Supporting Information

pK_a Data-driven Insights to Multiple Linear Regression Hydrolysis QSARs: Applicability to Perfluorinated Alkyl Esters

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Summary: 32 pages, 22 tables, 6 figures, 1 scheme

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Supplementary Tables

Table S1. Counts of Specific Molecular Substructures on the PFASSTRUCT list of 14,735 PFAS.[a,b]

Synthetic organic chemical/substructure	No. Molecules
PFAS I (EPA OPPT 2021)[c]	9139
PFAS II (OECD 2021)[d]	13477
PFAS (R_f of C_6 or more)[e]	3445
Carboxylic acid esters	1125
αPFCA esters	254
PFECA esters	39
αPFOH esters (α-perfluorinated alcohol esters)	51
n:2 FTOH esters	77
n:2 FTAc esters	58
n:2 FTCA esters	13
n:2 FTUCA esters	3
Carboxylic acids	1146
αPFCA	269
PFECAs (includes HPFO-DA and similar chemicals)	88
n:2 FTCAs	16
n:1 FTUCAs	17
n:2 FTUCAs	8
Alcohols	1436
αPFOHs (α-perfluorinated alcohols)	30
n:2 FTOHs	33
PFEs (Perfluoroethers)	740
Acrylates (carboxylic acids and carboxylates)	379
FASAs	876
FASA ethyl acrylates	30

[a]ChemAxon batch command line execution of evaluator was used as a tool in determining presence of substructure in each molecule. [b]The substructures of PFAS I and PFAS II are provided in scheme 1. [c]Based on the EPA OPPT 2021 working definition, the structure contains the unit R-CF_2-CF(R1)(R2), where R does not include hydrogen and the carbon-carbon bond is saturated (note: branching, heteroatoms, and cyclic structures are included). [d]Based on the OECD 2021 definition, at least one CF_2 (perfluorinated methylene group) or one CF_3 (perfluorinated methyl group) without any H/Cl/Br/I atom attached. [e]R_f is a perfluoroalkyl group: $R_f = (CF_2)_xCF_3$ where $C_n = C_{x+1}$.

Table S2. List of SMARTS used for identifying various functional groups of PFAS.[a]

Category	SMARTS
PFAS I (EPA)	[F][C]([F])([!#1:1])[C]([F])([!#1:1])[!#1:1]
PFAS II (OECD)	[F][C]([F])([!#1!#17!#35!#53:1])[!#1!#17!#35!#53:1]
PFAS (R_f of C_6 or more)	[!#1:1]C(F)([F])C(F)([F])C(F)([F])C(F)([F])C(F)([F])C(F)([F])[!#1:1]
Carboxylic acid esters	[C,c,R][C](=[O])[O][C,c,R]
αPFCA esters	[!H;!I;!Cl;!Br]C(F)([F])C(=O)O[H]
PFECA esters	[Si,C,N,S,P,O,F]C(F)([F])O[C](F)[C](=O)O[C,c]
αPFOH esters	[*]C(F)(F)OC([C,c])=O'
n:2 FTOH esters	[C,F]C(F)(F)C([H])([H])C([H])([H])OC([C])=O
n:2 FTAc esters	[*,H]C([*,H])([*,H])C(=C(([*,H])[*,H]))C(=O)OCCC(F)([*,H])F
n:2 FTCA esters	[*]C(F)(F)C([H])([H])C([H])([H])[C](=O)O[C,c]
n:2 FTUCA esters	[*][C](F)(F)[C]([H])=C([H])C(=O)O[C,c]
Carboxylic acids	[CX3:1](=[O:2])[OX2H1:3]
αPFCA	[*]C(F)(F)C([H])([H])C([H])([H])[C](=O)O[H]
PFECAs	[Si,C,N,S,P,O,F]C(F)([F])O[C](F)[C](=O)O[H]
n:2 FTCAs	[*]C(F)(F)C([H])([H])C([H])([H])[C](=O)O[C,c]
n:1 FTUCAs	[*][C](F)(F)[C]([F])=C([H])C(=O)O[H]
n:2 FTUCAs	[*][C](F)(F)[C]([H])=C([H])C(=O)O[H]
Alcohols	[C:1][OH;!$(OC~[!#1!#6]):2]
αPFOHs	[*][C,R](F)([F])O[H]
n:2 FTOHs	[C,F]C(F)(F)C([H])([H])C([H])([H])O[H]
PFEs	[Si,C,N,S,P,O,F]C(F)([F])O[C,c]([F])([*])[*]
Acrylates	C([*,H])([*,H])=C([*,H])C(=O)[O][H,*]
FASA	NS(=O)(=O)C(F)(F)C(F)([*])
FASA ethyl acrylates	[H,*]N(CCOC(=O)C([H,*])=C([H,*])[H,*])S(=O)(=O)C(F)(F)[*]

[a]Batch function used to evaluate: evaluate -e "match('SMARTS')" input > output

Table S3. Values of the regression coefficient (Coeff.) and p-values for the linear-regression analysis of carboxylic acid ester hydrolysis rate constants against various physicochemical and molecular descriptors for relevant models.[42]

	CAE QSAR1		*CAE QSAR2*	
Variable	*Coeff.*	*p-value*	*Coeff.*	*p-value*
Intercept	-8.696	7.98E-03	-2.159	4.41E-01
[a]pK_a OC=O	-1.754	3.78E-07	-1.312	2.54E-05
[b]pK_a COOH	-0.936	2.14E-30	-1.062	3.17E-44
[c]pK_a OH	-0.336	4.32E-39	-0.399	1.61E-71
[d]SH *COOH	-15.008	1.94E-27	-14.240	1.02E-28
[e]SH *OH	-19.093	4.19E-28	-17.973	4.34E-31
[f]SEI *OH	6.914	2.64E-15	6.642	6.34E-16
[g]SEI C=O*	18.338	1.62E-16	16.062	6.74E-16
[h]ρ *C=O	-3.731	1.37E-05	-3.836	2.02E-06
[i]*E* COOH	0.031	2.16E-06	0.030	8.89E-08
[j]opt-*E* COOH	-0.022	8.35E-04	-0.022	1.44E-04
[k]μ COOH	-0.084	1.06E-05	-0.094	1.65E-07
[l]AAC	-0.143	1.13E-09	-0.135	1.65E-18
[m]Sum π χ	0.015	6.94E-04	-	-
[n]molec α	-0.067	1.09E-12	-	-
[o]molec α OH	0.049	2.23E-04	-	-

[a]Basic micro pKa on carbonyl (parent compound); [b]Acidic macro pKa of the carboxylic acid product; [c]Acidic macro pKa of the alcohol product; [d]Steric hindrance at the carbon of carboxylic acid product; [e]Steric hindrance at the alcohol product; [f]Steric effect index at the oxygen of the alcohol product; [g]Steric effect index at the oxygen of the carbonyl group (on parent compound); [h]Charge density ($C \cdot m^{-3}$) on the carbon of the carbonyl group (on parent compound); [i]Single-point Merck Molecular Forcefield Energy in kcal/mol (MMFF94 version from 1994) on carboxylic acid product; [j]Optimized MMFF94 Energy on carboxylic acid product; [k]Dipole moment of carboxylic acid product; [l]Aromatic atom count; [m]Sum of pi electronegativity on parent compound; [n]Molecular polarizability of parent molecule ($C \cdot m^2 \cdot V^{-1}$); [o]Molecular polarizability of alcohol product ($C \cdot m^2 \cdot V^{-1}$)

Table S4. Root Mean Square Error for Predicted log(k1) from CAE QSAR 1 and CAE QSAR 2 with all descriptor values calculated using ChemAxon Marvin calculators.

		QSAR1	QSAR2
pH 9	All	1.416494	1.130273
	PFAS II	1.345982	1.182599
	FTAcs	0.912266	0.647586
	FASA	2.418323	1.437348
pH 7	All	1.011943	1.394045
	PFAS II	0.844474	0.660192
	FTAcs	1.525993	2.421298
	FASA	0.26995	1.4645

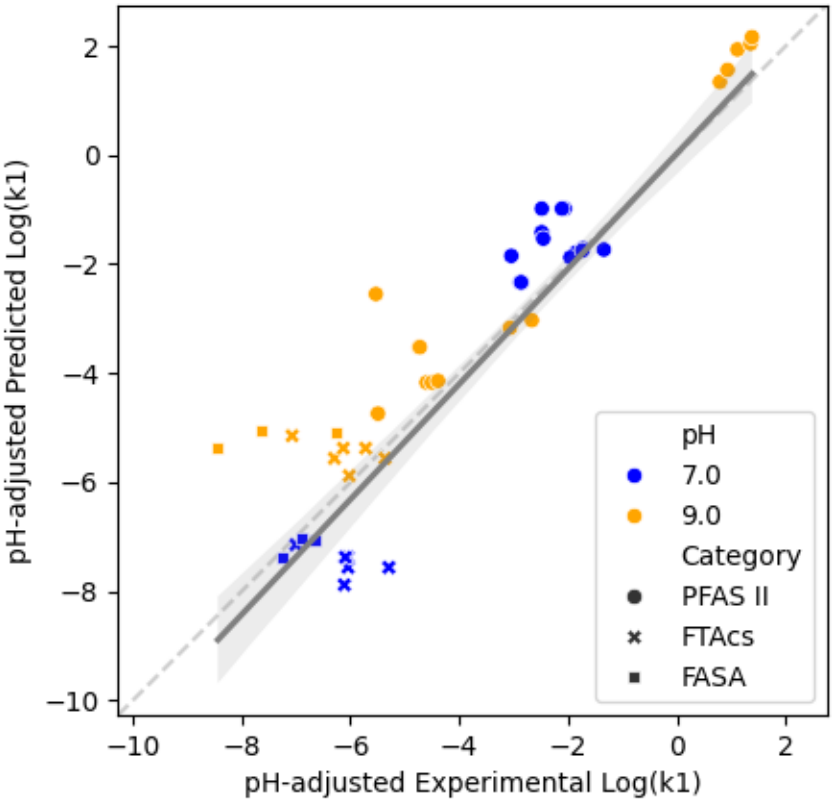

Figure S1. Predicted first-order rate constants from CAE QSAR 1 for hydrolysis at pH 7 and 9 plotted against literature-reported hydrolysis rate constants adjusted to pH values of 7 or 9. Dashed line shows y=x slope, and solid line is the linear regression trendline. All descriptor values calculated with ChemAxon Marvin calculators.

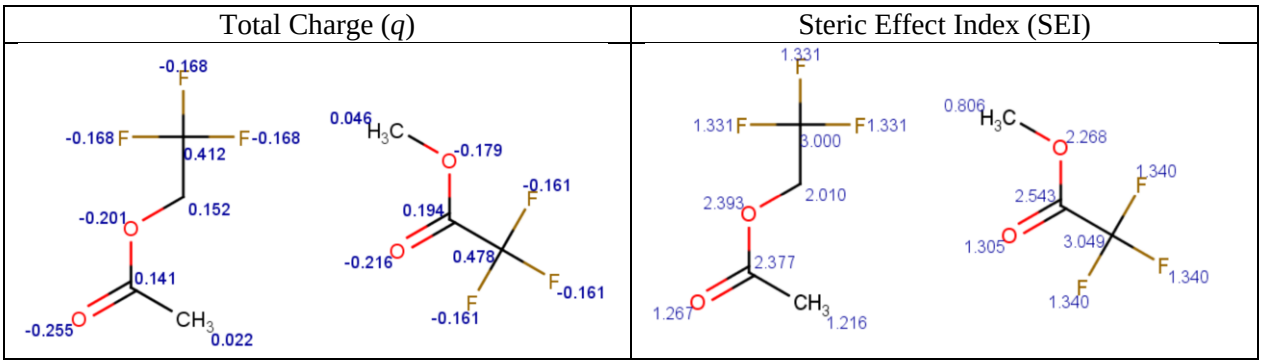

Figure S2. Charge and steric effect index values of trifluoroethyl acetate and methyl trifluoroacetate calculated using ChemAxon Marvin calculators.

Table S5. List of applicable training data from previous work (composed of fluorinated compounds and acrylates).[42]

Chemical Name	**SMILES**	**exp log(k)**	**CAE QSAR2**
Fluorinated Compounds			
o-Fluorophenyl acetate	CC(=O)OC1=C(F)C=CC=C1	0.44	0.67
m-Fluorophenyl acetate	CC(=O)OC1=CC(F)=CC=C1	0.45	0.75
p-Fluorophenyl acetate	CC(=O)OC1=CC=C(F)C=C1	0.18	0.48
Ethyl Difluoroacetate	FC(F)C(=O)OCC	3.65	3.10
Ethyl Fluoroacetate	FCC(=O)OCC	1.08	1.32
Trifluoroethyl acetate	CC(=O)OCC(F)(F)F	0.28	0.93
Ethyl 4-fluorobenzoate	CCOC(=O)C1=CC=C(F)C=C1	-1.41	-1.71
trifluoromethyl 2-phenylacetate	O=C(CC1=CC=CC=C1)OCC(F)(F)F	0.61	0.88
1,1,1,3,3,3-hexafluoropropan-2-yl 2-phenylacetate	O=C(CC1=CC=CC=C1)OC(C(F)(F)F)(C(F)(F)F)	1.93	1.81
Acrylates			
Methyl acrylate	C=CC(=O)OC	-0.85	-0.93
Ethyl acrylate	C=CC(=O)OCC	-1.11	-1.35
Butyl acrylate	C=CC(=O)OCCCC	-1.28	-1.48
Phenyl acrylate	C=CC(=O)Oc1ccccc1	-0.12	-0.42
p-Chlorophenyl acrylate	C=CC(=O)Oc1ccc(Cl)cc1	0.30	0.04
p-Acetylphenyl Acrylate	C=CC(=O)Oc1ccc(C(=O)C)cc1	0.55	0.52
m-Nitrophenyl acrylate	C=CC(=O)Oc1cc(N(=O)=O)ccc1	0.75	0.34
p-Nitrophenyl acrylate	C=CC(=O)Oc1ccc(N(=O)=O)cc1	0.95	0.75
Methyl methacrylate	C=C(C)C(=O)OC	-1.23	-1.55
Methyl 3,3-Dimethylacrylate	C(C)(C)=CC(=O)OC	-2.27	-1.68

Table S6. Measured and Predicted Half-lives for Various Perfluorinated Compounds which Satisfy Only the OECD 2021 Definition (see PFAS II) with Corrections (Temperature at 25˚C[a] and pH at 7 or 9[b]) Applied to Experimental Values.

Compound name	Chain length			expt.	pred.	ref.
Monomers (k_b)	***R1***	***R2***	***pH[b]***	***$t_{1/2}$***	***$t_{1/2@pH9}$***	
trifluoroethyl acetate	C1	CF1	>7	7.71 h[c]	2.6 h	[43]
trifluoroethyl acetate	C1	CF1	10.6	6.15 h	2.6 h	[44]
trifluoroethyl 2-phenylacetate	C1	CF1	7.4	4.73 h	2.3 h	[45]
1,1,1,3,3,3-hexafluoropropan-2-yl 2-Ph-acetate	C1	CF1	7.4	13.5 m	14.9 m	[45]
2,2,2-trifluoroethyl 4-nitrobenzoate	C0	CF1	8.6	5.37 m	22.4 m	[46]
2,2,2-trifluoroethyl 3-methyl-4-nitrobenzoate	C1	CF1	11.6	2.73 d	5.9 m	[46]
2,2,2-trifluoroethyl 1-acetylpyrrolidine-2-carboxylate	C0	CF1	8,11	10.4 h[c]	32.4 m	[47]
4-methylphenyl 2,2,2-trifluoroacetate	CF1	C1	5-9.9	0.11 s	0.12 s	[48]
phenyl 2,2,2-trifluoroacetate	CF1	C0	5-9.9	0.08 s	0.07 s	[48]
4-fluorophenyl 2,2,2-trifluoroacetate	CF1	C0	9	0.05 s	0.03 s	[48]
4-chlorophenyl 2,2,2-trifluoroacetate	CF1	C0	9	0.03 s	0.02 s	[48]
3-chlorophenyl 2,2,2-trifluoroacetate	CF1	C0	9	0.03 s	0.02 s	[48]
fluazifop-butyl	CF1	C4	9,9,9	2.51 d[c]	13.5 h	[49]
Monomer (k_n)	***R1***	***R2***	***pH[b]***	***$t_{1/2}$***	***$t_{1/2@pH7}$***	
methyl trifluoroacetate (corrected from 14.95˚C)	CF1	C1	7	1.33 m	26.5 s	[50]
methyl trifluoroacetate	CF1	C1	7	1.50 m	26.5 s	[44]
methyl trifluoroacetate	CF1	C1	7	3.52 m	26.5 s	[51]
ethyl trifluoroacetate	CF1	C2	7	3.51 m	1.2 m	[50]
ethyl trifluoroacetate (corrected from 22.03˚C)	CF1	C2	7	3.53 m	1.2 m	[50]
ethyl trifluoroacetate (corrected from 14.95˚C)	CF1	C2	7	3.54 m	1.2 m	[50]
s-propyl trifluoroacetate (corrected from 14.95˚C)	CF1	C2	7	12.8 m	3.4 m	[50]
i-propyl trifluoroacetate	CF1	C2	7	3.31 m	1.6 m	[51]
t-butyl trifluoroacetate (corrected from 14.95˚C)	CF1	C2	7	8.86 m	11.0 m	[50]
t-butyl trifluoroacetate	CF1	C2	7	8.20 m	11.0 m	[52]
t-butyl trifluoroacetate (corrected from 24.77˚C)	CF1	C2	7	8.48 m	11.0 m	[52]
4-nitrobenzyl trifluoroacetate	CF1	C1	7	15.3 s	37.6 s[d]	[50]
4-chlorobenzyl trifluoroacetate	CF1	C1	7	37.0 s	35.6 s[d]	[50]
benzyl trifluoroacetate	CF1	C1	7	49.9 s	42.7 s[d]	[50]
4-methylbenzyl trifluoroacetate	CF1	C1	7	63.0 s	52.3 s[d]	[50]
4-methoxylbenzyl trifluoroacetate	CF1	C1	7	38.0 s	39.1 s[d]	[50]

[a]C# and CF# are H-substituted and F-substituted chain lengths on R1 or R2 group of R_1COOR_2; Experimental values were corrected to 25˚C using the Arrhenius equation; $t_{1/2}$ is half-life in s = seconds, m = minutes, h = hours, d = days, y = years; Predicted Half-lives were determined based on CAE QSAR2 unless stated otherwise [b]Initial pH reported before correction to pH 7 and 9, for k_n, and k_b, respectively. [c]Average value. [d]Predicted half-life determined based on CAE QSAR1.

Table S7. Measured and Predicted Hydrolysis Half-lives for Various Polyfluorinated Compounds at 25˚C which Satisfy the 2021 PFAS Definitions from EPA OPPT and OECD.[a]

Compound Acronym	Chain length			expt. $t_{1/2}$[b]	pred. $t_{1/2}$	ref.
Monomers (basic conditions)	***R1***	***R2***	***pH$_{exp}$***	***@pH$_{exp}$***	***@pH9***	
6:2 FTAc	C2	CF6	9	1.87 d	20.1 d	[53]
6:2 FTAc (corrected from 50˚C)	C2	CF6	9	15.8 d	20.1 d	[53]
6:2 FTMAc (corrected from 20˚C)	C3	CF6	9	8.4 d	38.2 d	
8:2 FTAc (corrected from 30˚C)	C2	CF8	9	10.8 d	22.5 d	[54]
8:2 FTAc (corrected from 20˚C)	C2	CF8	9	4.2 d	22.5 d	[54]
10:2 FTAc (corrected from 30˚C)	C2	CF10	9	94.5 d	23.0 d	[54]
N-MeFBSEAc[d]	C2	CF4	9	5.99 y	15.1 d	[55]
N-MeFBSEAc[e]	C2	CF4	9	11.5 d	N/A	[55]
N-MeFBSEAc[f]	C2	CF4	9	12.4 d	N/A	[55]
N-MeFOSEAc[c]	C2	CF8	9	346 d	20.4 d	[56]
N-MeFOSEAc[c]	C2	CF8	11	80.6 d	20.4 d	[56]
N-EtFOSEAc[c]	C2	CF8	9	15.0 d	20.7 d	[56]
Monomer (neutral conditions)	***R1***	***R2***	***pH$_{exp}$***	***@pH$_{exp}$***	***@pH7***	
6:2 FTAc	C2	CF6	7	1.58 d	5.51 y	[53]
6:2 FTAc (corrected from 50˚C)	C2	CF6	7	8.92 d	5.51 y	[53]
6:2 FTMAc (corrected from 20˚C)	C3	CF6	7	10.4 d	10.5 y	[53]
8:2 FTAc (corrected from 30˚C)	C2	CF8	7	9.97 d	6.17 y	[54]
8:2 FTAc (corrected from 20˚C)	C2	CF8	7	8.97 d	6.17 y	[54]
10:2 FTAc (corrected from 30˚C)	C2	CF10	7	80.8 d	6.29 y	[54]
N-MeFBSEAc[d]	C2	CF4	7	143 d	4.14 y	[55]
N-MeFOSEAc[c]	C2	CF8	7	64.4 d	5.58 y	[56]
N-EtFOSEAc[c]	C2	CF8	7	35 d	5.67 y	[57]
Monomer (acidic conditions)	***R1***	***R2***	***pH$_{exp}$***	***@pH$_{exp}$***		
6:2 FTAc	C2	CF6	4	1.55 d		[53]
6:2 FTAc (corrected from 50˚C)	C3	CF6	4	39.1 d		[53]
8:2 FTAc (corrected from 30˚C)	C2	CF8	4	3.91 d		[54]
8:2 FTAc (corrected from 20˚C)	C2	CF8	4	10.2 d		[54]
10:2 FTAc (corrected from 50˚C)	C2	CF10	4	4.55 y		[54]
N-MeFBSEAc[d]	C2	CF4	4	56.4 y		[55]
N-MeFOSEAc[c]	C2	CF8	5	18.2 y		[56]
N-EtFOSEAc[c]	C2	CF8	4	42.0 d		[56]

[a]C# and CF# are H-substituted and F-substituted chain lengths on R1 or R2 group of R_1COOR_2; Experimental values were corrected to 25˚C using the Arrhenius equation; $t_{1/2}$ is half-life in s = seconds, m = minutes, h = hours, d = days, y = years; FTAc = fluorotelomer acrylate, FTMAc = fluorotelomer methacrylate, N-MeFBSEAc = N-Methyl perfluorobutane sulfonamidoethyl acrylate, N-MeFOSEAc = N-Methyl perfluorooctane sulfonamidoethyl acrylate, N-EtFOSEAc = N-Ethyl perfluorooctane sulfonamidoethyl acrylate. [b]Without pH corrections applied. [c]Half-life based on disappearance rate of parent. [d]Half-life based on formation of N-MeFBSE alcohol CAE hydrolysis product (corrected from 50˚C). [e]Half-life based on formation of FBSA product due to hydrolysis at the sulfonamide site. [f]Half-life based on formation of MeFBSA product due to hydrolysis at the sulfonamide site.

Table S8. Measured and Predicted Half-lives for Various Perfluorinated Polymers at 25˚C which Satisfy the 2021 Definitions from EPA OPPT and/or OECD (See PFAS I and PFAS II).[a]

Polymers	R_f		expt. $t_{1/2}$[b]	expt. $t_{1/2}$	pred. $t_{1/2}$	ref.
Fluorotelomer Acrylates	***R2***	***pH_{exp}***	***@pH_{exp}***	***@pH_{conv}*** [c]	***@pH9***	
p(PFOAc)	CF6	12.3	≥1.44 h	*≥120 d*	16 d	58
p(HFBAc)	CF3	12	≥1.11 h	*≥46.3 d*	2.0 d	58
p(PFOAc-co-DEGDVE) not grafted[d,e]	CF6	12.3	<4.32 m	<6.01 d	16 d	58
p(HFBAc-co-DEGDVE) not grafted[d,e]	CF3	12.3	<4.32 m	<6.01 d	2.0 d	58
p(PFOAc-co-DEGDVE) grafted[d,e]	CF6	12.3	4.95 h	1.1 y		58
p(HFBAc-co-DEGDVE) grafted[d,e]	CF3	12.3	1.30 h	109 d		58
FTP4 aged on cotton (8:2 FTOH)	CF8	10	5.50 y	55.0 y		59
FTP in waste & surface water (8:2 FTOH) [d]	CF8	6	59.2 d	7.24 d		60
FTP in waste & surface water (8:2 FTOH) [d]	CF8	8	52.6 d	6.44 d	9.7 d	60
FTP in waste & surface water (8:2 FTOH) [d]	CF8	10	6.97 d	85.3 d	9.7 d	60
acrylate FTP Solids (8:2 FTOH)	CF8	12	263 d	719 y		61
acrylate FTP Solids (10:2 FTOH)	CF10	12	230 d	631 y		61
acrylate FTP Solids (8:2 FTOH)	CF8	11	5.40 y	537 y		61
acrylate FTP Solids (10:2 FTOH)	CF10	11	5.10 y	509 y		61
acrylate FTP Solids (8:2 FTOH)	CF8	10	18.8 y	188 y		61
acrylate FTP Solids (10:2 FTOH)	CF10	10	17.9 y	179 y		61
acrylate FTP Solids (8:2 FTOH)	CF8	9	46.8 y	46.8 y	9.7 d	61
acrylate FTP Solids (10:2 FTOH)	CF10	9	44.0 y	44.0 y	10.3 d	61
acrylate FTP Solids (8:2 FTOH)	CF8	8	57.0 y	5.70 y		61
acrylate FTP Solids (10:2 FTOH)	CF10	8	49.3 y	4.93 y		61
acrylate FTP Solids (8:2 FTOH)	CF8	7	50.0 y	50.0 y		61
acrylate FTP Solids (10:2 FTOH)	CF10	7	56.5 y	56.5 y		61
acrylate FTP Solids (8:2 FTOH)	CF8	6	41.8 y	4.20 y		61
acrylate FTP Solids (10:2 FTOH)	CF10	6	67.6 y	6.76 y		61
acrylate FTP Solids (8:2 FTOH)	CF8	5	71.9 y	71.9 y		61
acrylate FTP Solids (10:2 FTOH)	CF10	5	107 y	107 y		61
Cellulose[e]	***R1***	***pH_{exp}***	***@pH_{exp}***	***@pH9***	***@pH9***	
Perfluoro octanoyl	CF7	7	12.7 h	7.6 m	1.56 m[f]	62
Perfluoro octanoyl (DS = 0.36)	CF7	7.5	23.1 s	0.73 s	2.94 s[f]	62
Perfluoro octanoyl (DS = 0.21)	CF7	7.5	13.9 s	0.44 s	2.94 s[f]	62
Trifluoroacetylated (with stirring)						
- distilled H_2O solution[d]	CF1	7	<16.2 h (100%)	<9.7 m (100%)	2.8 m	63
- distilled H_2O and DMF	CF1	7	<6.0 m (100%)	<3.6 s (100%)	2.7 s	64
Trifluoroacetylated (no stirring)	CF1	7	~ 1 d	~ 14.7 m	2.8 m	63
Pentafluorobenzoylated (with stirring)						65
- (filter paper)	CF0	7	>>4 d			
- (pulp fiber)	CF0	7	>4 d (40%)	>57.6 m (40%)	45 m	65

-	(plant-derived)	CF0	9	>5 h (25%)	>5 h (25%)	4.7 h, 13 h	65
-	(plant-derived)	CF0	4	Stable			65

[a] $t_{1/2}$ is half-life in s = seconds, m = minutes, h = hours, d = days, y = year; p(PFOAc) = poly(1H,1H,2H,2H-perfluorooctyl acrylate), p(HFBAc) = poly(2,2,3,4,4,4-hexafluorobutyl acrylate), co-DEGDVE = crosslinking with di(ethylene glycol)divinyl ether; Prediction for polymers determined by using acrylate monomer for FTP acrylates and H-termination for cellulose; Predicted half-lives calculated using CAE QSAR2; Rough estimates provided for experimental values of cellulose along with estimated % conversion, if available. Best half-life prediction(s) are shown for cellulose. [b]Without pH corrections applied. [c]Based on correction to pH 5, 7, and 9 for acidic, neutral, and basic conditions, respectively. [d]Experimental values were corrected for temperature using the Arrhenius equation. [e]All experimental values measured at pH 7 or greater were adjusted to pH 9. [f]Calculated based on experimental pK_a value of 2.3.

Scheme S1. Reaction Equations for Polymer Synthesis. (a) and (b) are Proposed Synthetic Pathways for Fluorotelomer Polymers Taken from Ref.[60]. (c) determined from ref.[58]

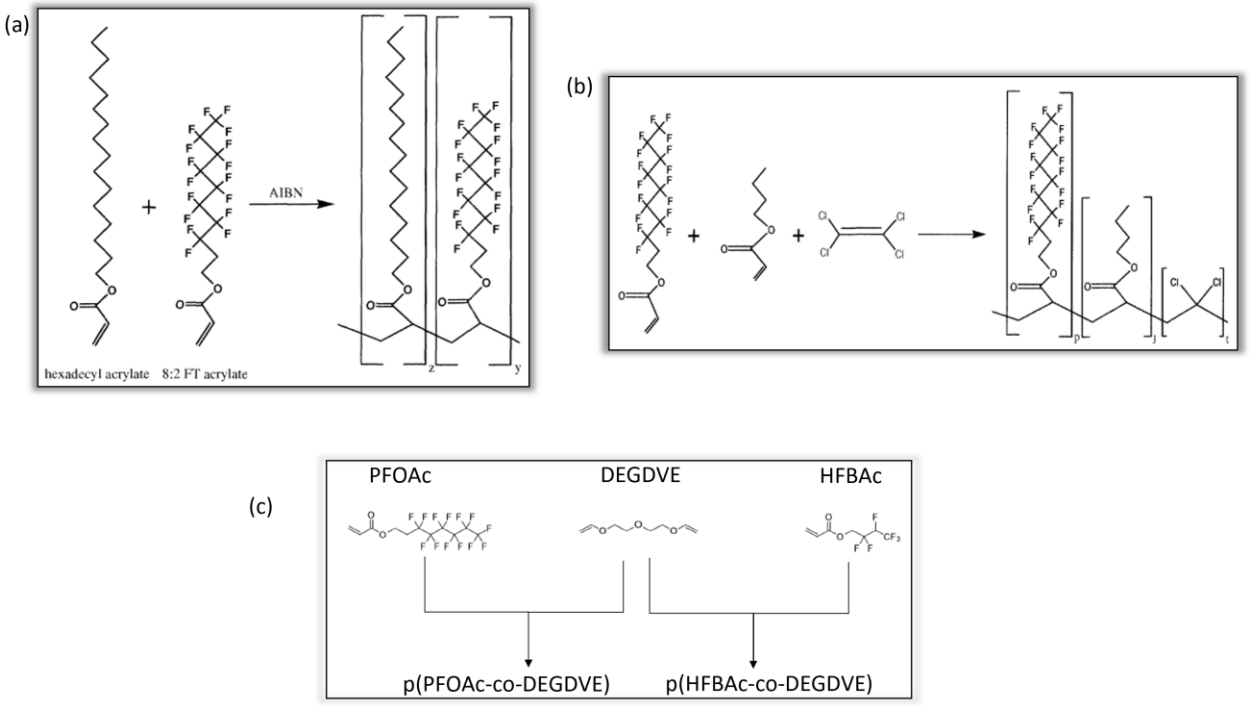

Table S9. Measured half-lives for various perfluorinated compounds under neutral conditions and in 70% acetone. Data taken from ref[66].

Compound name	Chain lengths			Expt.
Monomer (k_n)	***R1***	***R2***	***pH***	***$t_{1/2}$***
methyl trifluoroacetate	CF1	C1	7	1.5 h
ethyl trifluoroacetate	CF1	C2	7	4.8 h
propyl trifluoroacetate	CF1	C3	7	7.1 h
butyl trifluoroacetate	CF1	C4	7	8.4 h
pentyl trifluoroacetate	CF1	C5	7	9.8 h
hexyl trifluoroacetate	CF1	C6	7	10.9 h
decyl trifluoroacetate	CF1	C10	7	14.4 h
ethyl pentafluoropropionate	CF2	C2	7	2.9 d
ethyl heptafluorobutyrate	CF3	C2	7	6.1 d

[a]C# and CF# are H-substituted and F-substituted chain lengths on R1 or R2 group of R_1COOR_2; $t_{1/2}$ is half-life in h = hours or d = days.

Table S10. Statistical analysis for various trifluoroacetates under neutral conditions and 70% acetone.[a]

Metric	CAE QSAR2	CAE QSAR1	HYDROWIN	SPARC
R	0.92	0.95	0.92	0.92
R^2	0.85	0.90	0.84	0.85
MAE	2.538 (0.187)[b]	3.114 (0.152)[b]	1.55	0.731
MaxError	2.907	3.486	2.092	1.053
MinError	2.305	2.899	0.915	0.288
DoE[c]	0.602	0.586	1.178	0.765

[a]All models shown here resulted in over estimation of log k_b value for each compound. [b]Corrected MAE values were determined by subtracting the original MAE value for each trifluoroacetate compound. [c]Deviation of error (MaxError – MinError)

Additional Notes:

Table S9 shows that the predicted neutral hydrolysis rates are overpredicted by about 1 to 3 log units using various models. However, most of the prediction models maintain correlation. CAE QSAR1 and CAE QSAR2 perform slightly better the other models in terms of correlation. Also, the deviation of errors (DoE) are lower compared to SPARC and HYDROWIN. The models with the lowest to highest deviations are CAE QSAR1 (0.586) < CAE QSAR2 (0.602) < SPARC (0.765) < HYDROWIN (1.178). Correction to the CAE models for solvent effects may be applied to compounds containing perfluorinated alpha-carbon of ester function, $C_\alpha(C=O)O$. This may be useful for adjusting model for solvent effects based on MAE.

Table S11. Root Mean Square Error for predicted hydrolysis log(k1) from **CAE QSAR 1** with pK_a descriptor values calculated from ChemAxon, MolGpKa, OPERA, and pkasolver; all other descriptor values calculated with ChemAxon Marvin calculators.

		ChemAxon	MolGpKa	OPERA	pkasolver
pH 9	All	1.422	2.109	3.311	3.061
	PFAS II	1.340	1.947	2.668	1.873
	FTAcs	0.912	1.799	3.178	4.016
	FASA	2.418	3.323	6.090	5.744
pH 7	All	1.012	2.307	2.552	1.885
	PFAS II	0.844	2.834	2.702	1.430
	FTAcs	1.526	0.703	1.295	2.069
	FASA	0.270	0.727	3.538	3.183

Table S12. Root Mean Square Error for predicted hydrolysis log(k1) from **CAE QSAR 2** with pK_a descriptor values calculated from ChemAxon, MolGpKa, OPERA, and pkasolver; all other descriptor values calculated with ChemAxon Marvin calculators.

		ChemAxon	MolGpKa	OPERA	pkasolver
pH 9	All	1.080	1.686	3.175	2.963
	PFAS II	1.123	1.725	2.788	2.138
	FTAcs	0.648	1.009	2.612	3.613
	FASA	1.437	2.379	5.588	5.187
pH 7	All	1.394	2.119	2.212	1.532
	PFAS II	0.660	2.531	2.414	1.170
	FTAcs	2.421	1.229	0.765	1.654
	FASA	1.464	0.455	3.021	2.608

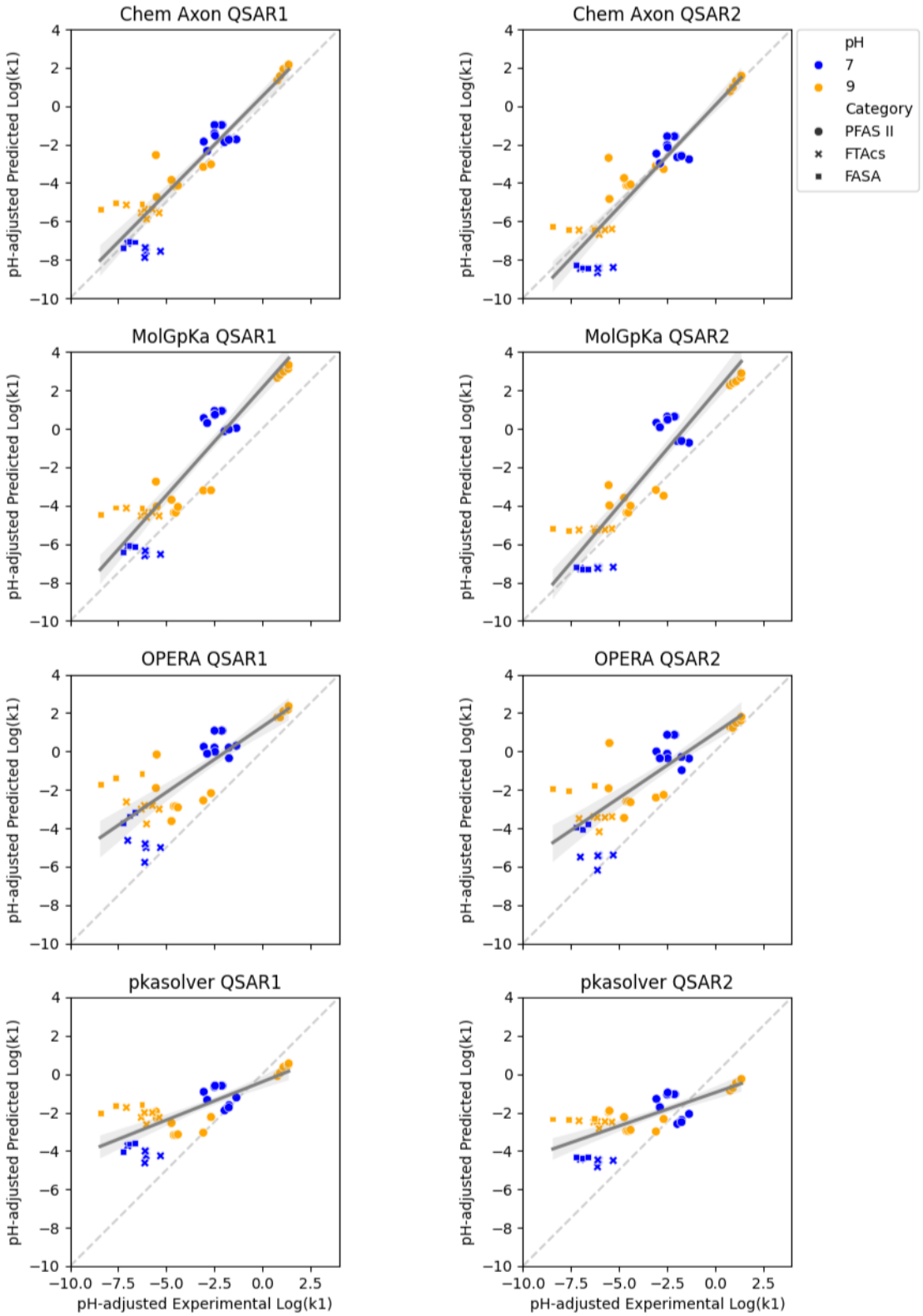

Figure S3. Predicted first-order hydrolysis rate constants from CAE QSAR 1 (on the left) and CAE QSAR 2 (on the right) calculated at pH 7 (blue symbols) and 9 (yellow symbols) plotted against

literature-reported hydrolysis rate constants adjusted to pH values of 7 or 9. Multi-panel figure compares results for estimated macro pK_a values from four different tools: ChemAxon, MolGpKa, OPERA, and pkasolver (top to bottom). Dashed line shows y=x slope, and solid line is the linear regression trendline.

Table S13. Experimental and calculated pK_a values for carboxylic acids of PFAS including perfluoroalkyl carboxylic acids (PFCAs), perfluoroalkyl ether carboxylic acid (PFECA), fluorotelomer carboxylic acids and unsaturated carboxylic acids (FTCA and FTUCA), and perfluoroalkyl benzoic acid using various applications.

ID no.	Name/Category	Abbr.	R_f	Expt. pK_a	Chemaxon	SPARC	Pkasolver	MolGpKa	OPERA	Ref no.
	αPFCAs									
1	Trifluoroacetic acid	TFA	C1	0.20	0.95	1.13	2.55	-0.4	0.72	[1]
2	Trifluoroacetic acid	TFA	C1	0.25[f]	0.95	1.13	2.55	-0.4	0.72	[2]
3	Trifluoroacetic acid	TFA	C1	0.30	0.95	1.13	2.55	-0.4	0.72	[2]
4	Trifluoroacetic acid	TFA	C1	0.47	0.95	1.13	2.55	-0.4	0.72	[3]
5	Trifluoroacetic acid	TFA	C1	0.54[a]	0.95	1.13	2.55	-0.4	0.72	[4, 5]
6	Trifluoroacetic acid	TFA	C1	0.62[f]	0.95	1.13	2.55	-0.4	0.72	[4, 5]
7	Pentafluoropropionic acid	PFPrA	C2	0.44[a]	1.37	0.11	2.44	0	0.81	[4, 5]
8	Pentafluoropropionic acid	PFPrA	C2	0.54[f]	1.37	0.11	2.44	0	0.81	[4, 5]
9	Pentafluoropropionic acid	PFPrA	C2	-0.42	1.37	0.11	2.44	0	0.81	[5, 6]
10	Pentafluoropropionic acid	PFPrA	C2	1.78[a]	1.37	0.11	2.44	0	0.81	[7]
11	Pentafluoropropionic acid	PFPrA	C2	1.44[c]	1.37	0.11	2.44	0	0.81	[7]
12	Pentafluoropropionic acid	PFPrA	C2	2.32[d]	1.37	0.11	2.44	0	0.81	[7]
13	Heptafluorobutanoic acid	PFBA	C3	0.19[f]	1.07	0.06	2.43	0.1	-0.21	[2]
14	Heptafluorobutanoic acid	PFBA	C3	0.38[a]	1.07	0.06	2.43	0.1	-0.21	[4, 5]
15	Heptafluorobutanoic acid	PFBA	C3	0.42[f]	1.07	0.06	2.43	0.1	-0.21	[4, 5]
16	Heptafluorobutanoic acid	PFBA	C3	1.44[a]	1.07	0.06	2.43	0.1	-0.21	[7]
17	Heptafluorobutanoic acid	PFBA	C3	1.51[d]	1.07	0.06	2.43	0.1	-0.21	[7]
18	Heptafluorobutanoic acid	PFBA	C3	≤1.60	1.07	0.06	2.43	0.1	-0.21	[8]
19	Perfluoropentanoic acid	PFPeA	C4	0.64[a]	0.34	-0.10	2.51	0.1	-0.80	[4, 5]
20	Perfluoropentanoic acid	PFPeA	C4	0.43[f]	0.34	-0.10	2.51	0.1	-0.80	[4, 5]
21	Perfluoropentanoic acid	PFPeA	C4	2.27[e]	0.34	-0.10	2.51	0.1	-0.80	[7]
22	Perfluoropentanoic acid	PFPeA	C4	≤1.60	0.34	-0.10	2.51	0.1	-0.80	[8]
23	Perfluorohexanoic acid	PFHxA	C5	0.89[a]	-0.78	-0.17	2.61	0.1	0.20	[4, 5]
24	Perfluorohexanoic acid	PFHxA	C5	0.75[f]	-0.78	-0.17	2.61	0.1	0.20	[4, 5]
25	Perfluorohexanoic acid	PFHxA	C5	2.17[e]	-0.78	-0.17	2.61	0.1	0.20	[7]
26	Perfluorohexanoic acid	PFHxA	C5	≤1.60	-0.78	-0.17	2.61	0.1	0.20	[8]
27	Perfluoroheptanoic acid	PFHpA	C6	2.26[e]	-2.29	-0.20	2.72	0.1	0.06	[7]
28	Perfluoroheptanoic acid	PFHpA	C6	≤1.60	-2.29	-0.20	2.72	0.1	0.06	[8]
29	Perfluorooctanoic acid	PFOA	C7	2.75	-4.2	-0.21	2.83	0.1	0.34	[9]
30	Perfluorooctanoic acid	PFOA	C7	2.80[e]	-4.2	-0.21	2.83	0.1	0.34	[9, 10]
31	Perfluorooctanoic acid	PFOA	C7	1.01	-4.2	-0.21	2.83	0.1	0.34	[5, 11]
32	Perfluorooctanoic acid	PFOA	C7	2.30[e]	-4.2	-0.21	2.83	0.1	0.34	[7]

33	Perfluorooctanoic acid	PFOA	C7	2.50	-4.2	-0.21	2.83	0.1	0.34	[12]
34	Perfluorooctanoic acid	PFOA	C7	0.50	-4.2	-0.21	2.83	0.1	0.34	[8]
35	Perfluorooctanoic acid	PFOA	C7	≤1.60	-4.2	-0.21	2.83	0.1	0.34	[8]
36	Perfluorooctanoic acid	PFOA	C7	≤0.42	-4.2	-0.21	2.83	0.1	0.34	[13]
37	Perfluorooctanoic acid	PFOA	C7	1.31	-4.2	-0.21	2.83	0.1	0.34	[14]
38	Perfluorooctanoic acid	PFOA	C7	<1	-4.2	-0.21	2.83	0.1	0.34	[15]
39	Perfluorononanoic Acid	PFNA	C8	2.58[b]	-6.51	-0.21	2.92	0.1	0.23	[4, 7]
40	Perfluorononanoic Acid	PFNA	C8	2.34[e]	-6.51	-0.21	2.92	0.1	0.23	[7]
41	Perfluorononanoic Acid	PFNA	C8	≤1.60	-6.51	-0.21	2.92	0.1	0.23	[8]
42	Perfluorodecanoic Acid	PFDA	C9	2.61[b]	-5.2	-0.22	3.01	0.1	0.40	[4, 7]
43	Perfluorodecanoic Acid	PFDA	C9	2.44[e]	-5.2	-0.22	3.01	0.1	0.40	[7]
44	Perfluorodecanoic Acid	PFDA	C9	≤1.60	-5.2	-0.22	3.01	0.1	0.40	[8]
45	Perfluoroundecanoic acid	PFUnDA	C10	3.13[b]	-5.2	-0.22	3.09	0.1	0.54	[4, 7]
46	Perfluoroundecanoic acid	PFUnDA	C10	≤1.60	-5.2	-0.22	3.09	0.1	0.54	[8]
47	GenX [2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoate]	HFPO-DA (PFECA)	C3	2.84	-0.77	-0.06	2.69	0	-0.73	[16]
	FTCAs and FTUCAs									
48	3,3,3-Trifluoropropanoic acid	1:1 FTCA (TFP)	C1	2.92[a]	2.95	3.12	2.98	3.1	2.22	[2]
49	3,3,3-Trifluoropropionic acid	1:1 FTCA (TFP)	C1	3.02[f]	2.95	3.12	2.98	3.1	2.22	[2]
50	4,4,4-Trifluorobutanoic acid	1:2 FTCA (TFB)	C1	4.00[a]	3.41	4.25	3.87	4.1	2.64	[2]
51	4,4,4-Trifluorobutanoic acid	1:2 FTCA (TFB)	C1	4.16[f]	3.41	4.25	3.87	4.1	2.64	[2]
52	4,4,4-Trifluorobutanoic acid	1:2 FTCA (TFB)	C1	4.00[a]	3.41	4.25	3.87	4.1	2.64	[17]
53	5,5,5-Trifluoropentanoic acid	1:3 FTCA (TFV)	C1	4.49	3.7	4.57	4.03	4.5	2.13	[18]
54	(2E)-4,4,4-trifluorobut-2-enoic acid	1:2 FTUCA	C1	3.35	3.4	3.30	3.55	2.8	2.52	[19]
55	(2E)-4,4,4-trifluorobut-2-enoic acid	1:2 FTUCA	C1	3.48	3.4	3.30	3.55	2.8	2.52	[17]
56	(2E)-4,4,5,5,6,6,6-heptafluorohex-2-enoic acid	3:2 FTUCA	C3	3.23	2.76	3.19	3.38	2.8	1.64	[17]
57	4,4,5,5,6,6,6-heptafluorohexanoic acid	3:2 FTCA	C3	4.18	2.71	4.01	3.63	4.20	3.06	[17]
58	2-Perfluorohexylethanoic acid	6:2 FTCA	C6	3.17	-1.06	2.82	3.07	3.20	2.72	[13]
59	2H,2H,3H,3H-Perfluorodecanoic acid	7:3 FTCA	C7	5.12[e]	0.11	3.96	3.56	4.2	3.36	[10]
60	5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-pentadecafluoroundecanoic acid	7:4 FTCA	C7	5.63[e]	1.62	4.46	3.83	4.6	3.36	[10]
61	6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-pentadecafluorododecanoic acid	7:5 FTCA	C7	5.8[e]	2.79	4.63	3.97	4.7	3.37	[10]
62	7,7,8,8,9,9,10,10,11,11,12,12,13,13,13-pentadecafluorotridecanoic acid	7:6 FTCA	C7	5.95[e]	3.65	4.69	4	4.8	3.25	[10]
63	8,8,9,9,10,10,11,11,12,12,13,13,14,14,14-pentadecafluorotetradecanoic acid	7:7 FTCA	C7	6.26[e]	4.23	4.72	4.04	4.8	3.03	[10]
64	(E)-6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-pentadecafluorododec-4-enoic acid	7:4 FTUCA	C7	5.4[e]	2.74	4.54	3.97	4.5	3.54	[10]

65	(E)-7,7,8,8,9,9,10,10,11,11,12,12,13,13,13-pentadecafluorotridec-5-enoic acid	7:5 FTUCA	C7	5.83[e]	3.59	4.65	4.06	4.7	1.55	[10]
	Perfluoroalkyl benzoic acid									
66	3-Trifluoromethylbenzoic acid	3-PFMeBA	C1	3.75	3.94	3.50	3.53	3.7	2.59	[5]

[a]Determined by potentiometric titration of PFCAs aqueous solution. [b]Determined by measurement of PFCAs solubility change with pH.
[c]Determined by potentiometric titration of PFCAs solution of methanol. [d]Determined by potentiometric titration of PFCAs solution of acetonitrile.
[e]Determined by potentiometric titration of PFCAs solution of 50% ethanol. [f]Determined by limited conductimetry.

Table S14. Experimental and calculated pK_a values for FTOHs using various applications.

ID no.	Name	Abbr.	R_f/ branching[a]	Expt. pK_a	Chemaxon	SPARC	Pkasolver	MolGpka	OPERA	Ref no.
1	2,2,2-Trifluoroethanol	1:1 FTOH	C1/1˚	12.50	11.49	12.43	9.49	12.30	9.22	20
2	2,2,2-Trifluoroethanol	1:1 FTOH	C1/1˚	12.43	11.49	12.43	9.49	12.30	9.22	21
3	2,2,2-Trifluoroethanol	1:1 FTOH	C1/1˚	12.37	11.49	12.43	9.49	12.30	9.22	21
4	2,2,2-Trifluoroethanol	1:1 FTOH	C1/1˚	11.40	11.49	12.43	9.49	12.30	9.22	22
5	2,2,2-Trifluoroethanol	1:1 FTOH	C1/1˚	12.80	11.49	12.43	9.49	12.30	9.22	23
6	2,2,2-Trifluoroethanol	1:1 FTOH	C1/1˚	12.40	11.49	12.43	9.49	12.30	9.22	24
7	2,2,2-Trifluoroethanol	1:1 FTOH	C1/1˚	11.30	11.49	12.43	9.49	12.30	9.22	21
8	3-Amino-1,1,1-trifluoropropan-2-ol	1:1 FTOH	C1	12.29	11.22	12.10	8.95	10.90	8.42	25
9	3-(Diethylamino)-1,1,1-trifluoro-2-propanol	1:1 FTOH	C1	12.56	11.06	12.07	8.61	12.00	8.87	25
10	Hexafluoro-2-methyl-2-propanol	1:1 FTOH	C1/2˚	9.60	8.08	9.21	9.03	9.90	9.55	24
11	2H-Perfluoro-2-propanol	1:1 FTOH	C1/2˚	9.30	7.97	9.18	8.59	9.10	7.52	24
12	1-Chloro-1,1,3,3,3-pentafluoro-2-(trifluoromethyl)propan-2-ol	1:1 FTOH	C1/3˚	5.30	5.31	5.73	8.13	8.40	7.78	24
13	1,1,1,3,3,3-Hexafluoro-2-(trichloromethyl)propan-2-ol	1:1 FTOH	C1/3˚	5.10	6.10	5.36	7.74	8.70	7.68	24
14	Perfluoropinacol	1:1 FTOH	C1/2˚(2)	5.95	6.33	6.18	6.64	8.00	6.25	26
15	1,1,1,3,3,3-Hexafluoropropane-2,2-diol	1:1 FTOH	C1/2˚(2)	6.58	6.00	7.37	9.18	7.80	2.60	26
16	3,3-Dibromo-1,1,1-Trifluoropropane-2,2-Diol	1:1 FTOH	C1	7.69	8.23	7.92	9.81	8.30	2.97	26
17	1,1,1-Trifluoro-2-propanol	1:1 FTOH	C1	11.80	11.58	12.46	9.22	12.50	4.98	21
18	1,1,1-Trifluoro-2-propanol	1:1 FTOH	C1	11.22	11.58	12.46	9.22	12.50	4.98	22
19	1,1,1-Trifluoro-2-methylpropan-2-ol	1:1 FTOH	C1	11.60	11.59	14.32	9.90	12.60	5.87	22
20	Perfluoro-tert-butanol	1:1 FTOH	C1/3˚	5.20	4.91	5.89	8.28	8.30	7.64	24
21	Perfluoro-tert-butanol	1:1 FTOH	C1/3˚	5.40	4.91	5.89	8.28	8.30	7.64	27
22	1,1,1,3,3,3-hexafluoro-2-(pyridin-2-ylamino)propan-2-ol	1:1 FTOH	C1	5.71	5.96	7.69	8.68	8.60	7.81	27
23	2-(aminomethyl)-1,1,1,3,3,3-hexafluoropropan-2-ol	1:1 FTOH	C1	5.35	6.49	6.65	8.72	9.00	8.44	27
24	1,1,1,3,3,3-Hexafluoro-2-[(methylamino)methyl]propan-2-ol	1:1 FTOH	C1	5.61	6.34	6.68	8.73	9.10	9.37	27
25	4-amino-1,1,1-trifluoro-2-(trifluoromethyl)butan-2-ol	1:1 FTOH	C1	6.39	7.85	7.59	8.99	9.50	9.14	27
26	2,2,3,3-tetrafluoro-1-propanol	1:1 FTOH	C1/1˚	12.74	12.65	12.40	8.09	12.80	9.96	23
27	Heptafluorobutanol	3:1 FTOH	C3/1˚	11.40	12.61	12.06	8.40	12.70	8.38	21
28	1,1,1,2,2,3,3,5,5,6,6,7,7,7-tetradecafluoroheptan-4-ol	3:1 FTOH	C3/2˚	10.60	9.87	8.37	7.75	9.90	7.38	21
29	2,2,3,3,3-Pentafluoro-1-propanol	2:1 FTOH	C2/1˚	11.35	12.52	12.35	8.97	12.60	9.44	23

[a]Branching of various chain lengths of R_f were determined for analytical purposes in the main text.

Table S15. Experimental and calculated pK_a values for fatty acids using various applications.

ID no.	Name	C_n	pK_a Type	Expt. pK_a	Chemaxon	SPARC	Pkasolver	MolGpKa	OPERA	Ref no.
1	Acetic acid	C2	bulk	4.74	4.54	4.76	4.19	4.50	3.95	[2]
2	Acetic acid	C2	bulk	4.76	4.54	4.76	4.19	4.50	3.95	[28]
3	Propanoic acid	C3	bulk	4.87	4.75	4.73	4.64	4.70	4.74	[2]
4	Propanoic acid	C3	bulk	4.87	4.75	4.73	4.64	4.70	4.74	[28]
5	Butanoic acid	C4	bulk	4.82	4.91	4.73	4.73	4.70	4.87	[2]
6	Butanoic acid	C4	bulk	4.81	4.91	4.73	4.73	4.70	4.87	[28]
7	Pentanoic acid	C5	bulk	4.81	5.01	4.73	4.79	4.80	4.77	[28]
8	Hexanoic acid	C6	bulk	4.85	5.15	4.73	4.81	4.80	4.69	[28]
9	Heptanoic acid	C7	bulk	4.85	5.15	4.73	4.83	4.80	4.96	[28]
10	Octanoic acid	C8	bulk	4.80	5.19	4.73	4.83	4.80	5.06	[29]
11	Octanoic acid	C8	bulk	4.85	5.19	4.73	4.83	4.80	5.06	[28]
12	Octanoic acid	C8	surface	4.90	5.19	4.73	4.83	4.80	5.06	[30]
13	Nonanoic acid	C9	bulk	4.97	5.23	4.73	4.80	4.80	4.92	[28]
14	Nonanoic acid	C9	surface	5.80	5.23	4.73	4.80	4.80	4.92	[30]
15	Decanoic acid	C10	surface	6.10	4.95	4.73	4.78	4.80	5.06	[28]
16	Decanoic acid	C10	surface	6.40	4.95	4.73	4.78	4.80	5.06	[30]
17	Decanoic acid	C10	surface	6.80	4.95	4.73	4.78	4.80	5.06	[28]
18	Decanoic acid	C10	surface	7.20	4.95	4.73	4.78	4.80	5.06	[28]
19	Decanoic acid	C10	surface	6.17[a]	4.95	4.73	4.78	4.80	5.06	[10]
20	Lauric acid	C12	surface	5.30	4.95	4.73	4.85	4.80	5.19	[28]
21	Lauric acid	C12	surface	6.13[a]	4.95	4.73	4.85	4.80	5.19	[10]
22	Lauric acid	C12	surface	6.60	4.95	4.73	4.85	4.80	5.19	[28]
23	Lauric acid	C12	surface	7.00	4.95	4.73	4.85	4.80	5.19	[28]
24	Lauric acid	C12	surface	7.07	4.95	4.73	4.85	4.80	5.19	[28]
25	Lauric acid	C12	surface	7.50	4.95	4.73	4.85	4.80	5.19	[28]
26	Tetradecanoic acid	C14	surface	6.30	4.95	4.73	4.88	4.80	5.19	[28]
27	Tetradecanoic acid	C14	surface	7.88	4.95	4.73	4.88	4.80	5.19	[28]

28	Tetradecanoic acid	C14	surface	7.90	4.95	4.73	4.88	4.80	5.19	[28]
29	Tetradecanoic acid	C14	surface	8.15	4.95	4.73	4.88	4.80	5.19	[28]
30	Palmitic acid	C16	intrinsic	6.25	4.95	4.73	4.93	4.80	5.19	[31]
31	Palmitic acid	C16	surface	8.34	4.95	4.73	4.93	4.80	5.19	[28]
32	Palmitic acid	C16	surface	8.50	4.95	4.73	4.93	4.80	5.19	[28]
33	Palmitic acid	C16	surface	8.70	4.95	4.73	4.93	4.80	5.19	[28]
34	Palmitic acid	C16	surface	9.70	4.95	4.73	4.93	4.80	5.19	[28]
35	Stearic acid	C18	intrinsic	6.93	4.95	4.73	4.98	4.80	5.19	[31]
36	Stearic acid	C18	surface	8.00	4.95	4.73	4.98	4.80	5.19	[28]
37	Stearic acid	C18	surface	8.55	4.95	4.73	4.98	4.80	5.19	[28]
38	Stearic acid	C18	surface	9.50	4.95	4.73	4.98	4.80	5.19	[28]
39	Stearic acid	C18	surface	9.89	4.95	4.73	4.98	4.80	5.19	[28]
40	Stearic acid	C18	surface	10.20	4.95	4.73	4.98	4.80	5.19	[28]
41	Stearic acid	C18	surface	10.15	4.95	4.73	4.98	4.80	5.19	[32]
42	Arachidic acid	C20	intrinsic	7.28	4.95	4.73	5.04	4.80	5.19	[31]
43	Arachidic acid	C20	surface	9.82	4.95	4.73	5.04	4.80	5.19	[29]
44	Arachidic acid	C20	surface	11.00	4.95	4.73	5.04	4.80	5.19	[28]

[a]Determined by potentiometric titration of PFCAs solution of 50% ethanol.

Table S16. Experimental and calculated pK_a values for hydroxy groups (includes alcohols) using various applications.[a]

ID no.	Name	C_n	Expt. pK_a	Chem Axon	SPARC	Pkasolver	MolGpKa	OPERA	Ref no.
1	Methanol	C1	15.20	15.78	15.73	10.2	13.9	10.29	33
2	Methanol	C1	15.54	15.78	15.73	10.2	13.9	10.29	34
3	Methanol	C1	15.54	15.78	15.73	10.2	13.9	10.29	35
4	Ethanol	C2	15.90	16.47	15.75	9.79	13.9	12.31	34
5	Ethanol	C2	15.93	16.47	15.75	9.79	13.9	12.31	33
6	Propan-1-ol	C3	15.10	16.85	15.75	9.63	13.9	13.00	33
7	Propan-1-ol	C3	16.10	16.85	15.75	9.63	13.9	13.00	34
8	Propanol	C3	16.5	16.85	15.75	9.63	13.9	13.00	35
9	Propan-2-ol	C2	15.70	17.26	17.6	10.04	13.9	11.68	33
10	Propan-2-ol	C2	17.10	17.26	17.6	10.04	13.9	11.68	34
11	Butan-1-ol	C4	15.90	16.95	15.75	9.65	13.9	12.72	33
12	Butan-1-ol	C4	16.10	16.95	15.75	9.65	13.9	12.72	36
13	Butan-2-ol	C3	16.80	17.69	17.6	9.97	13.9	11.78	33
14	2-Methylpropan-1-ol	C3	15.95	17.33	15.75	10.25	13.9	12.87	33
15	2-Methylpropan-2-ol	C2	15.00	18.09	19.2	10.69	14	12.14	33
16	2-Methylpropan-2-ol	C2	16.00	18.09	19.2	10.69	14	12.14	34
17	2-Methyl-2-propanol	C3	17.00	18.09	19.2	10.69	14	12.14	35
18	Hexan-1-ol	C6	16.05	16.84	15.75	9.65	13.9	12.00	33
19	1-Hexadecanol	C16	16.20	16.95	15.75	9.45	13.9	11.82	37
20	Prop-2-yn-1-ol	C3	13.60	13.65	15.02	9.94	13.3		33
21	Prop-2-en-1-ol	C3	15.52	16.16	15.2	9.7	13.8	12.17	34
22	Propane-1,3-diol[b]	C3	15.10	15.6	15.41	9.6	13.7	11.88	34
23	Butane-1,4-diol[b]	C4	15.10	15.67	15.62	9.63	13.9	10.86	34
24	Butane-1,3-diol[b]	C4	14.90	15.41	15.41	9.55	13.8	12.24	34
25	2-Methoxyethan-1-ol	C2	14.80	15.12	14.95	9.68	13.8	11.60	34
26	2-Ethoxyethanol	C2	14.8	15.12	14.95	9.57	13.8	10.32	33
27	Prop-2-yn-1-ol	C3	13.55	13.65	15.02	9.94	13.3		34
28	Phenylmethanol	-	15.40	15.02	15.04	10.55	13.6		34

29	Cyclohexanol	-	16.84	18.18	17.6	9.78	13.9	11.078	[34]
30	Tricyclohexylmethanol	-	24.00	22.81	19.2	9.73	14.2	12.009	[35]
31	Diphenylmethanol	-	13.54	13.75	16.43	11.07	13.6	12.399	[34]

[a]Carbon chain lengths (C_n) determined based on longest possible hydrocarbon chain connected to an alcohol or hydroxyl group. [b]Multiple (two) hydroxy groups present in the molecule.

Table S17. Experimental and calculated pK_a values for various PFAS containing sulfonic acids, sulfonamides, amines, etc.

ID no.	Name	Abbr.	R_f	Expt. pK_a	Chemaxon	SPARC	Pkasolver	MolGpka	OPERA	Ref no.
1	Pentadecafluorooctanoic acid ammonium salt (ammonium pentadecafluorooctanoate)	APFO	C8	2.50	-4.20	0.15	2.83	0.10	0.34	[38]
2	1H, 1H, 2H, 2H-Perfluorooctanesulfonic acid	H4-PFOS (6:2 FTS)	C6	1.31	-2.72	0.36		1.40	1.23	[38]
3	1H, 1H, 2H, 2H-Perfluorodecanesulfonic acid	H4-PFDeS (8:2 FTS)	C8	1.32	-2.61	0.36		1.40	1.33	[38]
4	Perfluorobutane sulfonic acid	PFBS	C4	-6.00	-3.31	0.14		-2.90	-1.61	[38]
5	Perfluorohexane sulfonic acid	PFHxS	C6	-6.00	-3.32	0.14		-2.90	-1.64	[38]
6	Perfluorooctane sulfonic acid	PFOS	C8	-6.00	-3.32	0.14		-2.90	-1.64	[38]
7	Trifluoromethanesulfonic acid	PFMS	C1	-5.90	-3.43	0.99		-3.40	0.03	[5]
8	2,2,2-trifluoroethylamine		C1	5.70	5.25	6.11	5.50	6.30	7.87	[39]
9	3,3,3-trifluoropropylamine		C1	8.70	9.94	9.08	8.40	7.20	9.07	[39]
10	1,1,1-trifluoro-N-methylmethanesulfonamide		C1	7.56	6.38	7.11	7.95	7.00	6.86	[40]
11	Trifluoromethanesulfonamide		C1	6.33	6.19	6.09	6.60	6.5	7.04	[40]
12	1,1,1-Trifluoro-Nphenylmethanesulfonamide		C1	4.45	3.91	5.11	4.35	4.3	4.72	[40]
13	N-4-Chlorophenyl-1,1,1-trifluoromethanesulfonamide		C1	3.90	3.64	4.46	4.11	4	4.00	[40]
14	N-3-methylphenyl-1,1,1-trifluoromethanesulfonamide		C1	3.75	4	5.26	4.37	4.4	4.72	[40]
15	1,1,1-Trifluoro-N-3-trifluoromethylphenylmethanesulfonamide		C1	3.50	3.4	3.98	3.67	3.7	3.60	[40]
16	1,1,1-trifluoro-N-(4-methylsulfonylphenyl)methanesulfonamide		C1	2.84	2.35	3.04	3.64	3.3	3.56	[40]
17	Trifluoromethylphosphonic acid	PFMP	C1	1.16	-0.06	0.34	3.34	0.7	0.55	[5]

Table S18. Experimental and calculated pK_a values for various organofluorine carboxylic acids that do not satisfy PFAS I and PFAS II definitions.

ID no.	Name	R_f	No. of Perfluorinated C	Expt. pK_a	Chemaxon	SPARC	Pkasolver	MolGpka	OPERA	Ref no.
1	3-fluorobenzoic acid	C0	1	3.88	3.76	3.68	3.88	3.90	3.73	[5]
2	4-fluorobenzoic acid	C0	1	4.16	4.22	3.80	3.97	4.20	4.26	[5]
3	2-fluoroprop-2-enoic acid	C0	1	2.55	2.91	2.86	2.63	3.10	2.44	[19]
4	3,3-difluoroprop-2-enoic acid	C0	1	3.17	2.55	3.13	3.20	2.50	2.20	[19]
5	2,3,3-trifluoroprop-2-enoic acid	C0	2	1.80	1.35	1.96	2.48	1.10	1.02	[19]
6	2,3,3-trifluoroprop-2-enoic acid	C0	2	1.79	1.35	1.96	2.48	1.10	1.02	[19]
7	Difluoroacetic acid	C0	0	1.24	2.00	1.75	2.39	1.10	2.07	[2]
8	Fluoroacetic acid	C0	0	2.66	3.13	3.16	2.63	2.80	3.47	[2]
9	Pentafluorobenzoic acid	C0	5	1.48	2.05	1.46	3.72	1.7	4.12	[41]

Table S19. Experimental and calculated pK_a values for various organofluorine alcohols that do not satisfy PFAS I and PFAS II definitions.

ID no.	Name	R_f	Expt. pK_a	Chemaxon	SPARC	Pkasolver	MolGpka	OPERA	Ref no.
1	2,2-Difluoroethanol	C0	12.0	13.05	13.39	9.03	13.20	3.85	[23]
2	1,3-Dichloro-1,1,3,3-tetrafluoropropane-2,2-diol	C0	6.67	6.77	7.05	9.08	8.20	2.67	[26]
3	1,1,3-Trichloro-1,3,3-trifluoropropane-2,2-diol	C0	6.48	7.155	6.85	8.95	8.20	2.58	[26]
4	2,2-Propanediol, 1,1,3,3-tetrachloro-1,3-difluoro-	C0	6.42	7.54	6.69	8.91	8.20	3.05	[26]
5	1-chloro-1,1,3,3,3-pentafluoropropane-2,2-diol	C0	7.9	6.38	7.22	9.14	8.00	2.74	[26]
6	1,1,3,3-tetrafluoropropane-2,2-diol	C0	8.79	8.37	9.25	8.92	8.70	4.08	[26]

Table S20. Description of pK_a applications used in this work.

Application	Description
ChemAxon	Commercially available; uses QSPR method[68] Equation: $pK_a = a*Q + b*P + c*S+d$ Where, Q = partial charge increment; P = polarizability increment; S is sum of the structure specific increments; a,b,c, and d are regression coefficients specific to the ionization site[68]
SPARC	Commercially available; Uses a blend of linear free-energy relationships (LFER) and perturbed molecular orbital (PMO) method[67]
pkasolver	Open-source; Uses Graph Neural Network[69]
MolGpKa	Open-source; Uses Graph-convolution Neural Network[70]
OPERA	Open-source; Uses k-nearest neighbors (kNN) classification model combined with support vector machines (SVM) algorithml[71]

Table S21. Comparison of training data available in various open-sourced pK_a prediction applications for organic chemicals including various PFAS.[a]

Synthetic organic chemical/substructure	OPERA	MolGpKa	pkasolver
Total Training Datapoints (n)	6503	19998	5994
PFAS EPA definition	4[b]	19[c]	3[d]
PFAS OECD definition	40	1469	176
N atom	5414	18550	4958
N-H	3017	15822	3859
Amidic	645	12265	1217
Sulfonamide	221	2660	375
F atom	115	3840	584
-CF3	38	1393	155
Sulfonic acids	33	89	12
Perfluorosulfonic acids	0	1	0
αPFEs(Perfluoroethers)	1	1	1
FASAs	10	5	13
Carboxylic acids	1132	3162	939
αPFCA	1	0	0
PFECAs (includes HPFO-DA and similar chemicals)	0	0	0
n:1 and n:2 FTCAs	0	0	1
n:1 and n:2 FTUCAs	0	0	0
Alcohols	513	3388	788
αPFOHs (α-perfluorinated alcohols)	0	0	0
n:1 and n:2 FTOHs	0	0	0

[a] It should be noted for MolGpKa data, detection of molecules other than the target may occur so smaller molecules such as trifluoroacetic acid molecules in mixtures were removed for analysis; also, acids were deprotonated in pkasolver, so we took this into account in our analysis of acids to get the correct number of molecules; and only TFA and TFP (1:1 FTCA) were the only training datapoints found identical to collected data in this work. [b] All hydrazide ionizable groups; [c] Various types of ionizable groups including amides (especially sulfonamides) and hydroxy groups; [d] All nitrogen-based basic pK_a groups.

Table S22. Comparison of the average and range of pKa values of experimental data with values reported by other authors.

	Experimental pKa			Rayne & Forest (2010)	Wang et al. (2011)	Baggioli et al. (2018)
	Average	Min	Max	DFT	COSMOtherm	DFT
PFBA	0.79	0.19	1.60	-0.6 to 0.2	0.85	n/a
PFPeA	1.00	0.43	2.27	-0.5 to 0.2	0.81	n/a
PFHxA	1.18	0.75	2.17	-0.6 to 0.0	0.84	n/a
PFHpA	1.93	1.60	2.26	-0.4 to 0.0	0.82	n/a
PFOA	1.67	0.42	2.80	-0.9 to 0.2	0.9	-2.35 to 1.57
PFNA	2.17	1.60	2.58	-0.4 to -0.1	0.82	n/a
PFDA	2.22	1.60	2.61	-0.7 to -0.2	n/a	n/a

Additional Notes: Rayne & Forest (2010) calculated pK_a values for 20 different conformers at various DFT levels including B3LYP/6-311++G(d,p) and M062X/6-311++G(d,p) with the IEFPCM-UFF and SMD solvation models. Wang et al. (2011) calculated the pK_a of PFOA for two different conformers using COSMOtherm. Baggioli et al. (2018) used DFT functionals coupled with the def2-TZVP basis set.

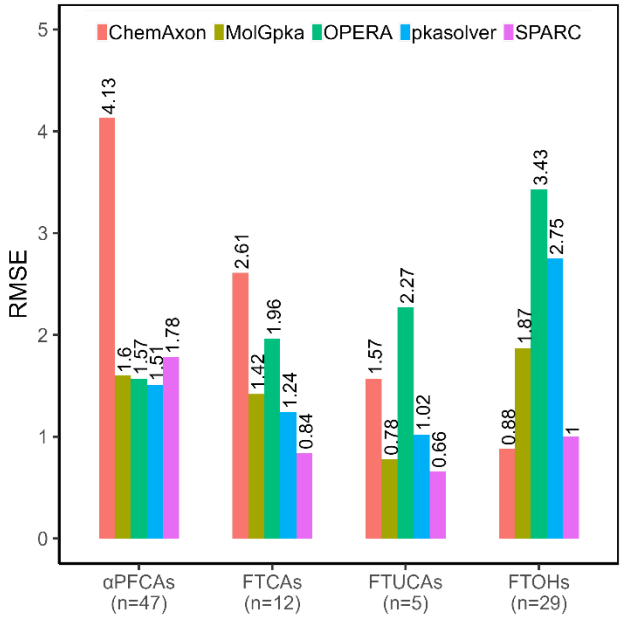

Figure S4. Mean Absolute Error for predicted pK_a values for PFCAs, FTCSa, FTUCAs, and FTOHs in our dataset

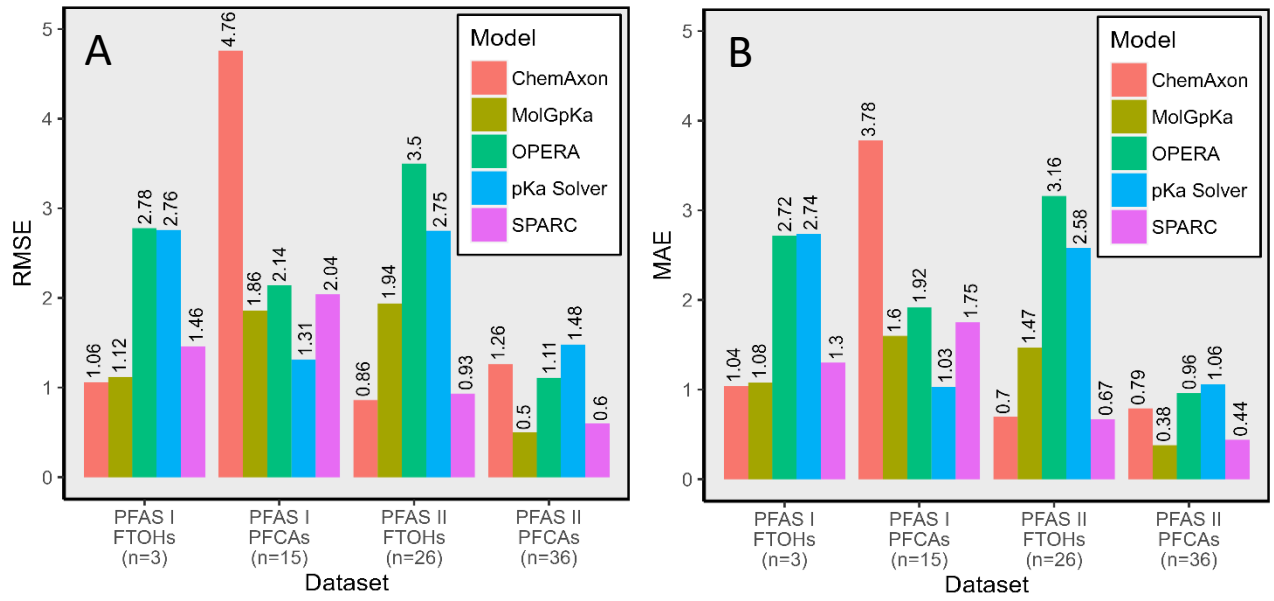

Figure S5. Performance of some available applications for pK_a predictions for FTOHs and PFCAs that satisfy the PFAS I or PFAS II definitions based on: (A) Root Mean Square Error, (B) Mean Absolute Error. Note that for PFAS I, perfluorinated chain length (R_f) ranged from C1-C10 and for PFAS II, only single perfluorinated carbon atom in carbon chain or R_f of C1.

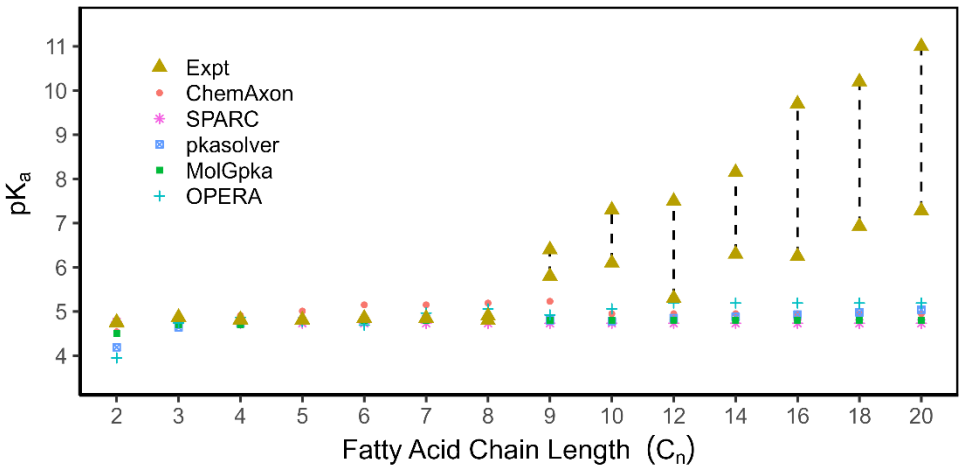

Figure S6. Performance of some available applications for pK_a predictions of fatty acids. Experimental ranges are indicated by the dashed lines ranges (---) between lower and upper reported values.

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