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Polycyclic aromatic hydrocarbon skin permeation efficiency *in vitro* is lower through human than pigskin and decreases with lipophilicity

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ABSTRACT

Polycyclic aromatic hydrocarbons (PAH) are persistent environmental pollutants, which occasionally appear as contaminants in consumer products. Upon dermal contact, transfer of PAH into the *stratum corneum* (s.c.) and migration through the skin may occur, resulting in this class of highly toxic compounds to become bioavailable. In this study, dermal penetration through human and porcine skin of 24 PAH, comprising broad molar mass (*M*: 152–302 g/mol) and octanol-water partition coefficient (log*P*: 3.9–7.3) ranges, was evaluated *via* Franz diffusion cell *in vitro* assays. More lipophilic and potentially more toxic PAH had decreased permeation rates through the rather lipophilic s.c. into the more hydrophilic viable (epi-)dermis. Furthermore, human skin was less permeable than pigskin, a commonly used surrogate in skin penetration studies. In particular, the s.c. of human skin retains a greater share of PAH, an effect that is more pronounced for smaller PAH. Additionally, we compared the skin permeation kinetics of different PAH in pigskin. While small PAH ($M < 230$ g/mol, log$P < 6$) permeate the skin quickly and are detected in the receptor fluid after 2 h, large PAH ($M > 252$ g/mol, log$P \geq 6$) do not fully permeate the skin up to 48 h. This indicates that highly lipophilic PAH do not become bioavailable as readily as their smaller congeners when transferred to the skin surface. Our data suggest that pigskin could be used as a surrogate for worst case scenario estimates of dermal PAH permeation through human skin.

1. Introduction

Polycyclic aromatic hydrocarbons (PAH) are associated with numerous health risks (Kamal et al., 2015). Many PAH are considered to be potentially carcinogenic (IARC, 2010, 2018; Kamal et al., 2015; Kim et al., 2013; Rocha et al., 2021; WHO, 2010), including the risk of inducing skin cancer after dermal exposure (Boffetta et al., 1997). For example, benzo[*a*]pyrene (B[*a*]P) is classified as a class 1 carcinogen, whereas certain dibenzopyrenes are suspected to be even more potent toxins (Collins et al., 1998). Apart from cancer, PAH are also linked to endocrine disruption (Zhang et al., 2016), heart disease (Burstyn et al., 2005) and immunosuppression (van Grevenynghe et al., 2005), among other adverse effects (Sousa et al., 2022; WHO, 2010). Hence, multiple regulations have been implemented to limit the exposure to PAH (EC, 2006; EC, 2013; EC, 2023; US-EPA, 2021). Nonetheless, as persistent organic pollutants, PAH are ubiquitous in the environment (Haney et al., 2020; Hutzler et al., 2011; Lao et al. 2018a, 2018b; Whitehead et al., 2011) and occasionally also found as contaminants in consumer products, in particular those containing carbon black or extender oils (Alawi et al., 2018; Bartsch et al., 2017; Folgado de Lucena et al., 2018). When PAH come into contact with skin, they can become bioavailable by diffusion through the stratum corneum (s.c.) into the viable epidermis

Abbreviations: B[*a*]P, benzo[*a*]pyrene; FDC, Franz diffusion cell; GC-MS/MS, gas chromatography coupled to tandem mass spectrometry; log*P*, logarithmic octanol-water partition coefficient; *M*, molar mass; OECD, Organisation for Economic Co-operation and Development; PAH, polycyclic aromatic hydrocarbons; s.c., *stratum corneum*; SI, supporting information; TEWL, trans-epidermal water loss.

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and dermis layers (Bartsch, 2018; Bartsch et al., 2016; Simon et al., 2023b).

Skin penetration is investigated either *in vivo* or *in vitro*. *In vivo* studies come with the drawback of exposing humans or animals to harmful substances and avoidable risks. Hence, *in vitro* studies involving the well-established Franz diffusion cell (FDC) assay remain an important pillar of skin penetration research (Franz, 1975; Ng et al., 2010). The FDC provides a simple set-up where the target substance, usually embedded or dissolved in a matrix, is spiked onto skin or skin models. The receptor chamber beneath is filled with a water-based fluid to mimic the subcutaneous layers and to provide a reservoir for fully permeating substances. The distribution of the substance within the skin and its concentration in the receptor compartment after specified incubation times give insights into the skin permeability.

The gold standard for FDC assays is human skin. However, human skin is not always readily available because it must be donated from plastic surgery patients (Bartsch et al., 2016; Hagvall et al., 2021) or corpses (Ellison et al., 2020, 2021). Synthetic or lab-grown skin models are alternatives that find increasing utilization in research (Lemoine et al., 2021; Ng et al., 2010), but are not yet recommended for skin permeation studies within a regulatory context (OECD, 2011). Pigskin is the most common alternative to human skin because it shares crucial properties with human skin. Thus, pigskin often provides comparable results for penetration-relevant parameters such as lag time and diffusion or partition coefficients (Gerstel et al., 2016; Herkenne et al., 2006; Rothe et al., 2017; SCCS, 2010). In addition, its procurement is relatively easy (Hopf et al., 2020). Yet, differences between human and pigskin remain (Khiao In et al., 2019). Studies have shown that pigskin is more permeable for certain substances than human skin (Barbero and Frasch, 2009; Rothe et al., 2017). A comprehensive comparison of the penetration of PAH into human and pigskin has not yet been reported.

It has been suggested that higher molecular mass (M) PAH (five or more rings: large PAH) feature lower penetration rates and fluxes through the skin than PAH with lower M (two to three rings: small PAH, Moody et al., 2011; Sartorelli et al. 1998, 1999, 2001). However, these studies either rely on small sample sizes ($n \leq 2$), involved non-human skin or reported PAH concentrations only in the receptor fluid, thus lacking information about the distribution profiles within individual skin compartments.

Here, we compiled the data of several FDC assays from a set of 24 dermally applied PAH of various ring numbers (2.5–6, $M = 152$–302 g/mol, Table A1 and Figure A1 in the Supporting Information (SI) A). Human and pigskin were incubated with PAH solutions in acetonitrile for 24 h. Pigskin was additionally incubated for various incubation times (2 h, 4 h, 16 h, 48 h), yielding insights into the migration kinetics. Subsequently, the five upper s.c. layers of treated skin samples were tape-stripped to analyze them separately from the remaining skin and the receptor fluid for their PAH content. Quantification was realized by gas chromatography coupled to tandem mass spectrometry (GC-MS/MS). Finally, the distribution of PAH in the skin layers was correlated to their logarithmic octanol-water partition coefficients (log$P$).

2. Methods

The data presented here is a compilation of quality controls which were run in parallel to FDC assays aiming to investigate dermal PAH penetration from consumer products with foreseeable skin contact (Bartsch et al., 2016). The concentration of each PAH applied to the skin specimens in acetonitrile was set at 1000 ng/ml. The method used and the materials and chemicals applied were published in the former study. Below, the method is briefly summarized for clarity.

2.1. Skin

Human skin was obtained from plastic surgery at Charité, Berlin and originated from female abdomen. The proposal to conduct permeation studies with human skin samples was reviewed and approved by an independent ethics committee (Ethics Commission Charité, Berlin, No. EA2/090/14, July 22, 2014). Flank pigskin was obtained from VION food GmbH (Perleberg, Germany) and delivered on ice. The un-scalded skin was taken from deceased pigs that would have not been used for food production. Both skin types were stored at −20 °C until use.

2.2. Franz diffusion cell assay

An FDC consists of a donor chamber for the application of a target substance in a matrix and a receptor chamber. The receptor chamber is filled with a liquid and jacketed by a water circulation system to keep the skin at a constant temperature. The skin or skin model is placed over the receptor chamber and fixed by the donor chamber cap with a clamp. Substances that reach the receptor fluid can be considered to become bioavailable. In the present study, the temperature of the receptor compartment was held at 33 ± 1 °C, which corresponds to average skin surface temperature of 32–35 °C (Lee et al., 2019). The receptor chamber was filled with an isotonic saline solution (9 g/l sodium chloride), which is considered to be a good approximation for hypodermal bodily fluids (Hoorn, 2017).

The skin was cut with a dermatome to a thickness of 300 μm and placed atop the receptor chamber. The donor cap was fixed onto the skin, resulting in an exposure area of 1.76 cm^2. The trans-epidermal water loss (TEWL) was measured to ensure skin integrity according to guideline 428 of the Organisation for Economic Co-operation and Development (OECD, 2004). If the TEWL of a skin sample was greater than 30% of the mean TEWL for the specific skin type as previously confirmed by validation experiments, the skin specimen was eliminated from the study (Bartsch et al., 2016). 50 μl of a solution containing a mixture of PAH in acetonitrile (1000 ng/ml, see Table A1 of SI A for a list of all 24 PAH) were applied onto the skin (corresponding to a dermal dose of 28 ng/cm^2) and incubated for the denoted time intervals (2–48 h, Table 1). For negative controls, 50 μl of pure acetonitrile were applied.

After the specified incubation times, all samples were spiked with internal standards (selected deuterated PAH, assignment of analytes to internal standards: Table A1 of SI A). The donor chamber was rinsed with saline solution (9 g/l sodium chloride), and the skin was removed from the assembly and stripped with five tape strips, which were then pooled. One tape strip was shown to remove one layer of the s.c. (Simon et al., 2023a), thus, the five upper s.c. layers were analyzed collectively. The tape strips were extracted using acetonitrile, which was re-extracted with *n*-hexane. This double extraction proved beneficial in minimizing matrix effects caused by the extraction of adhesive from the tape. The remaining skin was extracted using ethyl acetate and the receptor fluid was subjected to a solid phase extraction (reversed phase C18) followed by elution of the PAH with dichloromethane. All obtained extracts were then concentrated under a nitrogen stream, re-dissolved in acetonitrile and analyzed for their PAH content by GC-MS/MS. Further details on the measurement procedure are provided in a previous publication (Bartsch et al., 2016). This yielded PAH concentrations in three compartments: (i) upper s.c. (derived from five tape strips), (ii) remaining skin and (iii) receptor fluid.

Table 1
Number of replicates (n) of Franz diffusion cell assays performed per skin type and incubation time.

Incubation time	Origin of skin	n
2 h	pig	3
4 h	pig	3
16 h	pig	3
24 h	pig	9
24 h	human	13
48 h	pig	3

2.3. Data analysis

The data were analyzed using the statistical programming language R (version 4.2.2). Data were subjected to a Shapiro-Wilk normality test. If the data was not normally distributed, the data was tested for outliers using the Grubb's outlier test. If the test was positive, the outlier was removed. The mean and standard deviation for each PAH, skin species, compartment and incubation time were calculated from the purged data set. The results of all statistical tests are summarized in the SI B (sheets 1 and 2). Based on the amount of each PAH that penetrated into the skin (sum of all compartments, including the receptor fluid), the distribution ratio of the PAH in each compartment was calculated.

Equation (1) was used to fit the data and highlight the relationship of two variables, y and x, with u and w as regression parameters:

$$y = u \cdot e^{-x} + w. \quad (1)$$

3. Results and discussion

We compared the migration of a broad range of PAH from acetonitrile into human skin and one of its most common surrogates in skin penetration studies, pigskin (SCCS, 2010; Simon and Maibach, 2000). Furthermore, PAH were incubated on pigskin for different periods to produce a kinetic profile for each of the investigated PAH. The smallest and least lipophilic PAH in this study are acenaphthylene (M = 152 g/mol, log$P$ = 4.0, Lu et al., 2008) and acenaphthene (M = 154 g/mol, log$P$ = 3.9, Lu et al., 2008), the largest and most lipophilic PAH are the dibenzopyrenes (M = 302 g/mol, log$P$ = 7.2–7.3, PubChem, 2023b, c, d, e; US-EPA, 2012). A comprehensive list of all 24 investigated PAH is provided in Table A1 and Figure A1 (SI A). For the investigated PAH, log$P$ and M are linearly related (Figure A2 and equation (A.1), SI A). The data comprising the quantified mass, amount and ratio of each PAH at each incubation time for both species and all compartments are summarized in Sheet 3 of SI B.

The regulatory limit of the PAH content in consumer products with prolonged or repetitive short-term dermal contact is 1 mg/kg (0.5 mg/kg for toys) in the European Union (EC, 2023). However, significantly higher values in the range of up to ca. 50–270 mg/kg were measured in certain consumer products in the past (Bartsch et al., 2017; BVL, 2017). When these products are in contact with skin, dermal exposure in the range of the spiked PAH doses applied in this study (28 ng/cm^2) are expected (for example, after 24 h of skin contact, a hammer handle containing 166 mg/kg B[a]P released 102 ng/cm^2 of this PAH, Bartsch et al., 2016). In different exposure scenarios, certain sub-populations such as firefighters can be dermally exposed to even higher amounts of airborne PAH (between 4 and 1200 ng/cm^2, Sousa et al., 2022).

Previous research has shown that high concentrations of multiple PAH as well as rather complex matrices as application media (Bourgart et al., 2019; Hopf et al., 2018) can both diminish dermal penetration rates of PAH. However, the applied doses in the present study were 50-fold (Bourgart et al., 2019) and 5000-fold (Hopf et al., 2018) lower than in those studies and PAH were applied in solvent-based solutions, not in complex mixtures. Here, we investigated the relative distribution in the different skin compartments. Hence, in the following sections, we base our discussion on relative amounts normalized to the total amounts of each PAH that penetrated into the skin. This also allows for a better comparison between individual PAH in the different compartments. In addition, it compensates for the relatively high deviations that were occasionally observed in the recoveries for PAHs detected in the skin and receptor compartments compared to the amounts applied to the skin (Sheet 3 of SI B).

3.1. Distribution of dermally applied polycyclic aromatic hydrocarbons in human and pigskin

The more lipophilic the PAH, the more it is retained by the s.c. (see Fig. 1 for incubation time of 24 h; for other incubation times in pigskin, see Figure A.3, SI A). When skin migration of B[a]P and dibenzopyrenes was compared in a previous study, a similar effect was observed (Bartsch et al., 2016). Since log$P$ and M of the investigated PAH are correlated linearly, these results can be equally interpreted for the molar mass. However, since hydrophilic substances exceeding M of the most massive PAH investigated in this study were shown to efficiently permeate the skin (Ellison et al., 2020, 2021; Potts and Guy, 1992), lipophilicity is presumably a more relevant factor.

We recently demonstrated that partition coefficients characterizing the distribution of PAH between squalane and the s.c. are dependent on M and log$P$ of the respective PAH (Simon et al., 2023b). Highly lipophilic PAH partition more readily from this lipophilic matrix (log$P$ = 15.6, ACD/Labs, 2021) into the s.c. Therefore, a similar but more pronounced trend is expected for acetonitrile (log$P$ = −0.3, PubChem, 2023a), since more lipophilic compounds should partition more readily from this rather polar solvent into the hydrophobic s.c. Similarly, partition coefficients of a wide range of lipophilic (log$P$ > 3) substances for aqueous matrices and the s.c. were shown to positively correlate with log$P$ (Figure A.4 in SI A). Regarding PAH permeation into deeper skin layers, the influence of the application medium should be less relevant. However, during incubation, acetonitrile could have penetrated into the skin, selectively enhancing the permeation of smaller, less lipophilic PAH.

Since the s.c. is a relatively lipophilic matrix (Raykar et al., 1988), more lipophilic PAH should also be retained more efficiently by the s.c.

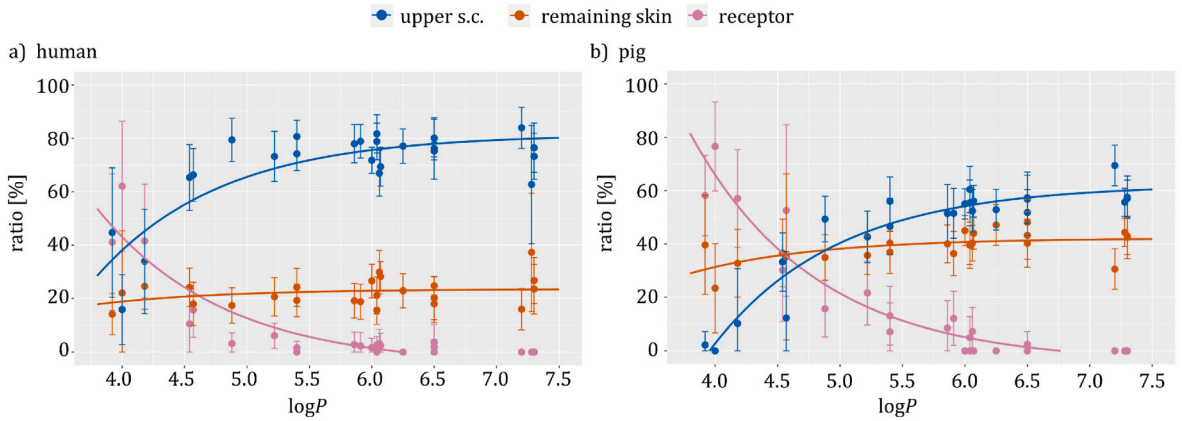

Fig. 1. Distribution ratio of polycyclic aromatic hydrocarbons in each compartment to total amount found in the skin (*stratum corneum* (s.c.), remaining skin) and receptor fluid after 24 h incubation time *versus* logarithmic octanol-water partition coefficient (log$P$). Means ± standard deviation. Curves represent data fitted to equation (1). a) Human skin (n = 13). b) Pigskin (n = 9). For other incubation times in pigskin (n = 3), see SI A, Figure A3.

at the s.c./viable epidermis boundary layer. This was confirmed experimentally: after 24 h incubation time, PAH with lower log*P* permeate the entire viable (epi-)dermis and are detected predominantly in the receptor fluid of the FDC. This effect is stronger for pigskin than for human skin. Contrarily, large PAH do not permeate the skin completely within the investigated time frame and were not found in the receptor fluid. Alternative receptor solutions that include solubility enhancers such as, for example, albumin might better dissolve these highly lipophilic PAH. Nonetheless, only minor permeation was observed even at very high applied dermal doses in the range of 6 μg/cm^2 when 50 mg/ml BSA were included in the receptor solution (Simon et al., 2023b). Since the rather aqueous layers of the viable epidermis and dermis are localized below the s.c., lipophilic substances would still have to overcome this barrier.

The ratio of the amount of each PAH in the three compartments — upper s.c., remaining skin and receptor fluid — can be approximated by fitting equation (1) to the data (Fig. 1; parameters: SI B, Sheet 4). When plotted, these curves help visualize the dependence of individual distribution ratios on log*P*. Furthermore, they show that the distribution ratios of PAH in each compartment approach a limit at about log*P* = 6.0. The distribution does not further change for larger PAH, regardless of the biological species (pig or human). A possible explanation could be favored partitioning of more lipophilic PAH into the rather lipophilic s.c. as opposed to the more aqueous epidermis beneath. Another hypothesis is a difference in the interaction with skin proteins. If larger PAH have higher affinities to these proteins, they would also be retained stronger. In principle, further physico-chemical properties could also modulate the penetration process. For example, it was shown that the molecular volume correlates with the flux of PAH through the skin, although we found no statistically relevant differences in our data (Alalaiwe et al., 2020).

The fraction detected in the remaining skin does not change substantially with log*P* values for either human or pigskin. The applied tape stripping procedure involving five tape strips only removes the five upper s.c. layers from the remaining skin (Simon et al., 2023a), which thus contains a large part of the s.c. as well as the s.c./viable epidermis boundary layer. Hence, both small and medium PAH that penetrate into the viable epidermis as well as large PAH, that are predominantly retained in the s.c. are found in this compartment.

3.2. Comparison of PAH permeation through human and pigskin

Human skin retains small PAH more effectively than pigskin. This is reflected in the greater share of small PAH in the receptor fluid after an incubation time of 24 h in pigskin than in human skin (Fig. 1). The same is true for the amount residing in the remaining skin, which on average is lower for human skin. These results are in accordance with previous studies on lipophilic compounds. For example, a study on heptane, hexadecane and xylene (log*P* > 3) found higher permeability coefficients for these three substances in pigskin than in human skin (Singh et al., 2002).

The regression curve (equation (1)), fitting the ratios of the relative amounts of PAH detected in human *versus* porcine s.c. as a function of log*P* asymptotically reaches a limit at 0.60 for highly lipophilic PAH (Fig. 2; values: Sheet 5, parameters of fit: Sheet 6 of SI B). Hence, for more lipophilic PAH, porcine s.c. better emulates human s.c. It was formerly demonstrated that lipids in the human s.c. are packed differently (orthorhombic lateral packing) and denser than in porcine s.c. (hexagonal lateral packing) even though the molar ratio of different lipids is approximately equal (Caussin et al., 2008). These more closely packed lipids could slow down the diffusion of smaller PAH in human s.c. Larger PAH, on the other hand, are retained more similarly by the s.c. of both species and the difference is less pronounced. We previously determined diffusion coefficients of PAH in porcine s.c., which were similar for PAH with log*P* > 4, while naphthalene (log*P* = 3.4) showed a significantly higher diffusion coefficient (Simon et al., 2023b). This might hint to a change of the diffusion mechanism above a given log*P* value and thus more closely related diffusion rates in human and porcine s.c.

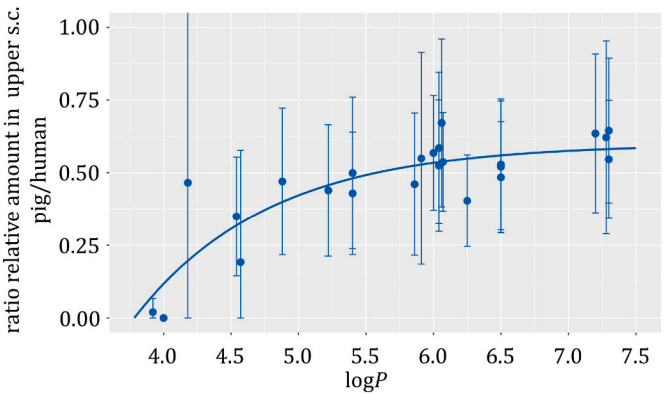

Fig. 2. Ratio of the relative amount of polycyclic aromatic hydrocarbons (PAH) found in human *stratum corneum* (s.c.) to the amount found in porcine s.c. at 24 h incubation time *versus* the logarithmic octanol-water partition coefficient (log*P*) of PAH. Means ± standard deviation. Curve represents data fitted to equation (1). Upper limit of fluorene standard deviation: 1.45.

The anatomical site where the skin samples were obtained, however, does not seem to play a significant role in the composition of the s.c., as previous studies have shown (Khiao In et al., 2019). Furthermore, it has been reported that freezing does not significantly alter the penetration characteristics of human skin (Jacques-Jamin et al., 2017). Contrarily, pigskin was shown to be affected: freezing and storage at −20 °C increased the permeability up to 25% compared to fresh skin of the lipophilic model substance methyl salicylate (Morin et al., 2023). This is supported by a direct comparison of rat, rabbit and pigskin revealing the latter to be especially vulnerable to freezing (Sintov and Greenberg, 2014). Since we used frozen skin specimens, this effect could add to the observed higher permeation rates of PAH through pigskin compared to human skin.

3.3. Skin penetration kinetics of polycyclic aromatic hydrocarbons

In general, less lipophilic PAH permeate the skin faster than more lipophilic PAH. This is evident from the relatively high amounts of small PAH detected in the receptor compartment after incubation times of only 2 h, whereas large PAH are mostly retained by the upper s.c. up to 48 h and do not permeate into the receptor fluid at all. For example, after 2 h almost 60% of the amount of acenaphthene (a small, 2.5-ringed PAH, Fig. 3a) recovered from the skin and receptor compartments is detected in the receptor fluid and less than 20% remain in the upper s.c. Contrarily, after the same incubation time, dibenzo[*a*,*l*]pyrene (a large, 6-ringed PAH, Fig. 3c) is recovered to more than 75% in the upper s.c. and levels out at about 70% after 4 h, whereas it was not detectable in the receptor fluid even after 48 h. Because no considerable change in the distribution pattern was detected over a period of more than 40 h, we suspect that large PAH would not fully permeate the skin even after extended incubation times. Of note, such long exposure times are less likely to reflect realistic exposure scenarios involving PAH transfer *via* dermal contact to consumer products. Nonetheless, PAH that accumulate in the s.c. but do not penetrate deeper in the investigated time frame could form a reservoir from where migration into the skin at later time points seems possible. The turnover of s.c. cell layers is about 14 days, which leaves up to two weeks for an accumulated compound to partition into the viable skin (Milstone, 2004).

The kinetic analysis for medium PAH such as pyrene (Fig. 3b) revealed that after 2 h, only about 4% of the anmount of pyrene that penetrated into the skin reach the receptor fluid, nearly 70% are retained by the upper s.c. and 28% reside in the remaining skin. After 16

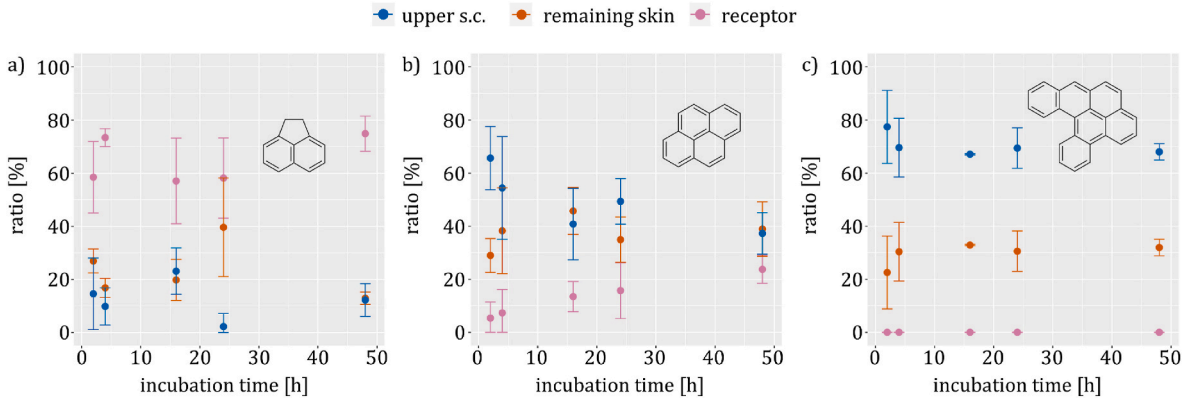

Fig. 3. Distribution ratio of selected polycyclic aromatic hydrocarbons (PAH) in each compartment to total amount found in the skin and the receptor fluid at different incubation times in pigskin. Means ± standard deviation. 24 h: $n = 9$; other incubation times: $n = 3$. a) acenaphthene (154 g/mol, log$P$ = 3.92), b) pyrene (202 g/mol, log$P$ = 4.88) and c) dibenzo[*a,l*]pyrene (302 g/mol, log$P$ = 7.20). For all other PAH, see SI A, Figures A5 to A7.

h, however, 14% reach the receptor fluid and the rest is about evenly distributed between upper s.c. and the remaining skin. After 48 h, almost a quarter of the amount of pyrene migrates into the receptor fluid. Results for skin penetration kinetics of all other investigated PAH are presented in Figures A.5–A.7 (SI A) and show similar trends.

4. Conclusion

By means of *in vitro* FDC assays involving human and pigskin, we showed that skin penetration efficiency of a broad range of PAH depends largely on log$P$, and thus, also correlates with M. At incubation times resembling time frames realistic for dermal exposure to consumer products that may be contaminated with PAH, small and to a lesser extent also medium PAH were found to reach the receptor fluid relatively fast (for example, within 2–4 h). For highly lipophilic PAH, on the other hand, the upper s.c. represents the most important barrier for permeation of PAH through the skin. These larger PAH do not partition significantly from the rather lipophilic s.c. into the more aqueous viable epidermis, and are retained effectively by the s.c. up to 48 h. This is supported by their recovery in the upper s.c. and the remaining skin, which contains a large fraction of the s.c. Since large PAH did not reach the receptor fluid in FDC assays, they would presumably not be transferred into systemic circulation *in vivo*, but eventually be removed over time by desquamation of the contaminated layers. On the other hand, formation of a reservoir in the s.c. and subsequent migration into the skin over a longer period cannot be ruled out. Furthermore, we showed that pigskin is more permeable for PAH than human skin, whereas this difference is more pronounced for small and less lipophilic PAH.

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Ethics vote on the usage of human tissue

The proposal to conduct permeation studies with human skin samples was reviewed and approved by an independent ethics committee (Ethics Commission Charité, Berlin, No. EA2/090/14, July 22, 2014). Informed consent was obtained for experimentation with these skin samples from donors, respecting their privacy rights by anonymization. Experiments were in line with all relevant laws and institutional guidelines.

CRediT authorship contribution statement

Konstantin Simon: Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Conceptualization. **Nastasia Bartsch:** Methodology, Investigation, Formal analysis, Conceptualization. **Lidia Schneider:** Methodology, Investigation, Formal analysis. **Valerie van de Weijgert:** Investigation, Formal analysis. **Christoph Hutzler:** Methodology, Conceptualization. **Andreas Luch:** Writing – review & editing, Resources, Funding acquisition. **Alexander Roloff:** Writing – review & editing, Writing – original draft, Supervision.

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. We report no conflicts of interests. All data were collected at the German Federal Institut for Risk Assessment (BfR).

Data availability

All data relevant for the publication can be found in Supporting Information B.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.119118.

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