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Dermal uptake: An important pathway of human exposure to perfluoroalkyl substances?☆

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ABSTRACT

Per- and polyfluoroalkyl substances (PFAS) have been produced and used in a broad range of products since the 1950s. This class, comprising of thousands of chemicals, have been used in many different products ranging from firefighting foam to personal care products and clothes. Even at relatively low levels of exposure, PFAS have been linked to various health effects in humans such as lower birth weight, increased serum cholesterol levels, and reduced antibody response to vaccination. Human biomonitoring data demonstrates ubiquitous exposure to PFAS across all age groups. This has been attributed to PFAS-contaminated water and dietary intake, as well as inadvertent ingestion of indoor dust for adults and toddlers. *In utero* exposure and breast milk have been indicated as important exposure pathways for foetuses and nursing infants. More recently, PFAS have been identified in a wide range of products, many of which come in contact with skin (e.g., cosmetics and fabrics). Despite this, few studies have evaluated dermal uptake as a possible route for human exposure and little is known about the dermal absorption potential of different PFAS. This article critically investigates the current state-of-knowledge on human exposure to PFAS, highlighting the lack of dermal exposure data. Additionally, the different approaches for dermal uptake assessment studies are discussed and the available literature on human dermal absorption of PFAS is critically reviewed and compared to other halogenated contaminants, e.g., brominated flame retardants and its implications for dermal exposure to PFAS. Finally, the urgent need for dermal permeation and uptake studies for a wide range of PFAS and their precursors is highlighted and recommendations for future research to advance the current understanding of human dermal exposure to PFAS are discussed.

1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are a class of thousands of chemical substances. These chemicals have been produced since the 1950s and still find use in a wide variety of industrial applications and consumer products. The perfluoroalkyl moiety is both chemically and thermally stable, as well as having hydrophobic and lipophobic properties. This makes this chemical class very useful and enduring when incorporated as surfactants in firefighting foams and coatings, as well as polymers used in textiles and food packaging materials (Buck et al., 2011; Glüge et al., 2020). More recent studies have highlighted less well-known applications of PFAS. This includes their use in cosmetic products, such as powders, foundations, sunblocks and more. These products were found to contain perfluorinated carboxylic acids (PFCAs) and polyfluoroalkyl phosphate esters (PAPs) among other fluorinated ingredients (Schultes et al., 2018). PFAS have been identified in other personal care products e.g., hair products, hand sanitisers, and makeup removers and have even been used in guitar strings and piano keys (Glüge et al., 2020). PFAS have been identified in ski wax products, with a study from Sweden reporting high levels of PFAS, including 9 different ski wax products containing perfluorooctanoic acid (PFOA) above the EU limit value of 25 ng/g, which promulgated in July 2020 (Fang et al., 2020). Another notable use of PFAS is in water-repellent clothing, which have been found to contain both PFCAs and perfluoroalkyl sulfonic acids (PFSAs) as well as fluorotelomer alcohols (FTOHs) (Greenpeace, 2016, 2013; 2012; van der Veen et al., 2020). FTOHs are a class of PFAS, which can be biotransformed in various living organisms to more stable compounds such as PFCAs and are hence often referred to as precursor compounds. For example, several *in vivo* and *in vitro* studies suggest that 8-2 fluorotelomer alcohol (8-2 FTOH) is metabolised to perfluoropentanoic acid (PFPeA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), PFOA, and perfluorononanoic acid

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(PFNA). The levels and profiles of resulting metabolites vary between species, suggesting possible pathways for indirect exposure to certain PFAS via precursors (Chen et al., 2020; Fasano et al., 2009; Xie et al., 2020).

In 2001, Giesy and Kannan published one of the first studies highlighting the global distribution of perfluorooctanesulfonic acid (PFOS), caused by the widespread use and production of PFAS. They identified PFOS in the tissue of wildlife, such as fish, birds, and marine mammals in samples collected in both North America and Europe (Giesy and Kannan, 2001). Around the same time, a different study identified four PFAS (PFOS, PFOA, perfluorohexanesulfonate (PFHxS), and perfluorooctanesulfonylamide (PFOSA) in human serum (Hansen et al., 2001).

A recent report by the European Food Safety Authority (EFSA) highlighted a number of possible adverse human health effects of PFAS. As the liver plays a part in the reabsorption of PFAS there have been studies on the possible effects of PFAS on liver function (EFSA CONTAM Panel, 2020). Salihovic et al. (2018) performed a longitudinal population-based study of 1016 individuals from Sweden. The first samples were collected within two months of each participant's 70th birthday with follow up samples collected at 75 years and 80 years. Statistical analysis of the results revealed a positive association between plasma concentrations of PFHpA, PFOA, PFNA, and PFOS and those of alanine aminotransferase (ALT). Increased ALT activity is a clinical marker for impaired liver function. Additionally, the study found positive associations of PFHpA, PFOA, PFNA, perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUnDA) with alkaline phosphatase (ALP) - another marker suggestive of liver dysfunction (Salihovic et al., 2018). These results suggest a possible link between serum concentrations of PFAS and impaired liver function; however, further studies are needed to confirm this. Furthermore, a link between PFOA, PFOS, and PFNA exposure and increased cholesterol levels in serum has been reported (EFSA CONTAM Panel, 2020).

Some studies have suggested that prenatal exposure to PFAS could lead to lower birth weight and increase the risk of preterm birth. A study on the Danish National Birth Cohort which includes maternal samples drawn in the first and second trimester, found a consistent negative association between PFOS and PFOA and birth weight as well as a nearly 2-fold increase in the risk of preterm birth (within the higher quartiles of exposure) (Meng et al., 2018). Similarly, a birth cohort study in eastern Massachusetts, found concentrations of PFNA and PFOS in the plasma of expecting mothers at the early stages of their pregnancies to display a weak inverse association with birth weight and an increased risk of preterm delivery (Sagiv et al., 2018). Both Meng et al. (2018) and Sagiv et al. (2018) used samples collected before 2003 (1996–2002 and 1999–2002 respectively) when environmental levels were at their peak. Thus, the concentrations found in these studies were higher than those found in more recent studies. For example, a study on a Spanish birth cohort revealed a possible negative association between concentrations of PFAS in maternal plasma and birth weight. However, this was not statistically significant (Manzano-Salgado et al., 2017). Yet, taking into consideration the difference in concentrations of PFAS in serum, the EFSA CONTAM Panel found that "there may well be a causal association between PFOS and PFOA and birth weight" (EFSA CONTAM Panel, 2020).

Another significant health effect of PFAS in humans is reduced antibody response to vaccination. Studies on birth cohorts from the Faroe Islands found negative correlations between vaccine antibodies against diphtheria and tetanus at ages 5 and 7 years and concentrations of PFAS in both maternal pregnancy and children's serum at 5 years (Grandjean et al., 2017, 2012). Similarly, Abraham et al. (2020) conducted a study on samples from a German cohort collected in the late 1990s and found significant associations between concentrations of PFOA in serum and adjusted levels of vaccine antibodies against tetanus, diphtheria and *Haemophilus influenza* type b (Abraham et al., 2020).

Studies on highly exposed cohorts have also linked PFAS exposure and endocrine disruption, e.g. thyroid toxicity and some cancers (Barry et al., 2013; Winquist and Steenland, 2014). The C8 study of a population from the US that was highly exposed to PFOA through their drinking water, found that the high PFOA exposure in this group was associated with increased risk of functional thyroid disease, as well as kidney and testicular cancers (Winquist and Steenland, 2014; Barry et al., 2013). Nevertheless, as noted recently, both these adverse effects are only detected at high levels of exposure and there is insufficient evidence to suggest association between PFAS exposure at lower levels and cancers or thyroid disease (EFSA CONTAM Panel, 2020).

A consistency of effects to PFAS exposure is seen between epidemiological studies and *in vivo* animal studies. Animals treated with repeat doses of PFAS revealed similar health effects to human studies. Animals exposed to PFCAs were found to have increased liver weights, disturbed lipid metabolism, elevated ALP and ALT as well as disrupted thyroid hormone levels. Similarly, for PFSA exposed animals, observed changes were increased liver weight, disruption in thyroid hormones and alterations to the kidneys (PFBS only) as well as changes in lipid metabolism, necrosis and inflammation of the liver for higher exposure groups (EFSA CONTAM Panel, 2020).

Based on these findings, in September 2020, EFSA proposed a group tolerable weekly intake of 4.4 ng (kg bw)$^{-1}$ for the sum of PFOA, PFOS, PFNA, and PFHxS. EFSA also noted various reports suggesting PFAS could have a wider impact on human health but further studies are needed to confirm these findings (EFSA CONTAM Panel, 2020). Currently, two PFAS are listed under the Stockholm Convention on persistent organic pollutants (POPs). PFOS, including its salts and perfluorooctane sulfonyl fluoride (PFOSF) are listed in Annex B (Restriction); while PFOA, its salts and PFOA-related compounds (including precursor compounds) are listed in Annex A (Elimination) (Stockholm Convention, 2019). Moreover, the POPs Review Committee has recommended that PFHxS, its salts and PFHxS-related compounds should also be listed in Annex A (POPRC, 2019).

Half-lives of PFAS in humans range from a few days for short-chained PFAS up to several years for long-chained PFAS (Table 1). The long half-lives of PFAS are due to their ability to interact with various transporters involved in reabsorption processes in the liver, intestine and kidneys (EFSA CONTAM Panel, 2020). The physicochemical properties - e.g. the octanol-water partitioning coefficient - of PFAS can affect their absorption in humans (Lipinski et al., 2001). While perfluoroalkyl acids (PFAAs) are not metabolised in humans, precursor compounds such as 8:2 FTOH and PFOSA can be biotransformed to PFOA and PFOS, respectively and thus contribute to human exposure to these compounds (Nilsson et al., 2013; Vestergren et al., 2008a). Currently, studies investigating human exposure routes of PFAS suggest the main pathways for human exposure are: diet and drinking water, followed by indoor dust and air (Haug et al., 2011; Poothong et al., 2020; Vestergren et al., 2008a). However, few studies have included dermal uptake as a possible route for human exposure. This is partly because very few studies have examined the dermal permeation ability of PFAS (Fasano et al., 2005; Franko et al., 2012). Other studies however, have revealed dermal absorption to be a significant contributor to the total human exposure to chemicals such as brominated flame retardants (Abdallah and Harrad, 2018; Pawar et al., 2017).

Recent studies highlight the use of PFAS in various consumer products that come in prolonged contact with human skin. This includes anything from cosmetics to water repellent clothing (Glüge et al., 2020; Greenpeace, 2016; Schultes et al., 2018; van der Veen et al., 2020; Whitehead et al., 2021). However, the extent of dermal absorption upon skin contact with these consumer products and its significance as a pathway of human exposure to PFAS is currently unknown. The limited understanding of the dermal exposure route may constitute a serious knowledge gap, especially in light of the use of PFAS at relatively high concentrations in consumer products that come in contact with human skin for prolonged periods.

Against this backdrop, the present review discusses the various

Table 1
Geometric mean (GM) values of PFAS half-lives in humans.

PFAS	Mean Half-life (years)	Gender	Volume distribution (mL/kg)[a]	Reference
PFOA	3.6	Both	170	Fu et al. (2016)
	2.7	Both	N/A[b]	Li et al. (2018)
	3.5	Both	N/A	Olsen et al. (2007)
	1.5	Young females	170	Zhang et al. (2013)
	1.2	Males and older females	170	Zhang et al. (2013)
	3.3	Both	N/A	Brede et al. (2010)
	2.3	Both	N/A	Bartell et al. (2010)
	8.2–14.5	Both	N/A	Yeung et al., 2013a
PFBS	0.07 (25.8 days)	Both	N/A	Olsen et al. (2009)
PFHxS	1.7	Both	230	Fu et al. (2016)
	5.3	Both	N/A	Li et al. (2018)
	7.3	Both	N/A	Olsen et al. (2007)
	7.1	Young females	230	Zhang et al. (2013)
	25	Males and older females	230	Zhang et al. (2013)
PFOS	1.9	Both	230	Fu et al. (2016)
	3.4	Both	N/A	Li et al. (2018)
	4.8	Both	N/A	Olsen et al. (2007)
	5.8	Young females	230	Zhang et al. (2013)
	18	Males and older females	230	Zhang et al. (2013)
	4.7	Males	230	Wong et al. (2014)
	3.7	Females (non-menstruating)	230	Wong et al. (2014)
	4.0	Females (menstruating)	230	Wong et al. (2014)
	4.3–4.8	Both	N/A	Yeung et al. (2013b)
PFNA	1.7	Young females	170	Zhang et al. (2013)
	3.2	Males and older females	170	Zhang et al. (2013)
PFDA	4	Young females	170	Zhang et al. (2013)
	7.1	Males and older females	170	Zhang et al. (2013)
PFUnDA	4	Young females	170	Zhang et al. (2013)
	7.4	Males and older females	170	Zhang et al. (2013)

[a] The volume distribution is defined as the total amount of a substance in the body divided by its concentration in the serum. The half-lives are often calculated based on the volume distribution (Fu et al., 2016; Zhang et al., 2013).
[b] Not available.

routes of human exposure to PFAS and their relative contribution to overall human exposure. The current state-of-knowledge on dermal exposure to PFAS is discussed to understand the underlying reasons for paucity of data on this route. Additionally, different techniques for dermal exposure assessment are evaluated as potential approaches to address the existing research gap on human dermal exposure to PFAS.

2. The significance of different pathways of human exposure to PFAS

Different studies on the various pathways of external human exposure to PFAS have been conducted in different regions of the world (Haug et al., 2011; Kim et al., 2019; Trudel et al., 2008). Fig. 1 summarises the diverse pathways of human exposure to PFAS.

A recent study on PFAS concentrations in human milk from Ireland used a first-order pharmacokinetic (PK) model to examine the relationship between concentrations in human milk and predicted exposure intakes via different pathways. Median non-dietary intakes via inhalation of indoor air, dust ingestion, and drinking water, accounted for about 1.5% of the median total exposure to PFOS and ~6% of that for PFOA. This suggests that in Ireland at least, diet is the main exposure route for PFOS and PFOA, although the authors noted that dermal absorption (not studied directly) could also be an important contributor to the observed human body burdens of PFAS (Abdallah et al., 2020).

Similarly, a study on Norwegian women and infants focused on different exposure pathways of PFOS and PFOA in humans and related them to concentrations in serum (Haug et al., 2011). The study used a first-order PK model and three different exposure scenarios, with varying dust ingestion rates as well as biotransformation factors of precursor compounds. Diet was found to be the main source of exposure accounting for 67–84% of the median total intake of PFOA and 88–99% of PFOS intake in women. The only biotransformations considered were FOSAs/FOSEs to PFOS and FTOHs to PFOA; otherwise only direct exposure to PFOA and PFOS was considered. Drinking water represented 4.6–22% of PFOA and 0.13–3.3% of PFOS exposure. For participants in the highest dust ingestion scenario (200 mg/day), estimated indoor air inhalation and dust ingestion accounted for more than 40% of the PFOA and 61% of PFOS intake. However, for most participants the greatest exposure was from food consumption with indoor air and dust contributing as little as 1.2%–1.7% of overall exposure for PFOA and 0.7%–0.1% for PFOS respectively. When comparing the results of the PK model and measured concentrations in serum, the best agreement was seen for scenario 1, which suggested diet to be the predominant contributor to total exposure, followed by drinking water, dust ingestion, and air inhalation. Infant exposure to PFOA and PFOS was reported to be mainly due to PFAS in breast milk, representing over 90% of overall exposure for both PFOA and PFOS. Dust ingestion was found to be the second highest contributor to PFOA and PFOS exposure in infants, followed by air inhalation (Haug et al., 2011). This study did not take dermal absorption into account, based on the low skin absorption of ammonium perfluorooctanoate, (APOF) reported by Fasano et al. (Fasano et al., 2005; Haug et al., 2011). Tables 2 and 3 summarise the average values of various exposure routes found by different studies and Fig. 2 compares different exposure routes for infants and adults. A similar figure based on dietary exposure from USA has been presented by Ghassabian et al. (2022) (based on data from Wu and Kannan (2019)).

As part of another study of human exposure to consumer chemicals (A-TEAM), the daily intakes of PFAAs and precursor compounds, were evaluated for a cohort of 61 adults in Norway (Poothong et al., 2020). The aim was to characterise exposure to PFAS from dermal contact (based on hand wipe samples), diet, house dust, and indoor air as well as the relative contributions from different exposure pathways to concentrations in human serum. Dermal absorption was estimated by assuming that the total mass of PFAS available for dermal uptake was that on hands as identified via hand wipes and was constant over an exposure duration of 24 h. To avoid overestimation, this study only included dermal absorption from the hand wipe samples. Hand-to-mouth contact based on hand wipe samples was not included as dust ingestion was considered to include dust adhered to hands. The absorption factor of PFAS was adopted from a study which found that 48% of PFOA applied to the human epidermis had penetrated it (Franko et al., 2012). Poothong et al. (2020) concluded that: 91% of the total estimated intake

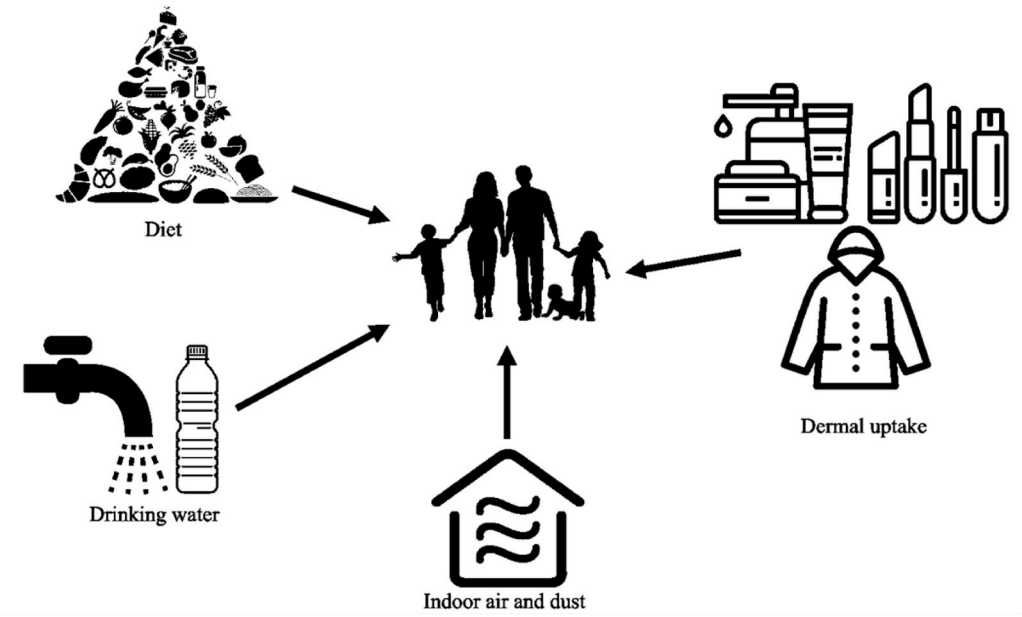

Fig. 1. The various pathways for external human exposure to PFAS.

Table 2
Summary of the median contributions (expressed as percentage of total exposure via all pathways considered[a]) of various exposure pathways to overall adult human exposure to PFOS and PFOA.

PFAS	Diet	Drinking water	Indoor air and/or dust	Hand-to-mouth contact	Dermal exposure	Reference
PFOA[b]	84	11	5.3	NM[c]	NM	Haug et al. (2011)
PFOS[b]	99	0.7	0.5	NM	NM	
PFOA	92	NM	7	NM	<1[f]	Poothong et al. (2020)
PFOS	95		3		<1	
PFOA	96	0.9	NM	2.6	NM	Kim et al. (2019)
PFOS	94	1.4	1	4	NM	
PFOA[d]	73[e]		25	2	NM	Trudel et al. (2008)
PFOS[d]	80[e]		15	5	NM	

[a] Numbers may not add to 100% due to rounding.
[b] The values shown are from exposure scenario 1 (estimated dust ingestion 50 mg/day and biotransformation of FOSA/FOSEs to PFOA: 1% and FTOH to PFOA: 0.02%).
[c] Not measured.
[d] Only direct exposure to PFOA and PFOS considered, high exposure scenarios.
[e] Diet and drinking water combined.
[f] Based on hand wipe samples and assuming 24 h constant exposure and an absorption factor of 48%.

Table 3
Summary of the median contributions (expressed as percentage of total exposure via all pathways considered[a]) of various exposure pathways to overall infant human exposure to PFOS and PFOA.

PFAS	Breast milk	Dust ingestion	Inhalation	Hand-to-mouth	Reference
PFOS	99	1.2	0.004		Haug et al. (2011)
PFOA	98	1.4	0.02		
PFOS	45	15		40	Trudel et al. (2008)
PFOA	35	20	2	40	

originated from diet, ingestion of house dust and inhalation of indoor air represented 3% and 2% of the total PFAAs respectively, while dermal absorption represented 0.3% of the total PFAS intake. On an individual PFAS basis, diet was the main source of exposure of PFOA, contributing to 92% of total exposure respectively followed by indoor air inhalation (4%), dust ingestion (3%), and dermal absorption (1%). Similarly, for PFOS, diet contributed to 95% of the total intake, followed by indoor air inhalation (3%), while dermal absorption and dust ingestion each contributed <1% of total exposure. The authors note a few limitations to their study, including the relatively small study group. Additionally, lack of knowledge on absorption and biotransformation rates of PFAS increases uncertainty. Finally, only dermal exposure through hands was considered. Depending on the source material e.g. clothing or cosmetics, dermal uptake could occur from a much larger area (Poothong et al., 2020).

A study by Kim et al. (2019) assessed individual-based exposure to PFAS via various exposure pathways. In this study, serum from 50 individuals was analysed along with one day composite food, drinking water, dust, and hand-wipe samples following both indoor and outdoor activity. Interestingly, a positive correlation was found between PFOA concentrations in serum and dust, indicating that dust was potentially a significant contributor to body burdens of PFAS in humans. For food and drinking water, the only PFAS that showed positive correlation to serum concentrations was PFUnDA. The outdoor hand-wipe samples revealed significant correlation with concentrations in serum for PFOA and PFUnDA as well as for total PFAS. However, the indoor hand-wipe samples revealed no correlation with concentrations in serum. The authors suggest that the uneven pattern of correlations between serum and the different external exposure metrics for the various target PFAS is due to the fact that only a single hand-wipe sample was collected for each individual, representing only 1 h of exposure whereas serum samples reflect long-term exposure (Kim et al., 2019). The authors also estimated the contribution of each exposure route to total PFOA and PFOS exposure on an individual basis. Only PFOA and PFOS were included as they were representative of PFAS with high detection frequencies in the samples analysed. For both PFOA and PFOS, food ingestion was the biggest contributor to the total body burden at 96% and 94% respectively. Indoor hand-to-mouth activity came second contributing to 2.4% of PFOA and 3.8% of PFOS intake. For PFOS intake, dust contributed 1% to the total intake, drinking water 1.4%, and outdoor hand-to-mouth activity 0.2%. This study did not consider dermal uptake as a possible

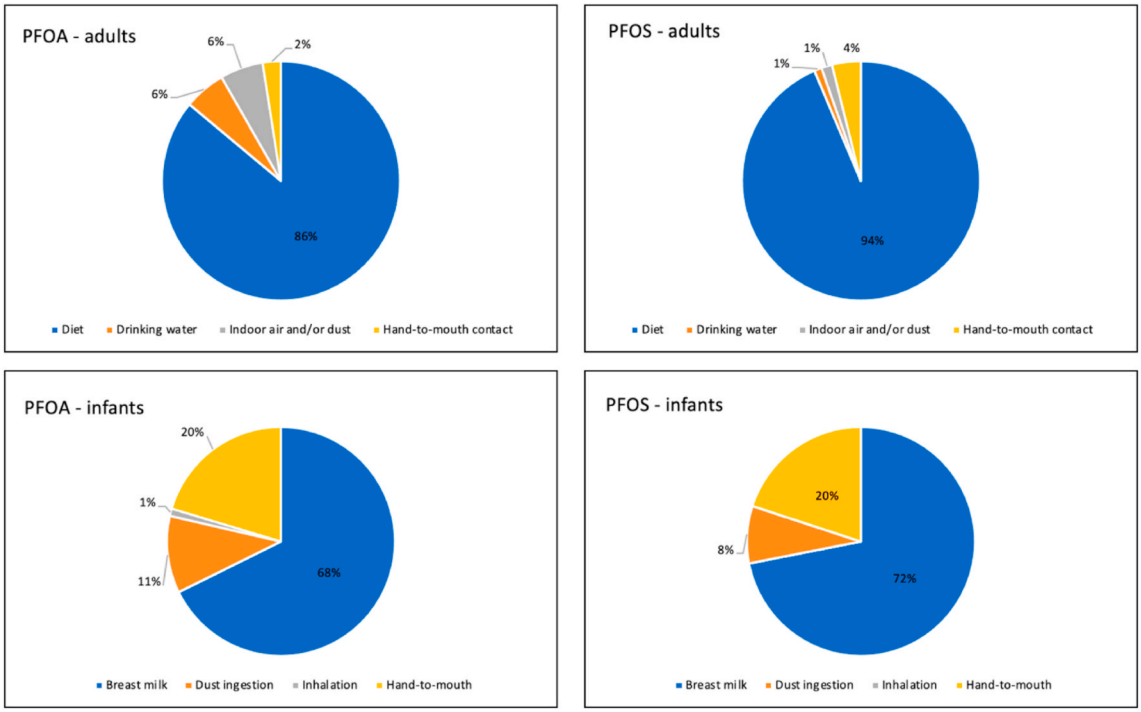

Fig. 2. Average relative percent contribution of different routes to overall daily human exposure to PFAS in adults and infants. A similar figure based on dietary exposure from USA was presented by Ghassabian et al. (2022) (based on data from (Wu and Kannan, 2019)).

exposure route (Kim et al., 2019).

A Scenario-Based Risk Assessment of exposure of North Americans showed similar results when investigating direct consumer exposure to PFOA and PFOS. The study found that under a high exposure scenario, food and water contributed to around 80% of adult PFOS exposure followed by dust ingestion (ca. 15%) and hand-to-mouth contact with mill treated carpets (ca. 5%). Similarly, around 73% of adult exposure to PFOA under the high exposure scenario was from diet, with most such exposure originating from food packaging. Under the same scenario, inhalation accounted for 15% of adult PFOA exposure, followed by dust ingestion (10%) and hand-to-mouth exposure (2%). For infants however, 45% of PFOS exposure was due to diet, followed by hand-to-mouth exposure (40%), and dust ingestion (15%). Infant PFOA exposure was mainly found to be due to hand-to-mouth exposure (40%) followed by diet (35%), and dust ingestion (20%) (Trudel et al., 2008).

Building upon the study of Trudel et al., Vestergren et al. (2008a, 2008b) performed a Scenario-Based Risk Assessment to quantify consumer exposure to precursor compounds in order to assess their contribution to total daily doses of PFOS and PFOA. To account for the metabolic transformation of precursors to PFOA and PFOS, the load of precursors absorbed into the human body was multiplied by a biotransformation factor. Due to the large variability of metabolic transformation between different studies, they used a modelling approach to generate biotransformation factors relevant to 3 different exposure scenarios (low, intermediate, and high) for each of the studied precursor groups. The possible routes for dermal exposure that this study included were: contact with treated clothing, deposition of spray droplets while using impregnation sprays, as well as skin contact with upholstery, and house dust deposited on skin. Looking at PFOS exposure for adults and teens, the study concluded that in both the low-exposure and intermediate scenarios, direct exposure to PFOS via diet was the main route of exposure, accounting for 99% and 94–98% respectively. For the intermediate group, precursor-based exposure was a minor pathway (2.3–5.4%). However, under the high-exposure scenario, precursor-based exposure was a substantial contributor to overall exposure to PFOS accounting for 60–80% of the total exposure. Direct exposure to PFOS accounted for only 18–46% under the high-exposure scenario. Similarly, direct PFOA exposure accounted for 92–100% of the total exposure of adults and teens in the low- and intermediate exposure scenarios. For the intermediate exposure scenario, precursor-based exposure was a minor pathway (4.3–7.7%). In contrast, in the high-exposure scenario, precursor-based exposure was more significant, accounting for 48–55% of the total PFOA exposure in adults and teens. Direct PFOA exposure was slightly less significant (36–45%) for adults and teens in the high-exposure group. Similar patterns were seen for children for both PFOS and PFOA exposures. The main routes of exposure in the low- and intermediate scenarios were direct exposure to PFOS/PFOA, with precursor-based exposures more significant for the high-exposure scenario (Vestergren et al., 2008b).

A report by Knepper et al. researched durable water repellent (DWR) clothing as a possible source of exposure to PFAS. One of the exposure pathways considered was dermal uptake via consumers using commercial impregnation sprays containing PFAS to treat DWR clothing. Other pathways of exposure considered were: inhalation of said impregnation sprays, dermal uptake from wearing treated clothes, hand-to-mouth transfer from treated clothes, inhalation of indoor air, and ingestion of indoor dust. It was concluded that overall exposure to PFAS via DWR was mainly attributable to inhalation of indoor air (for both indirect and direct exposure), followed by dust ingestion. Dermal uptake was found to be minimal, but this is likely attributed to the low absorption rate assumed (0.001% of the chemical absorbed per hour). In the absence of experimental data, the uptake of PFCAs and FTOHs was derived from a study by Fasano et al. (2005) that assessed *in vitro* human dermal absorption of ammonium perfluorooctanoate, which could be an underestimation. It was concluded that the overall exposure from DWR outdoor jackets contribute to a small part of the overall exposure to PFCAs compared to dietary intake for the general population. Still, taking into consideration the substantial variability in exposure to consumer products, this study concluded that DWR jackets could represent a source of elevated exposure to some population groups (Knepper et al., 2014).

3. The skin barrier

Skin is the body's largest organ, with the skin of a human adult having a surface area of approximately 2 m^2 and weighing around 5 kg. This multi-layered organ plays an essential role in protecting the body from the surrounding environment. While it is an effective barrier for exogenous molecules, the degree of protection is not complete (Godin and Touitou, 2007). Therefore, elucidating the potential significance of dermal uptake as a pathway of human exposure to chemical contaminants is an important area of research. Human skin is composed of 3 main layers: epidermis layer, dermis, and hypodermis. The outermost layer, the epidermis is a non-vascular layer that serves as a protective obstacle to penetration of chemicals to the underlying vascular dermis. Healthy human epidermis is made up of 4 layers: stratum corneum (SC), stratum granulosum, stratum spinosum, and stratum basale. It is with the outermost layer - the SC - where the barrier properties of the skin mainly lie. This highly hydrophobic layer is composed of differentiated non-nucleated cells, corneocytes, which are filled with keratins and embedded in the lipid domain. The main pathway of transdermal permeation of chemicals through the SC is via passive diffusion. This is greatly affected by the compound's physicochemical properties including: molecular weight, presence and number of hydrogen bond donors/acceptors, water solubility, and octanol-water partitioning coefficient. The general rules that a compound should follow are known as Lipinski's rule of 5 and chemicals should fulfil at least three of the four criteria in order to be absorbed effectively by the body (see Table 4). However, it is important to note that these rules were developed for evaluation of drug delivery; thus although a chemical may not obey completely these rules, some fraction may still be absorbed by the skin (Abdallah et al., 2015a; Knudsen et al., 2016; Lipinski et al., 2001). In order for a chemical to be available for absorption (e.g. through skin) it has to be in solution, i.e. dissolved into the body fluid (sweat/sebum) in contact with the skin to be bioaccessible. A portion of what is bioaccessible can then be absorbed and reach the systemic circulation, i.e. bioavailable (Pawar et al., 2017). Other factors that can affect percutaneous absorption of chemicals are e.g. exposure conditions (dose, duration, surface area, exposure frequency), conditions of the skin surface (hydration, temperature, pH) and application sites (regional variation in penetration) (Law et al., 2020). After a chemical passes through the SC, it may be metabolised *in situ* or move by diffusion through the viable epidermis and into the vascular dermis layer, where it enters the systemic circulation (Knudsen et al., 2016). Transdermal permeation may also occur via sweat glands and hair follicles directly to the dermis (Abdallah et al., 2015a). Chemicals retained in the epidermis may not reach the circulation but are removed by the natural desquamation process (Knudsen et al., 2016).

Table 4
Physicochemical properties of various PFAS compared to the Lipinski's rule of 5 criteria. The other two criteria are H bond donors (≤5) and H bond acceptors (≤10).

Lipinski's rule of 5	Average Mass (Da)	Log(Kow) Experimental[a,b]	Log(Kow) EPI suite[a]
	>500 Da	≤5	≤5
PFOA	414.07	5.91	6.3
PFOS	500.13	-[c]	-[c]
PFHxA	314.05	4.15	4.37
PFHxS	400.12	4.57	4.34
PFNA	464.08	6.79	7.27
PFBA	214.04	-[c]	2.43
PFBS	300.1	2.81	2.41
PFPeA	264.05	3.26	3.4
PFHpA	364.06	5.02	5.33
PFHpS	450.122	5.45	5.31

[a] Values taken from Chemspider (2021).
[b] Note that it is stated that these values are "old".
[c] Values missing.

Along with the SC, increasing evidence suggests that xenobiotic metabolizing enzymes, in addition to transport proteins, play an important role in the transdermal penetration process. Human epidermal keratinocytes have been found to express various transport associated enzymes as well as detoxifying metabolic enzymes (Baron et al., 2001). CYP450 enzymes are capable of metabolizing a wide variety of small molecular weight exogenous as well as endogenous compounds. Although CYP450 enzymes have been identified in both human keratinocytes and some 3D-Human Skin Equivalent (3D-HSE) models, the levels detected in skin are lower than those detected in liver cells (Oesch et al., 2014). However, relative levels of the xenobiotic metabolizing enzyme carboxylesterase 1 (CES 1) in whole skin and liver were 0.62 with no significant difference ($p = 0.21$) (van Eijl et al., 2012). Furthermore, Abdallah et al. (2019) performed a study on the *in vitro* dermal metabolism of 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (EH-TBB). The study revealed that human skin cells metabolised EH-TBB mainly to tetrabromobenzoic acid (TBBA) and concluded that the dermal metabolism of EH-TBB was catalysed by carboxylesterases rather than CYP450 (Abdallah et al., 2019). A study by Liu et al. demonstrated strong binding affinity of PFAS towards both CES 1 and CES 2 *in vitro*. PFAS tested were: PFHxA, PFOA, perfluorodecanoic acid (PFDA), perfluorododecanoic acid (PFthouDoA), perfluorotetradecanoic acid (PFTeDA), perfluorooctadecanoic acid (PFOcDA), PFOS, perfluorohexyl iodide (PFHxI), perfluorooctyl iodide (PFOI), the fluorotelomer alcohols 4:2 FTOH, 5:1 FTOH, 6:2 FTOH, 7:1 FTOH, and 6:2 fluorotelomer sulfonic acid (6:2 FTSA). The compounds with the greatest binding affinity which caused greater inhibition ability were longer chain PFAS: PFDoDA, PFTeDA, and PFTOcDA. The preliminary results suggested a relationship between carbon chain lengths and inhibition ability, with longer chain lengths showing greater CES 1 inhibition (Liu et al., 2020). The ability of these longer chain PFAS to inhibit the liver CES1 enzymes suggests a lesser risk of dermal absorption of those compounds and their metabolites. However, this must be interpreted with some caution as the inhibition of dermal CES1 at realistic environmentally relevant concentrations was not investigated. Moreover, the resulting metabolites from these chemicals, be it via the partially inhibited CES1 enzymes or other metabolic pathways (e.g., CYP450), have not been identified or risk assessed. Thus, it is still important to experimentally investigate the bioavailability and biotransformation of these long chain PFAS.

4. Methods for evaluation of human dermal uptake of chemical contaminants

4.1. *In vivo* methods

Dermal absorption studies are currently hindered by various difficulties. For example, several ethical and technical limitations are related to studies involving human volunteers. Although such studies would be the most reliable when evaluating human dermal absorption, their use has been, and likely will continue to be limited. *In vivo* studies were used to study the dermal absorption of PCBs (polychlorinated biphenyls) through various pathways. Three different studies were conducted using either rhesus monkeys and/or guinea pigs, in association with *in vitro exposure* using human cadaver skin. These studies provided important early insights into the dermal absorption, systemic elimination, and dermal wash efficiency of lipophilic environmental contaminants (Wester et al., 1993, 1990, 1983). However, there are increasing ethical restrictions on the use of animal studies in toxicological studies. Additional uncertainties exist with data derived from animal studies when applied to humans, due to interspecies variation in parameters such as: skin barrier function, intercellular subcutaneous lipids, hair follicles, etc (Abdallah et al., 2015b). Notwithstanding this, there are benefits to the use of *in vivo* animal models for dermal absorption studies as they represent a complete metabolic and physiological system (Abdallah et al., 2015a).

4.2. In vitro and ex vivo methods

With increasing restrictions on *in vivo* animal models due to factors such as ethical concerns, the use of such models is in decline. This has led to increased development and validation of various *in vitro* methods, which then aid the development of predictive pharmacokinetic models (Abdallah et al., 2015a). An example of an *in vitro* experimental configuration using Franz cells is illustrated in Fig. 3. Guidance documents for *in vitro* skin absorption studies are currently available from various institutions (OECD, 2004a, 2004b; U.S. EPA, 2004; WHO, 2006).

Various skin models have been applied for *in vitro* testing, using either excised human skin from surgery or cadavers (*ex vivo*) or animal (e.g. pig or rat) skin as well as reconstructed human skin models (Abdallah et al., 2015a; Sartorelli et al., 2000; van de Sandt et al., 2004). Several factors in the experimental configuration can affect the results of *in vitro* experiments. Different types of diffusion cells have been used in various studies. Both static and flow-through cells showed comparable results for dermal absorption rates of caffeine, benzoic acid, and testosterone. The OECD recommends the use of these three chemicals to establish the reliability and performance of test systems as they cover a wide range of hydrophobicities and have been thoroughly studied (OECD, 2004a; OECD, 2004b). The type of receptor fluid (intended to mimic the blood stream into which dermally-absorbed chemicals pass) used in studies, can also affect the outcome based on the physico-chemical properties of the tested chemicals. Specifically, the receptor fluid could become a rate-limiting factor in dermal permeation studies if the test compound is poorly soluble in the chosen receptor medium. According to the OECD guidelines, the solubility of the test chemical in the receptor fluid should not be the rate limiting step in the *in vitro* diffusion process (OECD, 2004a; 2004b). This is of particular importance for hydrophobic compounds, where use of simple saline solutions as the sole component of the receptor fluid, can prove problematic as it is likely to underestimate the dermal absorption rate of poorly water-soluble compounds (Abdallah et al., 2015a; Jakasa and Kezic, 2008; OECD, 2011). The use of bovine serum albumin (BSA, up to 5%) has been suggested to improve the solubility of hydrophobic compounds in the receptor fluid (OECD, 2011; Sartorelli et al., 2000). Overall, it is always preferable that the receptor fluid mimics as accurately as possible, the actual biological conditions in terms of composition and temperature (Abdallah et al., 2015a).

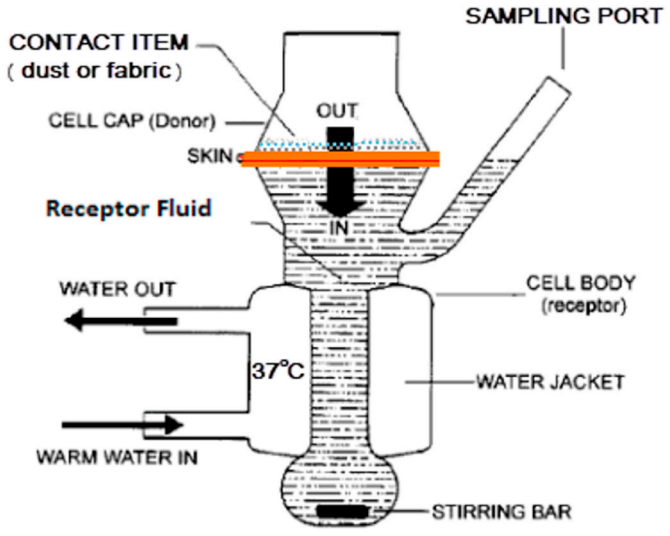

Fig. 3. *In vitro* dermal exposure experimental configuration using a Franz cell. The skin samples act as a barrier between the two compartments, the upper donor compartment and the lower receptor compartment. The receptor fluid should be kept at a temperature similar to human body temperature. Figure taken from Abdallah and Harrad (2018).

In vitro pig skin models show the most biological similarities with human skin models. The thickness of the skin layers, hair follicles, and blood vessel density, are all similarities shared by pig and human skin, as well as content of SC ceramides, elastin, and dermal collagen. As a waste product from meat production, pig skin can be easily acquired. Pig ear skin shows the closest structure to human skin layers and the permeability of pig ear skin has been shown to be comparable to that of human skin (Moniz et al., 2020).

For *ex vivo* dermal permeation experiments, freshly excised human skin (typically acquired from volunteers undergoing cosmetic surgery) is favoured over human cadaver skin although this is not always available (Van Gele et al., 2011). The skin permeability of fresh skin to tritiated water was not affected after storage for up to 3 days at 10 °C and for over a year for skin stored at −20 °C. However, storage at very low temperatures i.e. −80 °C has been shown to enhance the permeability of skin (OECD, 2004b). The types of *ex vivo* skin samples used for *in vitro* testing can vary from (1) full-thickness skin, composed of the SC, viable epidermis, and dermis, (2) split-thickness skin where the lower dermis has been discarded, and (3) epidermal membranes, which includes the viable epidermis and SC (Jakasa and Kezic, 2008). The thickness of skin samples used for dermal uptake testing could affect the variation in absorption of the tested compounds. Thicker skin, i.e. full-thickness and split-thickness samples, can result in a higher fraction of the chemical retained within the skin while thinner skin samples could show an increased flux (OECD, 2011; Wilkinson et al., 2006). According to OECD recommendations, the impact of this can be minimised by including all or part of the compound retained in the skin in the dermal absorption value (OECD, 2011).

A different approach, the Parallelogram, has also been applied for dermal absorption studies (Knudsen et al., 2019, 2016; Van Ravenzwaay and Leibold, 2004). In this approach, *in vivo* animal studies are combined with *ex vivo* animal, and human skin models. This allows for *in vivo* human exposure to be estimated as a function of *ex vivo* human exposure multiplied by a normalization factor based on the same dose applied to rat skin *in vivo* and *in vitro* (Fig. 4). This approach assumes the ratio of *in vivo* to *in vitro* dermal penetration of a chemical is the same through animal (i.e. rat) and human skin. It has been used to study the dermal uptake of brominated flame retardants (BFRs), such as novel BFRs (EH-TBB and BEH-TEBP) and tetrabromobisphenol A bis(2, 3-dibromopropyl) ether (TBBPA-BDBPE) (Knudsen et al., 2019, 2016).

4.3. 3D-Human Skin Equivalent models

3D-Human skin equivalent (3D-HSE) models were developed to overcome the ethical issues and differences between species, in addition to increasing restrictions on the use of laboratory animals in toxicological studies (Abdallah et al., 2015b, 2015c; Ackermann et al., 2010; Schäfer-Korting et al., 2008). There are two main types of 3D-HSE models. Reconstructed human epidermis (RHE) models consist of human keratinocytes cultured on an inert polycarbonate medium. The cells are cultured at the air-liquid interphase in a serum-free culture environment. Rapidly proliferating preparative keratinocyte cultures generate epidermal cells which are seeded on inert filter substrates. They are then raised to the air-liquid interface in a humidified-air incubator and the basal cells are fed by nutrient medium through the filter substratum (Abdallah et al., 2015a). A stratified epidermis is formed after 14 days which closely resembles human skin in terms of morphology, lipid composition, and differentiation markers (Abdallah et al., 2015a; Schäfer-Korting et al., 2008). Furthermore, studies have shown that 3D-HSE models display similar activity of enzymes involved in xenobiotic metabolism to those seen in real human skin samples (Hewitt et al., 2013; Wiegand et al., 2014).

Schafer-Korting et al. compared the permeability of three RHE models using 9 different compounds varying in physicochemical properties, including testosterone, caffeine, and benzoic acid (Schäfer-Korting et al., 2008). This was compared to the permeability of excised

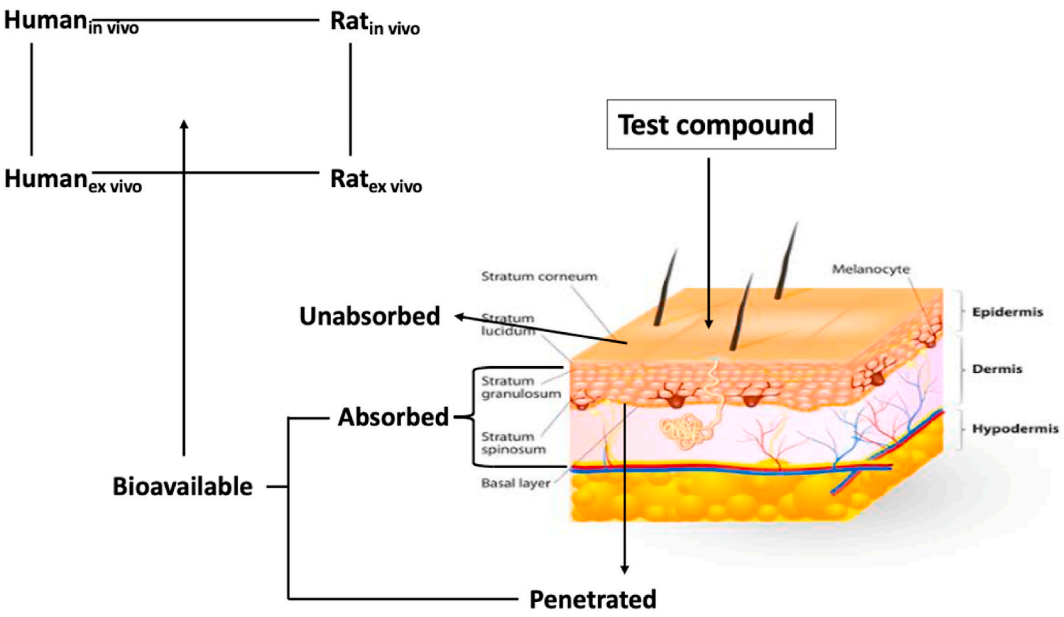

Fig. 4. Illustration of the parallelogram approach. Figure adapted from Knudsen et al. (2019)..

human epidermis and pig skin. Results showed that the 3D-HSE model proved more permeable than the human epidermis and pig skin, with the permeation coefficient (P_{app}) for one of the HSE models ranging from two– to seven-fold higher compared to P_{app} values of human epidermis sheets (HES), with the other 3D-HSE models tested showing a greater overestimation compared to HES. It is important to note that since this study was performed, available 3D-HSE models have improved according to developers, with models possessing "enhanced barrier function" now available. Notwithstanding this, the ranking of substance permeation through the human epidermis was similar to that of the HSE models as well as the pig skin, making 3D-HSE models feasible for *in vitro* dermal penetration studies (Schäfer-Korting et al., 2008). Since then, validated 3D-HSE protocols have been approved by the OECD and European Centre for Validation of Alternative Methods (ECVAM) for testing of skin irritation, phototoxicity and corrosion by xenobiotic chemicals (Abdallah et al., 2015b; OECD, 2004a, 2004b).

The second type of 3D-HSE models are full-thickness (FT) models. These models consist of an epidermis, made up of keratinocytes and fibroblasts, a basement membrane, and a dermis. FT models present morphology and tissue functionality similar to those of human skin. For the prediction of biotransformation-linked toxic endpoints, the FT skin models may be better suited than RHE models, as the biotransformation of compounds within the skin can vary between the major cell types that make up the skin (Ackermann et al., 2010).

Ackerman et al. tested the percutaneous absorption of the Phenion® FT skin model (full thickness HSE model) for four compounds, namely the OECD recommended reference compounds: caffeine, benzoic acid, and testosterone, as well as nicotine (Ackermann et al., 2010; OECD, 2004b). The absorption of testosterone and caffeine was compared to the absorption of pig skin. Results showed that the FT models were more permeable than pig skin (P_{app} values for FT models were 6–25 fold higher than th_{ose} obtained for pig skin), while still being comparable to RHE models when compared to previous studies, showing good data reproducibility (Ackermann et al., 2010).

Methods using 3D-Human Skin Equivalent (3D-HSE) models (RHE and FT types) have been developed for the evaluation of human dermal exposure to halogenated flame retardants i.e. brominated and chlorinated organophosphate flame retardants (Abdallah et al., 2016, 2015b). Additionally, methods using 3D-HSE models (FT models) have been developed for evaluation of dermal toxicity, e.g. of PFAS (Han et al., 2020) as well as for an *in vitro* genotoxicity assay, 3D Skin Comet assay for dermal exposure (Reisinger et al., 2018).

A comparison of two commercially available 3D-HSE models and human *ex vivo* skin, found no statistically significant differences when investigating the dermal bioavailability of BFRs at two exposure levels (500 ng/cm^2 and 1000 ng/cm^2). Comparison of the permeation coefficients revealed that the P_{app} for 3D-HSE models were only 1.1–1.3 times higher than those observed for *ex vivo* skin (Abdallah et al., 2015b). Similar results were obtained when comparing the dermal permeation of chlorinated organophosphate flame retardants (PFRs) using a 3D-HSE model, with that observed using human *ex vivo* skin. The difference in the absorbed fraction of the tested chemicals was 1.2–5.4% higher for 3D-HSE models compared to *ex vivo* human skin (Abdallah et al., 2016). While both studies found the 3D-HSE model showed less barrier function than *ex vivo* human skin, the differences were not statistically significant ($P > 0.05$) (Abdallah et al., 2016, 2015b).

As mentioned above, while they have not yet been employed to measure dermal uptake of PFAS, 3D-HSE models have been used to evaluate the dermal toxicity of PFCAs. This was done by repeated topical application for 6 days of two low dosages (0.25 mM and 2.5 mM) of PFPeA, PFHpA, PFHxA, and PFOA onto EpiDermFT full thickness models. This study also included *in vivo* tests, where rats were treated with PFHpA at different doses (0, 250 and 1000 mg/kg b.w.) for 6 h a day for 2 weeks. Each application site was shaved before application and covered with bandages after application. The results of the *in vitro* study revealed that 2.5 mM PFOA could induce keratinocyte membrane perturbation, however this was not found sufficient to cause cell death. Additionally, 2.5 mM PFOA-treated tissues showed decreased skin thickness compared to controls. The *in vivo* study revealed an 86% mortality in the 1000 mg/kg/day group during the treatment period with signs of ulceration and inflammatory cell infiltration at the application cites. The lower dose group (250 mg/kg/day) however, showed minimal to slight epidermal hyperplasia and parakeratosis, although minimal to slight ulceration was seen in a minority in the group (Han et al., 2020).

5. Dermal bioavailability and bioaccessibility of halogenated organic pollutants and their significance to overall human exposure

While little is currently known about dermal absorption of PFAS, recent studies on other halogenated organic pollutants exposure suggest

dermal absorption could be a significant contributor to body burdens e.g. for chlorinated and brominated flame retardants (Abdallah et al., 2016; Abdallah and Harrad, 2018).

A study on exposure of Americans to polybrominated diphenyl ethers (PBDEs) using a PK model assumed that 3% of PBDEs in soil that adhered to skin were absorbed. The study found that dermal uptake was the second biggest contributor to the total body burden of PBDEs (following dust ingestion) (Lorber, 2008). Similarly, Trudel et al. investigated total consumer exposure to PBDEs, both in North America and Europe as well as the most important exposure pathways. They found that for North Americans, dermal uptake from dust could play a significant role (up to 40% for those exposed at the 99th percentile level) in total human exposure to PBDEs (Trudel et al., 2011). These studies based their dermal absorption factor on reported dermal absorption of either dioxins or polychlorinated biphenyls from soil in laboratory animal models and neither study considered possible dermal absorption from contact with BFR-treated materials (Lorber, 2008; Trudel et al., 2011).

Other *in vitro* studies on BFR exposure via dermal uptake showed that their absorption varied according to the physicochemical properties of each compound. The general trends seen were a negative correlation between a compound's absorbed fraction and its log K_{OW}, while a positive corelation was observed between log K_{OW} and the fraction retained within the skin tissue (Abdallah and Harrad, 2018; Frederiksen et al., 2016). Moreover, Abdallah and Harrad (2018) found that the total dermal uptake of BFRs was not only caused by contact with dust but also, and to a greater extent, via contact with treated fabrics in consumer products, such as sofas. This study used exposure parameters from the USEPA exposure factors handbook and typical apparel in summer and winter to estimate the exposure to dust and fabric. They assumed contact with indoor dust to be for 6 h/day for adults and 9 h/day for toddlers (assuming toddlers have greater proximity to the floor and lower hygiene standards) and contact with sofa fabric for 4 h/day for adults and 2 h/day for toddlers (assuming toddlers display greater physical activity than adults – i.e. less sedentary). In fact, they considered the values assigned to dermal uptake from dust in previous studies to be overestimates, especially for adults. This then led to an inflated estimation of the relative contribution of the dermal pathway via contact with dust to the overall daily exposure to BFRs. Conversely, in some cases the total dermal uptake of BFRs was an underestimation due to overlooking dermal uptake via contact with consumer products (e.g. fabrics), according to their findings. For example, based on a conservative estimate, they found the dermal uptake of penta-BDE for an adult via contact with a flame-retarded sofa to be 8.1 ng/kg bw/day during summer which exceeds the estimated average total exposure via all pathways of American adults by Lorber (5.4 ng/kg bw/day) and Trudel et al. (3.1 ng/kg bw/day) (Abdallah and Harrad, 2018; Lorber, 2008; Trudel et al., 2011). However, the contribution of dermal uptake of toddlers via contact with a sofa was less significant compared to the adult group. Abdallah and Harrad found the dermal uptake for toddlers (1–5 years) to be 6.1 ng/kg bw/day, which was lower than the total exposure of toddlers (1–5 years) reported by Lorber (34.5 ng/kg bw/day) and Trudel et al. (10 ng/kg bw/day). These latter two studies included: BDE-28, BDE-47, BDE-99, BDE-100, BDE-153, BDE-154, BDE-183, and BDE-209; while the study by Abdallah and Harrad included the same compounds excluding BDE-183, and BDE-209 which could explain the difference in results to some extent (Abdallah and Harrad, 2018; Lorber, 2008; Trudel et al., 2011).

Other studies have supported the potential importance of the dermal pathway (Liu et al., 2017; Watkins et al., 2011). A study of exposure to PBDEs in office environments revealed positive correlations between PBDEs in indoor dust, hand wipes and serum samples. This could either be explained by dermal absorption and/or ingestion due to hand-to-mouth contact (Watkins et al., 2011). Similarly, an estimation of human exposure to halogenated flame retardants using skin wipes, suggested that dermal absorption could be a significant route of human exposure (Liu et al., 2017).

For a chemical present in a matrix such as dust or a consumer product/material to become dermally bioavailable (i.e. transported through the skin and reach the bloodstream), it has first to be released into surface skin fluids (a mixture of sweat and sebum), as it is from such skin fluids that dermal uptake occurs. The total mass of a given chemical that is released from the source matrix into the body fluid (referred to as bioaccessible) will likely not all be absorbed through the skin and reach the circulation. Therefore, bioaccessibility data in combination with dermal absorption data is needed to establish the ability of a chemical present in a matrix to be released from that matrix and become available for absorption by the skin (Pawar et al., 2017). Assessment of the dermal bioavailability of BFRs found a negative correlation between dermal penetration and the octanol:water partition coefficient (expressed as Log K_{OW}) (Abdallah et al., 2015b). Conversely, a positive correlation was found between Log K_{OW} and the fraction of BFRs remaining within the skin tissue after 24 h exposure. This is likely caused by the time needed for more hydrophobic and higher molecular weight BFRs to reach from the stratum corneum through the aqueous-based epidermis implying higher resistance to diffusion of highly hydrophobic compounds (Abdallah and Harrad, 2018).

Furthermore, studies on different dosing vehicles used when determining dermal penetration of chemicals, found small differences in percutaneous penetration when exposing skin to chemicals dissolved in acetone, 30% acetone in water, and 20% Tween 80 in water. Although the differences were not statistically significant, more hydrophilic compounds showed higher penetration abilities in 20% Tween 80 in water. This could possibly be relevant to human exposure as several polar and non-polar compounds are naturally present in human skin surface film liquid (sweat/sebum mixture) (Abdallah et al., 2015b; Abdallah et al., 2016).

Pawar et al. (2017) assessed the bioaccessibility of FRs. The study found that compound-specific physicochemical properties (mainly log K_{OW} and water solubility) as well as the composition of the synthetic sweat/sebum mixture used were the factors that most greatly influenced the bioaccessibility of the target compounds. The compounds examined were: α-, β-, and γ-hexabromocyclododecane (HBCDD), tetrabromobisphenol A (TBBPA), tris-2-chloroethyl phosphate (TCEP), tris (1-chloro-2-propyl) phosphate (TCIPP), and tris- 1,3-dichloropropyl phosphate (TDCIPP). Additionally, this study established that the presence of cosmetics such as moisturising cream, sunscreen lotion, shower gel, and body spray significantly impacted the bioaccessibility of all but one (TBBPA) of the target FRs. The presence of all tested cosmetics decreased the bioaccessibility of HBCDs while an increased bioaccessibility of TCEP, TCIPP, and TDCIPP was observed when combined with shower gel and sunscreen (Pawar et al., 2017). A different study (Abdallah and Harrad, 2018) found that a further factor affecting dermal absorption of BFRs, was the type of matrix with which dermal contact occurs (dust or fabrics). The study revealed greater dermally absorbed mass after 24 h contact with fabrics in comparison to contact with indoor dust. However, when expressed as a percentage of the applied dose in the contact material, the fraction absorbed from fabrics was significantly lower than from indoor dust. Thus, they concluded that when expressed as a percentage of the applied dose, dermal absorption was influenced by both the applied dose and the contact matrix. Additionally, the degree of skin hydration during exposure also affected the dermal uptake of BFRs. More "sweaty" skin led to higher absorption of PBDEs and hexabromocyclododecane (HBCDD), likely caused by the lipophilic sebum components in the skin fluid mixture (Abdallah and Harrad, 2018).

6. The potential of dermal uptake as a pathway of human exposure to PFAS

Few studies have explored the possible dermal penetration of PFAS. An *in vitro* study of the permeability of APOF through human skin used human epidermal membranes and degassed physiological saline (0.9% NaCl) as receptor fluid. Analysis of the receptor fluid revealed that only

0.048 ± 0.01% of the applied APOF had penetrated the skin after a 48 h exposure period (Fasano et al., 2005). Importantly, the use of saline solution as receptor fluid does not accurately mimic actual biological conditions. This could reduce diffusion of chemicals to the receptor fluid leading to an underestimation of dermal absorption (Abdallah et al., 2015a; Jakasa and Kezic, 2008; OECD, 2011). Furthermore, this study only analysed the receptor fluid samples, and not the skin samples themselves, skin washes, or donor/receptor compartment washes.

A study by Franko et al. (2012) used both *ex vivo* human full-thickness and epidermis skin samples exposed to a single dose of 50 μL solution 0.1 mg/μL PFOA in acetone solution for 24 h. HEPES-buffered Hanks balanced salt solution (HBSS) consisting of 5.96 g HEPES, 0.32 g $NaHCO_3$, and 0.05 g gentamicin sulphate added to 1 L of Hanks balanced salt solution (pH adjusted to 7.4) was used as a receptor fluid. The skin patches were washed with solvent prior to analysis of the receptor fluid and skin samples. Analysis of the receptor fluid samples revealed that 24% of the applied PFOA had penetrated human skin epidermis samples after 24 h of exposure. When including PFOA found within the skin samples (skin depot), the total absorbable fraction of PFOA was found to be 48% and 69% for epidermis and full-thickness skin samples respectively (Franko et al., 2012). Varying the pH of the PFOA dosing solutions revealed a great difference in the median permeability coefficient of the free acid (5.5×10^{-2} cm/h) and the charged species (4.4×10^{-5} cm/h) (Franko et al., 2012). Thus, the effect of PFOA ionisation state on dermal penetration could explain the different results of these two studies (Fasano et al., 2005; Franko et al., 2012).

Two studies from the same laboratory examined the effects of topically applied PFOA and PFBS in murine models (Shane et al., 2020; Weatherly et al., 2021).The first study topically applied PFOA in acetone on the dorsal surface of each ear in concentrations ranging from 0.5 to 2% w/v. After 4 days of dermal exposure (2%) the IgM antibody response was significantly reduced. Additionally, dermal exposure to PFOA caused a significant decrease in thymus (1 and 2%) and spleen weight (0.5–2%) as well as an increased liver weight (0.5–2%). This study raises concern on the potential adverse effects of dermal exposure and the immunotoxicity of PFOA after dermal exposure (Shane et al., 2020). Similarly, in the other study PFBA in acetone was topically applied on the dorsal surface of each ear in concentrations ranging from 3.75 to 7.5% v/v for 28 day or 15% v/v for 15-day exposures. At all exposure levels significant increases in liver and kidney weights were seen as well as altered serum chemistries. The adverse effects seen after dermal exposure to PFBA were similar to those reported for oral PFBA exposure and dermal and oral PFOA exposure. The authors note that as the study was conducted for hazard identification the highest non-overtly toxic concentrations were selected for exposure (Weatherly et al., 2021). It is important to keep in mind that mouse skin differs from human skin in relation to skin barrier function, hair follicles etc. However, murine models can still give a good indication for potential human exposure.

Although little is known about the function of influx transport proteins in human skin, e.g. their interaction in uptake of xenobiotics, various transporter proteins have been identified in human skin. For example, the solute carrier transporter, SCL21 family genes encode various organic anion transporter polypeptides (OATP) family transporters, which can mediate absorption, distribution, and excretion of an array of environmental toxins and clinically used drugs (Fujiwara et al., 2015). The expression of various OATPs as well as organic anion transporters (OAT, e.g. OAT4) has been confirmed in the skin (Fujiwara et al., 2015; Schiffer et al., 2003). Interestingly, many of the same OATPs are expressed in the liver, where they have been demonstrated to be able to transport PFBS, PFHxS, and PFOS, as well as PFOA and PFNA (Zhao et al., 2016). Furthermore, OAT4 has been linked to placental transfer of PFAS, with studies suggesting the chain length of a PFAS being related to its binding affinity to OAT4 (Kummu et al., 2015; Lu et al., 2021).

Hand wipes have been used to evaluate PFAS exposure through dermal and hand-to-mouth contact. In a study conducted in Oslo, Norway, hand wipe samples collected to evaluate indoor PFAS exposure and composite samples from both hands of 60 adults were analysed (Poothong et al., 2019). The exposure via dermal absorption was calculated based on body weight, the results of the hand wipe samples, time (set to 24 h exposure), and fraction of PFAS absorbed through the skin over 24 h (48%), which was based on the previous findings of Franko et al. (2012) on dermal absorption of PFOA. These calculations generated estimates of the daily dermal uptake of PFOA and PFOS of 11 ng (kg bw)$^{-1}$ and 3.6 ng (kg bw)$^{-1}$ respectively (Poothong et al., 2019). Importantly, the Poothong et al. (2019) study only accounted for the PFAS found on hand wipes and did not take into account the presence and dermal uptake of PFAS on other areas of the skin, for example due to the use of cosmetics. Additionally, the study was based on samples collected at one time point only; and therefore, did not account for daily/temporal fluctuations (e.g. seasonal differences in dust loading and varying use of products on different days and/or seasons). Moreover, assuming a 24 h exposure to a fixed dose does not reflect variations in dust/PFAS loading on the hands due to washing frequency and/or hand-to-mouth behaviour and other hand contact events. Therefore, the actual dermal uptake and relative significance of dermal exposure to PFAS could deviate substantially from these estimates.

A recent Spanish study on PFAS concentrations in breast milk also estimated the possible exposure routes associated with the breastmilk PFAS levels (Serrano et al., 2021). The study participants filled out a questionnaire disclosing information such as their socio-demographic characteristics, diet, lifestyle, and use of personal care products. A multivariate regression analysis was then used to evaluate factors related to individual and total PFAS concentrations. This revealed a positive association between PFAS levels in breast milk and the use of various personal care products suggesting dermal uptake as a source of PFAS exposure. Positive association was seen both for short- and long-chain PFAS and personal care products such as cosmetics, skin care and hair products, perfume and deodorant. Additionally, foundation use was positively associated with the sum of PFOA, PFOS, PFNA and PFHxS concentrations. The authors discuss how the current knowledge regarding dermal exposure to PFAS have led to it being a considered as minor contribution to total human exposure in many exposure assessments. They suggest this should be reconsidered as newer studies such as this one identify positive associations between PFAS levels and the use of personal care products. Furthermore, various studies have identified PFAS in products that come in contact with the skin i.e. personal care products (Glüge et al., 2020; Schultes et al., 2018). The authors do acknowledge the small sample size of this study (n = 82) as a limiting factor as it reduces the capacity to detect possible determinants of PFAS exposure, especially for compounds with a low detection frequency. Additionally, the questionnaire used was not specifically designed for exhaustive investigation of sources of PFAS exposure which could have prevented identifications of other possible pathways. Finally, the large number of explanatory factors evaluated could have revealed some false statistically significant associations and that a possible bias may have resulted from a misreporting of dietary intakes and other factors. However, the authors state that misclassification was unlikely to be driven by exposure levels (Serrano et al., 2021).

Furthermore, biomonitoring studies from both Norway and Belgium have identified positive associations between PFAS (e.g. PFNA, PFTrDA, PFBS and 6:2 diPAP) serum levels and the use of personal care products (Colles et al., 2020; Thépaut et al., 2021).

7. Possible sources of human exposure via the dermal pathway

A growing number of studies reveal sources and scenarios for which dermal exposure to PFAS can occur. Studies on PFAS and their potential precursors in various consumer products and clothing could indicate dermal absorption as a potentially important route of human exposure (Fujii et al., 2013; Greenpeace, 2016, 2013; 2012; Schultes et al., 2018;

van der Veen et al., 2020; Whitehead et al., 2021). A report on several cosmetics revealed that some products, e.g., foundations and powders, contained 25 different PFAS. The compounds most frequently detected in the samples were PFHpA and PFHxA, along with polyfluoroalkyl phosphate esters (PAPs). Up to 470 μg g^{-1} of total PAPs were identified in products that listed combinations of PAPs as an ingredient. However, the total identified PFAS only represented a small fraction of the extractable organic fluorine (EOF) in the samples when analysed by combustion ion chromatography (CIC) (Schultes et al., 2018). Moreover, a recent study on fluorinated compounds in North American cosmetics identified up to 13 different PFAS in various cosmetic products such as mascaras, foundations, and lip products. Targeted PFAS analysis was conducted using LC-MS/MS and GC/MS, while total (organic and inorganic) fluorine concentrations were measured by particle-induced gamma-ray emission (PIGE) spectroscopy (Whitehead et al., 2021). Another study reported total PFCA concentrations to range from not detected up to 5.9 μg g^{-1} in cosmetics and up to 19 μg g^{-1} in sunscreens (Fujii et al., 2013). This study did not include the analysis of PAPs or EOF, thus the total concentration of fluorinated compounds in the samples tested is unknown. Moreover, a recent paper highlighted the wide range of products that contain PFAS (Glüge et al., 2020). The authors identified many consumer products that come in contact with the skin such as: hand sanitiser, cosmetics (body lotion, foundation, blush, eye cream, eye pencil, eye shadow, mascara, lipstick, moisturiser, nail polish, makeup remover, powder, shampoo, hair cream, conditioner, hair spray, hair mousse, shaving cream, and sunscreen), as well as guitar strings and piano keys.

Another potential source of exposure is dermal contact with water repellent clothing, e.g., rain jackets, rain pants, and footwear. Three different studies by Greenpeace found PFAS in outdoor clothing and hiking gear. When testing various samples of outdoor clothing they found that most of the samples contained some form of PFAS, such as PFOA, PFBS, and PFHxA, as well as 8:2 FTOH and 6:2 FTOH (Greenpeace, 2016, 2013, 2012). Furthermore, a recent study on the effect of weathering on water repellent clothing revealed an increase in concentrations of most perfluoroalkyl acids (PFAAs) in weathered articles compared to those in the original unweathered samples. Moreover, an increase in volatile PFAS such as 6:2 FTOH and 8:2 FTOH was also seen in some samples after weathering. The authors suggest a few explanations for the increase in volatile PFAS caused by weathering. One proposed explanation was the degradation of fluorotelomer based polymers with fluorinated alcohol and/or acrylate side chains. Other suggestions were that previously non-extractable organic fluorine was rendered extractable by weathering, or that other unknown precursors were degrading or transforming to the identified volatile PFAS (van der Veen et al., 2020). A study of 160 textile samples from the United States compared PFAS concentrations determined via two different extraction methods. Firstly, the textile samples were extracted by a simple solvent extraction and the second used an oxidative treatment. This second method, the total oxidizable precursor (TOP) assay helps with the analysis of unknown precursors. The samples included water repellent textiles, flame retarded textiles and infant clothing. Before oxidation, the sum concentration of 13 PFAAs (C4, C6, C8 and C10 PFSAs and C4–C12 PFCAs) ranged from <LOD to 63.7 μg/m^2 (mean value: 3.18 μg/m^2), with the highest PFAS concentrations seen in flame retarded textiles, followed by water repellent textiles and infant clothes. In samples analysed after the oxidative treatment, the sum PFAA levels were 10-fold higher than in the samples before oxidation, suggesting the use of PFAA precursors in textiles. This study estimated the dermal exposure to PFAAs in infant clothing based on the concentration of PFAAs found in the clothing, the total body surface for infants (2543 cm^2), the daily migration rate of PFAAs from textiles to the skin (0.001 1/day) and the penetration rate of PFAAs into the body (0.5, unitless). None of the PFAAs exceeded the proposed reference dose (RfD) of 20,000 pg/kg bw/day suggested by the USEPA for PFOA and PFOS in 2016 with the mean exposure doses of total PFAAs calculated based on values after TOP assay being 69.9 pg/kg bw/day (maximum 622 pg/kg bw/day) (Zhu and Kannan, 2020). Dermal exposure was only estimated based on PFAA levels from infant clothing which had the lowest PFAS concentrations of the three types of fabric samples analysed. Additionally, the US EPA announced in 2021 that they will be re-evaluating the RfD for PFOS and PFOA based on scientific data and new analysis indicating negative health effects occurring at much lower levels of exposure than previously thought (U.S. EPA, 2021).

8. Summary and recommendations

Studies have identified many different PFAS-containing consumer products such as fabrics and cosmetics that can come in contact with the skin. Additionally, studies on other halogenated organic pollutants suggest that contaminated dust contributes greatly to dermal exposure of those contaminants with dust also being a source of possible PFAS exposure. Previous studies show that structurally related brominated and chlorinated chemicals are dermally bioavailable and can result in significant contributions to the body burdens of these hazardous chemicals. While this may indicate dermal exposure as an important pathway of exposure to PFAS, especially with dermally relevant consumer applications i.e., water-proof fabrics and cosmetics, it is difficult to estimate the dermally absorbed fraction of PFAS based on those of chlorinated and brominated FRs. This is due to the unique physico-chemical properties of PFAS (due to the strength of the C–F bond) and the diverse nature of PFAS in terms of the large number of chemicals with varying numbers of carbon atoms, fluorine content and functional groups leading to a broad spectrum of physico-chemical properties within PFAS. Thus, dermal uptake experiments are urgently required to address this crucial research gap and provide necessary information on the dermal flux and permeability coefficients of major PFAS in different homologue groups (e.g., C_4–C_{14}, PFAAs, PFSAs … etc). Such information can then be applied in QSAR-modelling approaches to estimate dermal permeability coefficients for structurally-related PFAS with an acceptable level of confidence based on the relative similarity of physico-chemical properties among chemicals within the same PFAS homologous group.

3D-HSE models mimic human skin and provide an effective and ethical alternative to the issues associated with human dermal absorption studies. Notwithstanding this, our understanding of dermal absorption of PFAS remains incomplete and experimental data scarce. As knowledge and understanding of the health impact of PFAS increases, it is increasingly important to fill the knowledge gaps that exist regarding human dermal exposure to these chemicals. In the near future, it is important to test the dermal absorption of these chemicals in order to better understand the contribution of this pathway to total human exposure to PFAS. Experiments evaluating the bioavailability of PFAS, both as complex mixtures and single compounds, are ever more feasible with the use of 3D-HSE models. In combination with experiments assessing bioaccessibility, the use of such models to evaluate dermal bioavailability will provide substantial meaningful insights into human dermal absorption of PFAS. Finally, studies mimicking real life exposure scenarios where 3D-HSE models are combined with sweat/sebum mixtures that mimic skin fluids, to test dermal uptake from PFAS-containing materials, should be undertaken. The results from these tests, along with PK models delineating the relationship between external exposure via multiple pathways to human body burdens, can then give a clear picture of the dermal absorption of PFAS and to what extent this contributes to total human exposure.

Credit author statement

Oddný Ragnarsdóttir: Investigation, Writing – original draft, Writing – review & editing, Visualization, Data curation. **Mohamed Abdallah:** Validation, Conceptualization, Writing – review & editing, Resources. **Stuart Harrad:** Supervision, Conceptualization, Writing –

review & editing, Resources.

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.

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