and dust [1,] and their potential contamination with HBCDDs (Rani et al., 2013; Mao et al., 2021).

This knowledge gap can be attributed to several factors, including limited analytical methodologies, ethical constraints related to both *in vivo* and *in vitro* studies using human tissues, strict restrictions on the use of laboratory animals in toxicological studies and variabilities associated with the allometric scaling of dermatokinetic data from animals to humans due to inter-species differences in e.g., hair distribution and barrier function (Abdallah and Harrad, 2018). To overcome these challenges, 3-dimensional human skin equivalent (3D-HSE) models offer a sustainable new approach to study the dermal absorption of toxic chemicals in MPs.

3D-HSE models are fully differentiated, multi-layered, and commercially available dermal tissues that both physiologically and histologically mimic the human skin (Schäfer-Korting et al., 2008; Nitsche et al., 2022). They consist mainly of fibroblast and human keratinocytes obtained from consenting healthy human donors and cultured at the air–liquid interphase in a viable inert support which allows the growth and differentiation of cells in a culture medium (Schimek et al., 2018). The application of 3D-HSE models for testing skin permeation of topically applied substances and metabolism studies of xenobiotics have been confirmed (Sriram et al., 2018) due to their closely related physiological function and metabolic capacity to excised human skin (Alberti et al., 2017; Abdallah et al., 2015; Abafe et al., 2024). These models have been approved by the European Centre for the Validation of Alternatives Methods (ECVAM) and the Organization for Economic Co-operation and Development (OECD) for the testing of skin irritation, phototoxicity and corrosion potential of xenobiotics (Abou-Elwafa Abdallah and Harrad, 2022) and have been successfully applied to study the dermal uptake of various xenobiotics including polybrominated diphenyl ethers (PBDEs) in microplastics (Abafe et al., 2024), brominated and organophosphate flame retardants, both applied as free chemicals in solution (Abdallah et al., 2015) and in matrices relevant to human exposure, such as indoor dust and furniture fabrics (Abou-Elwafa Abdallah and Harrad, 2022).

Against this backdrop, the present study provides first experimental insights into the dermal absorption of HBCDDs additives in PS-MPs and evaluates the potential contribution of the dermal pathway to human body-burden of this toxic group of plastic additive chemicals, using an *in vitro* 3D–HSE model. The influence of different factors (e.g. the physicochemical properties of HBCDDs, and the degree of skin hydration) driving the dermal absorption of HBCDDs from PS-MPs were examined.

Materials and method

Chemicals and reagents

Solvents used e.g. hexane, ethyl acetate, isooctane, nonane and methanol were of HPLC grade obtained from Fisher Scientific, Loughborough, United Kingdom. Individual analytical standards of α-, β-, and γ-HBCDD, d_{18}-γ-HBCDD, and $^{13}C_{12}$-α-, β-, and γ-HBCDD were purchased from Wellington Laboratories Inc., Ontario, Canada.

Polystyrene microplastics

We produced microplastics from expanded polystyrene (EPS) in-house laboratory reference material, with known concentrations of α-, β-, and γ-hexabromocyclododecane (HBCDD) obtained from the National Institute for Environmental Studies (NIES, Tsukuba City, Ibaraki, Japan). Full details of the concentrations of HBCDDs in this material are presented in supplementary Table S1. Microplastics of particle size $<$ 0.45 mm was produced from the EPS panel using a Fritsch Pulverisette 0 cryo-vibratory micro mill (Idar-Oberstein, Germany). The EPS panel was divided into small cubes (~5 cm in length), which were frozen at −80 °C and transferred to a 50 mL stainless-steel grinding mortar 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 5 times, resulting in plastic particles of different sizes characterised using aluminium sieve of different mesh sizes. MPs with particle size ranging from $>$ 0.30–$<$ 0.45 mm which falls within MP particle size ranges frequently detected in indoor dust (Haque et al., 2024; Radzi et al., 2026) were used for the exposure assessment.

Three-dimensional human skin equivalent model tissue

Three-dimensional human skin equivalent (3D-HSE) EPISKIN™ RHE/FT/L/13 (surface area of 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.

Skin surface film liquid (SSFL)

The physiologically based SSFL was prepared as reported in a US patent (US20080311613A1) (Stefaniak B and Harvey J, 2008) using a combination of >25 organic and inorganic components (Abdallah et al., 2015). The SSFL comprising 1:1 sweat: sebum was prepared and the pH mixture was adjusted to the physiological pH of 5.3 ± 0.1 as described previously (Abdallah et al., 2015). To evaluate the influence of skin hydration on the dermal bioavailability of HBCDDs from skin contact with PS-MPs, we applied 50 μL/cm^2 and 10 μL/cm^2 of the SSFL to the surface of the skin to represent sweaty and dry skin exposure scenarios (Abafe et al., 2024; Abou-Elwafa Abdallah and Harrad, 2022).

Dermal exposure and uptake protocol

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 as previously described (Abafe et al., 2024). The permeation device was specifically designed for this 3D-HSE 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 Dulbecco's Modified Eagle Medium (DMEM) - based culture containing 5% bovine serum albumin (BSA)) for 30 mins in 5% CO_2 at 37 °C in an incubator. The skin was then moistened with SSFL (50 μL or 10 μL for wet and dry skin scenarios, respectively), and the PS-MPs (0.0103–0.0110 g) were evenly applied onto the surface of the skin in the donor compartment (see Table S1 for the average exposed dose of HBCDDs in the PS-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 each hour over 24 h of exposure period. At the end of the exposure experiment i.e., after 24 h, the surface of the skin was gently and rigorously wiped to remove all MP particles and washed with cotton buds impregnated in 1:1 ethyl acetate: hexane solution (2 mL x 5 times). Thereafter, the skin tissues were gently removed from the permeation device. The donor and receptor compartments were individually washed with 2 mL x 5 times 1:1 ethyl acetate: hexane mixture. The exposure experiment was simultaneously carried out in triplicate and all samples were stored at 4 ± 3 °C until analysis. The dermal uptake experiments generated five types of samples, namely: (a) receptor fluids, (b) skin wash with residual MPs, (c) skin tissue (d) donor compartment wash, and (e) receptor compartment wash. To simplify, concentrations of target HBCDDs in samples of (a) + (e) are presented as "absorbed", while those in samples (b) + (d) are presented as "unabsorbed", while concentrations of HBCDDs in samples (c) are presented as "accumulated within the skin tissue".

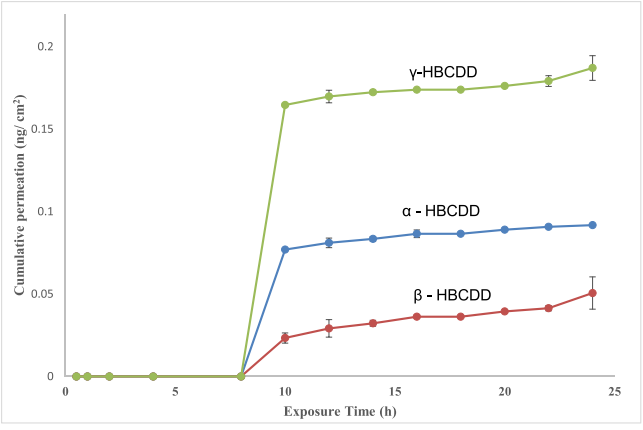

Fig. 1. Cumulative absorption of HBCDD isomers into the receptor fluid following 24 h exposure.

Sample extraction

Receptor fluid samples were spiked with 60 ng $^{13}C_{12}$-α-, β- and γ-HBCDD internal standard mixture. This was followed by the addition of 10 mL dichloromethane (DCM). The mixture was vortexed for 10 min followed by ultrasonication at 40 °C for 10 min and then centrifuged at 3900 rpm for 5 min. The organic phase was collected into a separate pre-cleaned and sterilised glass test-tube. The procedure was repeated twice. The collected extracts were evaporated to approximately 2 mL under a gentle stream of nitrogen set at 40 °C. Two mL of hexane was added to precipitate any dissolved plastic and then reduced to approximately 1 mL and reconstituted in 2 mL hexane to completely remove DCM followed by vortex-mixing. Approximately 3 mL of concentrated sulfuric acid was added to samples and then vortexed for 1 min. The mixtures were left to stand for at least 5 hr and then centrifuged at 3500 rpm for 5 min for phase separation. The organic layer was collected into a clean test tube. The sulfuric acid phase was further extracted twice with the addition of 2 mL n-hexane, vortexed for 2 min and centrifuged at 3500 rpm for 5 min. All the organic phase were combined and reduced to incipient dryness under a gentle stream of nitrogen at 40 °C. The extracts were reconstituted in 150 μL of methanol containing 250 pg μL^{-1} d_{18}-γ-HBCDD.

For the extraction of HBCDD from the original PS-MP sample ($n = 3$), residual PS-MP following exposure assessment i.e., (b) and skin tissue (c) were spiked with 100 ng $^{13}C_{12}$ α-, β- and γ-HBCDD followed by the addition of 3 mL DCM. The mixture was vortex for 2 min and sonicated for 5 min (The PS-MP dissolves completely in DCM for quantitative extraction of HBCDD from the polymer matrix). The mixture was evaporated to approximately 2 mL and washed with 2 mL n-hexane and evaporated under a gentle stream of nitrogen at 40 °C to approximately 1 mL. Dissolved PS was precipitated with 2 mL n-hexane followed by the addition of approximately 3 mL sulfuric acid and then vortexed for 2 min. The mixture was left to stand for at least 5 hr followed by centrifugation at 3500 rpm for 5 min. The organic layer was collected into a separate test-tube and the sulphuric acid phase was re-extracted twice with 2 mL n-hexane in each extraction cycle. All the organic layers were combined and evaporated to incipient dryness under a gentle stream of nitrogen at 40 °C. The extracts were reconstituted with 150 μL of methanol containing 250 pg μL^{-1} d18- γ-HBCDD.

LC-MS/MS Analysis

HBCDDs were measured using a Shimadzu LC–20AB Prominence binary pump liquid chromatograph equipped with a SIL-20A autosampler, a DGU-20A3 vacuum degasser coupled to an ABSciex API 2000 triple quadrupole mass spectrometer as previously described (Abafe et al., 2023). Briefly, chromatographic separation was achieved using Agilent Pursuit XRS3 C18 column (150 mm × 2 mm ID, 3 μm particle size) and a mobile phase of (A) Water (B) Methanol at a flow rate of 180 μL/min. Molecular ionisation was achieved using an electrospray ionisation source operated in negative-ion mode. Tandem MS/MS detection operated in the multiple reaction monitoring mode was used for quantitative determination of HBCDD isomers based on *m/z* 640.6→79, *m/z* 652.4→79 and *m/z* 657.7→79 for the native, $^{13}C_{12}$-labelled and

d_{18}-labelled diastereomers, respectively. The optimised LC–MS/MS parameters are summarised in supplementary Table S2.

Estimation of dermal permeation parameters and data analysis

All dermatokinetic parameters were estimated using data obtained from the partial steady-state kinetics for each of the HBCDD isomers, following the procedure described by Niedorf et al. (2008). To obtain the steady-state flux (J_{ss}) i.e., the quantitative description of the permeability of HBCDDs through the skin was obtained from Fick's first law of diffusion (Eq. (1)).

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

With J_{ss} measured in ng cm^{-2} hr^{-1}; Δm = permeated dose of HBCDD (ng); Δt (hr) = Time interval; A = Area (cm^2); K is the partition coefficient; D is the diffusion coefficient; ΔC (ng cm^{-2}) = the difference in concentration across the permeation membrane; and dx (cm) is the thickness of the permeation membrane.

Because the donor concentration (C_D) far exceeds the absorbed concentration (C_A) i.e., ($C_D \gg C_A$), which is consistent with infinite dosing configuration, ΔC was replaced by C_D , with an assumption of constant permeated mass per unit time. Consequently, for each HBCDD isomer, the cumulative permeated dose (ng cm^{-2}) in the receptor fluid per unit area of the exposed skin surface was plotted against time (hr). The partial steady-state conditions were evaluated by a linear regression line $R^2 > 0.9$, with the slope of the curve representing J_{ss}, as described by Niedorf et al. (2008). The time taken for each HBCDD isomer from the beginning of the permeation experiment i.e., from the start of exposure until reaching the receptor fluid with non-detectable fluxes, referred to as the lag time (T_{lag}) was determined according to Eq. (2).

$$T_{lag} = -\frac{b_o}{J_{ss}} \quad (2)$$

where b_o is the intercept of the y- axis. Similarly, the apparent permeability coefficient P_{app} (cm hr^{-1}), defined as the independent resistance against the permeation of HBCDDs was determined using Eq. (3).

$$P_{app} = \frac{D\ .\ K}{dx} = \frac{J_{ss}}{C_D} \quad (3)$$

The dermatokinetic parameters were determined using data generated under the wet skin exposure scenario. All statistical analyses were performed with XLSTAT version 2021.3.1 and Microsoft Office Excel 2021. The distribution of the data was normal confirmed by a Shapiro Wilk Test. A Paired Student's *t*-test between two datasets was used to determine the differences in skin permeation between the dry and wet skin exposure scenario, while the Mann Whitney U test was used to determine the differences among several datasets. Statistical significance was set as $p < 0.05$. The results of the experiments are presented as the arithmetic means of triplicate measurements ± standard deviations.

Assessment of dermal exposure to HBCDD through skin contact with microplastics

The daily dermal uptake (DU) of HBCDDs (ng kg^{-1} bw D^{-1}), through skin contact with polystyrene microplastics was estimated using Eq. (4).

$$DU = \frac{C\ \times\ MAF\ \times BSA\ \times\ AF\ \times EF}{Body\ weight\ (kg)} \quad (4)$$

where C is the HBCDD concentrations (ng g^{-1}) in PS MPs; MAF is the microplastic adherence factor in g $cm^{-2;}$ BSA is the body surface area (cm^{-2}), AF is the absorbed fraction of HBCDD (unitless); EF is the fraction of time exposed per day (hours per day an adult spend in contact with polystyrene microplastic), and BW is body weight in kg. The dermal uptake parameters used in this study are provided in supplementary material Table S3, as obtained from the US EPA exposure factor handbook (USEPA 2011). A number of exposure scenarios were applied as follows:

a) Exposure dose: We used two exposure doses of 0.01% w/w (i.e., the exposure dose in the PS-MP used in this study) and 1% w/w of HBCDDs in PS (which is within the range of typical concentration of HBCDDs in extruded polystyrene (Alaee et al., 2003; Stubbings and Harrad, 2019)) to exemplify low and high exposure dose scenarios, respectively.
b) Exposure Time – two exposure fractions (EF) were applied in this study. First, referred to as low-exposure scenario, assuming 6 h daily dermal exposure to microplastics e.g., through indoor dust, fabrics, atmospheric deposition etc., before washing or taking a shower. While a 12 h exposure time was used to depict a typical exposure scenario (i.e., 12 h daily exposure before taking a bath).
c) Summer: The summer season typifies the time of the year with increased exposed body surface area, as most people wear shorts and t-shirts, leaving substantial parts of the body exposed. Thus, we assumed that the head, forearms, hands, thigh, lower legs and feet are exposed to microplastics during this season, consistent with the study of Abdallah et al., 2018 (Abdallah and Harrad, 2018).
d) Winter: winter exemplifies the time of the year where most parts of the body are covered by people. Thus, we assumed that only the head, hands and feet are exposed to microplastics in the winter.

Following these scenarios, we applied the results of our 3D-dermal absorption model to obtain realistic evaluation of the DU of HBCDDs via contact with polystyrene microplastics. Since there are no definitive data on dermal contact with MPs, we employed parameters from the USEPA exposure factor handbook (Table S3).

Quality control and assurance

To ascertain the validity of the *in vitro* and analytical procedure, several quality assurance measures were undertaken. Each batch of absorption experiments was accompanied by both positive and negative controls ($n = 3$). For positive control, the EPISKIN™ tissue was exposed to Triton-X −100, which resulted in 100 ± 6% penetration; while the negative control involved the exposure of decabromodiphenyl ethane, which showed 0% permeation following 24 h of exposure. No HBCDD isomer was detected in the procedural blanks ($n = 3$), which consisted of the EPISKIN™ tissue exposed to the synthetic skin surface film liquids i.e., 1:1 artificial sweat: sebum mixture. The recoveries of both the internal standard and recovery determination standard (RDS) were within 90 ± 12%, reflecting the efficiency of the analytical protocol deployed. The uniformity of the distribution of the PS-MP particles on the surface of the skin was monitored using PerkinElmer™ Spotlight 400 microscopic FT-IR imaging system as previously described (Abafe et al., 2024). The method's limit of detection (LOD) and limit of quantitation (LOQ) were 0.04, 0.11, 0.27 pg g^{-1} and 0.13, 0.35, 0.82 pg g^{-1} for α, β, γ-HBCDD respectively.

Results and discussion

Mass balance and dermal bioavailable fractions of HBCDD

The mass balance recovery of HBCDD isomers from the analysis of the different types of samples generated from the dermal uptake experiment e.g., absorbed fraction (a) + (e), unabsorbed fraction (b) + (d) and accumulated within the skin tissue (c) following 24 h exposure to EPISKIN™ ranged between 79 ± 13.90 – 105 ± 3.20 % and 89 ± 16.10 – 96 ± 2.60 % for the dry and wet skin exposure scenarios (Table 1 & supplementary Table S4)). Most of the recovered HBCDDs were found in the skin wash (i.e., unabsorbed fraction) at an average of 81, 94 and 87

Table 1
Distribution and mass balance recovery (%) of HBCDDs following 24 h exposure of PS-MP to 3D-HSE.

	Dry Scenario			Wet Skin Scenario		
	α-HBCDD	β-HBCDD	γ-HBCDD	α-HBCDD	β-HBCDD	γ-HBCDD
Receptor Fluid (a)	ND	ND	ND	0.002 ± 0.0003	0.001 ± 0.0002	0.001 ± 0.0002
Receptor wash (e)	0.0042 ± 0.002	0.01 ± 0.003	0.001 ± 0.0003	ND	ND	ND
Donor wash (d)	0.15 ± 0.10	0.17 ± 0.12	0.16 ± 0.05	ND	ND	ND
Skin tissue (c)	0.12 ± 0.02	0.17 ± 0.01	0.12 ± 0.06	7.12 ± 0.06	5.14 ± 1.25	7.80 ± 0.90
Skin wash (b)	78.40 ± 13.73	104 ± 2.93	85.8 ± 13.20	83.6 ± 1.20	83.8 ± 14.88	87.8 ± 1.70
Total Recovery	79 ± 13.90	105 ± 3.20	86 ± 13.30	91 ± 1.26	89 ± 16.10	96 ± 2.60

% of the exposure dose for α, β and γ-HBCDD respectively, consistent with the infinite dosing conditions implemented in this study.

The bioavailability of all three isomers of HBCDDs was evident, albeit low (Fig. 1). The average levels measured in the receptor fluid following 24 h exposure were 0.10 ± 0.03 ng cm^{-2}, 0.07 ± 0.01 ng cm^{-2} and 0.36 ± 0.06 ng cm^{-2} which translates to 0.002, 0.001 and 0.001% of the dose of HBCDD in the exposed PS-MP for α, β and γ-HBCDD respectively. Whilst there is no study reporting the dermal uptake of HBCDD via skin exposure to microplastics, previous *in vitro* dermal bioavailability of HBCDDs in pure analytical standards exposed to human *ex vivo* and 3D-HSE models reported low dermal uptake of these chemicals. For instance, Frederiksen et al. (2016) reported low uptake of HBCDD i.e. ≤ 0.1% of the applied dose in both physiologically relevant receptor fluid and 50% alcohol-based receptor fluid (labelled as "worst-case scenario"), while Abdallah et al. (2015) reported as much as 3–6% absorption of 500 ng/cm^2 neat standard solutions of α, β and γ-HBCDDs exposed to 3D-HSE models and human *ex vivo* skin (Abdallah et al., 2015). For HBCDDs-contaminated dust and fabrics exposed to human *ex vivo* skin, the absorbed fraction of HBCDDs ranged from 1–6% in the receptor fluid (Abdallah and Harrad, 2018). While low percent absorption was evident in all studies, variations were attributed to several factors including, dose scenario (finite/infinite), dosing method (neat/solutions/ consumer products), exposure conditions (dry/wet skin) and duration (24–36 h), as well as the molecular weight and lipophilicity of the individual HBCDD isomers, and the hydrophobicity of the exposed matrix as described in Section 3.3 `Factors driving the dermal uptake of HBCDDs from polystyrene MPs'.

In the present study, the absorbable mass of HBCDDs accumulated in the skin tissue ranged between 309–2997 ng/cm^2 (Table S4). This translates to a percentage fraction of the exposure dose of 7.12, 5.14, and 7.8% respectively for α- β and γ–HBCDD. The higher % of γ-HBCDD accumulated within the skin tissue could be due in part to the relatively higher concentration of this isomer in the exposed PS-MP, which was approximately an order of magnitude higher than those of α and β-HBCDD. This is consistent with previous studies where the viable dermis and epidermis have been reported to act as a temporary site for the accumulation and subsequent absorption of lipophilic chemicals e.g., HBCDDs (Frederiksen et al., 2016) and PBDEs (Abdallah et al., 2015; Abafe et al., 2024). However, large molecules such as HBCDDs with slow absorption may be lost through metabolism or desquamation and other mechanisms during temporary storage in the dermis and epidermis (Frederiksen et al., 2016). Nonetheless, in the absence of any loss to desquamation or metabolism, some chemicals retained within the layers of the skin e.g., the *stratum corneum* will transfer continuously into the viable layers of the skin, thus the accumulated chemical would eventually become available for systemic absorption since dermal uptake is a dynamic process (Abafe et al., 2024; Frederiksen et al., 2016). This observation should be interpreted with caution since we only determined the concentration of HBCDDs in the entire skin tissue and not in separate layers of the skin and suggest the need to extend exposure assessment beyond the 24 h deployed in this study. The available literature data on the dermal uptake of this class of chemicals using 3D-HSE models and human *ex vivo* skin, reported a markedly higher fraction of up to 30% of the applied dose to accumulate in the skin (Abdallah et al., 2015). Frederiksen et al. 2016 (Frederiksen et al., 2016) reported the fraction of HBCDD accumulated within different layers of human *ex vivo* skin to range from 10–11% and 0.8–1% of the applied dose in the epidermis and dermis, respectively. Abdallah et al. (2015) found as much as 30% of the applied dose in the skin following exposure of α, β and γ-HBCDDs to human *ex vivo* skin. These values generally exceed those in this study, which could be due in part to the highly hydrophobic PS-MP exposed to 3D-HSE in the current study, rather than the pure analytical standards exposed directly to both human *ex vivo* skin and *in vitro* 3D-HSE in previous studies (Abdallah et al., 2015; Frederiksen et al., 2016). However, our results resemble those reported for the dermal uptake of HBCDDs from real environmental samples. For instance, Abdallah and Harrad (2018), reported between 3–10% and 18– 20% of the applied dose of HBCDDs in furniture fabrics and dust, respectively, to accumulate within the skin tissue after 24 h of exposure. This observation suggests that the nature of the matrix plays an important role in the dermal uptake of HBCDDs upon contact with skin, whereas more hydrophobic matrices render it difficult for HBCDDs to leach out and become available for absorption (i.e., *less bioaccessible*). This is in line with recently published study, which suggests that hydrophobic microplastics e.g., polyethylene (PE) and polypropylene (PP) could limit the availability of hydrophobic additive chemicals (polybrominated diphenyl ethers) for absorption by the skin tissue (Abafe et al., 2024).

Dermal absorption kinetics of HBCDDs in PS-MPs

Three parameters including the flux (Jss), defined as the rate of transfer of HBCDD per unit area; the apparent permeation coefficient (P_{app}), which determines the independent resistance against the permeation of HBCDD, and the lag time (T_{lag}) defined as the time it takes for HBCDD to cross the skin barrier to reach the receptor fluid without detectable flux, were estimated for HBCDD isomers in this study (Table 2). Partial steady-state data were obtained following 24 h exposure of EPISKIN™ to PS-MPs, with sampling conducted at several time-intervals to generate the time-permeation plots for each isomer (Fig. S1). The regression coefficients (R^2) of the steady-state data for all three isomers of HBCDD were > 0.90, consistent with the acceptance criteria for dermal uptake studies as reported by .Niedorf et al. (2008).

Percutaneous permeation only became slowly evident after 10 h of exposure until the experiment was terminated at 24 h (Fig. 1). The slow release of HBCDD from the PS-MPs followed by penetration through the skin barrier to the receptor fluid indicates low dermal uptake, which may be driven in part by the strong hydrophobic nature of PS, and the individual physicochemical properties of HBCDD isomers. This low dermal uptake under the studied protocol is evident by the low dermal

Table 2
Dermal uptake parameters of HBCDDs in polystyrene microplastics.

HBCDD Isomer	Flux (ng $cm^{-2}h^{-1}$)	P_{app} (cm h^{-1})	T_{lag} (h)
α-HBCDD	5.1E-03	5.3E-07	2.4
β-HBCDD	2.3E-03	3.7E-07	2.5
γ-HBCDD	7.0E-04	1.8E-08	3.3

flux (J_{ss}) 5.1 × 10^{-3}, 2.3 × 10^{-3} and 7.0 × 10^{-4} ng cm-^{2} h^{-1} obtained for α, β and γ-HBCDD, respectively. The apparent permeation coefficient P_{app} was 5.26 × 10^{-7}, 3.71 × 10^{-7} and 1.79 × 10^{-8} ng cm^{-2}, respectively for α, β and γ-HBCDD, with T_{lag} ranging from 2.4 to 3.3 h (Table 2). These data shows that dermal uptake of HBCDD is lowest (albeit at no statistically significant difference, $p = 0.446$) for γ-HBCDD even though it was characterised with a higher initial exposure dose, which was at least an order of magnitude more than the dose of α and β-isomers. The dermal uptake for γ -HBCDD is lowest when expressed as percentage of applied dose but it is highest when considered as absorbed mass. This is caused mainly by the large exposure dose of γ-HBCDD, compared to the other two isomers (Table S4).

Factors driving the dermal uptake of HBCDDs from polystyrene MPs

Influence of physicochemical properties

The percutaneous absorption of HBCDDs from PS is mostly driven by their physicochemical properties as demonstrated by the strong positive correlation obtained for the Log_{kow} and the dermatokinetic parameters (Fig. 2 and supplementary Table S5–8) e.g., J_{ss} ($r^2 = 0.71; p = 0.35$), P_{app} ($r^2 = 0.97; p = 0.12$) and T_{lag} ($r^2 = 0.80, p = 0.31$), as well as their water solubility and J_{ss} ($r^2 = 0.99, p = 0.07$), P_{app} ($r^2 = 0.79, p = 0.31$). The low water solubility especially for γ-HBCDD, in addition to the strong hydrophobic nature of PS could have influenced the strong dermal resistance and uptake of these toxic chemicals, by restricting the release of these chemicals from the MPs into the surface of the skin.

While it is known that the *stratum corneum* provides the barrier for human skin, within which the inter-corneocytes lipids deliver the main route for transdermal permeation of hydrophilic skin care and health products; for hydrophobic chemicals e.g., HBCDDs in highly hydrophobic matrices such as polystyrene microplastics, the dermal bioaccessibility of the chemical from the matrix is a rate limiting step for their dermal uptake (Abafe et al., 2024). This is evidenced by the long T_{lag} ranging from 2.4 to 3.3 h for HBCDDs, as well as their generally low bioaccessibility from polystyrene as previously reported (Abafe et al., 2023).

The skin penetration of six organophosphorus compounds with similar molecular weight have been shown to be driven by the individual physicochemical properties of the compound, dilution in water and the composition of the receptor fluid (Thors et al., 2016). Similarly, previous dermal uptake studies of neat solutions of HBCDDs attributed the long lag times observed to their lipophilicity, low polarity and low water solubility (Abdallah et al., 2015). In addition, Frederiksen et al. (2016) reported a significant decreasing trend of P_{app} with increase in

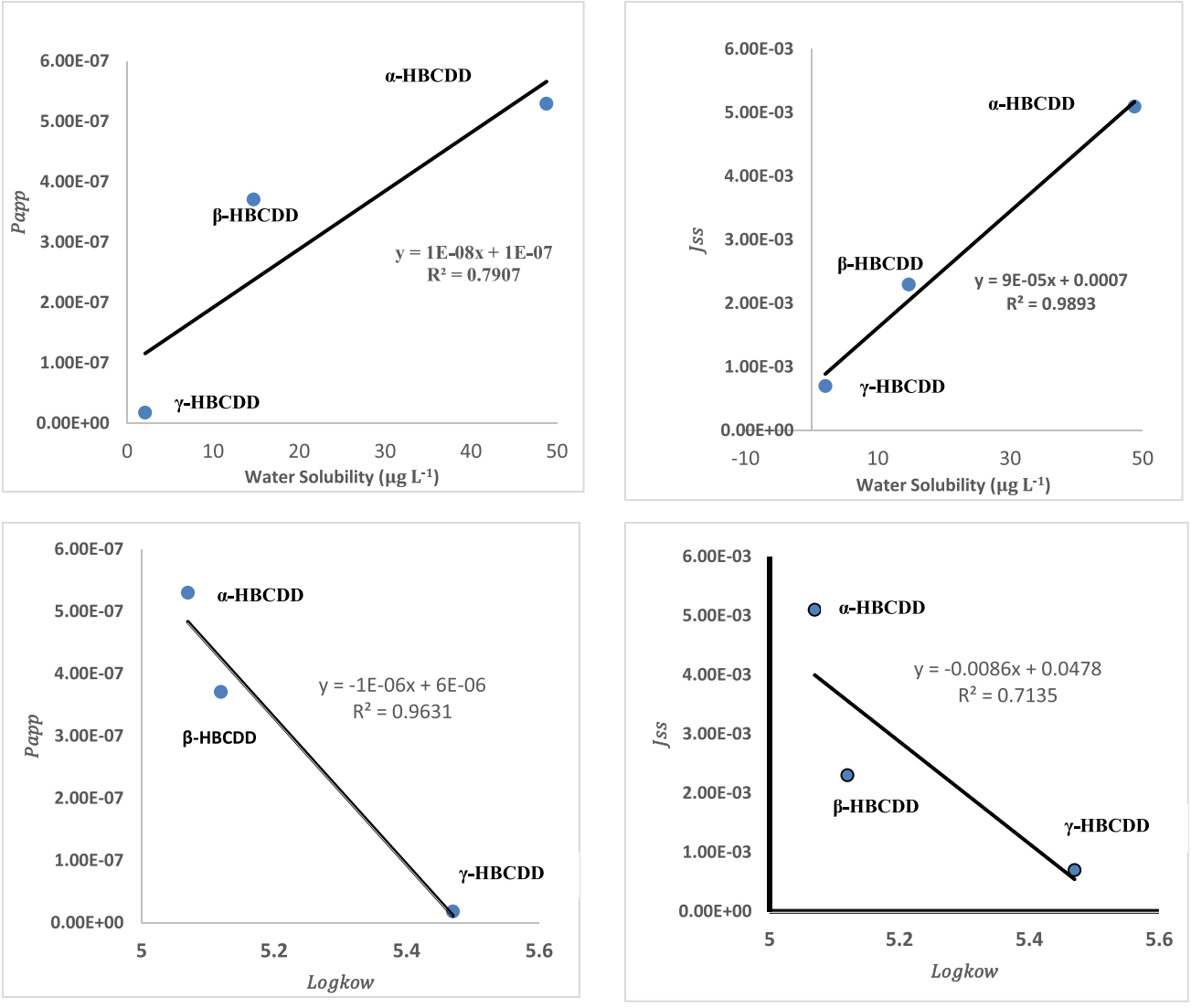

Fig. 2. Influence of physicochemical properties on the dermal absorption kinetics of HBCDDs from PS-MPs.

Log_{kow} of structurally different flame retardants including HBCDDs.

While most of these studies involved the application of neat solutions of the various chemicals in an appropriate dosing vehicle such as organic solvents, not much is known about the behaviour of these compounds in real-life exposure scenarios where the chemicals are embedded in a matrix e.g., the highly hydrophobic PS - MP that come into contact with the skin. However, we recently found a strong association between the physiochemical properties of PBDEs (with similar molecular weight and properties to HBCDDs) and their dermal uptake from polyethylene and polypropylene microplastics exposed to 3D-HSE, though the strong hydrophobicities of the matrices were shown to strongly influence the dermal uptake of PBDEs (Abafe et al., 2024).

Influence of skin hydration on the dermal bioavailability of HBCDD in MPs

To determine the influence of skin hydration on the dermal bioavailability of HBCDDs upon skin contact with PS MPs, we mimicked wet (i.e., sweaty) and dry skin exposure scenarios by applying 50 μL/cm^2 and 10 μL/cm^2 of the SSFL, respectively to the surface of the EPISKIN™ tissue at the start of the exposure experiment. While no quantifiable concentration of any of the HBCDD isomers were measured in the receptor fluid under the dry skin scenario, the concentration of HBCDDs in the sweaty skin scenario ranged from 0.07–0.36 ng cm^{-2} in the receptor fluid (Table 2). Similarly, as shown in Figure. S2, the percentage fraction of HBCDD accumulated within the skin tissue following 24 h exposure ranged between 0.12–0.17% and 5.14–7.80% for the dry and sweaty skin exposure scenarios, respectively. These results suggest that a sweaty skin facilitates the uptake of HBCDD from PS-MPs through dermal barriers to the blood stream.

Similarly, the concentrations of HBCDD retained within the skin tissues under the dry skin exposure scenario were 12, 10 and 45 ng g^{-1} for α, β and γ- HBCDDs, respectively. These values are between an order of magnitude or two lower than the concentrations found for the sweaty skin exposure scenario (Table S4). This indicates the influence of sweaty skin in driving the bioaccessibility of HBCDDs from PS-MPs into the skin tissues (Abdallah et al., 2015). This could be due in part to the potential for a sweaty skin to alter the lipid structure of the *stratum corneum*, as well as increase the adhesion of PS-MPs to the skin, thereby enhancing contact time and increase solubility of HBCDDs.

These results align with previous studies wherein more sweaty skin has been reported to be a major driver for the dermal uptake of xenobiotics. For instance, we previously found significantly higher bioavailable fractions of PBDEs following the exposure of PE and PP - MPs to the skin under sweaty skin exposure conditions compared to dry skin conditions (Abafe et al., 2024). Abdallah and Harrad (2018) made similar observations for neat standard solutions of brominated flame retardants exposed to sweaty and dry skin.

Dermal exposure assessment

The estimated daily dermal uptake (DU) of HBCDDs from PS-MPs (Table 3) varied largely depending on the exposure scenario. Under the conservative exposure scenario (i.e., low exposure dose), the DU of ΣHBCDDs ranged from 2–16 ng kg^{-1} bw d^{-1} (winter); 7–18 ng kg^{-1} bw d^{-1} (summer), among different exposure time scenarios. Substantially higher exposure was estimated under the more realistic exposure scenario (i.e., 1% HBCDD w/w, a typical concentration of HBCDDs found in EPS thermal insulation panels), with the DU ranging from 204 – 242 ng kg^{-1} bw d^{-1} (winter) and 760 – 904 ng kg^{-1} bw d^{-1} (summer) to 1292 – 1536 ng kg^{-1} bw d^{-1} (winter) and 1519 – 1806 ng kg^{-1} bw d^{-1} (summer), respectively for the low (6 h) and typical (12 h) exposure scenarios.

Although the lack of data on the dermal uptake of HBCDDs from skin contact with MPs makes it difficult to compare our results, our data show that the DU of HBCDDs from contact with PS-MPs (low exposure dose scenario) are similar to the estimated DU of HBCDDs arising from skin contact with furniture fabrics, but substantially higher than the DU from dust (Abdallah and Harrad, 2018). These results highlight that under a more realistic exposure dose of HBCDDs in PS-MPs (i.e., > 1% w/w typically found in technical formulation of extruded and expanded polystyrene) (Alaee et al., 2003; Stubbings and Harrad, 2019), the potential for increased risk is plausible. For instance, the European Food Safety Authority (EFSA) estimated that the human body burden of 2.35 μg kg^{-1} bw d^{-1} of HBCDDs, has the potential to cause neurodevelopmental effects in humans (Schrenk et al., 2021). This value is within the same order of magnitude as the estimated DU of HBCDDs under the realistic exposure scenario in summer (1.66 μg kg^{-1} bw d^{-1}).

Conclusion

The human dermal uptake of HBCDDs upon skin contact with polystyrene microplastics was experimentally determined for the first time. While α, β and γ- HBCDD bioavailability was low, it clearly occurred; moreover, as much as 8% of the initial dose of HBCDDs in the exposed PS MPs accumulated within the skin tissue, with γ -HBCDD accumulating the most. This could serve as a reservoir for the continuous release of HBCDDs into the blood stream. Each of the three isomers tested displayed very strong dermal resistance, especially γ- HBCDD. Such resistance could be attributed in part to the strong hydrophobicity of polystyrene which prolongs the release of HBCDDs from the exposed matrix i.e., *bioaccessibility*, as well as the physicochemical properties of HBCDDs such as their high Log_{kow} and low water solubility.

However, it is unclear if the skin tissue would be a reservoir for continuous release of HBCDDs post exposure since we terminated our exposure experiment after 24 h, which constitutes a limitation of the current study. However, it has been reported elsewhere that certain xenobiotics accumulated in the skin are lost to skin desquamation, as well as washed off during bathing in addition to loss to metabolic mechanisms such as debromination, hydroxylation or stereoisomerisation. An extended exposure beyond 24 h is recommended for future dermal uptake studies of hydrophobic chemicals from microplastics. Also, the metabolic fate and the distribution of HBCDDs across skin layers should be investigated. Overall, we provide the first experimental evidence of the risk arising from human dermal exposure to polystyrene microplastics, which is an important first step for regulators

Table 3
Daily dermal uptake of HBCDDs in Polystyrene Microplastics (ng kg^{-1} bw d^{-1}).

Exposure Dose in PS-MPs	HBCDD- isomer	Low-Exposure Duration (6 h)				Average Exposure Duration (12 h)			
		Summer		Winter		Summer		Winter	
Low (0.01% HBCDDs by weight)		Male	Female	Male	Female	Male	Female	Male	Female
	α - HBCDD	1.60	1.34	0.43	0.36	3.19	2.68	2.71	2.28
	β- HBCDD	1.02	0.86	0.27	0.23	2.04	1.72	1.74	1.46
	γ - HBCDD	6.42	5.40	1.72	1.45	12.83	10.8	11	9.18
	ΣHBCDD	9.04	7.6	2.42	2.04	18.1	15.2	15.5	13
Realistic (1% HBCDDs by weight)	α - HBCDD	160	134	43	36	319	268	271	228
	β- HBCDD	102	86	27	23	204	172	174	146
	γ - HBCDD	642	540	172	145	1283	1079	1091	918
	ΣHBCDD	904	760	242	204	1806	1519	1536	1292

and policy makers to legislate for polystyrene microplastics to safeguard public health from the deleterious effects of toxic HBCDDs.

CRediT authorship contribution statement

Ovokeroye Akpojevwe Abafe: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Stuart Harrad:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Mohamed Abou-Elwafa Abdallah:** Writing – review & editing, Validation, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

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.

Acknowledgment

This project was funded by the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska - Curie Individual Fellowship Grant Agreement Number 101026229.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.hazadv.2026.101277.

Data availability

Data will be made available on request.

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