An assessment of organic solvent based equilibrium partitioning methods for predicting the bioconcentration behavior of perfluorinated sulfonic acids, carboxylic acids, and sulfonamides

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ABSTRACT

SPARC, KOWWIN, and ALOGPS octanol-water partitioning (log K_{ow}) and distribution (log D) constants were calculated for all C_1 through C_8 and the straight chain C_9 through C_{15} perfluoroalkyl sulfonic acids (PFSAs) and carboxylic acids (PFCAs). Application of five established models for estimating bioconcentration factors (BCFs) were applied to the PFSA and PFCA log K_{ow} and log D data and compared to available field and laboratory BCF data. Wide variability was observed between the methods for estimating log K_{ow} and log D values, ranging up to several log units for particular congeners, and which was further compounded by additional variability introduced by the different BCF equations applied. With the exception of n-perfluorooctanecarboxylic acid (n-PFOA), whose experimental BCF was poorly modeled by all approaches, the experimental BCF values of the other PFSA and PFCA congeners were

reasonably approximated by the ALOGPS log P values in combination with any of the five log K_{ow} based BCF equations. The SPARC and KOWWIN log K_{ow} and log D values provided generally less accurate BCF estimates regardless of the BCF equation applied. However, the SPARC K_{ow} values did provide BCF estimates for PFSA congeners with errors <0.3 log units using any of the five BCF equations. Model lipophilic and proteinophilic solvent based distribution constant calculations for the PFSA and PFCA congeners with experimental BCFs exhibited similar relationships with their corresponding BCF values. For longer chain PFCA and PFSA congeners, increasing hydrophobicity of the perfluoroalkyl chain appears to be driving corresponding increases in BCF values. Perfluorooalkyl sulfonamides are expected to display similar chain length and branching pattern influences on BCFs, but no experimental data are currently available upon which to validate the estimated values which range widely between the various approaches by up to 10 log units. The amidic proton acidity on primary and secondary perfluoroalkyl sulfonamides will play a significant role in the partitioning of these compounds with both abiotic and biotic organic matter, and will need to be taken into account when assessing their environmental and biological fate.

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INTRODUCTION

Perfluorinated compounds (PFCs) are widely distributed environmental contaminants receiving increasing amounts of research and regulatory attention.[1-9] A wide range of PFCs are present in consumer and industrial products, including perfluoroalkyl sulfonic acids (PFSAs), perfluoroalkyl carboxylic acids (PFCAs), perfluoroalkyl telomers, sulfonamides, and phosphates, and their derivatives (Figure 1). In many cases, abiotic and biotic degradation pathways result in the production of PFSAs from sulfonamide precursors, and the production of PFCAs from any of these PFC classes as well as other compound groups (such as hydrofluorocarbons).[10-35] The PFSAs and PFCAs appear to be more persistent than their precursor compounds; and thus, these two classes are thought to represent highly recalcitrant degradation products for the large number of possible precursor PFC compounds released into the environment. Consequently, there is substantial interest in identifying, quantitating, and determining the degradation efficiencies for the range of PFSA and PFCA precursors known to be present in environmental systems. In addition, there is a corresponding need to better understand the biological fate of PFSAs and PFCAs, and in particular, their propensity to accumulate in biota [36, 37] where toxic effects [38-52] can be exerted.

Because of their relatively strong acid head groups, the PFSAs ($pK_a<<0$) and PFCAs ($pK_a<4$) have been grouped together as the perfluorinated acids (PFAs).[53-56] Many assessments of their environmental and toxicological fate are interpreted within this context of a hydrophilic head group that is ionized in most environmental and biological systems, coupled with a dual

hydrophobic/oleophobic perfluoroalkyl chain. These PFAs display surface active behavior, a property often intended and exploited by their industrial design and application,[57] that complicates predictive models regarding their distribution within various biotic and abiotic matrices. However, it is important to recognize that PFSAs and PFCAs are not the only acidic PFCs. We have recently shown [58] that the primary and secondary substituted amide protons of perfluoroalkylsulfonamides are also acidic at near neutral pH values, a factor that has been ignored by many research groups [10, 18, 59-64] that incorrectly treat all perfluoroalkyl sulfonamide groups as non-acidic moieties. For example, Kelly et al. [62] recently termed one well known member of this compound class, n-perfluorooctanesulfonamide (n-FOSA), as a "neutral lipophilic chemical", and then erroneously applied a log K_{ow}-log K_{oa} classification system for biological partitioning behavior based on the assumed non-ionizability of this substrate. n-FOSA likely has a pK_a value of between 6.2 [58] to 6.5,[65] and as such, will be substantially, if not entirely, ionized in relevant fresh and marine waters and in physiological fluids such as the blood. Unfortunately, the biological studies that have overlooked the ionizable amidic protons on perfluoroalkyl sulfonamides are also ignoring work published nearly three decades ago that has clearly linked sulfonamide group acidities to biological uptake and transfer patterns in aquatic organisms.[66] As such, any further understanding regarding the biological accumulation and activity of perfluoroalkyl sulfonamides, as well as environmental partitioning/degradation/treatment models, will need to explicitly include the acidity of any primary or secondary amide groups in the resulting modeling efforts, and recognize these compounds as additional members of the broader PFA classification.

At present, though, only the PFSAs and PFCAs have widely reported and reliable data describing their biological partitioning behavior.[37, 62, 67-81] These compounds prefer to partition into protein rich regions of living organisms, and are thus termed proteinophilic with both non-specific and specific binding modes.[7, 61, 74, 75, 81-97] Because of their ability to degrade in vivo to PFSAs and PFCAs,[98] unambiguous measurements of such descriptors as bioconcentration factors (BCFs) and bioaccumulation factors (BAFs) for the perfluoroalkyl sulfonamides, fluorotelomers, and phosphates are difficult to obtain. For the PFSAs and PFCAs, the large number of potential congeners within each longer chain perfluoroalkyl homologue group, and absence of corresponding authentic standards, also precludes detailed congener specific experimental assessments.[99] Consequently, there is a need to examine existing estimation methods for biological partitioning behavior, as well as develop and calibrate new methods, for application to these two PFA classes. In previous work,[100, 101] we developed a method for estimating the congener specific BCFs of the C_4 through C_8 PFSAs and PFCAs using molecular area and volume based proxies for the hydrophobicity of the perfluoroalkyl chains. Our prior approach was predicated on the assumption that the electrostatic contributions towards biological partitioning behavior are relatively constant regardless of perfluoroalkyl chain length or branching pattern within this homologue range. Part of this assumption was also based on the difficulty in computationally modeling electrostatic effects at the sulfonate and carboxylate head groups, a well-known issue that has confounded pK_a prediction methods [53, 55, 56] for these compounds.

However, no study has as yet comprehensively examined the application of established organic

solvent based equilibrium partitioning methods for predicting the bioconcentration behavior of PFAs. Indeed, prior work has effectively dismissed the application of such approaches without any detailed examination.[2, 6] This is likely because PFAs are known to be proteinophilic and display surfactant like behavior, in contrast to the dominant lipophilicity of most other halogenated organic contaminants, and also because most BCF structure-activity models have been trained with generally lipophilic compounds. We have chosen to apply existing empirically derived BCF estimation frameworks to the PFAs to investigate their potential accuracy, after which more informed decisions can be made as to the possible application of these existing structure-activity relationships to contaminants such as PFSAs and PFCAs. In particular, there are a number of well defined equations that use experimentally determined or estimated octanol-water partitioning constants (K_{ow}) to calculate corresponding BCF values. If any of these approaches were to reasonably predict the BCFs of PFAs, this would offer an opportunity to apply such models within regulatory frameworks to other non-lipophilic contaminants as part of an overall screening program.

This is a particularly important issue to investigate, since the field of contaminant science often progresses with first identifying compounds of concern in environmental systems, followed by a slow process of generating reliable physicochemical and biological partitioning data for even modest environmental assessments. For compounds that do not exhibit traditional lipophilic behavior, the acquisition of new experimental data and subsequent generation of new structure-activity relationships can take years to decades. It is of value for the research community to determine if some of the pre-existing biological partitioning estimation frameworks are

sufficiently robust to apply towards new contaminants such as the PFAs, as these frameworks may also then be applied to other non-traditional contaminant classes. Such findings would allow more rapid regulatory screening and environmental assessment/modeling processes, also accelerating the progression of various contaminant research fields. To investigate these issues, we utilize several established computational methods for predicting the K_{ow} values of all C_1 through C_8 and the straight chain C_9 though C_{15} PFSAs and PFCAs. We then apply five major K_{ow} based estimation equations to estimate the corresponding BCF values, and where available, compare the estimated BCFs with the limited experimental dataset. In addition, we also evaluate computationally generated amino acid based solvent systems as proteinophilic environment proxies by which to potentially develop more reliable BCF estimation models for PFSAs and PFCAs. Furthermore, despite the absence of experimental BCF data for the perfluoroalkyl sulfonamides, we have also used this conceptual approach to map the potential chemical space of BCFs for these compounds as well.

METHODS AND MATERIALS

Congener specific PFSA, PFCA, and perfluoroalkyl sulfonamide partitioning constants were calculated with the SPARC (http://ibmlc2.chem.uga.edu/sparc/; August 2007 release w4.0.1219-s4.0.1219),[102] KOWWIN (http://www.epa.gov/opptintr/exposure/pubs/episuite.htm; EPI Suite v.4.00), and ALOGPS 2.1 (http://www.vcclab.org/) [103-105] software programs using the SMILES molecular formula language [106, 107] as inputs for both solutes and solvents. Congener numbering systems for the PFC compounds under study are given in detail in ref. [108].

RESULTS AND DISCUSSION

To facilitate an assessment of existing solvent based equilibrium partitioning approaches towards predicting the BCFs of PFSAs and PFCAs, a review of the literature was undertaken to identify and constrain the range of reported experimental BCF values under laboratory and field conditions (Table 1). In this regard, we note the reviews of Boutonnet et al. [3] on trifluoroacetic acid (TFA) and Conder et al. [37] on the general biological partitioning behavior of longer chain members from these two PFA classes. These reviews contain important BCF data for several PFSA and PFCA congeners (notably TFA and n-perfluorooctane sulfonic acid [n-PFOS]) from industry technical reports that are not available in the open scientific literature. For TFA, no animal BCF data is available to the best of our knowledge, and the current BCF database appears limited to experiments and field data collected for a range of aquatic and terrestrial plant species. Evapotranspirative concentration of the generally non-volatile TFA has been raised as a potential concern in interpreting the BCF data in plants.[3] However, both terrestrial and aquatic plants have approximately equal reported BCF ranges for TFA (0.0 to 1.6 and 0.0 to 1.0, respectively), suggesting such effects do not lead to a significantly different BCF value in plants between these two matrices.

Using the SPARC, KOWWIN, and ALOGPS software programs, the logarithmic octanol-water partition constants (log $K_{ow(SPARC)}$, log $K_{ow(KOWWIN)}$, and log $P_{octanol:water(ALOGPS)}$) were then calculated for all C_1 through C_8 and the straight chain C_9 through C_{15} PFCA (Fig. 2) and PFSA (Fig. 3)

congeners. The SPARC program also allows estimation of the distribution constant for ionizable compounds (log $D_{octanol:water}$; see ref. [109] for a recent review on the application of log D values towards lipophilicity estimation) at varying pH values (we chose pH 7 for our examples, yielding log $D_{octanol:water,pH\ 7}$ as presented in Figures 2 and 3 and used in subsequent analyses). A log D approach is a more accurate theoretical reflection for the partitioning of acidic PFAs (pK_a values <0 for all PFSAs and <4 for all PFCAs studied to date) [53-56] between an aqueous and organic solvent at pH values where the substrates are substantially ionized. In addition, the log D approach can be tailored to a specific pH of interest, such as 8.1 for organic matter in marine systems and 7.4 for blood. However, existing octanol-water based partitioning models for BCF estimation are parametrized for measured and estimated K_{ow} values on generally non-ionizable compounds. Thus, we present the use of both log K_{ow} and log $D_{octanol:water}$ values in the current work for comparative purposes. As Figures 2(a) and 3(a) show, there is wide variability (up to several log units) between predicted octanol-water partitioning constants among the four methods for the C_1 through C_8 PFCAs and PFSAs, respectively. The ALOGPS log P method has only modest increases (<2 log units) between the straight chain C_8 through C_{15} congeners for both PFA classes, whereas the other approaches show log K_{ow}/D increases of up to, and exceeding, ten log units over this perfluoroalkyl chain length range. Furthermore, any log K_{ow}/D/P estimation approaches are continuously being changed over time as computational programs are retrained,[9] leading to temporal variation in estimates that may greatly impact the perceived accuracy at any point in time of any partitioning based approaches towards predicting the biological behavior of PFAs.

As a result, it is clear that the choice of log K_{ow}/D/P estimation approach, and the timing of the calculations, will have a significant - if not determinative - effect on how well the predicted biological partitioning behavior of PFSAs and PFCAs compares to field or laboratory data. These issues have been recently overlooked by Kelly et al.,[62] who examined the trophic level magnification and wildlife exposure for a number of individual straight chain perfluoroalkyl compounds, including PFSAs and PFCAs. Instead of performing updated SPARC calculations, these authors chose to cite a 2006 study by Arp et al. [110] as the source of SPARC calculated log K_{ow} and octanol-air (log K_{oa}) partitioning constants, and personal communication with Dr. David Ellis at Trent University as evidence that SPARC overestimates the log K_{ow} values of PFCAs by one unit. There are several discrepancies in the Kelly et al. data [62] used in their analysis that are worth noting. The SPARC log K_{ow} values were adjusted by one log unit for all congeners with the exception of the C_{13} PFCA (n-perfluorotetradecanoic acid, n-PFTA), for which only 0.2 units was subtracted. As well, the source of the log K_{oa} values for n-perfluorododecanoic acid (n-PFDoA) and n-PFTA are unknown as Arp et al. [110] do not report values for these compounds. Furthermore, the log K_{oa} values reported for n-PFOS and n-perfluorooctanesulfonamide (n-FOSA) appear to have come from Arp et al.'s [110] COSMOtherm estimates rather than their SPARC data. Since the work of Arp et al.,[110] the SPARC software program has been updated. Using the current version of SPARC, we have calculated the following log K_{ow} (also shown in Figures 2 and 3) and log K_{oa} values for the PFCAs and PFSAs discussed in Table S3 by Kelly et al. [62] (data presented as "Feb 2006"→"Apr 2009" SPARC values): log K_{ow}, n-perfluoroheptanoic acid (n-PFHpA), 3.82→5.36; n-perfluorooctanoic acid (n-PFOA), 4.59→6.26; n-perfluorononanoic acid (n-PFNA), 5.45→7.23; n-perfluorodecanoic acid (n-

PFDeA), 6.38→8.26; n-perfluoroundecanoic acid (n-PFUnA), 7.40→9.35; and n-PFOS, 5.26→4.67; log K_{oa}, n-PFHpA, 5.93→7.39; n-PFOA, 6.25→7.62; n-PFNA, 6.55→7.81; n-PFDeA, 6.82→7.96; n-PFUnA, 7.07→8.06; and n-PFOS, 6.17→6.02. Consequently, there are substantial changes in the SPARC predictions using the historical 2006 data from Arp et al. [110] and the current SPARC release. The importance of these temporal changes in SPARC estimated partitioning constants (and that from other computational methods) has been explored in greater detail in our recent review paper.[9]

Such temporal changes also can greatly influence the perceived biological behavior of these compounds. For example, using the log K_{ow}-log K_{oa} classification approach by Kelly et al.,[62] the current SPARC data presented herein indicates that n-PFOA and n-PFNA could be classified as high K_{ow}-high K_{oa} compounds, not low K_{ow}-high K_{oa} compounds as Kelly et al. [62] state, and that n-PFOS could potentially be classified as a low K_{ow}-low K_{oa} compound. Kelly et al. [62] use these classifications to make some important conclusions regarding the environmental behavior of these compounds, whereby n-PFOA, n-PFNA, and n-PFOS are "low K_{ow}-high K_{oa} compounds ($K_{ow} < 10^5$, $K_{oa} > 10^6$) ... expected to only biomagnify in air-breathing wildlife". It is uncertain why Kelly et al. [62] quote the 2006 SPARC values for the nine compounds of interest from Arp et al. [110] (although only seven of these compounds are data in Arp et al. [110]), rather than examine the correlations between their experimental data and values computed from the current SPARC version. Indeed, even in 2006, Arp et al. [110] noted that SPARC calculated physicochemical properties changed substantially between the two versions of the program used over the duration of their study ("spring 2005" versus "February 2006"), a finding further demonstrated in our

recent work [9] illustrating that a set of new 2009 SPARC log K_{ow} values exist for these PFA congeners (as well as some other perfluorinated compounds). The resulting significantly different sequence of 2005→2006→2009 SPARC values for these compounds means that SPARC derived log K_{ow} values for PFAs (as given in Figures 2 and 3) should be considered as "snapshots in time", and that - in the current absence of reliable experimental K_{ow} data for PFAs - any definitive conclusions regarding the perceived general applicability of log K_{ow} based biological partitioning models should be avoided until experimental data is available and the associated computational methods are then validated against such data.

Using the log K_{ow}/D/P values shown in Figures 2(a) and 3(a) for PFCAs and PFSAs, respectively, we applied the BCF estimation approaches set out by Dimitrov et al. (2002),[111] Veith et al. (1979) [112] and EC (1996),[113] Mackay (1982),[114] Veith and Kosian (1983),[115] and Bintein et al. (1993) [116] to predict the corresponding BCFs given in Figures 2(b)-(f) and 3(b)-(f). The combination of four different partitioning constant estimation programs with five different BCF estimation approaches results in 20 combinations of BCF prediction signatures for each of the two PFA classes. The application of the different BCF estimation equations to the pre-existing high variability in log K_{ow}/D/P values from the various software programs results in a similarly large BCF estimate variability that spans up to 10 orders of magnitude for some PFA congeners. Thus, this combinatorial BCF estimation approach highlights the current difficulty in determining whether such K_{ow} based BCF estimation approaches can be reliably applied to PFAs, and warrants caution against prematurely concluding that such approaches are of little potential [62] in understanding the biological partitioning behavior of PFAs - particularly for studies where

there are errors in translating the data values from one study to another, where only one computational approach is utilized on only a selected group of PFA congeners, where only one BCF estimation approach is applied, and/or where only one experimental dataset is investigated.

Based on the available field and laboratory BCF values reported for each PFA congener, we calculated corresponding average experimental BCF values and their range (Table 2) for use in evaluating the various BCF prediction approaches. When the errors between the estimated BCFs using the various method combinations are compared to these average BCF values, the ALOGPS log P estimation method generally outperforms the other log K_{ow}/D methods across the five BCF prediction frameworks. The ALOGPS log P method displays a reasonable average signed error range of 0.0 to 0.4 log BCF units for these eight PFA congeners and an average unsigned error range of 0.6 to 0.7 log BCF units, whereas the other methods have higher average signed errors ranging up to 3.1 log BCF units and average unsigned errors ranging up to 3.5 log BCF units. Reported experimental BCF values range up to 2.3 log units for particular PFA compounds, further confounding a clear determination regarding the accuracy of some traditional K_{ow} based BCF estimation approaches. A graphical comparison between the ALOGPS log P based BCF estimates for the five BCF prediction equations is shown in Figure 4. The greatest prediction error is observed for n-PFOA (all equations overpredict its BCF by at least two log units). n-Perfluorohexanesulfonic acid (n-PFHxS) is approximated within 0.7 to 1.2 log BCF units by the ALOGPS log P based approaches. All other PFA congeners with available experimental data have their BCF values reasonably predicted by existing K_{ow} based approaches and the ALOGPS log P values. We also note that the SPARC K_{ow} values did provide BCF estimates for n-PFHxS

and n-PFOS with errors <0.3 log units using any of the five BCF equations, strongly suggesting that this K_{ow} estimation program and existing BCF equations may provide a highly accurate pre-existing means of estimating BCF values for any PFSA congener. If this is the case, then our PFSA BCF data in Figure 3 using SPARC K_{ow} values may represent reasonably accurate BCF estimates for this important contaminant class. This finding would contradict earlier claims that K_{ow} based approaches would likely be of little value in estimating the biological partitioning behavior of PFSAs.[2, 6]

Regardless of the theoretical issues in applying a primarily lipophilic compound based BCF analytical framework to the proteinophilic PFAs, one must acknowledge that the K_{ow} based approaches provide a reasonable screening level of insight into the bioconcentration properties of PFAs in both plant and animal tissues based on the modest available experimental datasets. While we understand, and agree with, concerns over using K_{ow} based partitioning frameworks on PFAs, we also stress that there is no theoretical rationale behind much of the existing BCF estimation framework for lipophilic compounds. With such a wide diversity in the types (linear, curvilinear, gaussian, sigmoidal, etc.) and the values of the constants in the numerous BCF prediction equations for a wide range of compound classes, this field is based on empirical correlations between experimental BCF data and either experimentally determined or computationally estimated molecular properties. Thus, there is no reason to believe that some K_{ow} based BCF estimation approaches developed primarily for lipophilic compounds may not, perhaps coincidentally, also apply to proteinophilic compounds. Furthermore, many contaminants contain a variety of functional groups giving a resulting complex milieu of various

-philic/-phobic behaviors (i.e., hydrophobic, hydrophilic, proteinophilic, lipophilic, lipophobic, etc.) at the functional group scale. Identifying the overall net -philic/-phobic behavior of a compound based on its functional group components is a major challenge. As a result, while K_{ow} based approaches may appear, on face, to be less than theoretically satisfactory if applied to non-lipophilic contaminants such as PFAs, this discrimination does not appear to have any firm theoretical foundation, since a first principles analysis of the myriad K_{ow} based BCF methods for lipophilic compounds also does not exist.

The most promising means of estimating the congener specific biological and environmental partitioning behavior of PFSAs and PFCAs is through structure-activity relationships developed uniquely for these two contaminant classes.[100, 117] In Figure 5, we show the relationships between the experimentally obtained BCFs and various computationally estimated water-solvent partitioning constants. Included in this figure are the four log K_{ow}/D/P methods shown in Figures 2 and 3, as well as SPARC estimated log K partitioning constants at pH 7 for isoamyl acetate. Similar patterns of log K_{ow}/D/P versus BCF behavior are observed for the four octanol models and isoamyl acetate. The longer chain PFCAs display a consistent relationship between the respective log K_{ow}/D/P and BCF values regardless of solvent, which can either be approximated as second order polynomial equations with terminal curvature between n-PFOA and n-PFTA (as shown in Fig. 5), or as linear relationships between n-PFOA and n-PFDoA. In Figure 6, we also present the relationships between the experimental BCF values for these eight PFA congeners and the corresponding SPARC calculated log K_{ow}/D values in the twenty naturally occurring amino acids as model proteinophilic solvents. The lack of different log K_{ow}/D/P versus BCF

signatures for the various solvent models shows that such computational approaches are not predicting fundamentally different biological partitioning patterns whether the solvent model is lipophilic (i.e., n-octanol) or proteinophilic (i.e., the amino acids).

Distribution constants were also calculated using SPARC for n-PFHxS and n-PFOS using all 20 naturally occurring amino acids at pH 7 in solutions with ionic strengths of zero and 0.15 (near the ionic strength of blood). Increasing the ionic strength from zero to 0.15 uniformly decreases the corresponding log D value by a factor of 0.51 regardless of solvent model or PFSA congener. In general, we found that varying the ionic strength to values between zero and 0.15 generally varied the resulting SPARC log D value by a constant factor regardless of solvent model or solute. This suggests a constant, and solute/solvent independent, SPARC correction factor for ionic strength, so that if an appropriate proteinophilic solvent model for PFAs was found, calculations would only need to be conducted at a chosen ionic strength and could be corrected to any desired ionic strength through an appropriate correction factor. More importantly, SPARC currently does not calculate any relative differences in log D among various solvent model-solute combinations with varying ionic strength. Such differences likely exist, but are not currently incorporated into SPARC, and probing such differences would require more advanced solvation models – likely at the ab initio level. Furthermore, we found that SPARC log D constants were independent of temperature. Again, this does not reflect reality, and is a current limitation of the modeling software that would need to be investigated with more advanced solvation models incorporating explicit temperature dependencies.

In our previous work,[100, 101] we used computationally generated molecular area and volume based approaches to isolate the hydrophobic effects of the perfluoroalkyl chains on PFCAs and PFSAs that contribute to the net driving force (a sum of perfluoroalkyl hydrophobic and head group electrostatic effects; with a potential additional role from hydrogen bonding with the perfluoroalkyl chain) for partitioning to biological materials, thereby allowing for estimation of PFCA and PFSA BCFs for all C_4 through C_8 linear and branched congeners. Our findings suggested that linear PFA congeners should display significantly higher BCFs than the corresponding branched congeners. These findings have been subsequently confirmed by both field and laboratory based experimental studies.[67, 68, 72, 118, 119] The approximately linear relationships between the various log K_{ow}/D/P values for lipophilic and proteinophilic and n-PFOA through n-PFDoA experimental BCFs shown in Figures 5 and 6 are consistent with our prior BCF estimation approaches. Furthermore, all log K_{ow}/D/P estimation approaches used to construct Figures 2(a) and 3(a) predict higher BCFs for linear versus branched PFA congeners. Thus, application of any of the log K_{ow}/D/P versus BCF relationships in Figure 5 and corresponding log K_{ow}/D/P values from Figures 2 and 3 would yield a similar congener specific pattern of predicted PFCA and PFSA BCF values, respectively, for linear and branched congeners as we previously published using semiempirical computational methods.[100, 101] As we stressed in our prior work,[100, 101] various estimation methods will yield quite different relative intrahomologue BCFs based on branching of the perfluoroalkyl chain, as well as different BCFs for all members of a homologue group outside the very limited experimental training set shown in Table 1 (limited to the straight chain C_6 and C_8 PFSA and C_7 through C_{13} PFCAs) - a fact clearly demonstrated in Figures 2 and 3. Additional experimental values from both branched PFA

congeners of any perfluoroalkyl chain length and straight chain congeners outside the existing dataset ranges are required to calibrate any of the computationally based approaches in our current or previous [100, 101] work. However, it is clear from our extensive modeling efforts on a number of PFC classes, and the limited experimental database, that any process involving partitioning of PFCs to organic matter, whether abiotic or biotic, will result in a preferential fractionation towards a more linear congener profile across all homologues and PFC subclasses.

The relatively high BCF reported for TFA is difficult to reconcile with an extrapolation of the trend observed between n-PFOA and n-PFTA for all lipophilic solvents in Figure 5 and almost all amino acid model proteinophilic solvents in Figure 6. In Figure 6, asparagine and histidine model solvent log D values include TFA in the general PFCA trend, but the distribution of log D values across all PFCAs is too small for these two solvents to allow a reliable structure-activity relationship to be generated (i.e., a regression with a near infinite slope would result, leading to large corresponding uncertainties in the predicted BCF values, making the effort of little value). As noted above, only plant BCF data is available for TFA; and thus, we cannot say whether these BCF values are anomalously high compared to what would be observed for higher trophic level aquatic organisms. Little difference in the BCFs between benthic alga and rainbow trout was observed for n-PFOS (Table 1), and if this relationship also applies for TFA, we would expect TFA to bioconcentrate in all aquatic organisms. These comparisons highlight the need for further BCF testing on TFA in higher aquatic organisms, as there appears to be a possibility that the sharply declining trend in BCFs with decreasing perfluoroalkyl chain length reported for the longer chain PFCAs may slow sharply, or even reverse after reaching some minimum between

TFA and n-PFOA, as the chain length approaches its minimum at TFA. If TFA does have a BCF >1 in some higher organisms, this would be clear evidence for changing electrostatic contributions towards biological partitioning with changing perfluoroalkyl chain length, such that the much reduced hydrophobic contribution to bioconcentration in TFA (relatively to, for example, n-PFOA) has been more than compensated for by a large increase in the electrostatic contribution to proteinophilic bioconcentration, with the net result of TFA having a BCF equal to, or even greater than, the much more hydrophobic n-PFOA.

As we [53, 56] and others [54, 120] have discussed, the pK_a (a measure of electrostatic character at the head group) of PFCAs increases substantially in moving from TFA (pK_a about 0.5) to n-PFOA (pK_a between about 3 and 4). Consequently, the greater acidity of TFA compared to n-PFOA may reflect a proxy for corresponding increases in the electrostatic contribution to proteinophilic sorption behavior that the BCF data in Table 1 may also suggest. We stress, however, such discussions are hypothetical in the absence of clear BCF testwork on TFA showing whether it does, or does not, bioconcentrate in some higher aquatic organisms. With respect to the PFSAs, we expect all congeners to be strong acids (pK_a values <0),[21, 55] but any potential changes in the electrostatic character of the sulfonate head group with changing perfluoroalkyl chain length and/ or branching is poorly understood. One of the primary limitations in this regard are the disagreements between the various computational approaches. For example, we have shown that the semiempirical PM6 method predicts substantial chain branching effects on the pK_a values of both PFSAs and PFCAs, with branched congeners more acidic than their linear counterparts by up to several pK_a units.[21, 53] In contrast, SPARC predicts a small branching effect on pK_a.[21, 56]

Neither the PM6 method nor SPARC predict substantial chain length effects on the pK_a values of these two classes between C_1 and C_8, which is inconsistent with the known increasing pK_a with increasing straight chain length for the PFCAs, and in general, neither method adequately modeled the pK_a values of PFSAs or PFCAs.[21, 53, 55, 56] Ab initio computational approaches may offer some improved understanding regarding the electrostatic character of the PFA head groups, particularly the effects of chain length and branching, but additional experimental work is required for confirmation.

As the linearity of the n-PFOA through n-PFDoA log K_{ow}/D/P versus BCF relationships in Figures 5 and 6 illustrate, these computational approaches are likely assuming that the increasing length of the perfluoroalkyl chain (i.e., sequential addition of $-CF_2-$ groups to the end of the perfluoroalkyl chain) is driving the relatively constant increase in BCF values over this range, and that electrostatic contributions towards the net partitioning constant by the respective head groups are negligible. This finding is both consistent with our previous PFA modeling framework,[100, 101] as well as the hypotheses of Martin et al. [75] that, for the longer chain PFAs, increasing hydrophobicity of the perfluoroalkyl chain was driving the increasing BCF values with increasing chain length. Organic carbon normalized sediment-water partitioning constants (K_{oc}) determined by Higgins et al. for PFSAs and PFCAs also found a relatively constant hydrophobic contribution with increasing perfluoroalkyl chain length,[121, 122] consistent with our computational studies on these compounds,[117] further suggesting that hydrophobic interactions are dominating the change in organic matter partitioning seen with increasing perfluoroalkyl chain lengths.

On this point, we note that Kelly et al. [62] have recently made the statement that there are problems with "using a K_{ow} based (hydrophobicity) approach for evaluating bioaccumulation potential of PFAs." Lipophilicity, a subset of hydrophobicity, should not be confused with the more broader concept of hydrophobicity. It is widely stated, for example, that perfluoroalkyl groups are both oleophobic and hydrophobic, suggesting that hydrophobic compounds are not necessarily lipophilic. As the studies presented in Table 1 have shown, increasing perfluoroalkyl chain length correspondingly increases the partitioning of PFAs onto/into biological materials. While the electrostatic interaction between the carboxylate or sulfonate head group and proteinaceous materials clearly plays a major role in the partitioning behavior of PFAs, so does the hydrophobic driving force from an increasing perfluoroalkyl chain length. Although perfluoroalkyl chain length may contribute to variation in the electrostatic character of the head group at short chain lengths (such as TFA as discussed above), there does not appear to be a convincing rationale why increasing the perfluoroalkyl chain length from C_8 to C_9 would affect the electrostatic character of the head group to such an extent to explain the increase in biological partitioning behavior between these two compounds. The likely explanation for the difference in the biological partitioning behavior of longer chain PFAs, then, is most probably a hydrophobic rationale where the electrostatic contribution of the head group to protein partitioning is essentially constant for all longer chain PFAs, and the increasing hydrophobicity of the perfluoroalkyl chain with increasing chain length is driving the increase in partitioning constants.

As noted in the Introduction, there are - to the best of our knowledge - no reliable experimental

BCF measurements upon which to calibrate existing computational approaches for the perfluoroalkyl sulfonamides. In addition, the primary and secondary substituted perfluoroalkyl sulfonamides (e.g., SAs, NMeSAs, NEtSAs, SEs, and SAAs; see Figure 1 for structures) have acidic protons, and any examination of experimental data or use of estimation methods must keep this factor in mind. The PFSAs and PFCAs also clearly have acidic protons, and yet in some cases existing BCF estimation approaches designed primarily for non-ionic lipophilic compounds appear to reasonably approximate the biological partitioning behavior of these ionic and proteinophilic PFAs. Consequently, we chose to also examine the computationally estimated chemical space of perfluoroalkyl sulfonamide BCF behavior. Reasonably good consistency (in an approximately linear relationship) was obtained for the SPARC log K_{ow} and KOWWIN log K_{ow} values for all C_1 through C_{15} straight chain SAs, NMeSAs, NEtSAs, NNdiMeSAs, NNdiEtSAs, SEs, NMeSEs, NEtSEs, SAAs, NMeSAAs, and NEtSAAs (Figures 7 and 8). By comparison, the ALOGPS log $P_{octanol:water}$ values exhibit biphasic behavior which agrees with the corresponding SPARC and KOWWIN log K_{ow} values up to a perfluoroalkyl chain length of about six carbons for all sulfonamide classes. After this point, the ALOGPS log P values trend linearly with a smaller increase in value with increasing chain length, yielding differences in estimated log K_{ow} values by up to ten log units for the C_{15} chain length. No experimentally available octanol-water partitioning constants appear to be available for the sulfonamides upon which to calibrate these estimates. However, we have previously shown that SPARC estimates the log K_{oa} values of the two perfluoroalkyl sulfonamides for which experimental data are available,[9] suggesting that the corresponding log K_{ow} values may also be reliable.

For the acidic sulfonamides, the SPARC log D values also show an approximately linear relationship with increasing chain length similar to the SPARC and KOWWIN log K_{ow} values. The SPARC log D values are lower than, or equal to, the corresponding log K_{ow} values by amounts that correlate with the pK_a of the substrate, reflecting decreased partitioning into octanol due to substrate ionization. In other words, the lower the estimated pK_a value, the greater ionization would occur at pH 7, and the corresponding larger difference between the log K_{ow} and log D values. This difference between SPARC log K_{ow} and log D values reaches a maximum for the SAAs, which have carboxylate groups (pK_a values of about 4) that are entirely ionized at pH 7, and which also have acidic amide protons that can also ionize at near neutral pH values, resulting in overall contributions from dianionic structures at pH 7 having log D constants up to several log units lower than the corresponding log K_{ow} values. When the differences between computational methods are input into the various BCF estimation equations, resulting wide variation (up to ten log units) is observed in estimated BCF differences for each sulfonamide isomer. Consequently, the lack of any reliable experimental BCF data upon which to calibrate the methods, and the wide differences in BCF estimates obtained depending on the partitioning calculation and BCF framework combination, mean that there are currently no methods for determining which, if any, of our existing BCF estimation approaches results in a reasonably accurate sulfonamide BCF signature.

The importance of including the ionization of acidic primary and secondary substituted amide protons for the perfluoroalkyl sulfonamides when assessing abiotic or biotic partitioning behavior is illustrated in Figure 9. As we have previously shown,[58] increasing branching of the

perfluoroalkyl chain on sulfonamides is expected to significantly increase the pK_a of any amidic protons by up to several pK_a units. Increased branching of the perfluoroalkyl chain is also expected to significantly decrease the partitioning to organic matter.[100] Consequently, the linear C_8 SA **89** (i.e., n-FOSA) is expected to have a log D value for the non-ionized species that is significantly higher than for its highly branched 1,1',2,2'-tetramethylbutyl counterpart C_8 SA **23**, consistent with the results shown in Figure 9(a) at lower pH values. Chain branching reduces the acidity of C_8 SA **23** relative to C_8 SA **89**, leading to a difference in the log D values between these two congeners that is maximized at low and high pH values (Δlog D of about 3 log units) and minimized at near neutral pH values (Δlog D of about one log unit at a marine system pH of 8.1). Thus, the relative magnitudes of the log D values between various acidic perfluoroalkyl sulfonamide congeners (as well as any other acidic perfluoroalkyl compounds) depends not only on the perfluoroalkyl chain length and branching, and head group identity, but also the pH under consideration. This large number of competing influences that governs the overall resultant partitioning behavior of acidic PFCs to both abiotic and biotic organic matter must be taken into account in all relevant studies, otherwise spurious conclusions and incorrect interpretations of experimental data will occur. Addition of an amidic ethyl group to n-FOSA (giving C_8 NEtSA **89** or n-NEtFOSA) both increases its inherent log D value, and increases the amidic proton pK_a, leading to a Δlog D between n-FOSA and n-NEtFOSA that is minimized at low and high pH values (about 0.5 log unit difference) and maximized at near neutral pH values (up to two log units difference).

For the sulfonamidoethanols and sulfonamidoacetates, similar effects of chain length, branching,

and amidic group alkylation on pK_a values and log D values are predicted. The non-ionized C_8 SE **89** (i.e., n-FOSE) is moderately less lipophilic than its C_8 NEtSE **89** (i.e., n-NEtFOSE) counterpart, with a Δlog D of about 0.5 log units for the non-ionized n-FOSE (n-NEtFOSE does not have an acidic amide proton, and the alcohol moieties on all SE congeners are not acidic in environmentally and biologically relevant aqueous solutions) (Fig. 9(b)). Upon ionization of the amidic proton on n-FOSE at pH values >8, the Δlog D between these two compounds increases significantly to two log units. With regard to the SAAs, these compounds have carboxylate functions that will ionize at pH values <5 (pK_a values are about 4), and at near neutral pH values the carboxylate groups will be effectively ionized. For C_8 SAA **89** (i.e., n-FOSAA), the amidic proton has an estimated pK_a of 7.4, such that in vivo and in natural waters, substantial contributions from the dianionic species will be present (in marine systems with a pH >8, the dianionic species will be dominant). As shown in Figure 9(c), the ionization of the amidic proton on n-FOSAA has an insignificant effect on the log D compared to the C_8 NEtSAA **89** (i.e., n-NEtFOSAA), whose carboxylate group is expected to display similar ionization behavior as for n-FOSAA, though no amidic proton is present on n-NEtFOSAA to also ionize. It therefore appears that the partitioning behavior of both the secondary and tertiary substituted SAAs will be primarily governed by ionization of the carboxylate group, and the subsequent ionization at higher pH values of any amidic protons that may be present is not expected to have a significant additional impact on the non-specific (solubility-based) partitioning behavior. We do note, however, that any site specific partitioning behavior that involves direct binding/association between an anionic nitrogen atom on a sulfonamide and a corresponding positively charged receptor site will likely display a greater dependence on ionization of the amidic group than is

reflected in the pattern of SPARC log D values with increasing pH.

As expected based on our prior studies into the C_4 through C_8 congener specific BCFs for the PFSAs and PFCAs,[100] the perfluoroalkyl sulfonamides also display similar patterns of increasing BCF with increasing linearity and length of the perfluoroalkyl chains (Figure 10). These estimated BCFs use the ALOGPS log P values as inputs, and as we have previous shown with regard to our estimates of log K_{oc} values for the PFSAs and PFCAs,[117] the ALOGPS program generally estimates less intrahomologue log P variation than is observed for corresponding SPARC log K_{ow} or log D values. As a result, if SPARC log K_{ow} or log D values more accurately represent the intrahomologue variation in organic matter partitioning behavior than the ALOGPS values, we would expect greater intrahomologue BCF variability than is being shown in this representative figure. However, all computational approaches we have examined to date, and the limited experimental dataset for PFSAs and PFCAs, all consistently indicate that branched PFC congeners should display lower organic matter partitioning behavior compared to their more linear chain counterparts. Thus, we would reasonably expected branched perfluoroalkyl sulfonamides to have lower BCF values than linear congeners.

CONCLUSIONS

The SPARC, KOWWIN, and ALOGPS software programs were used to calculate the octanol-water partitioning and distribution constants for the C_1 through C_8 and the straight chain C_9 through C_{15} PFSAs and PFCAs. These programs predict widely variable K_{ow} values (up to

several log units), with ALOGPS predicting modest increases for the C_8 to C_{15} congeners while SPARC and KOWWIN predict substantial increases over this series. Several widely used BCF equations were applied to the calculated partitioning constants from these three computational programs, resulting in a wide range of estimated BCFs that range up to 10 orders of magnitude for some congeners. The ALOGPS program generally outperformed the other computational programs when used with any of the BCF prediction methods. Despite the limited experimental data set available for PFSAs, SPARC generated K_{ow} values appear to reasonably predict BCF values using all methods examined. Computational estimates of BCFs for the perfluoroalkyl sulfonamides are also predicted to increase with increasing linearity and chain length, regardless of partitioning estimation method and BCF framework used, although differences in magnitude up to 10 log BCF units were observed for some congeners due to the combination of partitioning constant and BCF estimation equation employed. There is currently no perfluoroalkyl sulfonamide BCF data available to determine whether any of the approaches examined accurately represent this class of compounds.

Predicted biological partitioning behavior of all perfluorinated compounds will vary substantially with the estimation approach and BCF framework employed. Temporal variability will also impact predicted BCFs and perceived accuracy, since the computational methods are regularly updated and retrained, resulting in potentially substantial differences between calculated values over time. For the PFSA and PFCA congeners with experimentally determined BCFs, model lipophilic and proteinophilic solvent based distribution constant values exhibited similar relationships with their corresponding BCF values. For longer chain PFCA and PFSA congeners,

increasing hydrophobicity of the perfluoroalkyl chain, rather than electrostatic effects, appears to be driving the observed increase in BCF values.

FIGURE CAPTIONS

Figure 1. General structures of the compounds under study.

Figure 2. Estimated C_1 through C_8 PFCA congener specific (a) SPARC log K_{ow} (circles), SPARC log $D_{octanol:water}$ (squares), KOWWIN log K_{ow} (up triangles), and ALOGPS log $P_{octanol:water}$ values (down triangles), and the corresponding estimated log BCF values using these partitioning constants with the (b) Dimitrov et al. (2002) [111], (c) Veith et al. (1979) [112] and EC (1996) [113], (d) Mackay (1982) [114], (e) Veith and Kosian (1983) [115], and (f) Bintein et al. (1993) [116] estimation approaches.

Figure 3. Estimated C_1 through C_8 PFSA congener specific (a) SPARC log K_{ow} (circles), SPARC log $D_{octanol:water}$ (squares), KOWWIN log K_{ow} (up triangles), and ALOGPS log $P_{octanol:water}$ values (down triangles), and the corresponding estimated log BCF values using these partitioning constants with the (b) Dimitrov et al. (2002) [111], (c) Veith et al. (1979) [112] and EC (1996) [113], (d) Mackay (1982) [114], (e) Veith and Kosian (1983) [115], and (f) Bintein et al. (1993) [116] estimation approaches.

Figure 4. Comparison between average experimental log BCF values for various PFA congeners (TFA, diamond; n-PFOA through n-PFTA, circles; n-PFHxS and n-PFOS, squares) and the predicted log BCF values using the corresponding ALOGPS log P estimates and the (a) Dimitrov et al. (2002) [111], (b) Veith et al. (1979) [112] and EC (1996) [113], (c) Mackay (1982) [114], (d) Veith

and Kosian (1983) [115], and (e) Bintein et al. (1993) [116] octanol-water partitioning based BCF estimation approaches. X-axis error bars represent the range of experimental log BCF values. Y-axis error bars reflect the estimated error in the ALOGPS log P values as determined by this software program.

Figure 5. Comparisons between the average experimental log BCF values for various PFA congeners (TFA, diamond; n-PFOA through n-PFTA, circles; n-PFHxS and n-PFOS, squares) and corresponding computationally estimated solvent:water partitioning constants for octanol ((a) SPARC log K_{ow}, (b) SPARC log $D_{octanol:water}$, (c) KOWWIN log K_{ow}, and (d) ALOGPS log $P_{octanol:water}$), and (e) isoamyl acetate. X-axis error bars reflect the estimated error in the ALOGPS log P values as determined by this software program. Y-axis error bars represent the range of experimental log BCF values.

Figure 6. Comparisons between the average experimental log BCF values for various PFA congeners (TFA, diamond; n-PFOA through n-PFTA, circles; n-PFHxS and n-PFOS, squares) and corresponding computationally estimated SPARC log K_{ow} (open symbols) and log D (closed symbols) using the 20 naturally occurring amino acids as model proteinophilic solvents. Y-axis error bars represent the range of experimental log BCF values.

Figure 7. Estimated straight chain C_1 through C_{15} SPARC log K_{ow} (circles), SPARC log $D_{octanol:water}$ (squares), KOWWIN log K_{ow} (up triangles), and ALOGPS log $P_{octanol:water}$ values (down triangles), and the corresponding estimated log BCF values using these partitioning constants

with the Dimitrov et al. (2002) [111], Veith et al. (1979) [112] and EC (1996) [113], Mackay (1982) [114], Veith and Kosian (1983) [115], and Bintein et al. (1993) [116] estimation approaches for the (a) SAs, (b) NMeSAs, (c) NEtSAs, (d) NNdiMeSAs, and (e) NNdiEtSAs.

Figure 8. Estimated straight chain C_1 through C_{15} SPARC log K_{ow} (circles), SPARC log $D_{octanol:water}$ (squares), KOWWIN log K_{ow} (up triangles), and ALOGPS log $P_{octanol:water}$ values (down triangles), and the corresponding estimated log BCF values using these partitioning constants with the Dimitrov et al. (2002) [111], Veith et al. (1979) [112] and EC (1996) [113], Mackay (1982) [114], Veith and Kosian (1983) [115], and Bintein et al. (1993) [116] estimation approaches for the (a) SEs, (b) NMeSEs, (c) NEtSEs, (d) SAAs, (e) NMeSAAs, and (f) NEtSAAs.

Figure 9. Representative pH dependent SPARC log $D_{octanol:water}$ plots for (a) the straight chain C_8 SA **89** (n-FOSA; circles), the branched 1,1',2,2'-tetramethylbutyl substituted C_8 SA **23** (FOSA **23**; squares), and the straight chain C_8 NEtSA **89** (n-N-EtFOSA; diamonds), (b) the straight chain C_8 SE **89** (n-FOSE; circles) and the straight chain C_8 NEtSE **89** (n-EtFOSE; squares), and (c) the straight chain C_8 SAA **89** (n-FOSAA; circles) and the straight chain C_8 NEtSAA **89** (n-EtFOSAA; squares).

Figure 10. Estimated (a) ALOGPS log P values and corresponding estimated log BCF values using these partitioning constants with the (b) Dimitrov et al. (2002) [111], (c) Veith et al. (1979) [112] and EC (1996) [113], (d) Mackay (1982) [114], (e) Veith and Kosian (1983) [115], and (f) Bintein et al. (1993) [116] estimation approaches for the SAs (circles), NMeSAs (squares), NEtSAs (up

triangles), SEs (down triangles), and SAAs (diamonds).

Table 1. Comparison between available experimental bioconcentration factors (BCFs) for various PFA congeners and the corresponding range of predicted values using the various octanol-water partitioning prediction methods and octanol-water partitioning based BCF estimation approaches as discussed in the text.

Compound	Predicted log BCF	Observed log BCF	Species	Ref.
TFA	-1.3 to 1.0	0.0 to 0.2	*Lemna gibba* (floating higher aquatic plant)	[3]
		0.0 to 0.3	spruce	[3]
		0.5 to 1.3	*Helianthus annuus* (sunflower plant)	[123]
		1.0	*Selenastrum capricornutum* (freshwater alga)	[3]
		1.2 to 1.4	*Glycine* spp. (soya)	[3]
		1.4 to 1.6	*Triticum aestivum* (wheat)	[3]
n-PFOA	2.6 to 5.0	-0.1 to 1.2	*Trachemys scripta elegans* (turtle) and *Chinemys reevesii* (turtle)	[77]
		0.3	*Pimephales promelas* (fathead minnow)	[37]
		0.5 to 1.0	*Cyprinus carpio* (common carp)	[37]
		0.6 to 1.4	*Oncorhynchus mykiss* (rainbow trout)	[75]
n-PFDeA	2.6 to 6.9	2.7 to 3.4	*Oncorhynchus mykiss* (rainbow trout)	[75]
n-PFUnA	1.4 to 8.0	3.4 to 4.0	*Oncorhynchus mykiss* (rainbow trout)	[75]
n-PFDoA	0.2 to 9.2	4.3 to 4.6	*Oncorhynchus mykiss* (rainbow trout)	[75]
n-PFTA	-2.5 to 11.7	4.4 to 4.5	*Oncorhynchus mykiss* (rainbow trout)	[75]
n-PFHxS	0.1 to 3.2	1.0 to 1.9	*Oncorhynchus mykiss* (rainbow trout)	[75]
n-PFOS	1.8 to 5.0	2.3	zooplankton	[71] in [37]
		2.8 to 3.0	benthic algae	[73] in [37]
		3.0 to 3.6	*Oncorhynchus mykiss* (rainbow trout)	[75]
		3.1 to 3.6	*Lepomis macrochirus* (bluegill sunfish)	[37]
		3.7 to 4.6	*Trachemys scripta elegans* (turtle) and *Chinemys reevesii* (turtle)	[77]
		3.9	*Micropterus dolomieui* (smallmouth bass) and *Micropterus salmoides* (largemouth bass)	[79]
		3.9	A range of fish species from Japan	[80] in [37]

Table 2. Comparison of predicted log BCF errors for various PFA congeners for which experimental data is available and using the range of octanol-water partitioning prediction methods and octanol-water partitioning based BCF estimation approaches as discussed in the text. Reported experimental log BCF values presented as the average across all available laboratory and field studies (log $BCF_{exp,avg}$) with the range in parentheses.

Compound	log $BCF_{exp,avg}$	Dimitrov et al. (2002) [111]				Bintein et al. (1993) [116]				Veith et al. (1979) [112] and EC (1996) [113]				Veith and Kosian (1983) [115]				Mackay (1982) [114]			
		SPARC log K_{ow}	SPARC log D	KOWWIN log K_{ow}	ALOGPS log P	SPARC log K_{ow}	SPARC log D	KOWWIN log K_{ow}	ALOGPS log P	SPARC log K_{ow}	SPARC log D	KOWWIN log K_{ow}	ALOGPS log P	SPARC log K_{ow}	SPARC log D	KOWWIN log K_{ow}	ALOGPS log P	SPARC log K_{ow}	SPARC log D	KOWWIN log K_{ow}	ALOGPS log P
TFA	0.8 (0.0 to 1.6)	0.0	-0.3	-0.3	-0.1	0.0	-1.6	-1.2	-0.4	0.0	-1.5	-1.1	-0.4	0.2	-1.2	-0.8	-0.2	-0.4	-2.1	-1.7	-0.8
n-PFOA	0.7 (-0.1 to 1.4)	3.1	2.0	3.1	2.0	3.6	2.5	3.6	2.5	4.0	2.3	4.0	2.3	3.9	2.4	3.9	2.3	4.3	2.4	4.3	2.3
n-PFDeA	3.1 (2.7 to 3.4)	-0.3	0.7	-0.3	0.0	-0.5	1.1	-0.4	0.5	3.3	1.7	3.2	0.4	3.1	1.6	3.1	0.4	3.9	2.0	3.9	0.5
n-PFUnA	3.7 (3.4 to 4.0)	-1.9	-0.3	-1.8	-0.3	-2.3	-0.3	-2.1	0.2	3.5	1.9	3.4	0.1	3.3	1.8	3.2	0.0	4.3	2.4	4.2	0.2
n-PFDoA	4.5 (4.3 to 4.6)	-3.4	-2.0	-3.2	-0.9	-4.2	-2.2	-3.9	-0.4	3.8	2.2	3.5	-0.4	3.4	2.0	3.2	-0.4	4.7	2.9	4.4	-0.2
n-PFTA	4.5 (4.4 to 4.5)	-4.0	-3.7	-3.9	-0.8	-6.9	-4.9	-5.9	-0.2	5.9	4.3	5.1	-0.1	5.4	4.0	4.7	-0.1	7.3	5.4	6.3	0.2
n-PFHxS	1.5 (1.0 to 1.9)	-0.1	-0.7	1.2	0.7	0.3	-1.0	1.7	1.2	0.2	-1.0	1.5	1.0	0.3	-0.7	1.6	1.1	0.0	-1.4	1.6	1.0
n-PFOS	3.4 (2.3 to 4.6)	-0.5	-1.6	0.3	-0.8	0.0	-1.1	0.8	-0.3	-0.1	-1.2	1.2	-0.5	-0.1	-1.1	1.2	-0.5	-0.1	-1.3	1.6	-0.5
	Avg. error (signed)	-0.9	-0.8	-0.6	0.0	-1.2	-0.9	-0.9	0.4	2.6	1.1	2.6	0.3	2.4	1.1	2.5	0.3	3.0	1.3	3.1	0.3
	Avg. error (unsigned)	1.7	1.4	1.8	0.7	2.2	1.8	2.5	0.7	2.6	2.0	2.9	0.6	2.5	1.8	2.7	0.6	3.1	2.5	3.5	0.7

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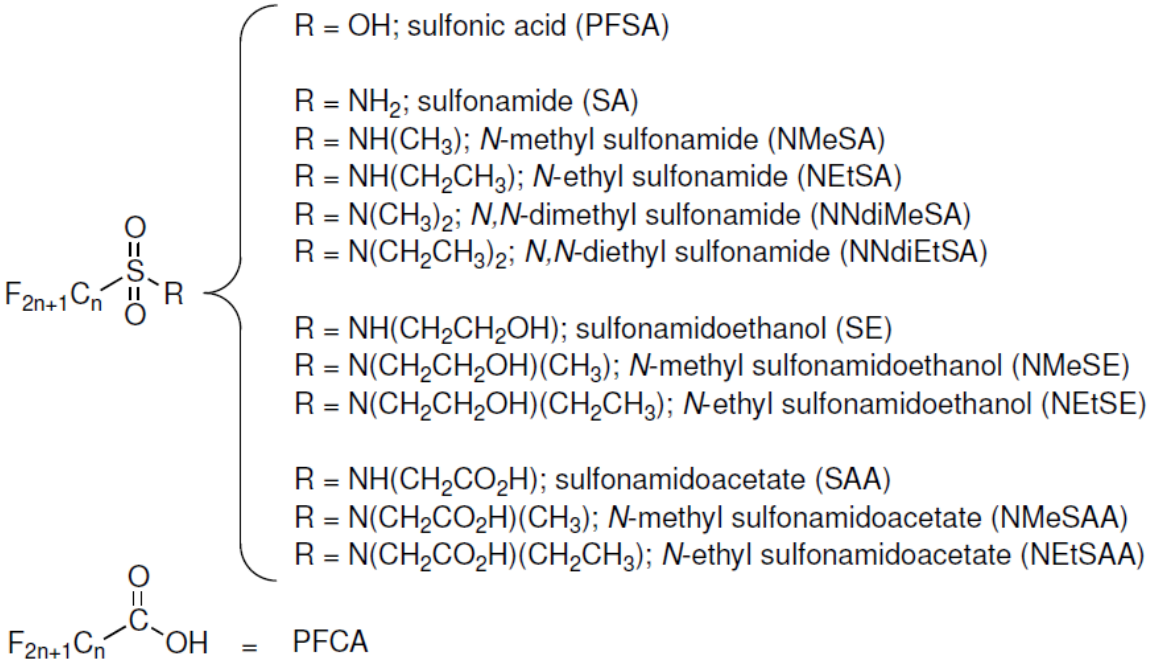


Fig. 1

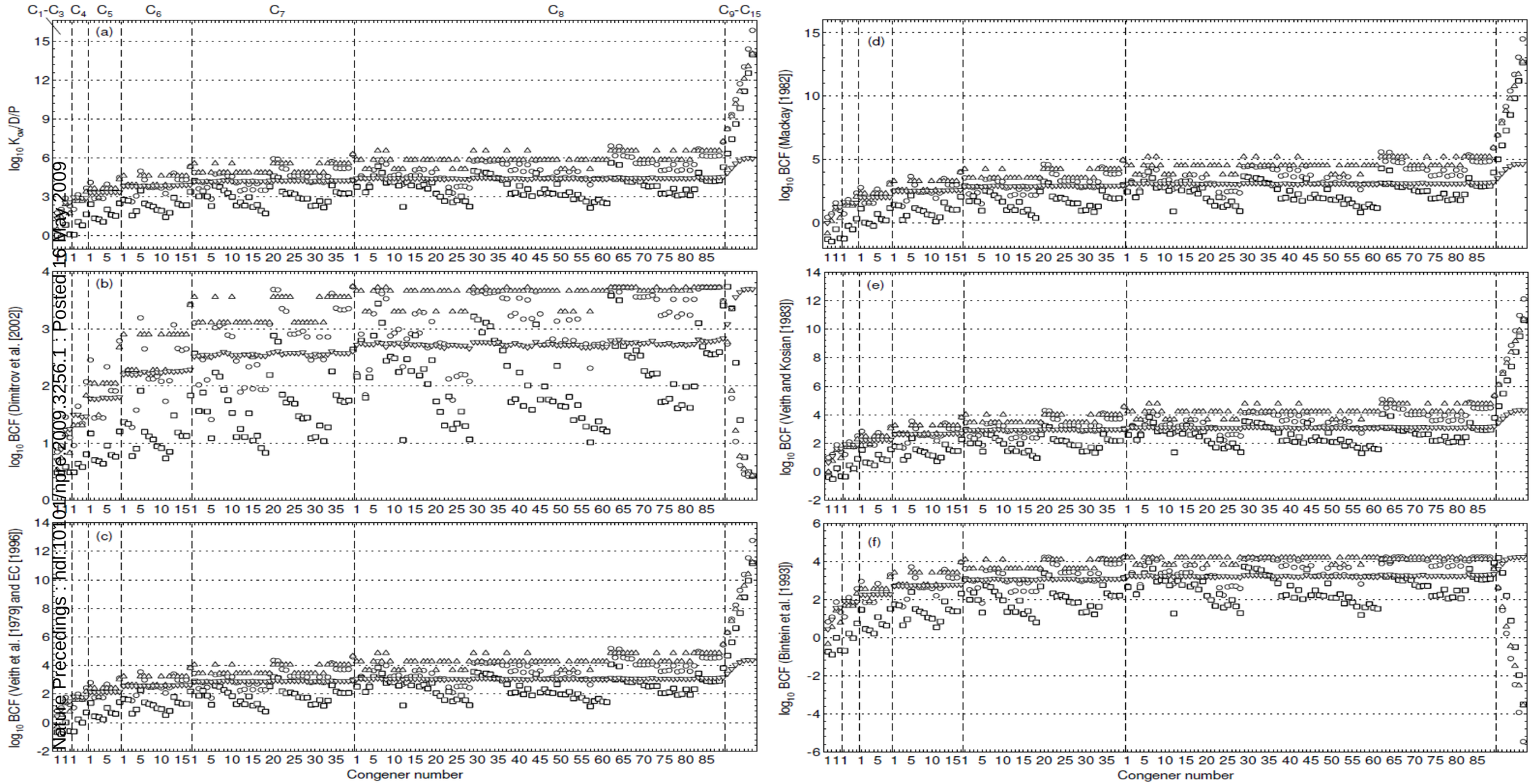


Fig. 2

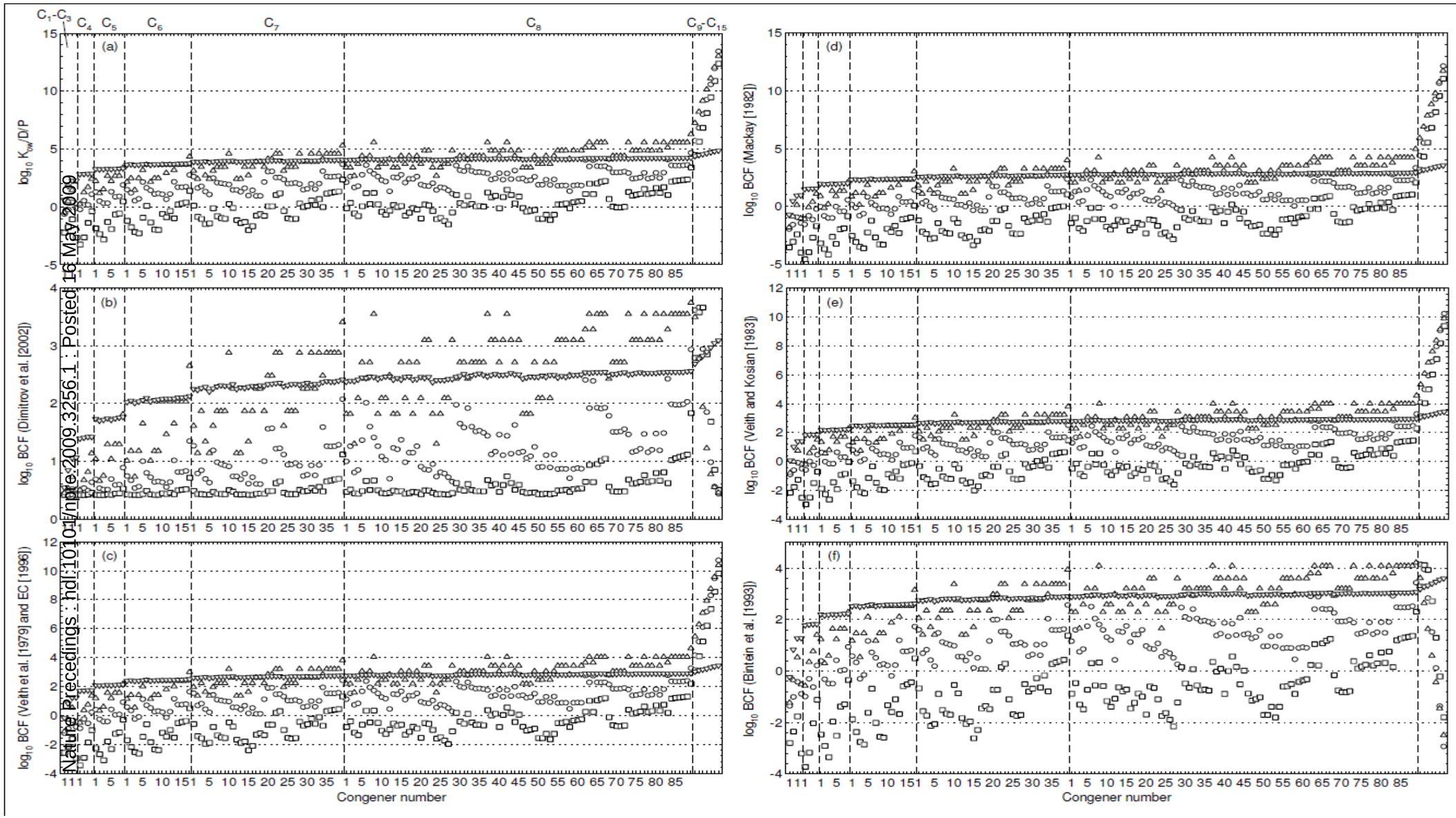
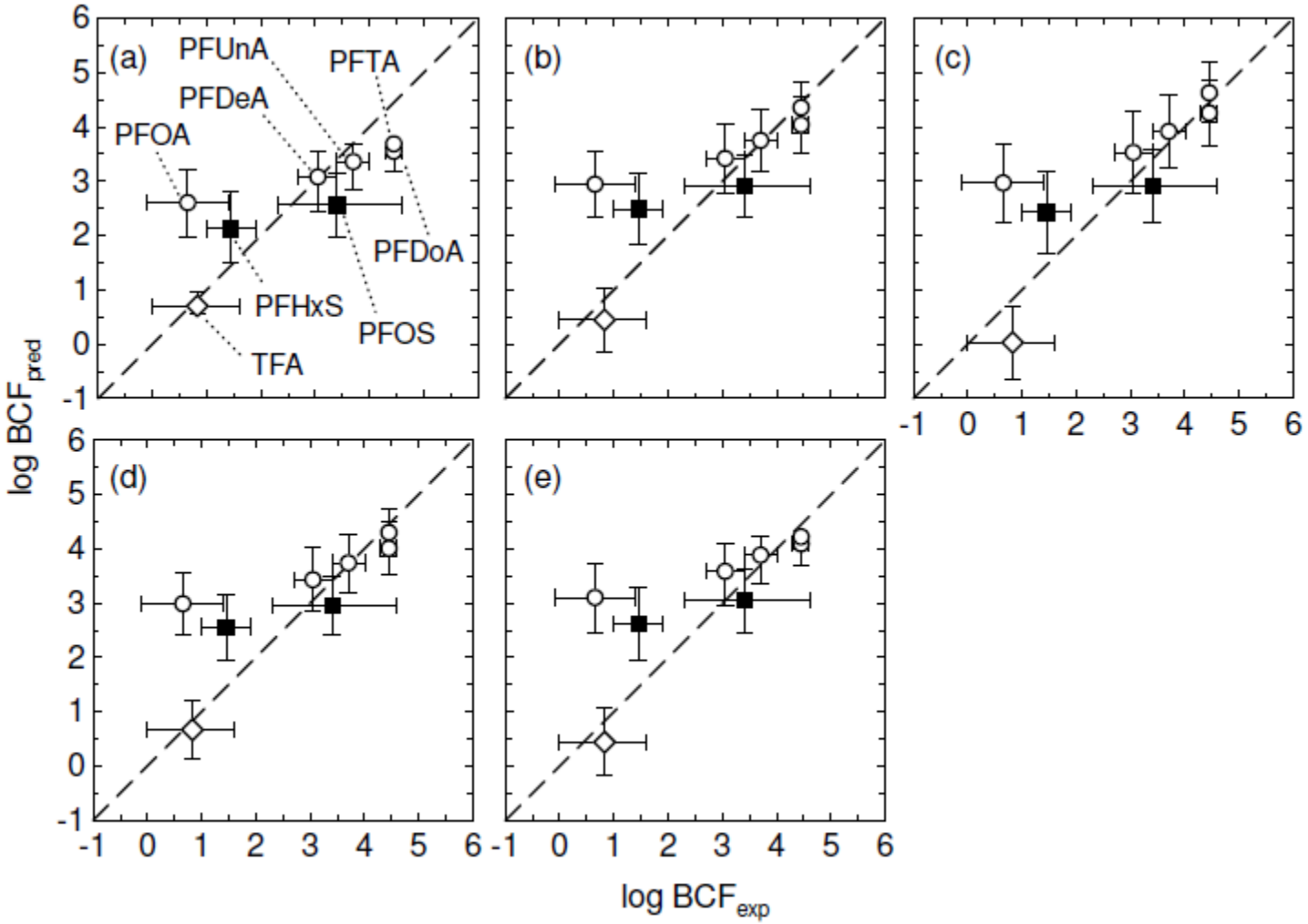


Fig. 3



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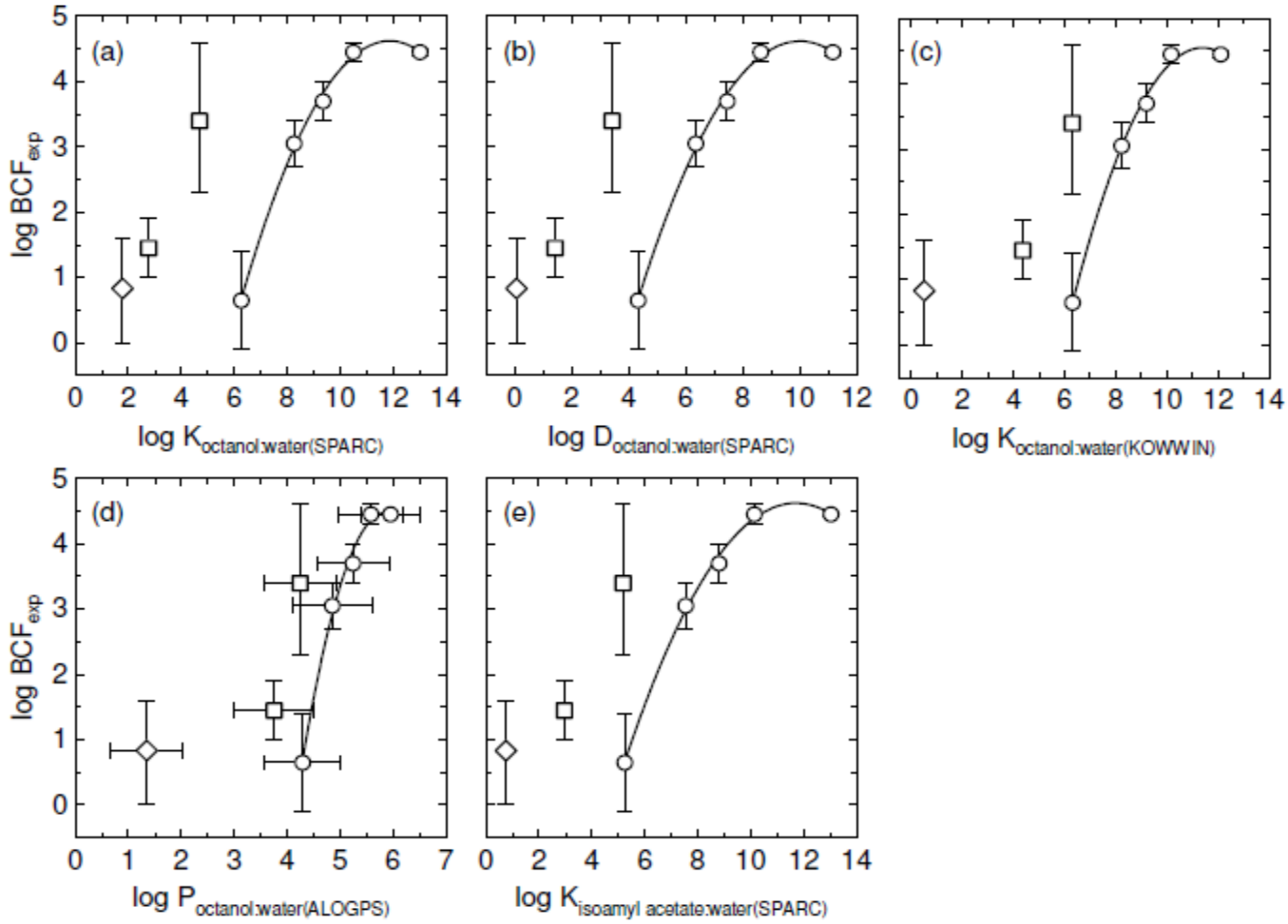
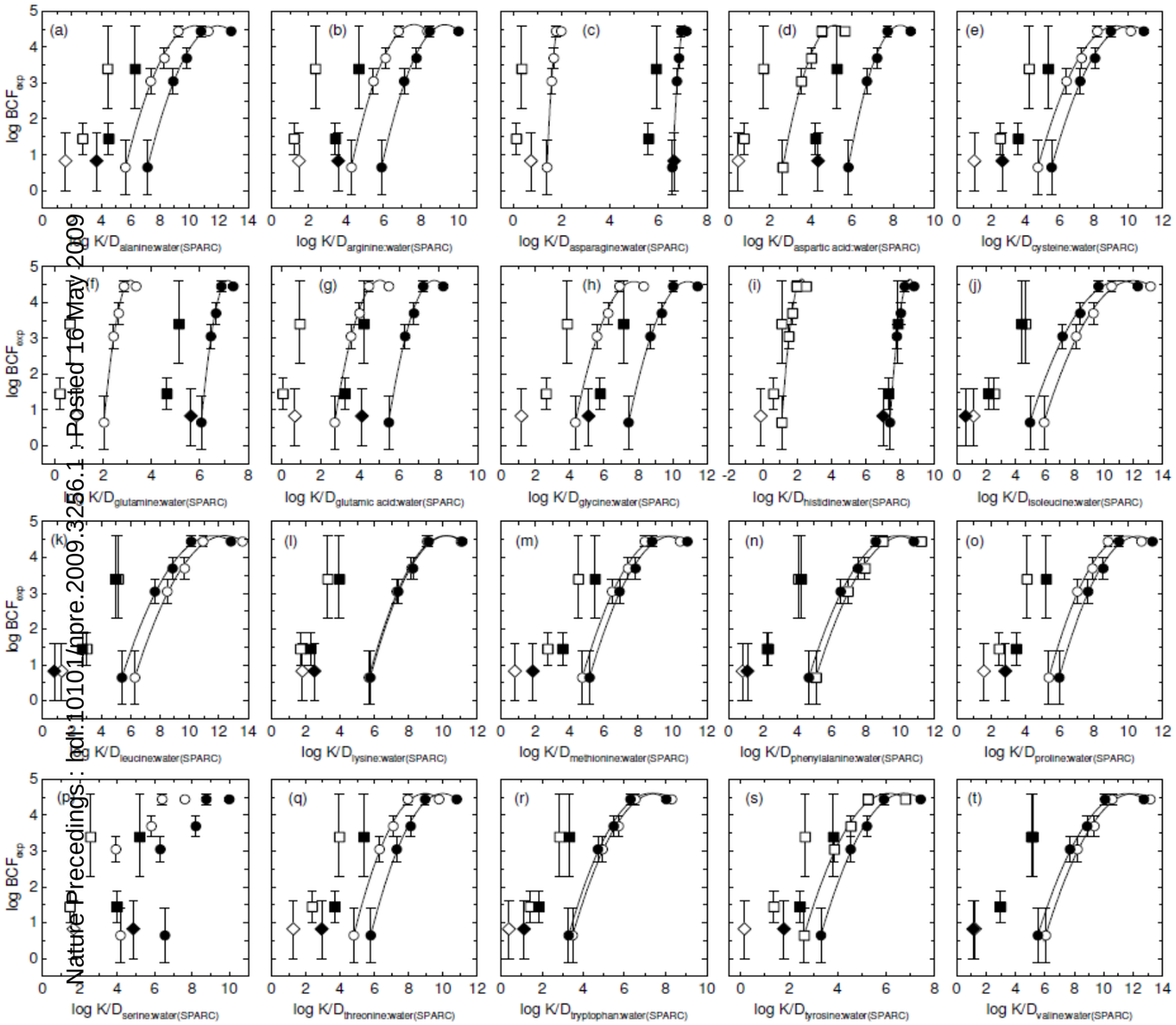


Fig. 5



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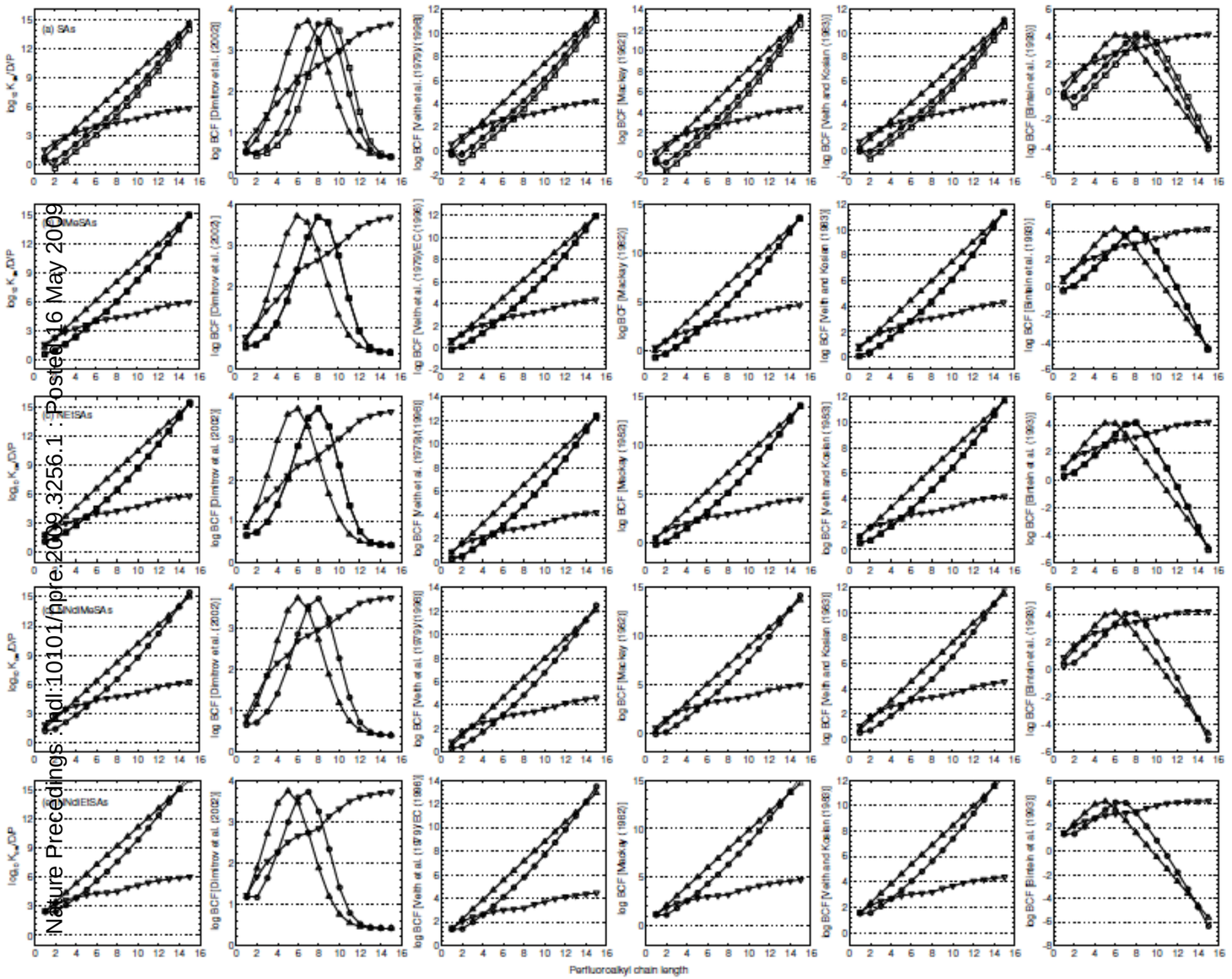

Fig. 7

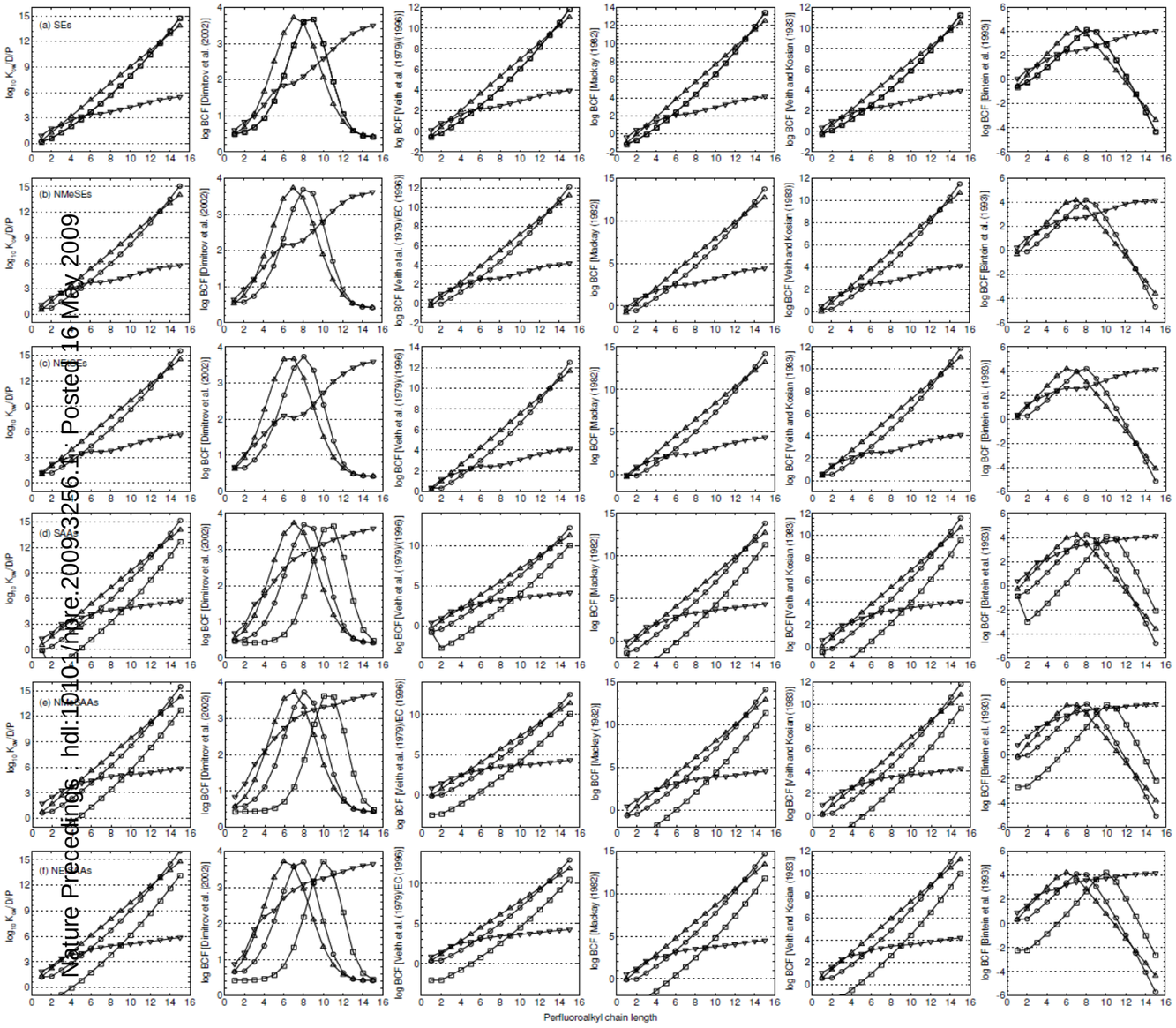

Fig. 8

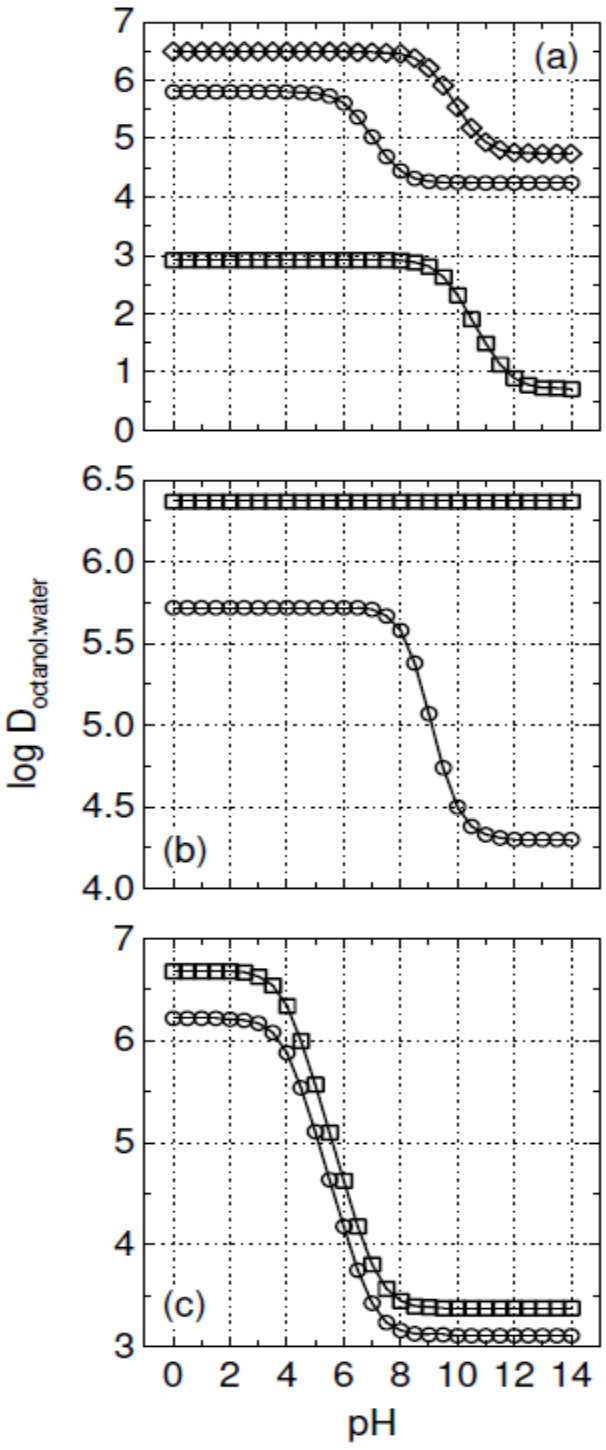

Fig. 9

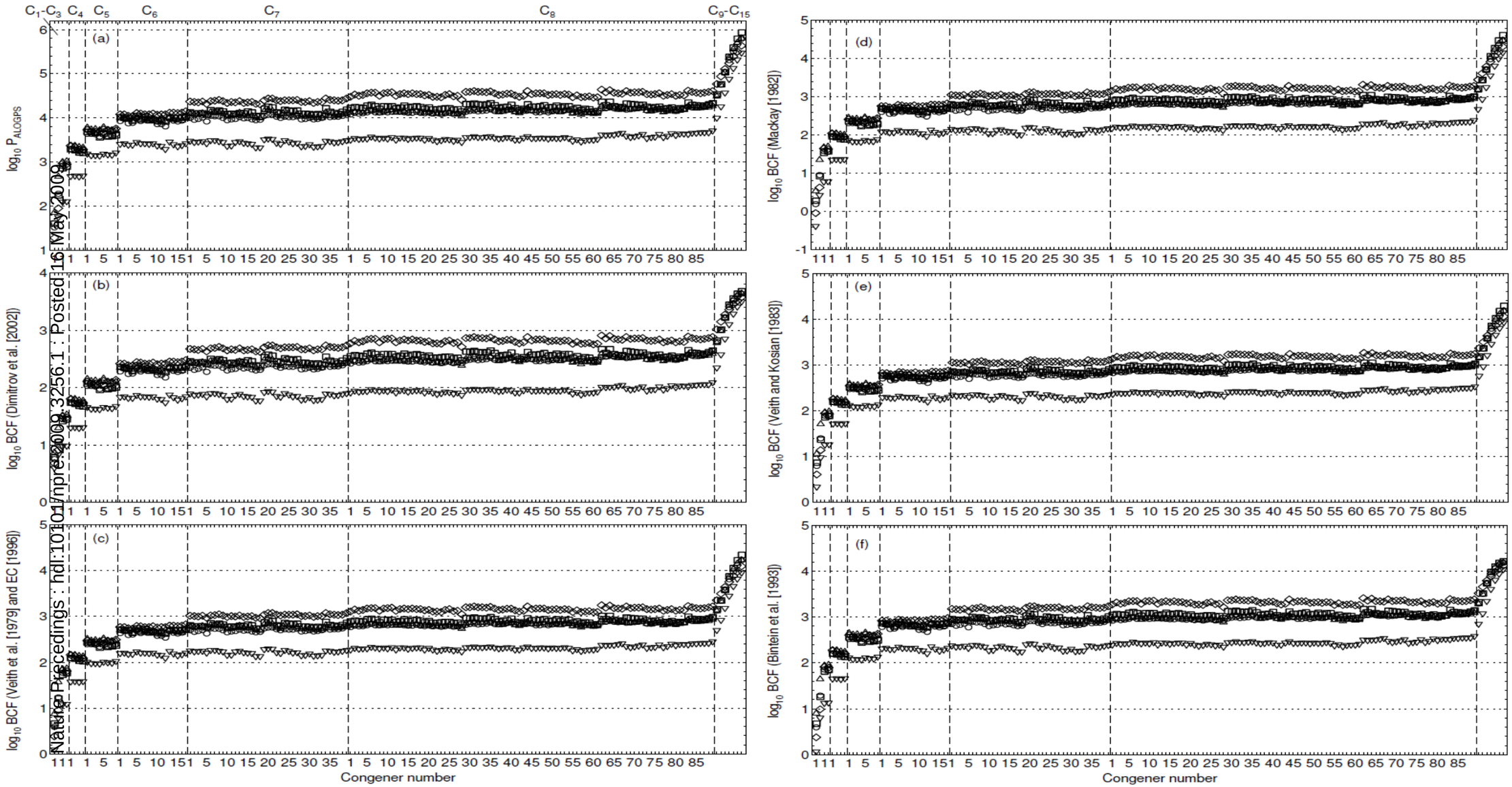

Fig. 10