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Considerations in Evaluating Dermal Absorption of Per- and Polyfluoroalkyl Substances (PFAS)

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Dermal absorption of PFAS is generally considered to be a minor uptake pathway relative to ingestion and inhalation because at the stratum corneum physiological pH of 5.5, PFAS exist in ionized forms that do not readily penetrate skin. However, findings are inconsistent across studies. Of three studies that measured dermal absorption of the PFAS perfluorooctanoic acid (PFOA) in humans or in human epidermal membranes, fractional absorption of PFOA ranged by three orders of magnitude: 0.048, 1.6, and 48% as reported by Fasano *et al.* (2005), Abraham and Monien (2022), and Franko *et al.* (2012), respectively. To understand the basis of this variability, we critically evaluated these studies to: (1) identify the most reliable dermal absorption factors for PFOA in humans, and (2) apply appropriate dermal absorption factors to estimate dermal exposures to children from soil and water contact at background levels of PFOA. For each study, we calculated the dimensionless ratio, Nderm, equivalent to experimental load/(steady-state flux x experimental duration). High values of Nderm indicate infinite dose conditions suitable for measuring steady-state flux, but percent absorption varies inversely with load. Low values of Nderm indicate finite dose conditions suitable for measuring dermal absorption relevant to realistic environmental or occupational exposures. We determined that the *in vitro* 0.048% dermal absorption of PFOA reported by Fasano *et al.* is likely an underestimate of dermal absorption potential, in part due to the viscosity of the aqueous vehicle. We also calculated a high value of Nderm (3,289), which indicates that the experimental conditions may not represent realistic finite dose exposures. In contrast, the *in vitro* 48% dermal absorption of PFOA reported by Franko *et al.* is likely an overestimate of dermal absorption potential because: (1) the vehicle solvent was acetone, which enhances dermal penetration of amphipathic compounds like PFAS, and (2) the experiment was conducted at an acidic pH of 2.25 at which PFOA is essentially fully un-ionized and exhibits 1,000-fold greater dermal permeability than the ionized form at pH 5.5 (*i.e.*, 5.5 x 10-2 and 4.4 x 10-5 cm/h, respectively). Accordingly, we calculated ~1,000-fold differences in steady-state flux (165 and 0.132 µg/[cm2-h]) and Nderm (0.592 and 740) for PFOA at pH 2.25 and 5.5. Abraham and Monien estimated dermal absorption of PFOA from an applied sunscreen to be 1.6%; however, the data were collected from a single human subject and the experimental conditions represented a worst-case exposure scenario (*i.e.*, the sunscreen was applied over the entire body surface and the subject did not shower for 48 hours afterwards). Nevertheless, we calculated Nderm = 0.704 suggesting the experiment was conducted under finite dose conditions. Based on the available data, we propose that the most plausible dermal absorption factors for PFOA are 1.6% absorption (after 48 hours) and permeability coefficient of 4.4 x 10-5 cm/h (after 24 hours) at pH 5.5. Applying these dermal absorption factors and background levels of PFOA in soil (0.124 µg/kg) and drinking water (30 ng/L), we estimated dermal exposures for children playing in mud and bathing to be 7.3 x 10-9 and 1.8 x 10-7 mg/kg-day, respectively. Our estimates reflect low dermal absorption of PFOA relative to absorption from ingestion. We believe our analysis is consistent with low dermal absorption of other PFAS based on their ionic properties at pH 5.5. Experimental studies of the dermal kinetics of other PFAS will provide more precise estimates of absorption parameters. Future studies should use non-viscous, non-acetone vehicle solvents at an environmentally relevant pH of 5.5, and test multiple doses of PFAS under both infinite and finite dose conditions to reliably measure steady-state flux and dermal absorption potential, respectively.