Dermal Absorption Studies of Perfluorinated Alkyl Substances

Final report

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Perfluorinated alkyl substances (PFAS) are highly persistent chemicals used in treatment of fabrics, in fire-fighting chemicals and many other applications. These compounds are a significant environmental concern due to their persistent nature and demonstrated toxicity, thus the uptake and accumulation of PFAS in biological systems is an important topic to study. Our approach makes use of an innovative technique of "tagging" PFAS with the radioisotope Fluorine-18 (^{18}F, half-life = 110 min) to generate [^{18}F]PFAS radiotracers [Burkemper et al, 2017], which allows for tracking of the biodistribution of these compounds in real time using Positron Emission Tomography (PET) and precise quantification of the amount of radiolabeled compound inside organs and tissues of interest.

For this project, we conducted the first dermal absorption studies with radiofluorinated PFAS to determine how quickly specific PFAS get absorbed through the skin of healthy mice by measuring the amount of radioactivity in blood samples over time. We will first attach the radioisotope ^{18}F onto commercially available PFAS such as perfluorooctanoic acid (PFOA), perfluorohexanoic acid (PFHxA), perfluorooctanesulfonic acid (PFOS) and perfluorobutanesulfonic acid (PFBS) as previously described in our article Burkemper *et.al.* 2017. Once purified, the compounds will be concentrated down to dryness and re-dissolved into a various solvents such as water, dimethyl sulfoxide (DMSO), and artificial sweat.

For this study SKH1-Hrhr mice were used to provide an immunocompetent, hairless model. Animals were purchased from Charles River with a jugular vein catheter (JVC) and vascular access button (VAB) surgically implanted to allow for easy blood draw and in low volumes. With proper care, the VAB has proven to be patent for >2 months (allows for multiple studies on same mouse).

A concentrated drop of the [^{18}F]PFAS was put onto the backs of healthy mice and covered in a modified rodent jacket to help prevent ingestion from grooming. Blood samples, 1-2 μL, will be taken from the VAB at various time points throughout the study (up to 8 hours after exposure). Each blood draw included magnetically holding the VAB, withdrawing the locking solution with a syringe, pulling a blood sample with a secondary syringe, then relocking the JVC. The collected blood was measured in a gamma counter to determine the amount of radioactivity that is circulating in the blood stream. Results are shown in Figures 1-3.

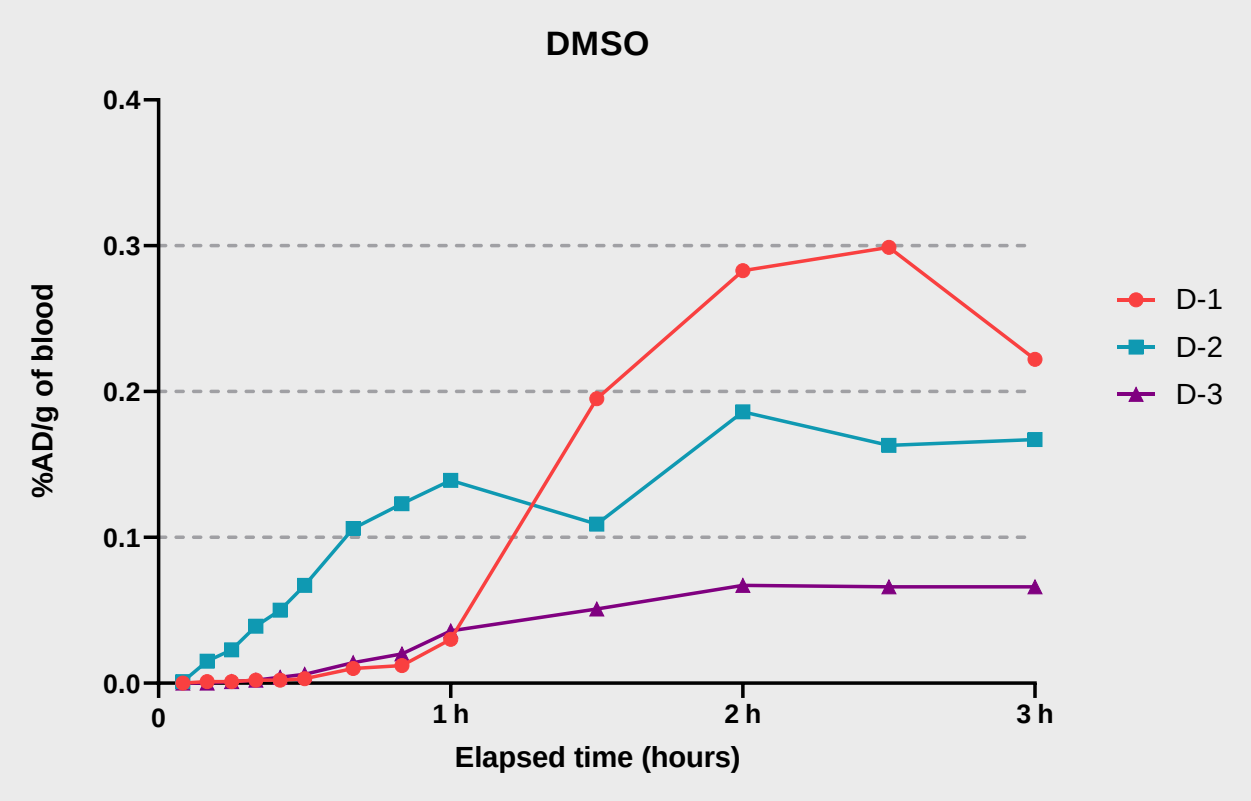

Figure 1. [^{18}F]PFAS blood curves for dermal administration in dimethyl sulfoxide (DMSO) as a carrier as a function of administered dose per gram (AD/g). DMSO is known to rapidly cross the skin barrier and thus should be considered a positive control. Curves shown are for individual animals. Peak blood activities are observed between two and three hours.

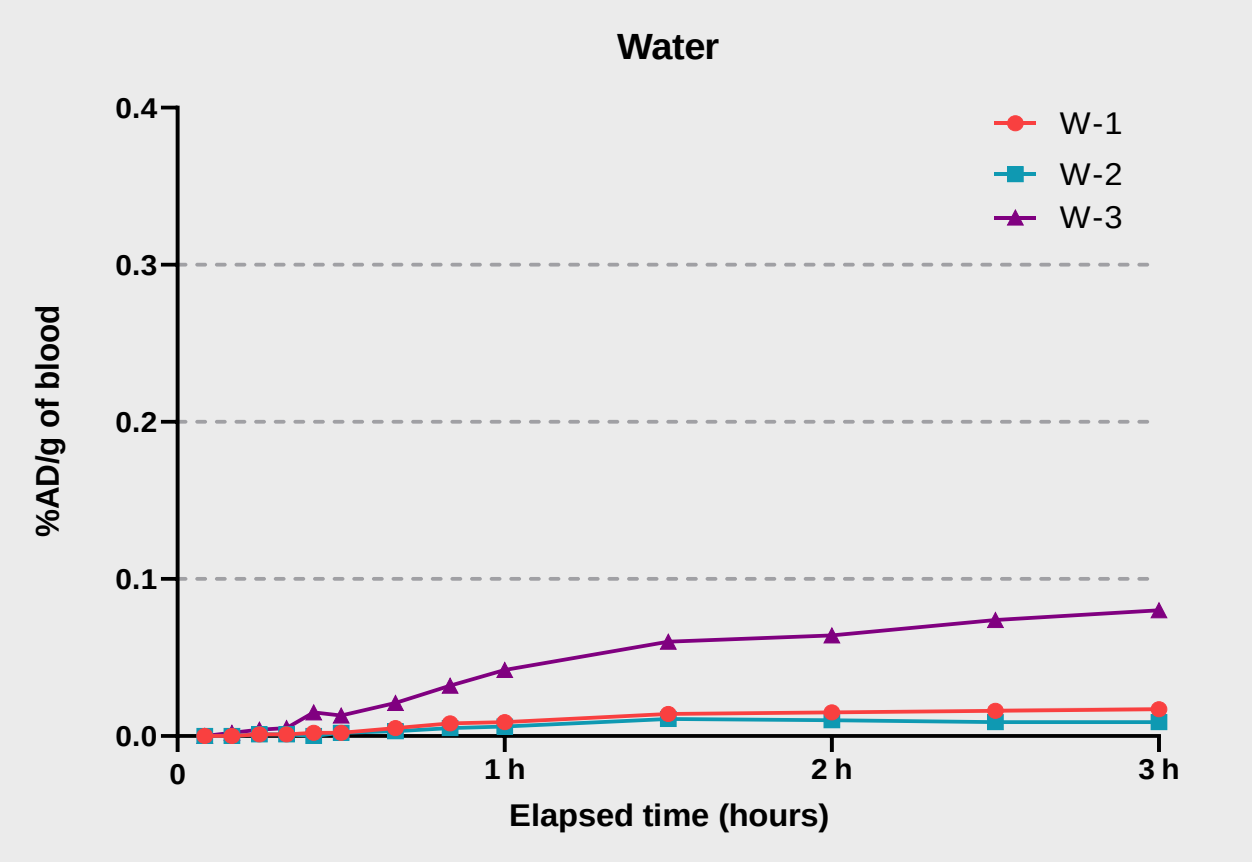

Figure 2 [^{18}F]PFAS blood curves for dermal administration in water as a carrier as a function of administered dose per gram (AD/g) . Curves shown are for individual animals. Peak blood activities were rising at three hours post administration suggesting slow absorption kinetics.

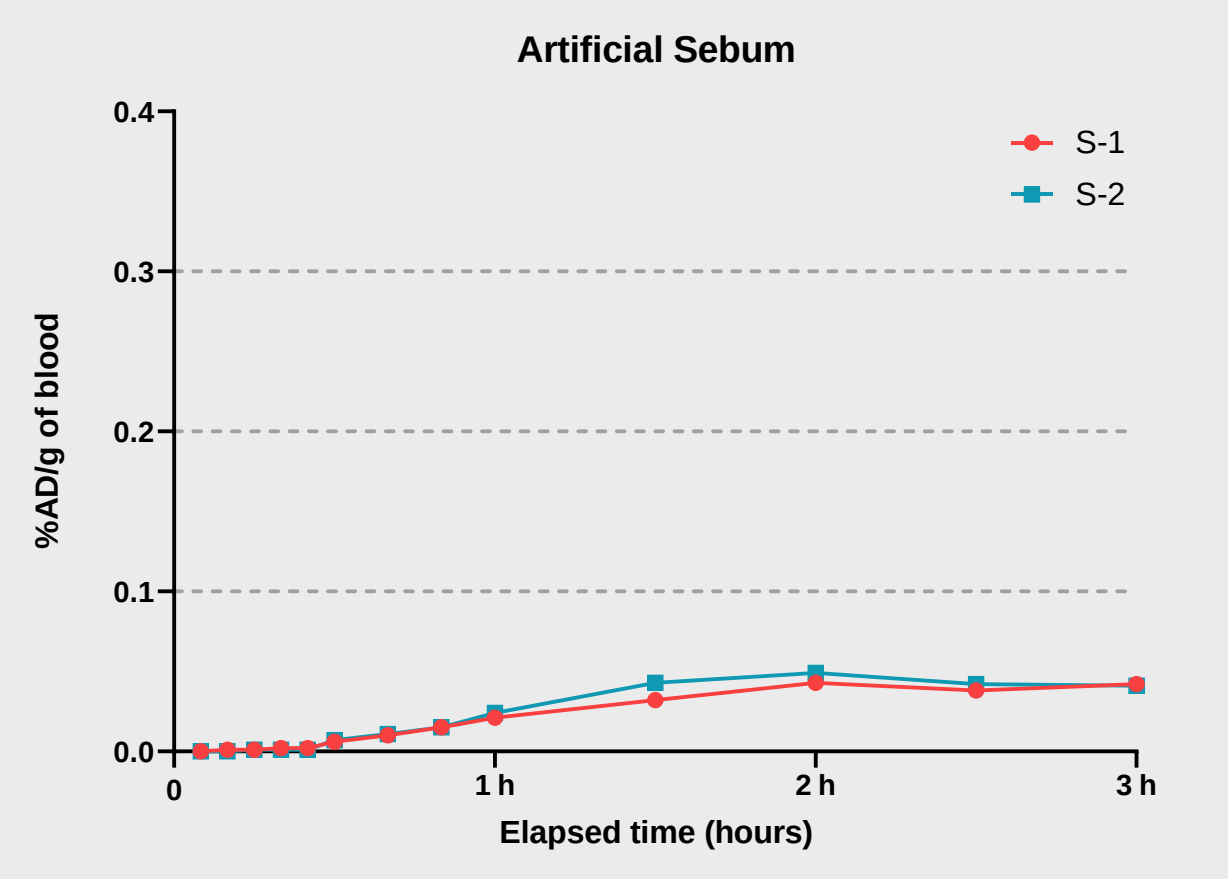

Figure 3. [^{18}F]PFAS blood curves for dermal administration in artificial sebum (sweat) as a carrier as a function of administered dose per gram (AD/g) . Curves shown are for individual animals. Peak blood activities were observed at two hours post administration and then remained relatively stable suggesting slow and sustained absorption kinetics.

Positron Emission Tomography/Computed Tomography (PET/CT) images were also collected following the kinetic study to investigate the uptake of [^{18}F]PFAS in various organs.

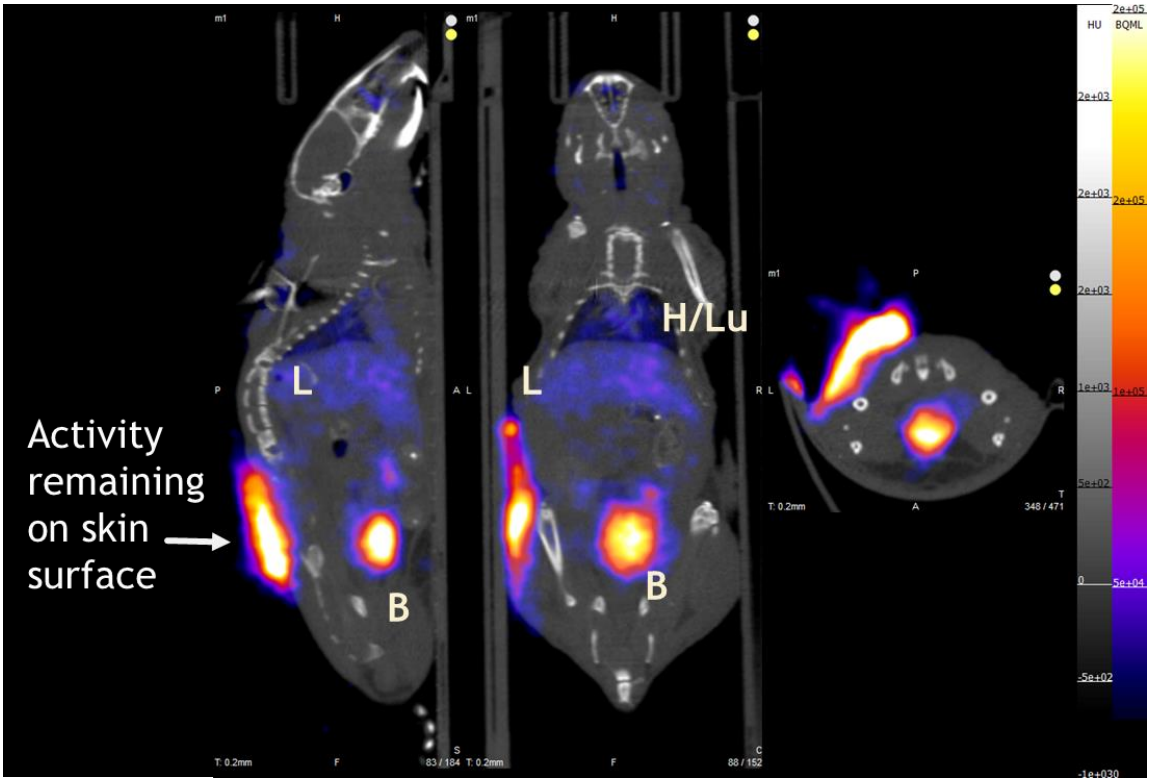

Figure 4. Small animal Positron Emission Tomography/Computed Tomography (PET/CT) of [^{18}F]PFAS distribution after dermal administration. Compound was observed in heart, lung, liver and bladder with the highest concentrations in the bladder (likely route of excretion) (L-Liver, H/Lu – Heart/Lung, B- Bladder)

Additional studies are ongoing and will determine if chain length, solvent composition and PFAS type results in different dermal absorption profiles of the PFAS studied. Using the data published from these experiments and dermal exposure data, toxicologists will be able to estimate for the first time, the extent of dermal absorption of PFAS in a mouse model. This provides estimates for human absorption values, and potentially could be followed up with *in vitro* human skin equivalent tests.

Reference: Burkemper, J.L.; Aweda, T.A.; Rosenberg, A.J.; Lunderberg, D.M.; Peaslee, G.F.; Lapi, S.E. *Environ. Sci. Tech. Lett.* **2017**, *4*, 211-215