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Dermal uptake of chlorinated organophosphate flame retardants via contact with furniture fabrics; implications for human exposure

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ABSTRACT

The chlorinated organophosphate flame retardants (Cl-PFRs): tris-(2-chloroethyl)-phosphate (TCEP), tris-(1-chloro-2-propyl)-phosphate (TCIPP) and tris-(1,3-dichloropropyl)-phosphate (TDCIPP), have been widely used in upholstered furniture despite their carcinogenic potential. Although Cl-PFRs are mainly added to furniture foam, they are present in the fabrics likely due to migration from the foam. While several studies have assessed human exposure to Cl-PFRs via different pathways, no information exists on dermal uptake of these chemicals through contact with fabrics. In the current study, dermal absorption of TCEP, TCIPP and TDCIPP from 3 UK domestic furniture fabrics was experimentally assessed for the first time using *in vitro* 3D-human skin equivalents (EpiSkin™) under different real-life exposure scenarios. Results revealed all 3 target Cl-PFRs were dermally bioavailable to varying degrees (3.5%–25.9% of exposure dose) following 24 h contact with the studied fabrics. Estimated permeability coefficients (K_P, cm h^{-1}) showed TCEP had the highest percutaneous penetration potential followed by TCIPP, then TDCIPP. Further investigation revealed human dermal uptake of Cl-PFRs can be influenced by several factors including: the specific physicochemical properties of the compound, the type of exposure matrix, the exposure dose and the degree of skin hydration at the point of contact. Exposure assessment revealed UK adults and toddlers can be exposed to 20.4 and 14.1 ng TCIPP/kg bw/day via contact with furniture fabrics in summer, which is higher than international average exposures via inhalation and dust ingestion for adults and dietary exposure for toddlers. Therefore, risk assessment studies for Cl-PFRs and future replacements should consider dermal contact with consumer products (e.g. furniture fabrics) as a potential significant human exposure pathway.

1. Introduction

Chlorinated organophosphate flame retardants (Cl-PFRs) include: tris-(2-chloroethyl)-phosphate (TCEP), tris-(1-chloro-2-propyl)-phosphate (TCIPP) and tris-(1,3-dichloropropyl)-phosphate (TDCIPP), in addition to other less widely used compounds (e.g. tetrekis (2-chloroethyl) dichloroisopentyl diphosphate (V6)). They are widely used to impart flame retardancy in foams deployed in domestic and office furniture, car upholstery, adult and child mattresses, and related products (ECHA, 2018). Several studies have reported various toxic effects of Cl-PFRs including immunotoxicity and disturbance of lipid metabolism in chicken embryos (Farhat et al., 2014), as well as reduced proliferation and growth of human neural stem cells and rat neuronal growth (Behl et al., 2015). TDCIPP was reported to cause reduced thyroid hormone levels in humans (Meeker and Stapleton, 2010), while high concentrations of TCEP have been associated with an increased risk of papillary thyroid cancer (Hoffman et al., 2017a). Both TCEP and TDCIPP were associated with induction of various types of tumours (Baril et al., 1998) leading to the classification of TCEP by the EU as a "potential human carcinogen" (carcinogen category 3), while TDCIPP is classified under regulation EC 1272/2008 as a category 2 carcinogen with hazard statement H351 "suspected of causing cancer" (ECHA, 2010). TCEP and TDCIPP are also listed as possible carcinogens under the State of California's Proposition 65 (OEHHA, 2021). While TCIPP has not been subjected to carcinogenicity testing, its structural resemblance to TDCIPP and TCEP increases the likelihood of comparable toxicity. TCIPP was classified as a hazardous substance by the EU due to evidence of reproductive and developmental toxicity (EU risk assessment reports, 2008).

The increasing concern over their potential adverse health effects has

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led to numerous studies investigating both external and internal human exposure to Cl-PFRs via different exposure pathways and assessing the risk associated with such exposure (Chupeau et al., 2020; Yang et al., 2020; Gbadamosi et al., 2021; Hou et al., 2021). Consistent with the paradigm that dermal exposure to FRs was of limited importance, attributed mainly to the lack of experimental data on this pathway compared to inhalation and ingestion, earlier EU risk assessment reports of Cl-PFRs concluded that dermal exposure was not of significance (EU risk assessment reports, 2008). However, few studies detected significant concentrations of various flame retardants in handwipes and highlighted the potential importance of dermal exposure; thereby shifted the focus of human exposure studies towards more careful evaluation of the dermal pathway (Allen et al., 2013; Keller et al., 2014; Stapleton et al., 2014; Hoffman et al., 2015). Two important *in vitro* studies (Abdallah et al., 2016; Frederiksen et al., 2018) indicated that substantial dermal absorption of Cl-PFRs was likely, thereby paving the way for a handful of studies using personal hand wipes and silicone wristbands to ascertain the significance of the dermal exposure pathway and its contribution to human body burdens of Cl-PFRs (Larsson et al., 2018; Phillips et al., 2018; Hammel et al., 2020; Hou et al., 2021). Pertinently, Phillips et al. concluded that dermal absorption was likely an important pathway of children's exposure on the basis of significant positive correlation between Cl-PFRs concentrations in hand wipes and their metabolites in paired urine samples (Phillips et al., 2018). The mounting evidence on the potential significance and magnitude of human dermal absorption of Cl-PFRs has led to the reassessment of the extent of exposure and thus risk by the European Chemicals Agency (ECHA), and their recommendation (currently in abeyance pending further toxicological data) that use of TCEP, TCIPP, and TDCIPP in foam in children's products (e.g. cot mattresses) be restricted to 0.1% by weight (1000 ppm) in view of the revised exposure level and evidence of carcinogenicity (ECHA, 2018). In the United States, the Children's Safe Product Act demands that TCEP, TDCIPP, and TCIPP in children's products to be recorded by manufacturers, and in 2017 restricted the concentration of TCEP and TDCIPP to 1000 ppm in children's' products and residential furniture (Blum et al., 2019). It is also worth mentioning that TCEP is currently undergoing risk evaluation at the U.S. EPA, under the Toxic Substances Control Act, including risk assessment via different exposure pathways and scenarios including dermal uptake (US EPA, 2021).

However, the current state of knowledge on human dermal uptake of Cl-PFRs and the resulting risk assessment is based mainly on exposure via contact with these chemicals in indoor dust and air, while very little is known about dermal absorption of PFRs through dermal contact with consumer products. A pertinent study by our research group highlighted the very substantial contribution (up to 61% of the overall daily intake for adults in summer) made by dermal exposure for a range of brominated flame retardants (BFRs) present in furniture fabrics (Abdallah and Harrad, 2018). Other studies demonstrated the ability of Cl-PFRs to migrate from flame retarded furniture foams and dissolve in artificial human sweat (Kjølholt et al., 2015; Lounis et al., 2019). In the UK and Ireland, Cl-PFRs (especially TCIPP and TDCIPP) are widely present in furniture foam (Stubbings and Harrad, 2018). Because furniture foam padding is almost always covered by fabrics, direct dermal contact with Cl-PFRs in foam occurs only rarely (e.g. in old/damaged furniture where fabric wear exposes the foam). Nevertheless, high concentrations of Cl-PFRs have been reported in furniture fabrics, which was attributed to migration from the underlying flame-retarded foam and/or the need to meet the strict UK/Ireland furniture flammability test for the fabric (Kjølholt et al., 2015; Stubbings et al., 2016; Wu et al., 2019). Thus a realistic exposure and risk assessment of Cl-PFRs dermal uptake should mainly consider contact with the covering fabric outer surface with which human contact occurs.

The paucity of experimental data on dermal absorption of environmental pollutants has been attributed to several reasons including ethical issues associated with both *in vivo* and *in vitro* studies using human tissues. In addition, uncertainties arise from interspecies variation and allometric extrapolation of dermal absorption data from animals to humans due to the difference in hair distribution and dermal barrier functions (Abdallah et al., 2015a). To overcome these challenges, our research group reported on the successful application of *in vitro* 3D-human skin equivalents (3D-HSE, e.g. EpiSkin™ and EpiDerm™ models) as alternatives to human/animal tissues to study human dermal absorption of various brominated flame retardants (Abdallah et al., 2015c, b). In another study, 3D-HSE (EpiSkin™) showed no statistically significant differences in percutaneous permeability to Cl-PFRs, applied as standard solutions of individual chemicals, compared to human *ex-vivo* skin (Abdallah et al., 2016). Three dimensional-human skin equivalents (3D-HSE) are cultured at the air-liquid interphase from primary human cells to produce fully differentiated, multi-layer tissues that mimic the original human skin physiologically and histologically (Figure SI-1) (Carlson et al., 2008; Ali et al., 2015). They were initially developed as alternatives to animal testing by the pharmaceutical industry and were successfully applied to study various topically applied drugs (Schaefer-Korting et al., 2008; Ackermann et al., 2010).

Against this backdrop, the objectives of the current study are: (a) to provide the first experimental data on the dermal absorption of TCEP, TCIPP and TDCIPP via contact with furniture fabrics using 3D-HSE (EpiSkin™) models; (b) to investigate the potential factors influencing human dermal uptake of Cl-PFRs from fabrics; and (c) to estimate human dermal uptake of TCEP, TCIPP and TDCIPP via contact with furniture fabric samples and evaluate the significance of this exposure pathway as a contributor to their human body burdens.

2. Materials and methods

2.1. Chemicals and reagents

All chemicals, solvents and reagents used for preparation, extraction, clean-up and instrumental analysis of samples were of UPLC grade, obtained from Fisher Scientific (Loughborough, UK). Standard solutions (50 μg/mL, >99% purity) of native and 13C-isotope labeled tris (2-chloroethyl) phosphate (TCEP), tris (2-chloroisopropyl) phosphate (TCPP) and tris (1,3-dichloro-2-propyl) phosphate (TDCIPP) were purchased from Wellington Laboratories (Guelph, ON, Canada). Florisil® SPE cartridges were purchased from Supelco™ (Bellefonte, Pennsylvania, USA). All culture medium components (Table SI-1) and simulated human skin surface film liquid (SSFL) components (Table SI-2) were purchased from Merck UK (Gillingham, Dorset, UK).

2.2. Furniture fabric samples

The current study applies 3 fabric samples chosen from an archived large group of foam, padding and fabric samples collected by our research group for a survey of flame retardants in UK upholstered furniture (Stubbings et al., 2016). The samples were chosen because they contained measurable high concentrations of the 3 target Cl-PFRs in the fabrics (which are relevant for direct dermal contact, rather than the foam), and originated from furniture items that were used in UK domestic settings (home armchair (UK-DF1), home sofa (UK-DF2) and office armchair (UK-DF3). Full description of the 3 fabric samples and the concentrations of target Cl-PFRs in each sample is provided in Table SI-3.

2.3. 3D-human skin equivalent tissues

The EPISKIN™ RHE/L/13 human skin equivalent kit was purchased from SkinEthic Laboratories (Lyon, France). The RHE/L/13 tissue constructs are 1.07 cm^2 tissues shipped on the 13th day of culture required for acceptable tissue differentiation (www.episkin.com). The kit includes maintenance medium (MM) - which is a proprietary DMEM (Dulbecco's Modified Eagle's Medium)-based medium that allows

acceptable differentiated morphology of the tissue for ~ 5 days upon receipt by end users. Upon receipt, the EPISKIN™ tissues were equilibrated overnight with their MM 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)

Physiologically-simulated skin surface film liquid (SSFL) was prepared according to a previously reported method and US patent using over 25 different chemical components (Stefaniak and Harvey, 2008) including electrolytes, amino acids, triglycerides, vitamins and squalene (Table SI-2). The SSFL composition (1:1 sweat/sebum) and pH (5.3 ± 0.1) were adjusted to reflect relevant human physiological conditions (Stefaniak and Harvey, 2006, 2008).

2.5. Dermal exposure protocol

The dermal exposure experiments were performed according to a previously published protocol (Abdallah et al., 2016; Abdallah and Harrad, 2018). In brief, 3D-HSE tissues (1.07 cm^2/tissue) were mounted in standard Franz-type diffusion cells with the *stratum corneum* facing up (Fig. 1). Each tissue was initially equilibrated with the maintenance medium for 30 min at 37 °C before the test fabric (0.5 cm^2) was applied onto the skin surface in the donor compartment. No further pressure or weight was applied on top of the fabric to avoid potential tearing or loss of the 3D-HSE tissue integrity. To study the influence of skin hydration on dermal uptake of target BFRs, the skin surface was "moistened" with 50 μL/cm^2 of SSFL for the "wet contact" experiments reflecting a "sweaty skin scenario"; while 10 μL/cm^2 was added in the respective "dry contact" experiments to reflect more "dry skin scenario". All experiments were performed in triplicate.

A DMEM-based culture medium (Table SI-1) was used as receptor fluid, maintained at 37 ± 1 °C and magnetically stirred throughout the exposure experiment (24 h). At fixed time points, aliquots of the receptor fluid (2 mL) were collected from the receptor compartment (4 mL capacity) and immediately replaced with fresh fluid. After 24 h, the fabric was removed, the entire receptor fluid was collected and the skin surface washed thoroughly with cotton buds impregnated in (1:1) hexane:ethyl acetate (5 times) to "wipe out" any unabsorbed Cl-PFRs on the skin surface. The skin tissues were removed from the permeation devices and both the donor and receptor compartments were washed separately (5 times x 2 mL) with (1:1 v/v) hexane:ethyl acetate. All samples were

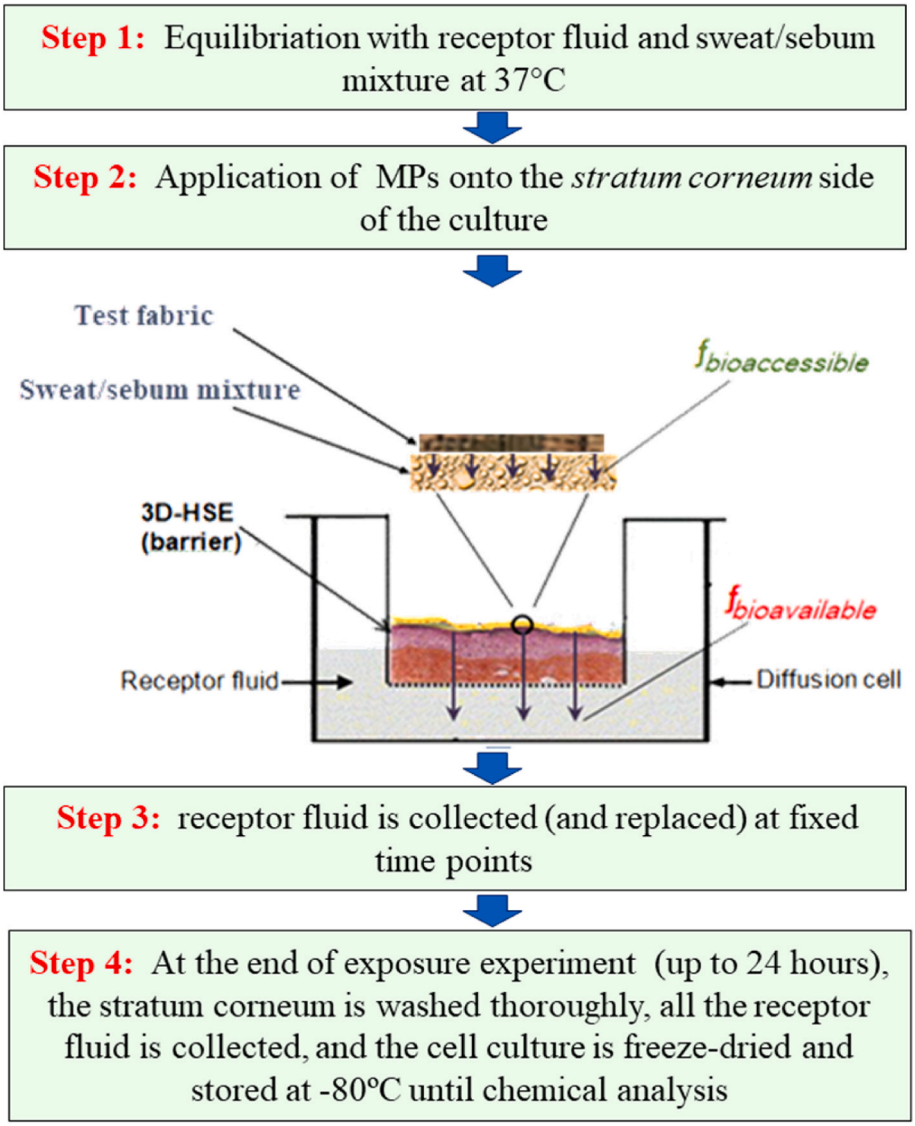


Fig. 1. Schematic representation of the *in vitro* 3D-HSE dermal absorption setup.

stored at −20 °C until chemical analysis of target Cl-PFRs.

For simplicity, concentrations of Cl-PFRs measured in the dermal exposure protocol samples were grouped under three major categories (Table 1): (*i*) The "absorbed" category (cumulative mass of target BFRs in the receptor fluid over 24 h + receptor compartment wash), (*ii*) the "skin" category (mass of target BFRs in the skin tissue) and (*iii*) the "unabsorbed" category (mass of target BFRs in the skin surface wash (cotton buds) + donor compartment wash).

2.6. Extraction, clean-up and chemical analysis

Each dermal exposure experiment generated 5 different types of samples: receptor fluid (different time points), skin tissue, cotton buds (used to thoroughly wipe the skin surface), donor and receptor compartment solvent washes. In addition, the applied test fabric sample was analysed at the end of the exposure experiment for a mass balance exercise conducted as a QA/QC measure (Table 2).

The extraction and clean-up of the collected samples were conducted according to a previously reported QuEChERs based method (Abdallah et al., 2016; Abdallah and Harrad, 2018). Quantification of target Cl-PFRs was conducted on a TRACE 1310™ GC coupled to an ISQ™ single quadrupole mass spectrometer (Thermo Fisher Scientific, Austin, TX, USA) operated in electron ionization (EI) mode according to a previously described method (Abdallah and Covaci, 2014). Full details of the extraction, clean-up and GC/MS analysis of the collected samples are provided in the SI section.

2.7. QA/QC

A multi-stage QA/QC protocol was applied to check the performance of the dermal absorption assay protocol. The handling instructions and performance characteristics of EpiSkin™ 3D-human skin equivalent (3D-HSE) were closely followed and the OECD guidelines for *in vitro* dermal absorption testing were also taken into consideration (OECD, 2004).

A "field" blank, comprising an EpiSkin™ tissue exposed to SSFL only and treated as a sample, was performed with each sample batch (n = 9). None of the target analytes were above the limit of detection (LOD) in the field blank samples. Good recoveries of the ^{13}C-labeled internal standard (>85%) in all sample types were obtained indicating high efficiency of the extraction method (Table SI-4). The accuracy and precision of the analytical method was tested via replicate analysis of matrix spikes of EpiSkin™ tissues, cotton buds and receptor fluid samples. Good results were obtained (Table SI-4) indicating suitability of the applied analytical protocol for quantification of target Cl-PFRs in the studied samples.

Based on the EpiSkin™ guidelines, the viability of the tissue was tested by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay using a standard kit purchased from the 3D-HSE provider. Acceptable MTT results (i.e. Formazan concentration ≥1.5 mg/mL) were achieved following 24 h of exposure under the specified test conditions, prior to dropping below the recommended level of Formazan at longer times. Both positive and negative control experiments were carried out alongside each sample batch. Positive controls involved the exposure of the test tissue to Triton-X-100 which showed ~100% permeation (n = 5; 98 ± 3%), while negative controls showed 0% penetration of decabromodiphenyl ethane after 24 h exposure. The integrity of the skin membrane was tested using the standard trans-

Table 1
Dermal bioavailability of target Cl-PFRs in the studied furniture fabric samples following 24 h exposure[e].

Fabric	Cl-PFR/ exposure dose	Absorbed[a]		Unabsorbed[b]		Skin[c]	
Wet skin (50 µL SSFL/ cm^2 skin)		ng	%	ng	%	ng	%
UK-DF1	TCIPP (57,250 ng)[d]	4190 (±280)[f]	**7.1**	52,880 (±490)	**89.4**	2070 (±75)	**3.5**
UK-DF2	TCEP (940 ng)	240 (±22)	**24.9**	710 (±30)	**73.6**	15 (±2)	**1.6**
	TCIPP (20290 ng)	1600 (±95)	**7.6**	18,735 (±265)	**88.8**	755 (±37)	**3.6**
UK-DF3	TDCIPP (13,930 ng)	671 (±42)	**4.8**	12,893 (±295)	**91.6**	663 (±44)	**4.8**
Dry skin (10 µL SSFL/ cm^2 skin)		Absorbed ng	%	Unabsorbed ng	%	Skin ng	%
UK-DF1	TCIPP (57,250 ng)	3310 (±260)	**5.6**	53,495 (±435)	**91.0**	1970 (±95)	**3.4**
UK-DF2	TCEP (940 ng)	230 (±18)	**24.0**	720 (±41)	**75.0**	10 (±1)	**1.0**
	TCIPP (20290 ng)	1300 (±105)	**6.1**	19,120 (±310)	**90.4**	720 (±46)	**3.4**
UK-DF3	TDCIPP (13,930 ng)	475 (±37)	**3.4**	13,255 (±305)	**94.0**	488 (±45)	**3.5**

[a] Cumulative absorbed mass/cm^2 of skin in the receptor fluid over 24 h + receptor compartment rinse.
[b] Unabsorbed mass in the fabric after 24 h + skin surface wipes + donor compartment rinse.
[c] Mass in the Episkin™ tissue after 24 h.
[d] Initial exposure dose in the donor compartment.
[e] All experiments were conducted in triplicate; results are provided as mean values.
[f] Standard deviation of 3 replicate measurements.

Table 2
Mass balance results (ng) for each of the conducted exposure protocols.

UK-DF1–TCIPP (app dose 57,246 ng)	Wet app (50 µL SSFL)	Dry app (10 µL SSFL)	UK-DF2–TCIPP (app dose 20,287 ng)	Wet app (50 µL SSFL)	Dry app (10 µL SSFL)
Receptor wash	31	35	Receptor wash	23	21
Receptor fluid	4156	3308	Receptor fluid	1579	1276
Skin wash	52,864	53,479	Skin wash	18,720	19,118
Donor wash	18	15	Donor wash	14	12
Skin	2072	1972	Skin	753	722
Sum	**59,141**	**58,774**	**Sum**	**21,089**	**21,137**
% of applied dose	**TCIPP**	**TCIPP**	**% of applied dose**	**TCIPP**	**TCIPP**
Receptor wash	0.05	0.06	Receptor wash	0.11	0.10
Receptor fluid	7.26	5.78	Receptor fluid	7.78	6.29
Skin wash	92.35	93.42	Skin wash	92.28	94.24
Donor wash	0.03	0.03	Donor wash	0.07	0.06
Skin	3.62	3.44	Skin	3.71	3.56
Sum	**103.31**	**102.67**	**Sum**	**103.95**	**104.19**
UK-DF2 – TCEP (app dose 937 ng)	Wet app (50 µL SSFL)	Dry app (10 µL SSFL)	UK-DF3–TDCIPP (app dose 13,932 ng)	Wet app (50 µL SSFL)	Dry app (10 µL SSFL)
Receptor wash	7	5	Receptor wash	12	9
Receptor fluid	236	224	Receptor fluid	659	466
Skin wash	706	719	Skin wash	12,886	13,249
Donor wash	3	<0.5	Donor wash	7	6
Skin	16	11	Skin	663	488
Sum	**968**	**959**	**Sum**	**14,227**	**14,218**
% of applied dose	**TCIPP**	**TCIPP**	**% of applied dose**	**TCIPP**	**TCIPP**
Receptor wash	0.75	0.53	Receptor wash	0.09	0.06
Receptor fluid	25.19	23.91	Receptor fluid	4.73	3.34
Skin wash	75.35	76.73	Skin wash	92.49	95.10
Donor wash	0.32	<0.01	Donor wash	0.05	0.04
Skin	1.71	1.17	Skin	4.76	3.50
Sum	**103.31**	**102.35**	**Sum**	**102.12**	**102.05**

epidermal electrical resistance (TEER) standard method (Guth et al., 2015). All EpiSkin™ tissues reported in this study passed all the above QA/QC tests.

2.8. Assessment of dermal absorption parameters for the studied Cl-PFRs

A quantitative description of test compound permeation through the skin barrier can be derived from Fick's first law of diffusion as follows (Niedorf et al., 2008):

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

Where J_{ss} = steady-state flux [ng cm-^{2} h^{-1}]; Δm = permeated mass [ng]; Δt = time interval [h]; D = diffusion coefficient [cm^2/h]; K = partition coefficient; A = area [cm^2]; Δc = concentration difference across the membrane [ng/cm^3]; Δx: thickness of membrane [cm].

When using infinite-dose configurations, i.e. in which the donor concentration far exceeds the concentration in the receptor compartment ($C_D \gg C_A$), ΔC can be replaced by the known donor concentration, C_D, and the permeated mass per time assumed constant. Therefore, the apparent permeation coefficient ($\boldsymbol{Kp}$, $\boldsymbol{cm\ h^{-1}}$), which represents an independent measure of the membrane resistance against permeation of the examined substance, can be calculated as:

$$Kp = \frac{J_{ss}}{C_D} \quad (2)$$

For each permeation experiment, Absorbed concentrations were plotted as cumulative absorption of the permeated compound in the receptor fluid versus time (hours). Steady state conditions were indicated by a linear regression line ($R^2 \geq 0.9$, figures SI-2 – SI-9), the slope of which represents the flux (J_{ss}). Determination of the start and upper boundary of the linear range (i.e. steady state conditions) was achieved according to a previously described method (figure SI-10) (Niedorf et al., 2008).

Following the contact of target Cl-PFRs with the skin, each compound needs to partition into the *stratum corneum* and diffuse through the epidermal cells before reaching the receptor fluid. This results in a lag time, t_{lag}, with non-detectable flux. The t_{lag} is represented by the time intercept (i.e. x-axis intercept) of the regression line over the linear region of the permeation curve (figures SI-2 – SI-9). Hence, t_{lag} can be calculated from equation (3):

$$t_{lag} = -\frac{b_0}{J_{ss}} \quad (3)$$

Where b_0 refers to the y-axis intercept of the linear regression line and J_{ss} is the slope. Full details are provided in the Supporting Information.

2.9. Dermal exposure assessment

Dermal uptake of the studied Cl-PFRs via contact with furniture fabrics was estimated using the general equation (USEPA, 2011):

$$\mathbf{DU} = \frac{\mathbf{C\ x\ BSA\ x\ AF\ x\ IEF}}{\mathbf{BW\ x\ 1000}} \quad (4)$$

Where DU = Daily dermal uptake (ng/kg bw/day), C = Cl-PFR concentration in the test fabric (ng/cm^2), BSA = Body surface area exposed (cm^2), AF = Absorbed fraction (unitless), IEF = indoor exposure fraction (hours per day spent in contact with flame-retarded fabric), BW = Body weight (kg).

The exposure parameters applied in equation (4) were obtained from the USEPA exposure factors handbook (Table SI-5) (USEPA, 2011). The following conservative dermal exposure scenarios were applied:

a) Summer: Assuming the back of the forearms, half the back of the thighs, lower legs and the palms of the hands exposed to armchair/sofa fabric at home (i.e. wearing a typical short and half-sleeved shirt) and only the back of the forearms, and the palms of the hands exposed to office armchair fabric (i.e. wearing a typical full-length trousers and short-sleeved shirt).
b) Winter: Assuming only the palms of the hands exposed to sofa fabric (i.e. wearing a typical full-length trousers and long-sleeve top).

3. Results and discussion

3.1. Dermal bioavailability of Cl-PFRs in furniture fabrics

All target Cl-PFRs were bioavailable to varying degrees following 24 h contact with the tested furniture fabrics under the specified exposure conditions for wet and dry skin (Table 1). TCEP showed the highest cumulative dermal absorption with 24.4% and 25.9% of the exposure dose becoming bioavailable after 24 h exposure in the dry and wet dermal skin scenarios, respectively. TDCIPP displayed the least percutaneous penetration with 3.5% and 4.8% bioavailability following 24 h contact with dry and wet skin. TCIPP was present in two of the tested fabrics (UK-DF1 and UK-DF2) with average bioavailability of 5.9% and 7.4% after 24 h contact with dry and wet skin (Table 1).

Interestingly, the opposite trend was observed for the mass of each chemical remaining within the skin tissue after 24 h exposure. TDCIPP showed more accumulation within the skin tissue (3.5–4.8% of exposure dose), followed by TCIPP (3.4–3.6%), while TCEP showed the least accumulation within the skin tissue (1.0–1.6%) (Table 1).

These results are consistent with two previous reports on dermal uptake of Cl-PFRs applied to both viable and cadaver human *ex vivo* skin as pure chemical standard solutions in organic solvents (i.e. no matrix) (Abdallah et al., 2016; Frederiksen et al., 2018). While Frederiksen et al. (2018) did not present their bioavailability results as percent of applied dose; the reported absorbed doses (ng/cm^2) in the receptor fluid after 24, 48 and 72 h exposure were in the order: TCEP > TCIPP > TDCIPP. The reverse order (i.e. TDCIPP > TCIPP > TCEP) was observed for accumulation of Cl-PFRs in the exposed *ex vivo* human skin tissues (Frederiksen et al., 2018). A previous study by our research group (Abdallah et al., 2016) reported the bioavailability of Cl-PFRs following 24 h exposure of viable human *ex vivo* skin in the order TCEP (28% of applied dose) > TCIPP (25%) > TDCIPP (13%), while the accumulated mass in the skin tissue after 24 h was in the reverse order TDCIPP (15% of applied dose) > TCIPP (11%) > TCEP (7%) (Abdallah et al., 2016).

The absorbed mass of target Cl-PFRs in the present study was higher than those reported previously by our research group (Abdallah et al., 2016) and by Frederiksen et al. (2018), which is attributable to the higher initial exposure dose in the test fabrics used in the current study (Table SI-3). Interestingly, when the absorbed mass was expressed as percent of the initial exposure dose, the percent of absorbed Cl-PFRs from tested fabrics (Table 1) were significantly lower ($P < 0.05$) than those reported previously upon dermal exposure to standard solutions of the same chemicals (in acetone) using the same experimental setup (Abdallah et al., 2016). This suggests the dermally absorbed fraction of Cl-PFRs varies with the type of matrix (i.e. fabrics) and is likely dependent on the relative ease by which the compound leaches out of this matrix to become available for absorption (i.e. become *bioaccessible*). A previous study revealed the main factors influencing dermal bioaccessibility of Cl-PFRs are: the composition of the SSFL (e.g. percent of sweat/sebum, presence and type of cosmetics) as well as the physicochemical properties of the exposure matrix (e.g. organic content) and the absorbed compound (e.g. log K_{OW}) (Pawar et al., 2017). It is worth mentioning that the observed lower absorbed fractions of Cl-PFRs from fabrics compared to those from standard solutions in organic solvents is in agreement with previous reports on the dermal absorption of brominated flame retardants (BFRs) (Frederiksen et al., 2016; Abdallah and Harrad, 2018).

TCIPP was present at elevated concentrations in two of the studied test fabrics (table SI-3). While the absorbed fractions of TCIPP varied

slightly between these two test fabrics (Table 1), the small number of samples precludes in-depth investigation of the impact of fabric polymer type and composition on the dermal bioavailability of Cl-PFRs. More research on a greater number of different fabric types is required to address this point.

3.2. Factors influencing human dermal uptake of Cl-PFRs from furniture fabrics

We investigated the impact of skin hydration on the dermal uptake of Cl-PFRs from furniture fabrics. In real life, substantial variability exists in both the volume and composition of SSFL per unit skin surface area. Human SSFL is composed mainly of a mixture of sweat and sebum, which are both important for the normal functioning of skin (Baker, 2019). 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 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 (Stefaniak and Harvey, 2008). Stefaniak et al. (2010) and Borelo et al. (Barel et al., 2014) reported that while the actual ratios *in vivo* vary by person, temperature and body area, 1:1 v/v of sweat:sebum mixture (used in the present study) is the most representative mix for *in vitro* dermal exposure experiments. Our results show increased dermal bioavailability of TCEP, TCIPP and TDCIPP from test fabrics upon contact with wet skin (50 μL SSFL/cm^2 skin) compared to the dry skin scenario (10 μL SSFL/cm^2 skin) (Table 1). This is likely associated with enhanced mass transfer of Cl-PFRs from the test fabric to the larger volume of SSFL, rendering them more available for absorption (i.e. more bioaccessible). Similar results of increased dermal uptake of organic pollutants from "sweaty" skin have been reported for polycyclic aromatic hydrocarbons (Sartorelli et al., 1999), pesticides (Williams et al., 2004) and brominated flame retardants (Abdallah and Harrad, 2018).

While the small number of target Cl-PFRs (3 compounds) precludes meaningful statistical analysis, our results revealed negative correlation between the absorbed fractions (expressed as percent of exposure dose) of target Cl-PFRs and their molecular weights (M.Wt) and log K_{OW} values, while a positive correlation was observed with their water solubility (table SI-6). This is generally in line with the principles of Lipinski's rule who reported that human absorption of chemical compounds is largely affected by their physicochemical properties including molecular weight, log K_{OW}, hydrogen bond donors and acceptors (Lipinski et al., 1997). In the present study, TCEP with the lowest M. Wt (285.5) and log K_{OW} (1.44) shows the highest bioavailability, while TDCIPP with the highest M. Wt (430.9) and log K_{OW} (3.80) has the lowest dermal absorption following 24 h exposure (Table 1). This is in line with the results of Frederiksen et al. who studied the dermal bioavailability of several organophosphate flame retardants (including our target Cl-PFRs) applied as mixture in an ethanol:toluene (4:1) solution and reported an increase in dermal permeation with decreasing log K_{OW} of the studied compounds.

To minimise the potential impact of the magnitude of exposure dose on the obtained results and for better comparison with pertinent studies, the steady state flux (J_{SS}, ng cm^{-2} h^{-1}) and dermal permeability coefficient (K_P, cm h^{-1}) were estimated for target Cl-PFRs (Table 3). Results show the apparent flux (J_{ss}) to vary widely between different studies depending on the initial exposure dose and exposure matrix/dosing solution, while slight variations are observed in the dermal permeability coefficient estimated for each Cl-PFR in different studies. It is well documented that the absolute value of K_P mainly depends on the specific experimental setup. However, an inter-laboratory comparison study revealed that even when.

K_P values of target compounds vary between laboratories, the rank order should not change within a confined group of compounds (van de Sandt et al., 2004). This is in line with the current knowledge on dermal permeability coefficients for Cl-PFRs where all studies have reported K_P values in the order TCEP > TCIPP > TDCIPP (Table 3).

Table 3
Dermal absorption parameters for target Cl-PFRs following 24 h exposure to the studied fabrics in the current study and comparison to pertinent studies.

The current study	J_{ss} (*ng cm^{-2} h^{-1}*)	K_p (*cm h^{-1}*) x 10^{-2}	t_{lag} (*h*)	Linear uptake range (*h*)	R^{2a}
	TCEP				
Fabric UK-DF2-Wet skin[b]	20	2.1	0.2	0.5–10	0.98
Fabric UK-DF2-Dry skin[c]	19	2	0.2	0.5–11	0.99
Frederiksen et al. (2018)[d] (Frederiksen et al., 2018)	10	0.6	N/A	N/A	N/A
Abdallah et al. (2016)[e] (Abdallah et al., 2016)	22	2.2	0.3	0.5–8	0.97
	TCIPP				
Fabric UK-DF1-Wet skin	361	0.6	0.5	1–12	0.97
Fabric UK-DF1-Dry skin	298	0.5	0.5	1–12	0.98
Fabric UK-DF2-Wet skin	125	0.6	0.6	1–12	0.98
Fabric UK-DF2-Dry skin	116	0.5	0.7	1–12	0.98
Frederiksen et al. (2018)	2.1	0.2	N/A	N/A	N/A
Abdallah et al. (2016)	16	1.6	0.3	0.5–10	0.98
	TDCIPP				
Fabric UK-DF3-Wet skin	31	0.2	1.8	2–22	0.98
Fabric UK-DF3-Dry skin	20	0.2	1.8	2–22	0.97
Frederiksen et al. (2018)	0.1	0.1	N/A	N/A	N/A
Abdallah et al. (2016)	5.4	0.5	2.9	4–22	0.96

[a] R^2 is the linearity coefficient. A minimum value of 0.9 is required to express linearity over the linear uptake range used to estimate the steady state flux (Niedorf et al., 2008).
[b] Wet skin scenario using 50 μL SSFL/cm^2 of skin.
[c] Dry skin scenario using 10 μL SSFL/cm^2 of skin.
[d] Direct exposure (*i.e. no matrix*) of human *ex vivo* skin to 1000 ng of each Cl-PFR in 500 μL of ethanol:toluene (4:1) mixture.
[e] Direct exposure of human *ex vivo* skin to 1000 ng of each Cl-PFR in 100 μL of acetone.

Overall, human dermal uptake of Cl-PFRs can be influenced by several factors including the physicochemical properties of the compound, the type of matrix, the exposure dose and the degree of skin hydration at the point of contact. Therefore, using a fixed ratio/percent to express the dermal uptake of Cl-PFRs, regardless of the contact matrix, exposure time, contaminant concentration and skin hydration is problematic and may lead to inaccurate results within a risk assessment context.

3.3. Human dermal exposure to Cl-PFRs via contact with furniture fabrics

The specific dermal absorption fractions for each Cl-PFR obtained from our *in vitro* exposure experiments were combined with exposure parameters from the USEPA exposure factor handbook (Table SI-5) (USEPA, 2011), and applied to equation (4) to estimate the daily human exposure via contact with the studied furniture fabrics. In the absence of definitive data on the duration of daily dermal contact with furniture fabrics in different microenvironments for different age groups, we adopted a conservative approach based on real-life exposure scenarios. We considered typical apparel in summer and winter (Table SI-5) assuming adults contact with sofa fabric for 4 h/day at home and with office armchair for 6 h/day. Due to their higher physical activity and play time, toddlers (4 years) were assumed to have dermal contact with sofa fabric for only 2 h/day at home. Results revealed significantly higher dermal uptake of all the studied Cl-PFRs in summer compared to winter for both adults and toddlers (Table 4). This can be explained by the larger skin surface area exposed during summer; resulting in more dermal contact with furniture fabrics. While the larger skin surface area resulted in higher dermal exposure in adults, this was relatively mitigated by the lower body weight of toddlers when exposure was

Table 4
Estimated human daily exposure (ng/kg bw/day) to target Cl-PFRs via dermal contact with tdest fabrics.

Wet Skin	Male adult[d]				Female adult				Male toddler[e]		Female toddler	
Cl-PFR	Scenario											
	Summer		Winter[c]		Summer		Winter		Summer	Winter	Summer	Winter
	Home[a]	Office[b]	Home	Office	Home	Office	Home	Office	Home	Home	Home	Home
TCEP	1.7	N/A[g]	0.3	N/A	1.4	N/A	0.3	N/A	1.2	0.3	1.2	0.3
TCIPP[f]	20.4	N/A	3.7	N/A	16.8	N/A	3.0	N/A	14.1	2.9	14.3	3.0
TDCIPP	N/A	3.0	N/A	1.3	N/A	2.3	N/A	1.0	N/A	N/A	N/A	N/A
Dry Skin	Male adult[d]				Female adult				Male toddler		Female toddler	
Cl-PFR	Scenario											
	Summer[a]		Winter[b]		Summer		Winter		Summer	Winter	Summer	Winter
	Home	Office	Home	Office	Home	Office	Home	Office	Home	Home	Home	Home
TCEP	1.6	N/A	0.3	N/A	1.3	N/A	0.2	N/A	1.1	0.2	1.1	0.2
TCIPP[f]	16.3	N/A	2.9	N/A	13.4	N/A	2.4	N/A	11.2	2.3	11.4	2.4
TDCIPP	N/A	2.1	N/A	0.9	N/A	1.7	N/A	0.7	N/A	N/A	N/A	N/A

[a] Assuming the back of the forearms, half the back of the thighs, lower legs and the palms of the hands exposed to sofa/armchair fabric (i.e. wearing a typical pair of shorts and short-sleeved shirt).
[b] Assuming the back of the forearms and the palms of the hands exposed to office armchair fabric (i.e. wearing a typical full-length trousers and short-sleeved shirt).
[c] Assuming only the palms of the hands exposed to sofa/armchair fabric (i.e. wearing typical full-length trousers and long-sleeve top).
[d] Assuming adult bodyweight of 70 kg, adults sit on sofa/armchair for 4 h/day at home and sit on office armchair for 6 h/day.
[e] Assuming toddler bodyweight of 15 kg, toddlers sit on sofa/armchair for 2 h/day at home (no office exposure).
[f] Mean of exposure estimates via UK-DF1 (home armchair) and UK-DF2 (home sofa).
[g] Not calculated because the target chemical was not detected in test fabrics from this microenvironment in the present study (n = 3) but has been detected in wider monitoring efforts.

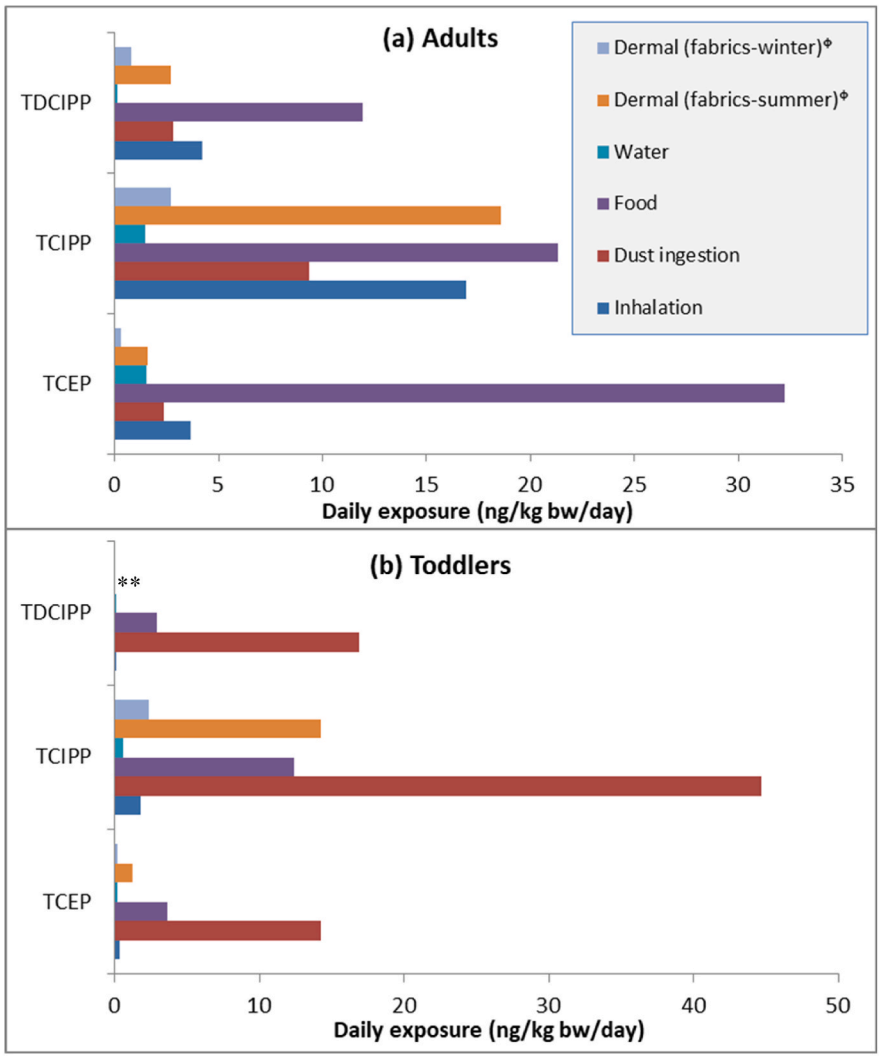
expressed per kg body weight (Table 4). It is reasonable to assume that the "wet skin" exposure scenario is more relevant to summer due to increased perspiration rate associated with higher temperatures in summer. Therefore, the highest dermal uptakes of 1.7, 20.4 and 3.0 ng/kg bw/day for TCEP, TCIPP and TDCIPP are expected for male adults during summer. Conversely, the lowest dermal uptakes are expected for toddlers during winter due to a combination of less exposed skin as a consequence of winter apparel and less sweaty "dry" skin (Table 4).

To evaluate the significance of dermal uptake of Cl-PFRs via contact with domestic UK furniture fabrics estimated here for the first time, we compared our results to previous studies assessing human exposure to these compounds via other exposure pathways in the UK. Brommer and Harrad reported median adult exposures to TCEP, TCIPP and TDCIPP of 0.03, 0.92 and 0.07 ng/kg bw/day, respectively via ingestion of indoor dust from different types of microenvironments in Birmingham, UK. The same study reported higher toddler exposures of 1.7, 43 and 4.0 ng/kg bw/day for TCEP, TCIPP and TDCIPP due to increased dust ingestion rates and lower body weight of toddlers (Brommer and Harrad, 2015). These results are generally lower than our current estimates for dermal exposure of UK adults to Cl-PFRs via contact with furniture fabrics, particularly in summer (Table 4). However, toddlers' exposure of 43 ng/kg bw/day TCIPP via dust ingestion is higher than our highest estimate of 14.3 ng/kg bw/day in summer under wet skin scenario. While this is in line with previous studies that highlighted the significance of dust ingestion as pathway of toddlers exposure to Cl-PFRs and similar contaminants (Hoffman et al., 2017b; Phillips et al., 2018), it is worth noting that these dust ingestion estimates assumed 100% absorption of intake which likely results in overestimation of the internal exposure dose (Fang and Stapleton, 2014). It should also be noted that EpiSkin™ tissue was reported to be more permeable to the target OPFRs (i.e. less barrier function) compared to human *ex vivo* skin model. Specifically, TCEP, TCIPP and TDCIPP showed enhanced absorption of 16%, 11% and 9%, respectively, in EpiSkin™ model compared to human *ex vivo* skin model. While this difference in percutaneous penetration was not statistically significant (Abdallah et al., 2016), this may still result in some overestimation of OPFRs dermally absorbed fraction via the EpiSkin™ model in the present study.

Ortiz-Carrizales reported median inhalation intakes of 7.4, 10.3, 0.05 ng/kg bw/day for TCEP, TCIPP and TDCIPP, respectively in UK adults, while toddlers were exposed to 8.3, 9.3, 0.04 ng/kg bw/day (Ortiz-Carrizales, 2018). These inhalation exposure results are generally within the range of our estimates for dermal exposure to TCIPP. However, higher inhalation exposure is reported for TCEP, while that for TDCIPP is lower than our estimates for dermal exposure via contact with furniture fabrics (Table 4). This may be explained by the specific vapour pressure (V_P) of both chemicals; whereby the high V_P of TCEP (1.1×10^{-4} *mm Hg*) and low V_P of TDCIPP (7.4×10^{-8} *mm Hg*) result in higher airborne concentrations of TCEP and low levels of TDCIPP (van der Veen and de Boer, 2012).

Assuming continuous 24 h exposure of the face, hands, forearms, legs and feet to indoor dust, Abdallah et al. reported UK adult dermal exposure to 0.1, 3.8 and 0.2 ng/kg bw/day of TCEP, TCIPP and TDCIPP, respectively via contact with indoor dust, while toddlers were exposed to 1.5, 32.9.1.6 ng/kg bw/day (Abdallah et al., 2016). These results are lower than our estimates for adult dermal exposure to Cl-PFRs via contact with furniture fabrics, yet higher than those for toddlers' exposure (Table 4). The high toddlers' exposure to Cl-PFRs via dermal contact with indoor dust may be attributed to more dust adhering to the toddlers' skin and higher exposed skin surface area to body weight ratio compared to adults (Abdallah et al., 2016).

To our knowledge, there exist no data on dietary exposure of the UK population to Cl-PFRs, which precludes national comparison of our results to this exposure pathway. A recent review article by Gbadamosi at al. reported mean global daily intakes of Cl-PFRs via different exposure pathways estimated from different studies worldwide (Gbadamosi et al., 2021). To place our results within an international context, we compared our mean estimates of UK adult and toddler exposure to target Cl-PFRs via dermal contact with the international mean daily exposures via different exposure pathways reported by Gbadamosi at al. (Gbadamosi et al., 2021) (Fig. 2). Unsurprisingly, dietary intake was the major pathway of exposure to all Cl-PFRs in adults, while dust ingestion was the predominant pathway in toddlers. Comparison with our results revealed dermal exposure to TCIPP via contact with furniture fabrics in summer is the second highest route of exposure to this contaminant following the predominant pathways of diet (adults) and dust ingestion (toddlers). For TCEP and TDCIPP, dermal exposure via contact with fabrics had less contribution to overall daily intake than other routes like dust ingestion, diet and inhalation, yet remained a significant exposure



ϕ Dermal uptake via contact with furniture fabrics (the present study).
** Not estimated in this study because TDCIPP was only detected in office furniture.

Fig. 2. Estimated mean international human exposure to Cl-PFRs from different pathways (ng/kg bw/day) (Gbadamosi et al., 2021) compared to their dermal uptake via contact with furniture fabrics (present study). ϕ Dermal uptake via contact with furniture fabrics (the present study). ** Not estimated in this study because TDCIPP was only detected in office furniture.

pathway that cannot be ignored, particularly in summer (Fig. 2). It is worth mentioning that the dermal exposure estimates in the present study have been calculated as uptake (i.e. factoring the bioaccessible fraction from the test fabric to SSFL then the bioavailable factor through EpiSkin™ tissue), while reported exposures via dust ingestion, diet and inhalation have assumed 100% absorption of intake (Gbadamosi et al., 2021). Moreover, the present study did not estimate the dermal uptake via contact with other potential Cl-PFR-containing fabrics (e.g. mattresses, pillows and child car-seats). Therefore, the daily exposure to Cl-PFRs via dermal contact with fabrics in the current study may be underestimated.

The present study provides the first experimental data on human dermal uptake of Cl-PFRs via contact with furniture fabrics using real-life exposure scenarios in both adults and toddlers. Results revealed this pathway can contribute substantially to human body burdens of Cl-PFRs, particularly in summer. Risk assessment studies for these chemicals and future structurally-similar replacements should consider dermal contact with flame-retarded consumer products (e.g. furniture fabrics) as a potential significant human exposure pathway.

Declaration of competing interest

The authors declare no conflict of interests associated with this paer.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.112847.

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