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Supplemental Material

Tap Water Contributions to Plasma Concentrations of Poly- and Perfluoroalkyl Substances (PFAS) in a Nationwide Prospective Cohort of U.S. Women

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Figure S4. Number of relevant industrial sites in Massachusetts from 1987 to 2015, as reported in EPA Toxic Release Inventory database. No information on the magnitudes of PFAS releases is available in this database so we identified relevant industrial sources following the methods outline in previous work using the North American Industrial Classification System (NAICS) code (Zhang et al. 2016). Full list of NAICS code is provided in Table S10.

References

Section S1: Supplemental information on methods

Literature review for toxicokinetic (TK) modeling parameters

We searched PubMed database for literature containing half-life and volume of distribution for the five PFASs included in the TK modeling. Search query was conducted in December 2017 using the terms ("rate of decline"[Title] OR "Fluorocarbons/pharmacokinetics"[MeSH Terms] OR "pharmacokinetics"[MeSH Terms] OR "toxicokinetics"[MeSH Terms] OR half-life[MeSH Terms] OR half-lives[MeSH Terms] OR "half life"[MeSH Terms] OR "half lives"[MeSH Terms] OR "serum and urine"[Title]) AND (PFOA[Title] OR PFOS[Text Word] OR PFHxS[Text Word] OR PFNA[Text Word] OR PFDA[Text Word] OR PFAS[Text Word] OR PFC[Text Word] OR "perfluoroalkyl*"[Text Word] OR "polyfluoroalkyl*"[Text Word] OR "perfluoroocta*"[Text Word] OR "perfluoronona*"[Text Word] OR "perfluorohexa*"[Text Word] OR "perfluorodeca*"[Text Word] OR "perfluooctanoic*"[Text Word]) AND (human[Title/Abstract] OR serum[Title/Abstract] OR "worker*"[Title/Abstract] NOT animal NOT teenager[Title/Abstract] NOT child*[Title/Abstract). 39 publications were found. After initial examination of titles and abstracts, 14 were deemed relevant. The references cited in the 14 studies were also examined for values of half-life and volume of distribution. Finally 9 studies were used to provide data on half-life and volume of distribution (Table S6 and Table S7).

Six studies reported values for estimated half-lives of PFASs in human plasma (Table S7). (Olsen et al. 2007) was the only study that reported half-lives for PFOS and PFHxS based on actual longitudinal observations of plasma concentrations. Other studies such has (Zhang et al. 2013) and (Worley et al. 2017) reported half-lives for PFOS and PFHxS based on urine elimination, but they were not included because urine elimination is not major elimination pathway for perfluoroalkyl sulfonates (Zhang et al. 2013).

Section S2: Supporting Tables and Figures

Table S1. Drinking water guideline levels for PFASs

Agency	Year	Guideline value (ng/L)	Reference
Sum of multiple PFASs			
Sweden	2014	90 for 11 PFASs	(Swedish National Food Agency 2014)
Denmark	2015	100 for 12 PFASs	(The Danish Environmental Protection Agency 2015)
Vermont, U.S.	2016	20 for five PFASs	(Vermont Department of Health 2018)
PFOS			
Michigan, U.S.	2013	11	(Michigan Department of Environmental Quality 2013)
New Jersey, U.S.	2018	13	(New Jersery Department of Environmental Protection 2018)
Minnesota, U.S.	2017	27	(Minnesota Department of Health 2017a)
Australia	2016	70	(Australian Department of Health 2016)
U.S. EPA	2016	70 for PFOS+PFOA	(U.S. Environmental Protection Agency 2016)
Germany	2006	100 for PFOS+PFOA	(German Ministry of Health 2006)
United Kingdom	2009	300	(U.K. Drinking Water Inspectorate 2009)
Netherland	2011	530	(National Institute for Public Health and the Environment (RIVM) 2010)
Canada	2016	600	(Health Canada 2016a)
PFOA			
New Jersey, U.S.	2017	14	(New Jersery Department of Environmental Protection 2017a)
Minnesota, U.S.	2018	35	(Minnesota Department of Health 2018a)
U.S. EPA	2016	70 for PFOS+PFOA	(U.S. Environmental Protection Agency 2016)
Germany	2006	100 for PFOS+PFOA	(German Ministry of Health 2006)
Canada	2016	200	(Health Canada 2016b)
United Kingdom	2009	300	(U.K. Drinking Water Inspectorate 2009)
Australia	2016	560	(Australian Department of Health 2016)
PFBS			
Minnesota, U.S.	2017	2000	(Minnesota Department of Health 2017b)
Canada	2016	15,000	(Health Canada 2016c)
PFBA			
Minnesota, U.S.	2017	7000	(Minnesota Department of Health 2018b)
Canada	2016	30,000	(Health Canada 2016c)
PFHxS			
Australia	2017	70	(Australian Department of Health 2016)
Canada	2016	200	(Health Canada 2016c)
PFNA			
New Jersey, U.S.	2017	13	(New Jersery Department of Environmental Protection 2017b)
Canada	2016	200	(Health Canada 2016c)

Table S2. Comparison of demographic, biometric and lifestyle factors for Nurses' Health Study participants included in this study and the full cohort.

		Matched plasma and tap water samples	Tap water samples only	Rest of cohort
n		110	115	121324
Age, yr		52.9 ± 6.4	54.6 ± 7.1	54.8 ± 7.2
White		105 (95%)	112 (97%)	113,725 (94%)
BMI, kg m^{-2}		25.8 ± 4.6	25.3 ± 4.7	25.9 ± 4.7
Weight, lb		152.6 ± 28.8	151.2 ± 29.8	136.4 ± 55.7
Parity				
	No birth	5 (5%)	5 (4%)	7,299 (6%)
	1-3 birth	69 (63%)	77 (67%)	74,769 (62%)
	3+ births	36 (33%)	33 (29%)	39,256 (32%)
Breastfeeding duration[b]				
	Never	43 (39%)	50 (43%)	51,098/100,768 (51%)
	< 12months	37 (34%)	39 (34%)	31,966/100,768 (32%)
	>= 12months	30 (27%)	26 (23%)	17,704/100,768 (18%)
Menstruation status				
	Premenopause	23 (21%)	21 (18%)	20,949 (17%)
	Postmenopause	87 (79%)	94 (82%)	94,128 (78%)
Seafood, servings day^{-1}		0.3 ± 0.3	0.3 ± 0.3	0.2 ± 0.3
Popcorn, servings day^{-1}		0.2 ± 0.2	0.1 ± 0.2	0.2 ± 0.4
Years residing at current location				
	<2	8 (7%)	6 (5%)	12,899/109,152 (12%)
	2~4	17 (15%)	17 (15%)	8,710/109,152 (8%)
	4~14	28 (25%)	46 (40%)	32,114/109,152 (29%)
	>14	57 (52%)	46 (40%)	55,429/109,152 (51%)

[a]Daily tap water consumption calculated as the sum of tap water consumed at all locations.
[b]Breastfeeding duration based on total months spent nursing all children reported in 1986 NHS questionnaire data.

Table S3. PFASs measured in drinking water and limits of detection (LOD)

Analyte[a]	Acronym	Carbon-chain length	Molecular ion	LOD (ng/L)
Carboxylic acids (PFCAs)				
Perfluoropentanoic acid	PFPeA	5	$F(CF_2)_4CO_2^-$	0.14 - 1.9
Perfluoroheptanoic acid	PFHpA	7	$F(CF_2)_6CO_2^-$	0.14 - 1.6
Linear perfluorooctanoic acid	nPFOA	8	$F(CF_2)_7CO_2^-$	0.17 - 0.8
Branched perfluorooctanoic acid	brPFOA	8	$F(CF_2)_7CO_2^-$	0.1 - 1.1
Linear perfluorononanoic acid	nPFNA	9	$F(CF_2)_8CO_2^-$	0.11 - 0.4
Branched perfluorononanoic acid	brPFNA	9	$F(CF_2)_8CO_2^-$	0.12 - 0.6
Perfluorodecanoic acid	PFDA	10	$F(CF_2)_9CO_2^-$	0.14 - 1.9
Perfluoroundecanoic acid	PFUnDA	11	$F(CF_2)_{10}CO_2^-$	0.14 - 2.2
Perfluorododecanoic acid	PFDoDA	12	$F(CF_2)_{11}CO_2^-$	0.27 - 6.0
Sulfonic acids (PFSAs)				
Perfluorobutane sulfonic acid	PFBS	4	$F(CF_2)_4SO_3^-$	0.14 - 0.5
Linear perfluorohexane sulfonic acid	nPFHxS	6	$F(CF_2)_6SO_3^-$	0.12 - 0.5
Branched perfluorohexane sulfonic acid	brPFHxS	6	$F(CF_2)_6SO_3^-$	0.14 - 0.9
Linear perflourooctane sulfonic acid	nPFOS	8	$F(CF_2)_8SO_3^-$	0.2 - 1.4
Branched perflourooctane sulfonic acid	brPFOS	8	$F(CF_2)_8SO_3^-$	0.28 - 1.2
Perfluorodecane sulfonic acid	PFDS	10	$F(CF_2)_{10}SO_3^-$	0.05 - 2.3

Table S4. LC-MS/MS and EOF recovery and precision results.

	University of Southern Denmark[1]			Harvard University[2]			Örebro University[3]		
	LOD (ng/mL)	% recovery	CV	LOD (ng/L)	% recovery	CV	LOD (ng/L)	% recovery	CV
Sample matrix	Human plasma			Water			Water		
PFCAs									
PFPeA	0.03	99.9	4.2	0.14-1.9	80.2	16	0.1	88.6	2.4
PFHxA	0.03	96.6	4.6	30.1	ND*	ND	0.1	90.7	2.2
PFHpA	0.03	106	11	0.14-1.6	97.9	15	0.1	90.9	2.7
PFOA	0.03	99.1	7.5	0.1 -1.1	88.4	9.6	0.1	90.4	1.6
PFNA	0.03	109	7.0	0.11 – 0.6	90.1	5.7	0.1	113	2.0
PFDA	0.03	89.9	11	0.14-1.9	87.6	9.2	0.1	89.1	3.9
PFUnDA	0.03	92.7	10	0.14-2.2	87.1	6.0	0.1	85.9	1.7
PFDoDA	0.03	106	18	0.27-6.0	85.8	7.3	0.1	76.7	4.6
PFSAs									
PFBS	0.03	ND	ND	0.14-0.5	90.1	15	0.1	87.4	2.4
PFHxS	0.03	104	4.0	0.12-0.9	94.9	12	0.1	90.1	4.4
PFOS	0.03	107	7.1	0.2-1.4	97.9	13	0.1	91.0	4.6

PreFOS									
N-EtFOSAA	0.03	87.7	11	Not measured			0.2	83.0	2.2
N-MeFOSAA	0.03	86.7	8.3	Not measured			0.4	86.0	2.6
EOF[4]	Not measured			Not measured			10	96.0	14

ND denotes below detection.
[1]This lab specializes in analysis of PFASs in human plasma.
[2]This lab specializes in analysis of PFASs in water.
[3]This lab specializes in analysis of Extractable Organic Fluorine (EOF)
[4]EOF assays were measured in the 5 tap water samples shown in Table S8 as a proxy measure of the total burden of fluorinated compounds.

Table S5. PFASs measured in plasma samples and coefficient of variation (CV%)

Analyte	CV %	CV by batch	Max CV %	Included in toxicokinetic model?
nPFOS	8.68	7.22	12.43	Used + Batch correction[a]
brPFOS	12.97	8.71	13.15	Used + Batch correction
PFNA	14.14	11.81	17.75	Used
N-MeFOSAA	20.27	18.9	22.02	Not measured in tap water
PFOA	22.27	14.26	25.29	Used + Batch correction
PFUnDA	29.36	22.15	41.25	Not Use
PFHxS	31.53	14.71	47.96	Used + Batch correction
PFDA	38.98	17.15	73.63	Not Used
PFDoDA	44.62	23.12	70.87	Not Used
N-EtFOSAA	49.71	41.17	62.14	Not Used
PFHpA	80.54	58.78	91.36	Not Used

[a]Batch effects were corrected following methods outlined by Rosner et al.(2008) A linear model was first fit to regress PFAS concentrations on batch indicator dummy variables. PFAS concentrations were then recalibrated by subtracting the difference between the coefficient of each individual batch and the average of the coefficients of all batches

Table S6. Summary of toxicokinetic model parameters

Parameter	Definition	Equation	Reference
$\frac{dC_{plasma,t}}{dt}$	Change in concentration of plasma PFAS over time (ng/mL/day)	$\frac{intake_t}{V_D} - k_E \times C_{plasma,t}$	
V_D	Volume of distribution (mL/kg)	PFOA: LN(ln(170), ln(1.7))[a]	(Thompson et al. 2010)
		PFNA: LN(ln(243.1), ln(48.9))	(Ohmori et al. 2003)
		nPFOS: LN(ln(230), ln(2.25))	(Thompson et al. 2010)
		brPFOS: LN(ln(230), ln(2.25))	(Thompson et al. 2010)
		PFHxS: LN(ln(213), ln(28))	(Sundström et al. 2012)
$t_{1/2}$	Half-life (year)	PFOA: LN(ln(4.7), ln(1.2))	Weighted average, see Table S7
		PFNA: LN(ln(2.7), ln(2.0))	Weighted average , see Table S7
		nPFOS: LN(ln(4.8), ln(1.1)	(Olsen et al. 2007)
		brPFOS: LN(ln(4.8), ln(1.1))	(Olsen et al. 2007)
		PFHxS: LN(ln(7.3), ln(1.1))	(Olsen et al. 2007)
k_E	Elimination rate (day^{-1})	$\frac{\ln(2)}{t_{1/2} * 365}$	
$C_{plasma,s.s.}$	Steady-state plasma PFASs (ng/mL)	$\frac{DW \times C_{water}}{bw \times V_D \times k_E}$	
DW	Drinking water intake (L/day)	Questionnaire data from 1990	This work
bw	Body weight (kg)	Questionnaire data from 1990	This work
C_{water}	Tap water PFASs in 1989/1990 (ng/L)	PFAS measured in water samples collected in 1989-90	This work

[a]LN(ln(GM), ln(variance)) stands for log-normal distribution with geometric mean (GM) and variance.

Table S7. Mean and variance of reported values on PFAS half-lives in human plasma or serum (in years)

Chemical	Ref	*n*	Arithmetic mean (AM)	Geometric Mean (GM)	95% CI (AM)	95% CI (GM)	Range	ln(GM)	ln(variance)
PFOA	(Bartell et al. 2010)	200		2.3		2.1-2.4	1.5-4.6	0.83	0.002
	(Olsen et al. 2007)	26	3.8	3.5	3.1-4.4	3.0-4.1		1.25	0.006
	(Seals et al. 2011)	602 (residents of Little Hocking)		2.9			2.5-3.0	1.06	0.002
	(Seals et al. 2011)	971 (residents of Lubeck)		8.5			5.9-10.3	2.14	0.015
	(Zhang et al. 2013)	20 (young female)	2.1	1.5			0.19-5.2	0.41	0.474
	(Zhang et al. 2013)	66 (old female and male)	2.6	1.2			0.059-14	0.18	1.008
	(Costa et al. 2009)	16	5.1	2.8			2.6-9.7	1.03	0.001
	(Worley et al. 2017)	45	3.9				3.5 - 4.1	1.36	0.001
Weighted average for PFOA[a]								*1.55*	*0.047*
PFNA	(Zhang et al. 2013)	16	2.5	1.7			0.38-7.7	0.53	0.249
	(Zhang et al. 2013)	50	4.3	3.2			0.34-20	1.16	0.558
Weighted average for PFNA[a]								*1.01*	*0.486*
PFOS	(Olsen et al. 2007)	26	5.4	4.8	3.9-6.9	4.0-5.8		1.57	0.008
PFHxS	(Olsen et al. 2007)	26	8.5	7.3	6.4-10.6	5.8-9.2		1.99	0.013

[a]When there are multiple human studies available for estimating the half-lives of PFASs, weighted average was calculated where the weight is the inverse of the variance of half-lives reported in each study.

Table S8. Drinking water samples collected in 2016

Site	Sampling location	Number of samples	Sampling date
MA1	Kitchen tap	2	10/4/2016
MA2	Kitchen tap	2	9/25/2016
MA3	Kitchen tap	2	9/30/2016
MA4	Kitchen tap	2	9/25/2016
MA5	Kitchen tap	2	10/2/2016

Note: water samples were used for a pilot analysis of EOF as a proxy for the total burden of fluorinated compounds in tap water.

Table S9. Search strategy used to identify PFAS industrial sources in Toxic Release Inventory

NAICS code	Description of Industry	Number of sites in US	Category in Figure S3
22132	Sewage treatment facilities	32	Waste treatment
562	Waste management and remediation	453	Waste treatment
313	Textile mills	956	Textile mills
322	Paper manufacturing	1455	Paper manufacturing
323	Printing and related support activities	991	Printing
324	Petroleum and coal products manufacturing	1549	Petroleum sector
3255	Paint, coating, and adhesive manufacturing	1747	Chemical manufacturing
32591	Printing ink manufacturing	324	Chemical manufacturing
3328	Metal coating, engraving, heat treating and allied activities	3313	Metal coating
3344	Semiconductor manufacturing	2199	Semiconductor manufacturing
48811	Airport operation	7	Airports and military bases
928110	National Security	439	Airports and military bases
PFOA stewardship program[a]		116	EPA PFOA stewardship program

[a]Note: Industrial sites participating in EPA PFOA stewardship program is identified by a combination of facility name and NAICS code. The facility name must have at least one of 3M, Arkema, Asahi, Basf, Clariant, Daikin, Dyneon, Dupont, Solvay Solexis. In addition, the NAICS code needs to be one of all other basic organic chemical manufacturing (325199), all other miscellaneous chemical product and preparation manufacturing (325998), plastic material and resin manufacturing (325211), custom compounding of purchased resins (325991), noncellulosic organic fiber manufacturing (325222), nonferrous metal (except aluminum) smelting and refining (331410).

Table S10. Modeled relative source contribution (%) of tap water to overall PFAS exposure among 110 Nurses' Health Study participants in 1989/1990.

Chemical	>LOD *n*	25th percentile[a]	Median	Mean	75th percentile
PFOA	49	7.7	11.6	19.2	20.1
PFNA	30	6.4	13.1	16.1	21.2
nPFOS	57	0.9	2.2	3.6	4.8
brPFOS	49	1.2	3	4.5	6.5
PFHxS	66	14.6	34.1	47.5	60.7

[a]25th percentile, median, mean and 75th percentile were calculated for individuals with tap water samples >LOD only

Table S11. Modeled relative source contribution (%) of tap water to overall PFAS exposure stratified by number of years living in the current residence.

Chemical	Years living in current residence	>LOD *n*	25th percentile[a]	Median	Mean	75th percentile
PFOA	<2	2	8.7	9.7	9.7	10.7
	2 ~ 4	6	4.8	8	10.6	17.7
	4 ~ 14	13	6.5	11.1	19.4	17.4
	>14	28	8.5	14.6	21.6	29.1
***p*-value**[b]	0.44					
PFNA	<2	0	/	/	/	/
	2 ~ 4	3	4	5.1	12.2	16.9
	4 ~ 14	9	7.4	19.7	17.7	23.6
	>14	18	7.2	12.7	16	20.1
p-value	0.54					
nPFOS	<2	3	1.2	1.3	2.2	2.7
	2 ~ 4	7	2.3	2.6	3	3.4
	4 ~ 14	14	0.8	2.2	3.4	5.9
	>14	33	0.8	2.2	3.9	5.1
p-value	0.97					
brPFOS	<2	2	2.4	3.7	3.7	4.9
	2 ~ 4	7	2.2	3	2.9	3.9
	4 ~ 14	12	1.3	4.1	5.6	7.9
	>14	28	1.2	2.4	4.5	6.7
p-value	0.92					
PFHxS	<2	3	20.3	24.1	35	44.2
	2 ~ 4	14	10.7	23.9	36.3	48.1
	4 ~ 14	17	18.3	36	48.7	67.8
	>14	32	16.2	36.8	52.9	58.3
p-value	0.78					

[a] 25^{th} percentile, median, mean and 75^{th} percentile were calculated for individuals with tap water samples >LOD only

[b] *p*-value was determined by the Kruskal-Wallis rank sum test of the difference between the RSC of tap water to plasma PFAS concentrations across different groups of years living in current residence

Table S12. Comparison of the relative source contribution (RSC) of tap water estimated using the deterministic toxicokinetic model and estimated using a Monte Carlo (MC) simulation.

%		>LOD *n*[a]	Median (95% PI)[b]	Mean (95% PI)	25th percentile (95% PI)	75th percentile (95% PI)
PFOA	Original[c]	49	11.6	19.2	7.7	20.1
	MC simulation[d]	49	12.0 (10.5, 13.7)	19.5 (18, 21.1)	6.7 (5.7, 7.7)	21.0 (17.3, 24.3)
PFNA	Original	30	13.1	16.1	6.4	21.2
	MC simulation	30	14.1 (8.7, 21.4)	24.3 (17.2, 34.5)	6.1 (3.7, 8.8)	30.5 (19.6, 45.7)
nPFOS	Original	57	2.2	3.6	0.9	4.8
	MC simulation	57	2.2 (2.0, 2.5)	3.5 (3.4, 3.7)	0.9 (0.8, 1.0)	4.6 (4.1, 5.2)
brPFOS	Original	49	3.0	4.5	1.2	6.4
	MC simulation	49	2.8 (2.5, 3.2)	4.5 (4.2, 4.7)	1.1 (1.0, 1.3)	6.4 (5.6, 7.3)
PFHxS	Original	66	34.1	47.5	14.6	60.7
	MC simulation	66	33.6 (28.9, 39)	52.9 (48.3, 58.4)	15.1 (12.6, 17.7)	64.8 (55.7, 75.7)

[a]RSC is only estimated for NHS participants whose tap water were detectable of respective PFASs.
[b]Mean and the 95% probability interval (PI) of the median, mean, 25th and 75th percentile RSC (%) from tap water, for NHS participants whose tap water were detectable of respective PFASs.
[c]Original is the same as Table S10. These are estimated RSC using the deterministic toxicokinetic model where input parameters (half-lives, volume of distribution, etc.) were set at the geometric mean stated in Table S7.
[d]MC simulation was conducted by iteratively drawing random values from the probability distribution of input parameter for 300 times, estimating RSC using the toxicokinetic model and generating the median, mean, 25th and 75th percentile among the NHS participants whose tap water were detectable of respective PFASs.

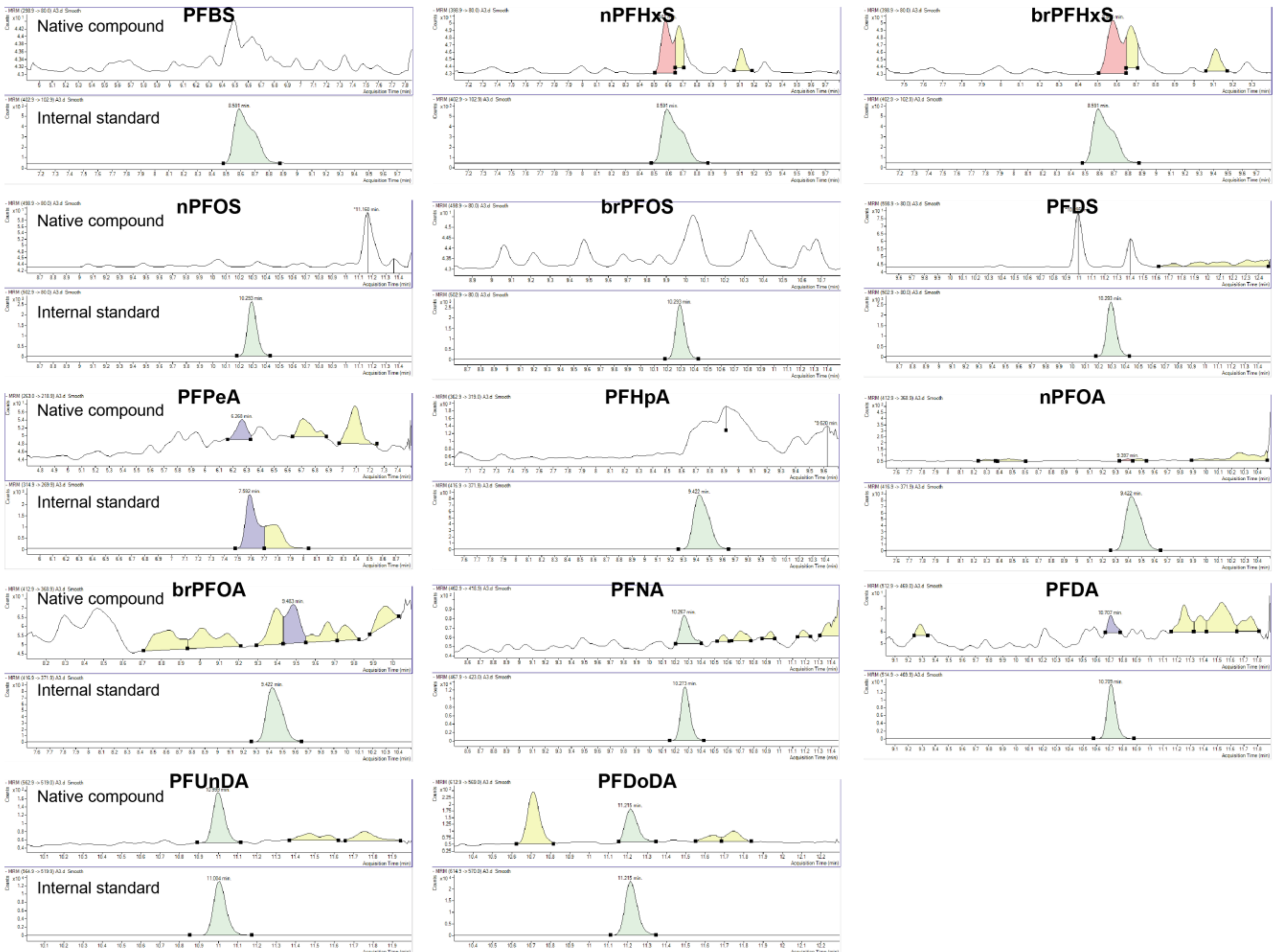

Figure S1. Chromatograms of PFASs in an extract of HDPE water sampling bottle, analyzed using an Agilent 6460 LC-MS/MS equipped with an online-SPE system (Agilent 1290 Infinity Flex Cube) in dynamic multiple reaction mode.

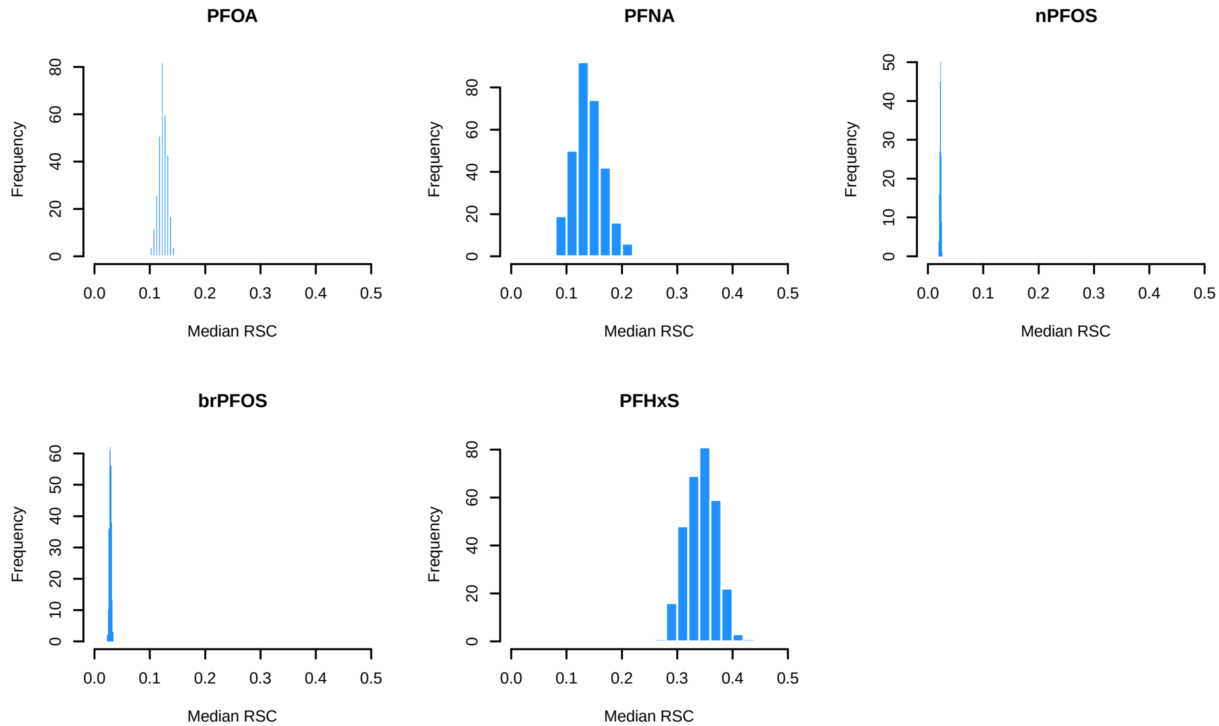

Figure S2. The distribution of estimated median relative source contribution from tap water among 300 Monte Carlo simulations that consider interindividual variability in TK parameters and drinking water consumption rates.

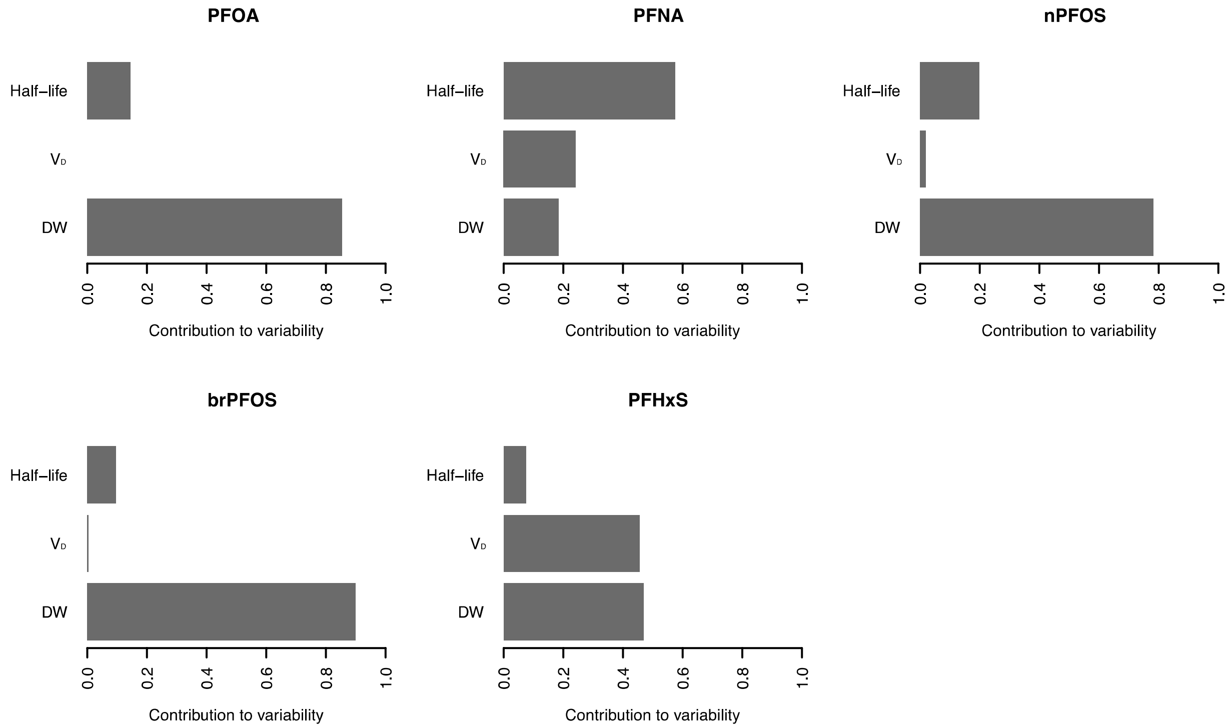

Figure S3. Sensitivity analysis showing contribution of each input parameter of the one-compartment toxicokinetic model to the variability of estimated relative source contribution of tap water. Contribution of different input parameters was calculated as the square of the correlation coefficient between input parameter and estimated RSC, normalized to the sum of the squared correlation coefficients (Wang et al. 2016). V_D stands for volume of distribution, DW stands for drinking water consumption rate.

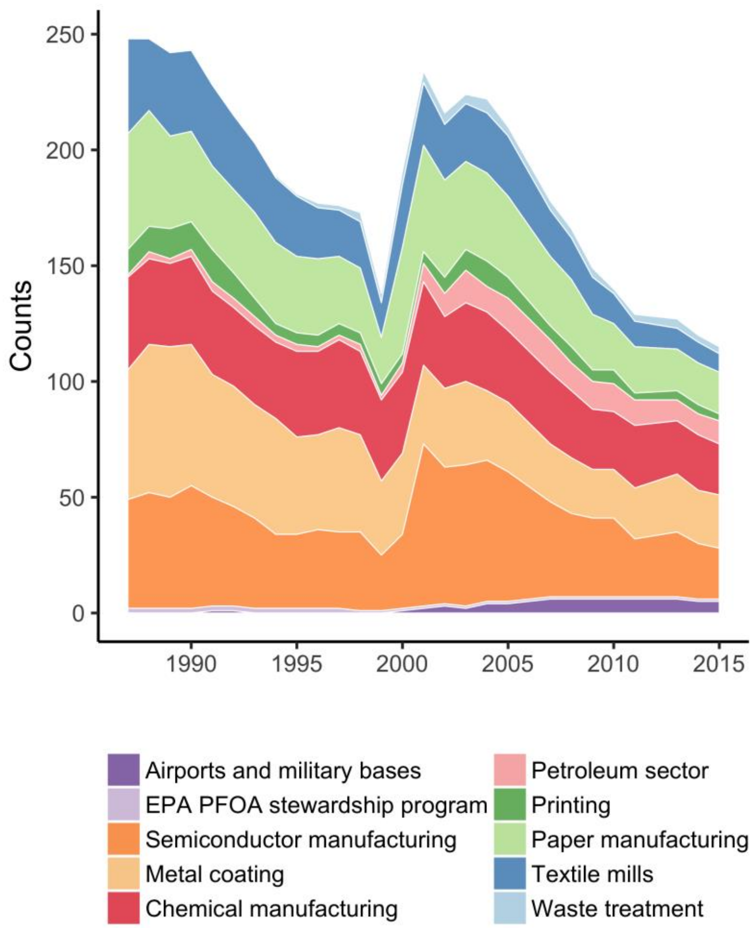

Figure S4. Number of relevant industrial sites in Massachusetts from 1987 to 2015, as reported in EPA Toxic Release Inventory database. No information on the magnitudes of PFAS releases is available in this database so we identified relevant industrial sources following the methods outline in previous work using the North American Industrial Classification System (NAICS) code (Zhang et al. 2016). Full list of NAICS code is provided in Table S10.

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