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ARTICLE *in* ENVIRONMENTAL SCIENCE & TECHNOLOGY · NOVEMBER 2012

Impact Factor: 5.33 · DOI: 10.1021/es304430r · Source: PubMed

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Potential Role of Phospholipids in Determining the Internal Tissue Distribution of Perfluoroalkyl Acids in Biota

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Studies characterizing and quantifying the bioaccumulation and internal tissue distribution of perfluoroalkyl acids (PFAAs) remain highly relevant from both a scientific and regulatory perspective. Unlike neutral hydrophobic organic contaminants which exhibit the highest wet weight concentrations in adipose tissue, the highest levels of PFAAs in biota are typically measured in liver and blood samples.[1] This pattern of internal tissue distribution is hypothesized to largely reflect the role of PFAA–protein interactions in determining the sorption capacity of the organism and its various organs. Based on recent work developing and evaluating a mechanistically based bioconcentration model for ionogenic organic chemicals (IOCs) in fish,[2] we propose an alternative hypothesis, namely that the bioaccumulation potential and internal tissue distribution of perfluoroalkyl acids (PFAAs) are strongly influenced by phospholipids. The objective of this Viewpoint is to encourage further empirical studies to evaluate this assertion.

Research into the interactions of PFAAs with proteins has predominantly focused on bovine serum albumin (BSA) and various fatty acid binding proteins (FABP). However, these data have yet to be used to derive a mechanistically based model capable of relating external concentrations of PFAAs to both internal concentrations and internal tissue distribution. It is already clear that bulk protein fraction in tissues cannot successfully explain the observed tissue distribution of PFAAs. For example, liver and muscle tissue have similar bulk protein contents,[3] whereas reported wet weight concentrations of PFAAs are typically many times higher in liver than in muscle.[1] These observations can be rationalized based on protein-water partitioning of PFAAs only if these interactions are highly protein-specific. This hypothesis implies that research efforts be directed toward isolating different tissue proteins and establishing protein-water distribution ratios for each one to complement studies with serum albumin and FABP. The potential importance of competition for binding sites on the protein under physiological conditions (i.e., in the presence of other endogenous ligands) is also a key consideration requiring further study.

Empirical studies characterizing interactions of various IOCs (including PFAAs) with phospholipids in membrane–water systems are also available in the scientific literature (e.g., refs 4 and 5). Most phospholipids present in biota (e.g., phosphatidylcholines) are zwitterionic at physiological pH with a positively charged choline group and a negatively charged phosphate group. Supportive electrostatic interactions with charged IOCs can therefore occur in addition to hydrophobic interactions.[4] Consequently, the difference between the membrane-water partition constant of the neutral and charged form (Δ_{MW} = 0.3–2 log units) is less than the difference between the (apparent) octanol–water partition constants (Δ_{OW} = 2–4 log units) and membrane-water distribution ratios (D_{MW}) are less sensitive to changes in pH than octanol–water distribution ratios (D_{OW}).[2,4] Assuming that D_{MW} and D_{OW} are reliable surrogates for sorption to phospholipids and neutral (storage) lipids in vivo respectively, phospholipids dominate the contribution of total lipid to an organism's sorption capacity for IOCs exhibiting a high degree of ionization at physiologically relevant pH.[2] Although there is some interspecies variability, phospholipids tend to be at least as prevalent as neutral (storage) lipids in most tissues with the exception of adipose tissue.[3] Ignoring the potential contribution of other biological macromolecules (e.g., proteins), the highest wet weight tissue concentrations of predominantly charged IOCs in long-term continuous exposure scenarios are therefore expected to be observed in tissues like liver, kidney and brain, which exhibit both a relatively high total lipid and phospholipid content.[3] By extension, regions within a particular tissue with higher phospholipid content are also expected to have higher wet weight concentrations. Tissues with relatively low phospholipid content but large volume (e.g., muscle) can still be relevant in terms of mass distribution though. Note that

Received: October 30, 2012
Revised: November 2, 2012
Accepted: November 2, 2012
Published: November 8, 2012

dx.doi.org/10.1021/es304430r | Environ. Sci. Technol. 2012, 46, 12285–12286

pharmacokinetic limitations to chemical transport imposed by the blood-brain and other diffusive barriers must also be taken into account.

Given that PFAAs are predominantly charged at physiologically relevant pH and have been shown to (i) correlate with extractable lipid content in some tissues (e.g., liver),[1] (ii) interact favorably with phospholipids in membrane-water systems,[5] and (iii) exhibit internal tissue distributions broadly consistent with expectations based on total phospholipid content (e.g., wet weight concentration in liver > muscle > adipose), we suggest that assessing the role of phospholipids in determining PFAA bioaccumulation behavior should be a priority. Note that the hypothesis that the internal tissue distribution of PFAAs is strongly influenced by phospholipid content may be most applicable to soft tissues and least applicable to whole blood, where interactions with serum proteins (e.g., albumin) may exert the key influence on total sorption capacity. In other words, we are not suggesting that phospholipid content is the sole explanatory factor behind observed internal tissue distributions in biota exposed to PFAAs; other classes of biological macromolecules are likely to play a role in vivo as will passive diffusion limitations and other pharmacokinetic considerations (e.g., active uptake/reabsorption pathways). Research targeted to further test the "PFAA-phospholipid hypothesis" will reveal its merits and limitations and thereby improve the understanding of the bioaccumulation potential of PFAAs. Studies including measurements of membrane-water partitioning of PFAAs and with more detailed extractable lipid analyses and correlations with observed wet weight concentrations are highly recommended.

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Notes

The authors declare no competing financial interest.

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