HHS Public Access
Author manuscript
Environ Sci Technol Lett. Author manuscript; available in PMC 2022 June 08.

Published in final edited form as:
Environ Sci Technol Lett. 2021 June 08; 8(6): 457–462. doi:10.1021/acs.estlett.1c00222.

Tissue-specific distribution of legacy and novel per- and polyfluoroalkyl substances in juvenile seabirds

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Abstract

Of the thousands of per- and polyfluoroalkyl substances (PFAS) in the environment, few have been investigated in detail. In this study, we analyzed 36 legacy and emerging PFAS in multiple seabird tissues collected from individuals from Massachusetts Bay, Narragansett Bay and the Cape Fear River Estuary. PFOS was the dominant compound across multiple tissues, while long-chain perfluorinated carboxylic acids (PFCAs) dominated in brain (mean = 44% of total concentrations). Emerging perfluoroalkyl ether acids (PFEAs)—Nafion byproduct-2 and PFO5DoDA – were detected in greater than 90% of tissues in birds obtained from a nesting region downstream from a major fluorochemical production site. Compound ratios, relative body burden calculations, and electrostatic surface potential calculations were used to describe partitioning behavior of PFEAs in different tissues. Novel PFEAs preferentially partition into blood compared to liver, and were documented in brain for the first time. PFO5DoDA showed a reduced preference for brain compared to PFCAs and Nafion BP2. These results suggest future monitoring efforts and toxicological studies should focus on novel PFAS and long-chain PFCAs in multiple tissues beyond liver and blood, while exploring the unique binding mechanisms driving uptake of multi-ether PFEAs.

Graphical Abstract

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Author Contributions

The manuscript was primarily drafted by A. Robuck and finalized through contributions of all authors. Sample analysis and data interpretation were carried out through contributions of all authors. All authors have given approval to the final version of the manuscript.

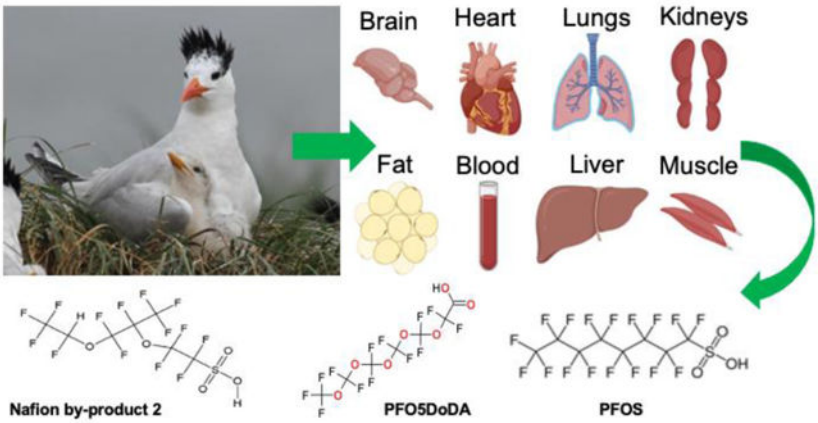
ASSOCIATED CONTENT

Supporting Information.

The following files are available free of charge.

Additional summary data, analyte list (Excel workbook)

Additional text describing methods, quality assurance, and providing additional figures in support of the text (PDF)



Keywords

PFOS; PFAS; seabirds; bioaccumulation; partitioning

Introduction

Per- and polyfluoroalkyl substances (PFAS) are manmade chemicals associated with adverse effects in biota; global biomonitoring studies document the pervasive accumulation of these compounds in wildlife[1–4]. The majority of these studies measured PFAS in select matrices only, such as serum, liver, feather, or egg[5–7]. These studies provide snapshots of PFAS levels in single tissue compartments but cannot assess total exposure across multiple tissues and organs.

Some research has recognized this shortcoming by measuring PFAS within multiple tissues of wild organisms, including tissues such as brain, lungs, heart, muscle, kidney, gonads, and adipose tissue (fat) [8–14]. Such work demonstrates highly unique partitioning behavior of PFAS. Verreault et al. (2005) examined plasma, liver, egg, and brain from glaucous gull (*Larus hyperboreus*) adults and eggs from the Norwegian Arctic and determined perfluorooctanesulfonic acid (PFOS) concentrations were greatest in plasma, followed by approximately equal concentrations in liver and egg[9]. Investigations in herring gull (*Larus argentatus*) female adults and eggs from the Great Lakes (US) and common guillemot (*Uria aalgae*) adults, chicks, and eggs from the Baltic Sea subsequently found adult and chick liver to contain higher concentrations of PFOS compared to plasma or muscle[10,15]. Results from other taxa also suggest blood, liver, and kidney contain the highest concentrations of multiple perfluoroalkyl acids (PFAAs), with some indication of preferential uptake of long-chain perfluoroalkyl carboxylic acids (PFCAs, $C_nF_{2n+1}COOH$, $n \geq 7$) in the brains of marine mammals[8,14,16]. This is in stark contrast to the behavior of hydrophobic organic chemicals like polychlorinated biphenyls (PCBs), which prefer fatty tissue storage.

Tissue-specific measurements also help constrain drivers of PFAS uptake and internal distribution. Empirical data from tissue-specific studies, modeling efforts, and data from controlled laboratory studies indicate interactions with specific proteins like albumin and liver fatty acid binding protein (L-FABP) determine the partitioning of PFAS in liver,

kidney, and blood matrices[17,18]. Non-specific phospholipid-mediated pathways have also been hypothesized to drive PFAA uptake in brain and liver[18–20]. These mechanisms are poorly described empirically and mechanistically across different taxa.

Notably, little or no information exists evaluating tissue-specific behavior of novel and replacement PFAS [11,12], such as per- and polyfluoroalkyl ether acids (PFEAs) [21]. We hence analyzed legacy and novel PFAS in 8 different tissues in seabirds from the U.S. Atlantic Coast to conduct the first study examining the tissue-specific distribution of select PFEAs. The aims of this study were to (i) derive the tissue distributions of 36 legacy and emerging PFAS in birds from three habitats and (ii) evaluate partitioning behavior of PFEAs, relative to PFAAs in different tissues. We hypothesized that novel ether-containing PFAS would be detected less frequently and at lower concentrations in all tissue matrices compared to legacy PFCA and PFSA homologs.

Materials and Methods

Sample Collection

Deceased immature seabirds including Royal Terns, Sandwich Terns, Laughing Gulls, and Brown Pelicans were collected from the Cape Fear River Estuary (CFRE) in southeastern North Carolina (n = 12), downstream from a major fluoropolymer production facility. Herring Gulls (n = 4) were obtained from urbanized Narragansett Bay and Great Shearwaters (n = 6) were obtained from offshore Massachusetts Bay. All birds were freshly or recently deceased, with little or no apparent decomposition. These species generally rely on small forage fish and marine invertebrates for food. All individuals were less than six months old, aged 1 – 5 months. The total sample set (n = 20 individuals), while seeemingly small, is larger than the number of individuals used in prior tissue-specific work (e.g. 5[22], 8[10], 5–10[15], or 4[13] individuals). More details about the appropriateness of our unique sample set, and particulars about each seabird species, individual, and location are provided in the Supplementary Information (SI) and in previous work (Tables S1, S2, Fig. S1)[9,15]. Tissues or samples collected included heart, brain, kidney, lungs, adipose fat, liver, whole blood, and pectoral muscle. 11/160 tissue samples (livers from CFRE individuals) were also reported in previous work from our group, but over 93% of the sample set is investigated here for the first time[23].

PFAS analysis via HRMS

A total of 36 PFAS were assessed in 160 seabird tissue samples from 20 immature seabird individuals via targeted and suspect screening (Table S4). PFAS were extracted and analyzed following a previously described HRMS workflow[23–26] using a Thermo Orbitrap Fusion mass spectrometer (ThermoFisher Scientific, Waltham, MA). Further details about sample preparation, analysis, quantification, and quality control are available in the SI.

Data treatment, statistical analysis, and structural comparison

Data manipulation and statistical analyses were performed in R version 3.6.1 (R Core Team, 2020)[27]. Concentrations were converted to a wet weight, per gram basis for ease of comparability. Reporting limits (RLs) were determined by comparison to process blank

values plus three times the standard deviation; in the absence of blank concentrations, the lowest calibration curve point was used. Responses below RLs were considered zero for summation purposes. Summary statistics, compound ratios, tissue-blood ratios, and relative body burdens were calculated for compounds found in greater than 50% of samples in at least one tissue as described in the SI; non-detects were substituted with zeros to avoid artificial inflation of derived statistics and ratios given the small sample size per tissue and habitat. As a result, ratio calculations are conservative and may underestimate true values. Compound ratios in multiple tissues of CFRE birds (n = 12, 96 tissues) were compared using ANOVA with post hoc application of Tukey's test with Bonferroni correction for multiple testing. Additionally, TURBO-MOLE software included in the COSMOconf software suite was used to evaluate differences in electrostatic surface potential between the lowest energy conformers of PFOS, PFOA, Nafion BP2 and PFO5DoDA. These visualizations portray a molecule's probable surface charge as a three-dimensional surface, providing insight about likely molecular interactions [28].

Results and Discussion

Detection of PFAS by tissue and region

17 of 36 analytes were detected in at least one seabird tissue (Fig. 1, Table S3). The largest number of analytes and the highest detection frequencies across each tissue type were observed in individuals from the Cape Fear sample set (Fig. 1).

PFOS and PFCA concentrations across multiple tissues

PFOS was detected at the highest mean concentration in most tissues when it was detected, and dominated sum totals in most tissues (Fig. S4, Tables S5, S7). Considering birds from all habitats, the highest mean concentrations of PFOS were observed in liver, kidney, lungs, and blood across all habitats (Fig. S2, Tables S5). High PFOS abundances in these relative to other tissues have been reported in wildlife from regions unimpacted by PFOS point sources [9,10,15]. PFOS was found in all CFRE tissues examined, and at the highest concentrations (up to 480 ng/g in blood) (Tables S5). High levels of PFOS have also been observed in fish and human serum samples from the wider Cape Fear region [26,29,30].

CFRE birds displayed the largest number of PFCA detections across multiple tissues (Fig. 1). PFUdA was the most abundant PFCA in liver, with a mean concentration of 10, 10, and 5 ng/g in CFRE, Massachusetts Bay, and Narragansett Bay livers, respectively (Fig. S2, Tables S5). PFTrDA was the most abundant PFCA detected in the lungs and brain of Massachusetts Bay individuals, at a mean concentration of 19 ng/g in both tissues, higher than or similar to concentrations observed in other tissue-specific research involving seabirds[9,10,15].

PFEA concentrations across multiple tissues of CFRE birds

PFEAs were detected in multiple tissues in birds from two habitats but were by far most abundant in CFRE birds. PFEAs made up the largest single proportion of total PFAS in fat (54% in CFRE birds), dominated by Nafion BP2, but concentrations were lower in fat compared to other tissues (Fig. S4, Tables S5). The highest PFEA levels were found in brain of CFRE individuals, with a maximum of 360 ng/g Nafion BP2 (Tables

S5). Mean concentrations of Nafion BP2 in blood from CFRE individuals (mean = 21 ng/ml) were approximately 70 times higher than Nafion BP2 levels observed in striped bass from the Cape Fear River (mean = 0.3 ng/ml)[26], and about 7 times higher than Nafion BP2 concentrations observed in human serum from Wilmington, NC (median = 2.7 ng/ml), a community where upstream industrial PFAS discharges in the Cape Fear River are known to impact finished drinking water[31]. Mean PFO5DoDA concentrations in blood of CFRE chicks (mean = 27 ng/ml) were about 90 times higher than in human serum from Wilmington residents (median = 0.3 ng/ml). PFEA concentrations in CFRE bird blood are also approximately two orders of magnitude higher than concentrations observed in humans surrounding a fluoropolymer production site in China (Nafion BP2 median = 0.097 ng/ml, PFO5DoDA median = 0.987 ng/ml), which were found to be associated with altered glucose, cholesterol, and other enzymes and proteins in human serum[32]. The higher observed concentrations in birds may be related to dose as a function of body weight and maternal offloading, with the smaller birds evidencing higher tissue concentrations when subjected to the same air/water dose.

Relative body burdens by tissue and body weight

We derived relative body burdens (RBBs) as the product of PFAS concentrations, organ weights, and total body weight (Eq. S1). The highest RBB of PFOS was found in liver, followed by blood and muscle (Fig. 2, Fig. S3).

In muscle, the high RBB of PFOS is likely driven by the large mass fraction of this component (~15 – 20% of body weight) whereas in blood (~10%) and liver (4 – 6%) the large RBB also results from the increased PFOS affinity for these tissues via specific uptake mechanisms including albumin, L-FABP, and membrane phospholipids[17,33,34]. RBBs also suggest a chain-length dependence of PFCA accumulation in liver and brain (Fig. 2). C_9 PFNA had the highest relative mass in liver, with decreasing relative mass with increasing chain length (Fig. 2). C_{12} PFDoDA and C_{13} PFTrDA showed significantly decreased relative masses in liver and increased mass in brain compared to C_9 – C_{11} PFCAs. These trends were likely driven by relative binding affinity of PFCAs with specific proteins in brain and blood-brain membrane transport pathways [14,17,34]. The largest RBBs of Nafion BP2, PFO4DA, PFO5DoDA were found in blood of CFRE individuals, driven by the large mass fraction of this compartment coupled with relatively high concentrations of PFEAs in whole blood (Fig. 2).

Legacy and novel PFAS in brain

10 compounds were detected in at least one brain sample and 8 detected in at least 50% of brain samples, demonstrating that multiple PFAS can migrate across the blood-brain barrier. PFOS displayed the highest mean concentration in brain, and PFCAs made up the largest fraction observed in brain (44% of total concentration across all birds), with PFUdA found at mean concentrations of 13, 8, and 3 ng/g in brains from CFRE, Massachusetts Bay, and Narragansett Bay individuals, respectively. The dominance of PFCAs was particularly notable in brains from Massachusetts Bay and Narragansett Bay individuals in which [PFOS] was lower, with PFCAs constituting a mean of 57% of total concentrations observed in brains (n = 6) (Tables S5). Pairwise concentration comparison suggests PFTrDA is

preferentially taken up into the brain compared to structurally analogous $C_9 – C_{12}$ PFCAs (Table S6). Similar results for long-chain PFCAs in marine mammals brain[14] have been hypothesized to be driven by phospholipid-mediated uptake.

Nafion byproduct-2, PFO4DA, and PFO5DoDA were all detected in brain tissue of individuals from the CFRE, with detection frequencies of 80%, 60%, and 100%, respectively. Migration across the blood-brain barrier (BBB) is highly restricted for ionic species like PFAAs and PFEAs, and is thought to occur via active transport pathways.[35] Empirical observations in marine mammals and birds demonstrate the presence of long-chain PFCAs, PFOS, and PFDS in brain tissue, suggesting BBB transport of PFCAs with C >9 or PFSAs with C ≥ 8 is possible, whether by OATP1A2 or another unspecified transport pathway related to or mediated by phospholipid interactions[9,13,14].

Our results indicate that ether-based PFAS chemistries readily migrate across the highly selective blood-brain barrier in vertebrate wild animals subject to environmentally relevant PFEA exposures. Data from polar bears[16], frogs[36], and mice[37] suggest some legacy PFAS (PFOS, PFCAs) are associated with alterations of neurochemical signaling and proteins critical for brain development, with uncertain long-term implications. Modeling suggests ether-based PFAS have similar or higher toxic potency compared to PFAAs[38]. Further research is required to examine PFEA impacts in the brain, given their proven ability to migrate into this tissue compartment.

Decreased preference of PFO5DoDA for brain

Concentration ratios facilitate the evaluation of compound partitioning between different tissues, as compounds subject to similar exposure and distribution pathways across multiple tissues likely share similar ratios between different tissues and vice versa. Using concentration ratios, we note that PFO5DoDA, a PFOA substitute with a backbone incorporating multiple ether linkages, partitions differently into brain than in other tissues compared to PFUdA, PFTrDA, PFOS, and Nafion BP2 (Fig. 3, Table S6).

This suggests a combination of structural features, such as the inclusion of multiple ether linkages (>2) that increase backbone flexibility, the molecular size of PFO5DoDA (11-member backbone), and/or the -COOH head group, reduce transport across the BBB compared to other examined PFAAs and the PFESA Nafion BP2. We consider the ether-linkages, molecular size, and/or increased backbone flexibility of PFO5DoDA to be the most important features for its accumulation in brain, given that the -COOH functional group is also present in long-chain PFCAs that preferentially partition to brain. The ether-based chemicals distribute across most other tissues in a similar manner as long-chain PFAA analogues, with a preference for blood and kidney apparent in some comparisons (Table S6).

Relative sorption strength of PFEAs to proteins

The high PFAS concentrations observed in blood suggests albumin may offer increased binding opportunity for PFEAs via its multiple binding sites with distinct binding affinities that favor a range of PFAS chain lengths and functional groups[28,39]. We used quantum chemical calculations performed via COSMOconf/TURBOMOLE to explore this hypothesis; these calculations allowed the comparison of electrostatic surface potential

between the lowest energy PFEA conformations and their respective PFAA homologues (Table S9). Nafion BP2 possessed increased probabilities of positive surface charge density compared to PFOS, and reduced probabilities of neutral surface charge. Given the sensitivity of binding cavity interactions to charge, we hypothesize that these aberrations in charge potential between PFEAs and PFAAs may result in a reduced ability for Nafion BP2 to engage in hydrophobic interactions in the L-FABP active site. This could help explain the reduced presence of Nafion BP2 in liver compared to blood. However, PFO5DoDA possessed an increased probability of neutral surface charge compared to PFOA, but was found at higher concentrations in blood compared to liver. Steric effects may drive differences in binding of PFO5DoDA to L-FABP compared to C8 - C10 PFAAs, which were found at higher concentrations in liver compared to blood in CFRE individuals. Sheng et al. (2018) found that several ether- and chlorine-containing emerging PFAS were structurally distorted during the binding process in orientations distinct from the “head-out” binding observed for PFAAs; they also interacted with a different suite of amino acid residues[40].

Based on calculated and observational results observed across this study, we suggest multi-ether PFEAs engage with the L-FABP active site in a way distinct from the structural deformation and binding interactions observed between L-FABP and long-chain PFAAs. These differences may reduce the favorability of interaction in the primary L-FABP cavity, leading to reduced liver concentrations compared to blood (Figs. S3, S4). Alternatively, phospholipid binding is an additionally important mechanism driving PFAS accumulation in liver, in tandem with L-FABP interactions[18]. The multi-ether PFAS, with altered electron densities or conformational behavior compared to PFAAs, may be less likely to engage with uptake pathways that favor phospholipid-like species with a distinctly hydrophobic tail and a hydrophilic head group.

Implications

This study is the first to document the internal distribution behavior of PFEAs in any vertebrate organism, and details the presence of PFAAs and PFEAs in multiple tissues and organs of young seabirds. Multi-ether PFEAs were generally most abundant in blood rather than liver; we suggest compounds containing multiple ether linkages may find more flexible binding sites within serum albumin compared to the primary active site of L-FABP. Little research to date has examined the binding behavior of multi-ether PFEAs, which is needed considering their burgeoning environmental relevance and continued incorporation in industrial processes. Overall, we note that continued reliance on ether-based PFAS may not translate to reduced tissue accumulation of PFAS as our work indicates ether-based chemicals are readily transported to multiple body compartments such as the brain, with unknown biological consequences. Our results also reinforce the utility of birds to better understand environmental distributions and internal partitioning of PFAS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We thank the Northeast Fisheries Observer Program, Gina Shield, Johanna Pedersen, Michael Moore, Lindsay Addison, Matthew McIver, the Wildlife Clinic of Rhode Island, and Kevin Powers for assistance obtaining and necropsying bird samples used in this studyWe acknowledge the help of Detlef Knappe (NCSU) in making this study feasible, Michaela Cashman, Diane Nacci, and Steve Rego (all US EPA) for critical feedback prior to peer review. The TOC art was created with BioRender.com, with the tern photo provided courtesy of Lindsay Addison. We thank Andrea Ebert and Kai Uwe Goss (Both UFZ Leipzig) for assistance with COSMOconf analysis and interpretation. Although EPA employees contributed to this article, the research presented was not funded by EPA and was conceived, designed, and implemented by URI. EPA's role was limited to advising PFAS analysis and therefore not subject to EPA's quality system requirements. Consequently, the views, interpretations, and conclusions expressed in the article are solely those of the authors and do not necessarily reflect or represent EPA's views or policies.

Funding Sources

A. Robuck acknowledges support from the National Oceanic and Atmospheric Administration Dr. Nancy Foster Scholarship program, the Robert and Patricia Switzer Foundation, the STEEP Superfund Research Program (NIEHS Award Number P42ES027706), and the Oak Ridge Institute for Science and Education (ORISE) program.

ABBREVIATIONS

PFOS	Perfluorooctanesulfonic acid
PFAAs	Perfluoroalkyl acids
PFEAs	Per- and polyfluoroalkyl ether acids

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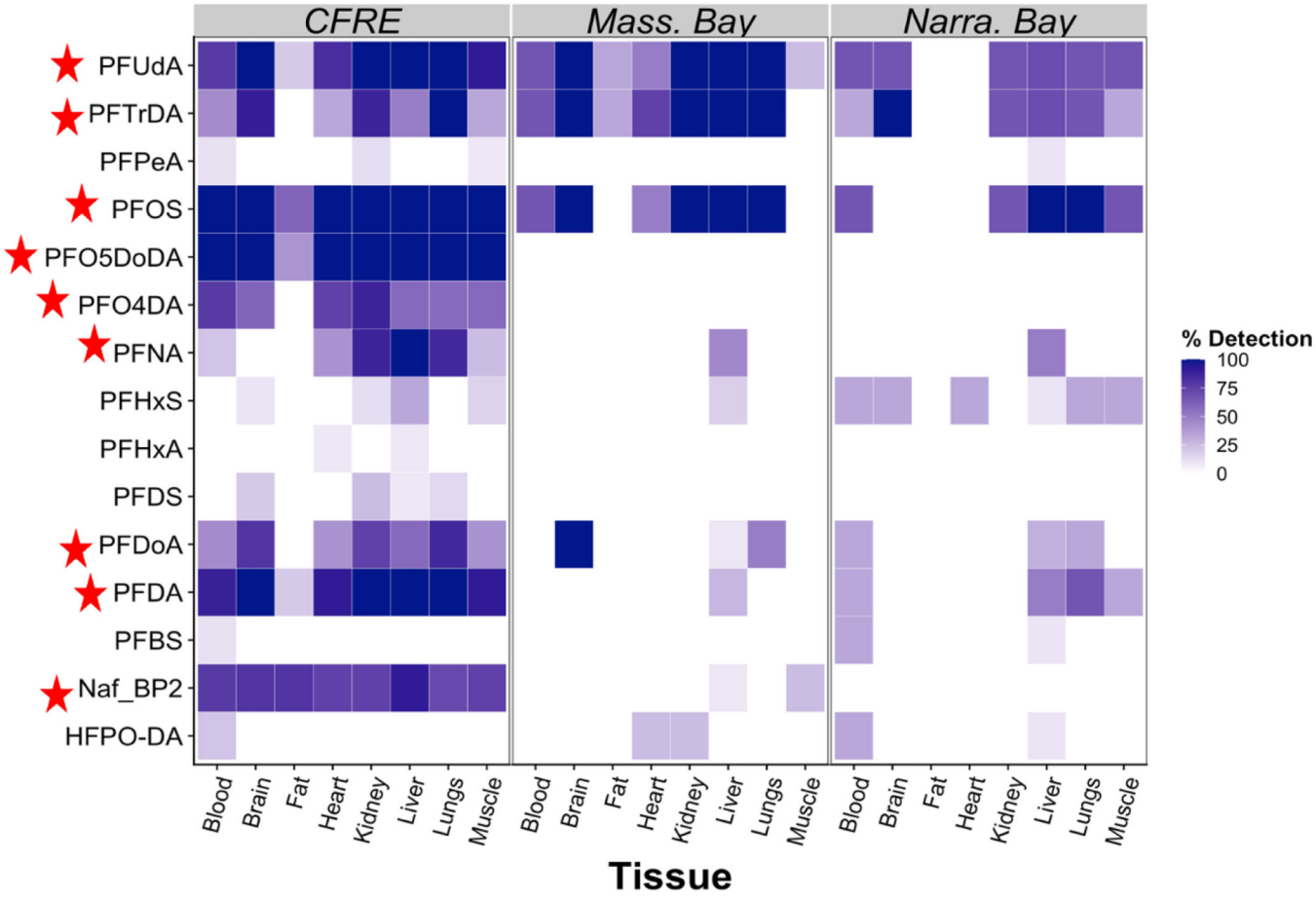

Figure 1.

Detection frequencies by habitat and tissue type, including 15 compounds that were found at least two samples. Nine PFAS (Nafion BP2, PFO5DoDA, PFO4DA, PFOS, PFNA, PFDA, PFUdA, PFDoA, and PFTrDA) were found in ≥ 50% of at least two tissues from at least one habitat, marked with a red star in the figure. See SI for compound abbreviations.

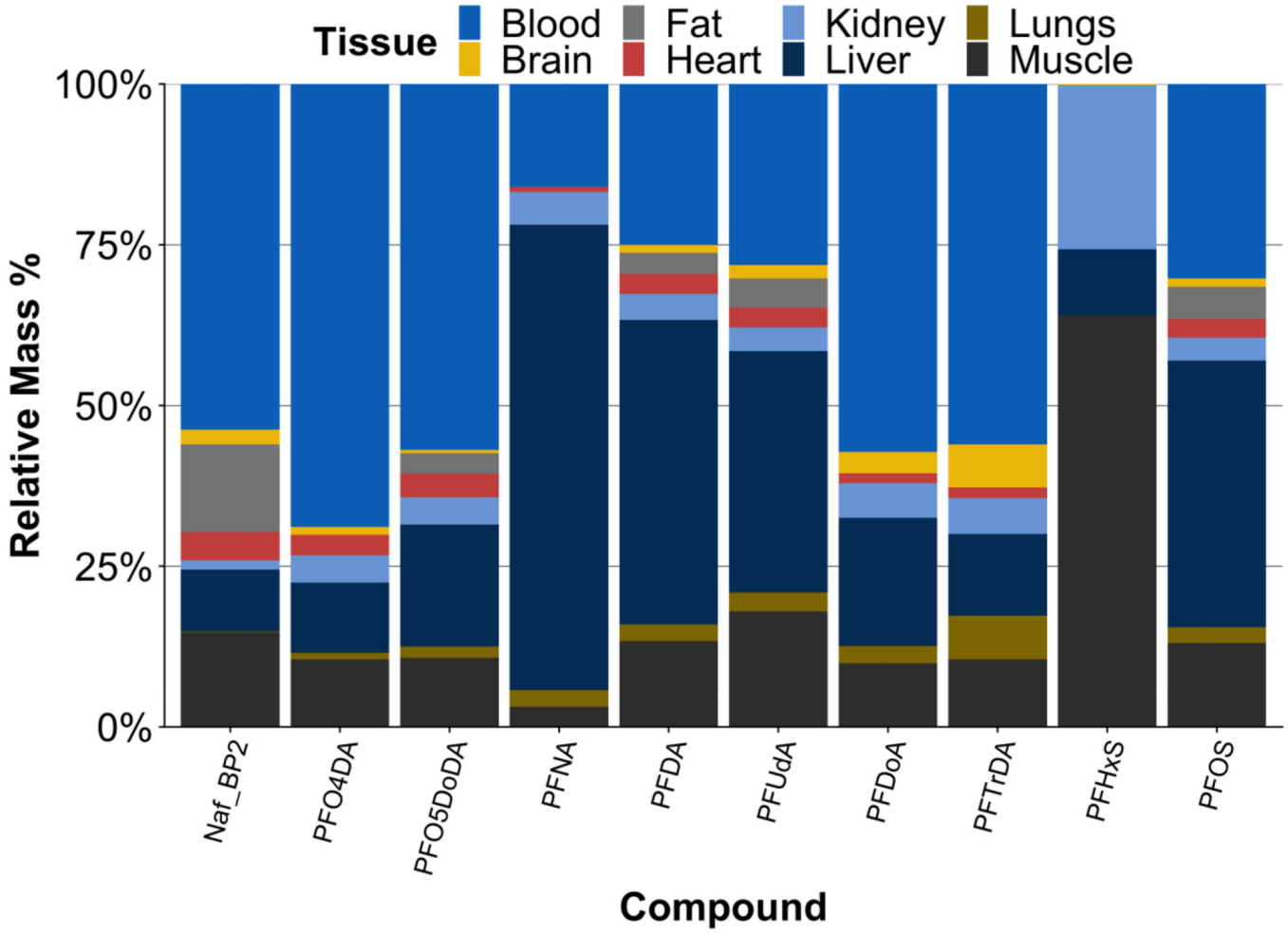

Figure 2.

Relative body burdens (RBBs) of each PFAS detected in more than 50% of samples in at least one tissue of CFRE individuals, stratified by tissue compartment. RBB data from other habitats is limited by lower detection frequencies, and is presented in Fig. S3.

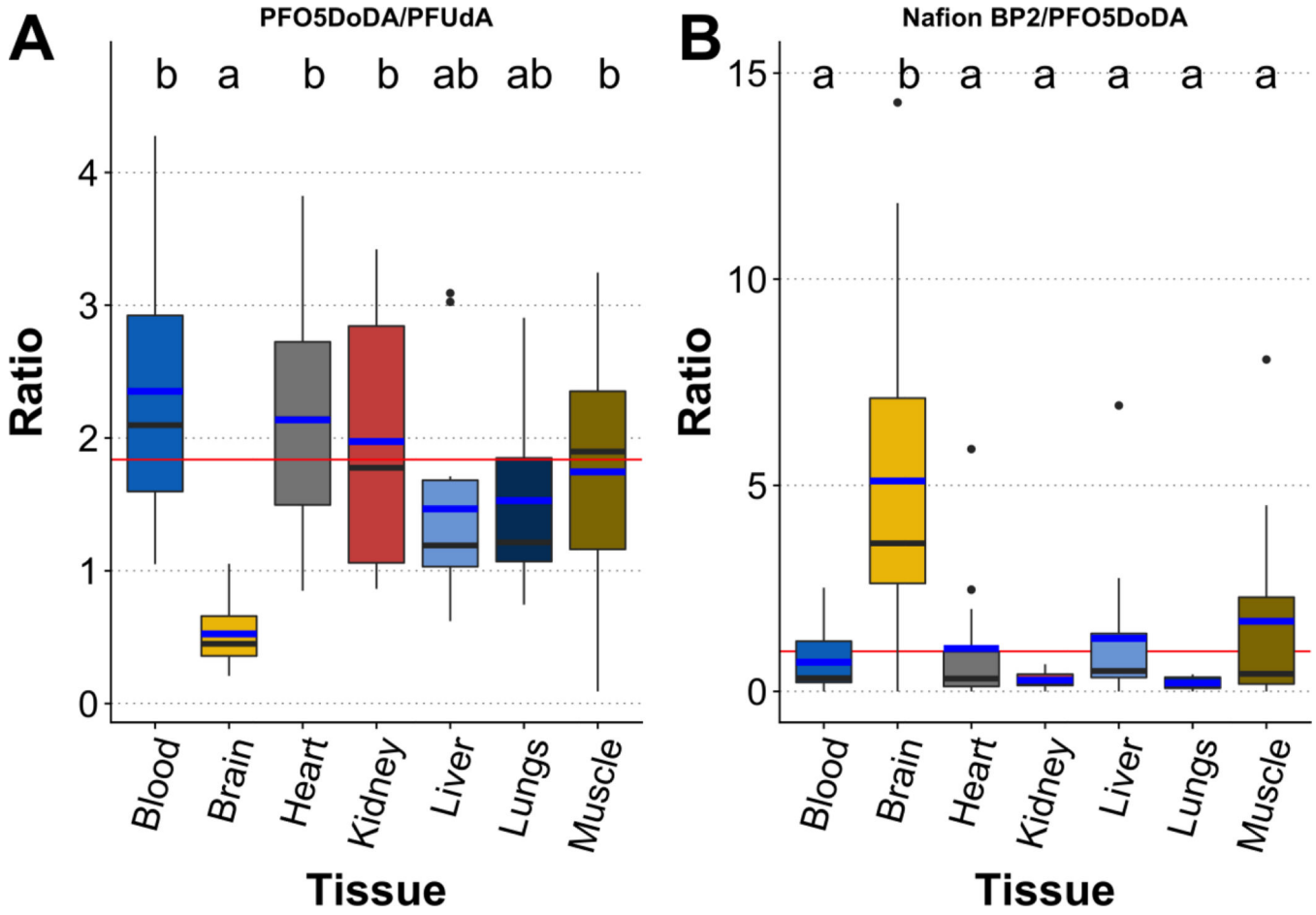

Figure 3.

Ratios of PFAS concentrations in seven tissues from all CFRE individuals, with A) presenting concentrations of PFO5DoDA divided by PFUdA and B) presenting concentrations of Nafion BP2 divided by concentrations of PFO5DoDA. Fat was excluded due to the very low detection frequency of PFO5DoDA and PFUdA in fat. The blue line within each box plot indicates the arithmetic mean while the black line indicates the median. The box hinges represent the first and third quartiles, and the whiskers indicate 1.5 times the interquartile range. Outliers are indicated by black dots. The red line indicates the mean of each concentration ratio including all tissues except brain. Common letters above each boxplot indicate tissues that share statistically indistinguishable concentration ratios as determined using Tukey's post-hoc test.