Supplementary information

Anthropogenic organic contaminants analysed in human blood and combined risk

Engelhardt A.J.[1*], Norström K.[2], Weiss J.M.[1]

[1]Department of Environmental Science (ACES), Exposure and Effects Unit, Stockholm University, Stockholm, Sweden [2]The Swedish Environmental Protection Agency, Stockholm, Sweden [*]corresponding author: josefin.engelhardt@aces.su.se, https://orcid.org/0000-0002-5277-6404

Journal: *Exposure and Health*

DOI: 10.1007/s12403-022-00507-y

Table of Tables

Table of Figures

Method

Literature search

In the literature searches, the title and abstracts were considered when selecting the articles to include. The selection criteria process when excluding pharmaceuticals was done based on the author's knowledge as well as how the use of the OC was described in the abstract. The results were sorted based on relevance according to each database and each page of the search was checked for relevant articles until only non-relevant articles and duplicates showed. It is possible that this is a limitation of the scope of the literature search.

Table S1 The details for the three literature searches and respective keywords used. See SI.Table 2 below for a list of each "compound_name" used in the literature search B.

Literature serach	**Database**	**Search words**	**Published year**	**Date**
A	EBSCO Discovery Service (EDS) through the Stockholm University library	(blood OR serum) AND human AND (sweden OR swedish) AND (contaminant OR chemical OR substance OR pollutant OR molecule)	2000-2019	2019-08-15
B	Google scholar	Human blood OR serum OR sera OR plasma "Compound_name"	2000-2019	2019-10-14 to 2019-10-18
C	PubMed	(blood OR serum) AND human AND (contaminant OR chemical OR substance OR pollutant OR molecule)	2000-2020	2020-06-30

Table S2 Search terms used for each search in literature search B, using Google Scholar as the database. The words can be everywhere in the article and only articles published between 2000-2019 were considered. Patents and citations were excluded.

Find articles…	**…with all words**	**…with the exact phrase**	**…with at least one of these words**	***Number of articles matching***	***Number of articles actually analysing human blood***	***Date of search***
Literature search no. 1	Human	2-Ethylhexyl salicylate	blood serum sera plasma	154	1	2019-10-14
Literature search no. 2	Human	Homomenthyl salicylate	blood serum sera plasma	67	0	2019-10-14

Literature search no. 3	Human	3-Benzylidene camphor	blood serum sera plasma	327	2	2019-10-14
Literature search no. 4	Human	4-Methyl benzylidene camphor	blood serum sera plasma	285	1	2019-10-14
Literature search no. 5	Human	Benzophenon-3	blood serum sera plasma	2690	4	2019-10-14
Literature search no. 6	Human	2,4-Dihydroxybenzophenone	blood serum sera plasma	421	3	2019-10-15
Literature search no. 7	Human	2,2'-Dihydroxy-4-methoxybenzophenone	blood serum sera plasma	157	0	2019-10-15
Literature search no. 8	Human	Ethylhexyl p-dimethylaminobenzoat	blood serum sera plasma	22	0	2019-10-15
Literature search no. 9	Human	Diethylamino hydroxybenzoyl hexyl benzoate	blood serum sera plasma	125	0	2019-10-15
Literature search no. 10	Human	Isoamyl p-methoxycinnamate	blood serum sera plasma	103	0	2019-10-15
Literature search no. 11	Human	Octyl methoxycinnamate	blood serum sera plasma	1200	0	2019-10-15
Literature search no. 12	Human	Octocrylene	blood serum sera plasma	1090	0	2019-10-15
Literature search no. 13	Human	Benzophenone	blood serum sera plasma	17700	0	2019-10-15
Literature search no. 14	Human	Dihydroactinidiolide	blood serum sera plasma	280	0	2019-10-15
Literature search no. 15	Human	Benzene, 1,1'-(3,3-dimethyl-1-butenylidene)bis 1,1,3-Trimethyl-3-phenylindan	blood serum sera plasma	0	0	2019-10-15
Literature search no. 16	Human	2-(2H-benzotriazol-2-yl)-4,6-di-tert-pentylphenol	blood serum sera plasma	24	0	2019-10-15
Literature search no. 17	Human	2-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol	blood serum sera plasma	15	0	2019-10-15

Literature search no. 18	Human	2,4-di-tert-butyl-6-(5-chlorobenzotriazol-2-yl)phenol	blood serum sera plasma	7	0	2019-10-15
Literature search no. 19	Human	2-(benzotriazol-2-yl)-4-methylphenol	blood serum sera plasma	9	0	2019-10-15
Literature search no. 20	Human	Chlorinated paraffins	blood serum sera plasma	1850	4	2019-10-18
Literature search no. 21	Human	Paraben	blood serum sera plasma	6470	10	2019-10-18

Statistics related to data in Fig 4

To prepare the data for Fig.4, each dataset corresponding to one OC was checked for normality using Shapiro-Wilk test, where the data is considered normally distributed when W > 0.05. ROUT's test was used to identify outliers, with Q=1.

Table S3 Sensitivity test to determine the influence of the LOQ values on the temporal trends. Bold values are non-significant *p*-values (>0.05). Different results in red means that depending on which choice is made, the temporal trend will change from significant to non-significant or vice versa. The equation for each trend is also presented.

OC name (Fig)	LOQ=0	LOQ/2	LOQ	Excluding LOQ
PFBS (Fig S1) **Different results**	Women *p*-value = 0.0001 Y = 0,02812*X - 54,85 Children *p*-value <0.0001 Y = 0,08818*X - 175,9	Women *p*-value **= 0.6768** Y = 0,01047*X - 19,94 Children *p*-value <0.0001 Y = 0,07838*X - 156,2	Women *p*-value **= 0.8910** Y = 0,003252*X - 5,344 Children *p*-value <0.0001 Y = 0,09150*X - 182,6	Women *p*-value = 0.0001 Y = 0,02812*X - 54,85 Children *p*-value <0.0001 Y = 0,08818*X - 175,9
PFDS (Fig S5)	Women *p*-value <0.0001 Y = -0,06291*X + 127,4	Women *p*-value = 0.0002 Y = -0,09963*X + 200,8	Women *p*-value = 0.0007 Y = -0,08593*X + 173,4	Women *p*-value <0.0001 Y = -0,06291*X + 127,4
PFHpA (Fig S7) **Different results**	Women *p*-value **= 0.2324** Y = -0,007000*X + 15,62 Men *p*-value **= 0.4111** Y = -0,01106*X + 24,00 Children *p*-value = 0.0005 Y = -0,02937*X + 61,09	Women *p*-value = 0.0293 Y = -0,01354*X + 28,72 Men *p*-value **= 0.6153** Y = -0,01046*X + 22,74 Children *p*-value <0.0001 Y = -0,03562*X + 73,67	Women *p*-value **= 0.1829** Y = -0,007955*X + 17,54 Men *p*-value **= 0.3720** Y = -0,01095*X + 23,78 Children *p*-value **= 0.1071** Y = -0,01376*X + 29,72	Women *p*-value **= 0.2324** Y = -0,007000*X + 15,62 Men *p*-value **= 0.4111** Y = -0,01106*X + 24,00 Children *p*-value = 0.0005 Y = -0,02937*X + 61,09
PFUnDA (Fis S8)	Women *p*-value = 0.0008	Women *p*-value = 0.0005	Women *p*-value = 0.0005	Women *p*-value = 0.0008

	Y = 0,007441*X - 12,55 Children *p*-value = 0.0003 Y = -0,02258*X + 47,64	Y = 0,008353*X - 14,39 Children *p*-value = 0.0005 Y = -0,02289*X + 48,28	Y = 0,007738*X - 13,15 Children *p*-value = 0.0003 Y = -0,02267*X + 47,83	Y = 0,007441*X - 12,55 Children *p*-value = 0.0003 Y = -0,02258*X + 47,64
PFTrDA (Fig S9)	Women *p*-value = 0.003 Y = 0,01357*X - 25,71	Women *p*-value = 0.001 Y = 0,01894*X - 36,51	Women *p*-value = 0.003 Y = 0,01368*X - 25,93	Women *p*-value = 0.003 Y = 0,01357*X - 25,71
PFDA (Fig S10)	Women *p*-value <0.0001 Y = 0,009006*X - 15,64	Women *p*-value <0.0001 Y = 0,01529*X - 28,28	Women *p*-value <0.0001 Y = 0,009947*X - 17,53	Women *p*-value <0.0001 Y = 0,009006*X - 15,64
BDE 47 (Fig S12a) **Different results**	Women *p*-value = 0.0183 Y = -0,03048*X + 62,11 Children *p*-value = **0.0561** Y = -0,1503*X + 303,9	Women *p*-value = 0.0230 Y = -0,01177*X + 24,54 Children *p*-value = **0.09** Y = -0,08628*X + 174,6	Women *p*-value = 0.0004 Y = -0,02118*X + 43,58 Children *p*-value = 0.0398 Y = -0,08686*X + 176,0	Women *p*-value = 0.0183 Y = -0,03048*X + 62,11 Children *p*-value = **0.0561** Y = -0,1503*X + 303,9
BDE 100 (Fig S12b)	Women *p*-value = 0.0006 Y = -0,06333*X + 127,4	Women *p*-value = 0.0015 Y = -0,03023*X + 60,86	Women *p*-value = 0.0003 Y = -0,03401*X + 68,61	Women *p*-value = 0.0006 Y = -0,06333*X + 127,4
BDE 99 (Fig S12c) **Different results**	Women *p*-value = 0.1849 Y = -0,02070*X + 42,13 Children *p*-value = **0.0896** Y = 0,07180*X - 144,0	Women *p*-value = **0.2276** Y = -0,008848*X + 18,26 Children *p*-value = **0.5748** Y = 0,01788*X - 35,48	Women *p*-value = **0.1163** Y = -0,01114*X + 23,03 Children *p*-value = **0.2205** Y = 0,03635*X - 72,46	Women *p*-value = 0.1849 Y = -0,02070*X + 42,13 Children *p*-value = **0.0896** Y = 0,07180*X - 144,0
BDE 209 (Fig S12d)	Children *p*-value = **0.6356** Y = -0,03100*X + 63,31	Children *p*-value = **0.4647** Y = -0,07736*X + 156,5	Children *p*-value = **0.4522** Y = -0,06661*X + 134,9	Children *p*-value = **0.6356** Y = -0,03100*X + 63,31
CB138 (Fig 5b) **Different results**	Women *p*-value = 0.0341 Y = -0,07699*X + 157,0	Women *p*-value = **0.1193** Y = -0,06156*X + 126,0	Women *p*-value = **0.0697** Y = -0,06622*X + 135,3	Women *p*-value = 0.0341 Y = -0,07699*X + 157,0
CB153 (Fig 5c)	Women *p*-value = **0.4118** Y = -0,01216*X + 27,17	Women *p*-value = **0.4690** Y = -0,01183*X + 26,46	Women *p*-value = **0.4320** Y = -0,01195*X + 26,71	Women *p*-value = **0.4118** Y = -0,01216*X + 27,17
HCB (Fig 7a)	Women *p*-value = **0.2681** Y = -0,01176*X + 25,61	Women *p*-value = **0.2465** Y = -0,01180*X + 25,68	Women *p*-value = **0.2487** Y = -0,01230*X + 26,72	Women *p*-value = **0.2681** Y = -0,01176*X + 25,61
p,p'-DDE (Fig 7a)	Women *p*-value = **0.3831** Y = -0,01467*X + 32,52	Women *p*-value = **0.4996** Y = -0,01362*X + 30,35	Women *p*-value = **0.4561** Y = -0,01387*X + 30,87	Women *p*-value = **0.3831** Y = -0,01467*X + 32,52

Table S4 The human biomonitoring guidance values (HBM-GVs) for the nine OCs (groups), critical effect they are based on and the data each reference value is based on.

Compound	**HBM-GV [pg/mL]**	**Critical effect**	**Data**	**Ref.**
PFOS	5000	• Birth weights of new-borns • Immunity after vaccination, immunological development	Based on epidemiological studies, HBM-GVs within range of critical effect	(Hölzer et al. 2021).
PFOA	2000	• Birth weights of new-borns • Immunity after vaccination, immunological development • Lipid metabolism • Time to desired pregnancy/waiting times to pregnancy >1 year • Thyroid metabolism	Based on epidemiological studies, HBM-GVs within range of critical effect	(Hölzer et al. 2021)
HCB	166	Liver toxicity (lowest value within range of BE-values for same endpoint)	Rat studies, **UF=1000** (sum of $UF_{LOAEL\text{-}to\text{-}NOAEL}$= 10; $UF_{Severity}$=10; $UF_{intravariability}$=10	(Aylward et al. 2010)
ΣPCBs[1]	3500	• Neurotoxic effects • Immunotoxic effects	Based on epidemiological studies	(Rauchfuss et al. 2013)
DDE & DDT	23,900	• Developmental toxicity • Liver toxicity	Rat studies **UF: 100** (sum of $UF_{interspecies}$=10; $UF_{intraspecies}$= 10)	(Kirman et al. 2011)
BDE99	3540	Neurodevelopmental effects on behaviour	Mouse study, **UF: 300** (sum of $UF_{intrahuman}$=10; $UF_{singe\text{-}dose\text{-}lifetime}$=3; $UF_{database\ deficiencies}$=10)	(Krishnan et al. 2011)
HBCDD	1600	Neurodevelopmental effects on behaviour	Animal studies, **UF:8** (sum of $UF_{intraspecies}$=3.2; $UF_{interspecies\ factor}$=2.5)	(German HBM Commission 2015)
ΣPCDD/F & dl-PCBs[2]	15	Effects on the reproductive system of male rats exposed *in utero*	Rat studies, **UF: 3** (sum of $UF_{LOAEL\text{-}to\text{-}NOAEL}$=3; $UF_{interspecies}$=1; $UF_{intraspecies}$=1	(Aylward et al. 2008)
PCP	40,000	Immunotoxicicy	Based on epidemiological studies	(German HBM Commission 1997)

[1] PCB-138, 153 and 180 concentrations in serum times 2, [2] The 12 dioxin-like PCBs, IUPAC No. 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169 and 189

Results

Table S5 POP distribution in the two databases

Database	HBDB	SEDB
POP	302 (54%)	95 (57%)
POP metabolite	51 (9.1%)	17 (10%)
Not POP	alkylphenols, bisphenols, CPs, flame retardants, PAHs, parabens, pesticides, PFASs, phthalates, solvents, UV-filters	bisphenols, flame retardants, pesticides, PFASs, phthalates

Table S6 Countries included in HBDB, the number of OCs and references analysed for each country

Country	Number of chemicals analysed	Number of references
Asia		
Bangladesh	9	1
Cambodia	17	2
China	100	12
India	55	2
Japan	210	49
Laos	21	1
Nepal	6	1
South Korea	79	12
Sri Lanka	9	1
Turkey	27	1
Uzbekistan	1	1
Vietnam	21	5
Europe		
Belgium	64	6
Czech Republic	6	1
Denmark	20	4
Estonia	6	1
Faroe Islands	40	4
France	43	6
Germany	198	10
Greece	2	1
Italy	65	2
Latvia	23	1
Norway	43	4
Poland	21	3
Portugal	16	2
Romania	26	1
Russia	73	5
Slovakia	51	5
Spain	41	6

Sweden	185	69
The Netherlands	20	3
Oceania		
Australia	14	4
New Zeeland	1	1
North America		
Canada	46	6
Mexico	6	1
USA	189	28
South America		
Brazil	1	1
Nicaragua	8	2

Table S7 Chemical groups reported to have been analysed in human blood divided into the Human Blood Database (HBDB) and Swedish Exposure Database (SEBD) and the time frame of corresponding blood sampling.

Compound group	**Time frame of blood sampling**	
	HBDB	**SEDB**
Alkylphenols	2008-2016	*n.a.* [a,b]
Bisphenols	1996-2017	1987-2008
Chlorinated paraffins	2012-2019	*n.a.* [a]
PCDD/Fs	1987-2019	1987-2004
Flame retardants	1988-2019	1991-2017
Flame-retardant metabolites	2002-2010	*n.a.* [a]
PAHs	2014	*n.a.* [a,b]
Parabens	2002-2017	*n.a.* [a,b]
PCBs	1967-2020	1988-2017
PCB metabolites	1967-2012	1991-2002
Personal care product ingredients	2002-2016	*n.a.* [a,b]
Pesticides	1988-2019	1988-2019
PFASs	1988-2020	1988-2019
Phthalates	2001-2009	2001-2008
Solvents	1998-2019	*n.a.* [a]
UV-filters	2010-2014	*n.a.* [a]

[a] *Not analyzed*

[b] *Analyzed in other human matrices in Sweden (Swedish Environmental Protections Agency 2019)*

Table S8 Selected OCs with number of studies and in parenthesis the number of individuals analysed for each OC, divided into women, men, both sexes and children and adolescents (0-20 years old).

Compound	Women	Men	Both sexes	Children and adolescents
CB138	13 (467)	7 (166)	10 (3162)	78 (1040)
CB153	19 (2701)	28 (2657)	10 (3368)	79 (1200)
CB180	5 (152)	7 (166)	10 (3162)	78 (1040)
PCDD/Fs	1 (497)	4 (544)	1 (1016)	*n.a.* [a]
PCP	2 (25)	3 (43)	*n.a.* [a]	*n.a.* [a]
p,p’-DDT	3 (137)	6 (166)	1 (79)	78 (1040)
p,p’-DDE	18 (2170)	27 (1459)	14 (3481)	79 (1200)
HCB	15 (1594)	13 (323)	14 (3750)	78 (1040)
BDE47	57 (1124)	12 (363)	6 (2349))	88 (1190)
BDE99	47 (683)	5 (197)	*n.a.* [a]	91 (1264)
BDE100	47 (685)	5 (197)	*n.a.* [a]	13 (224)
BDE209	43 (635)	5 (197)	*n.a.* [a]	13 (224)
PFOS	96 (3419)	9 (329)	6 (1476)	79 (1053)
PFOA	101 (3626)	10 (329)	10 (4014)	95 (1269)
BPA	12 (708)	1 (502)	*n.a.* [a]	*n.a.* [a]
Phthalates	3 (575)	1 (502)	*n.a.* [a]	*n.a.* [a]

[a] *Not analyzed*

Figures

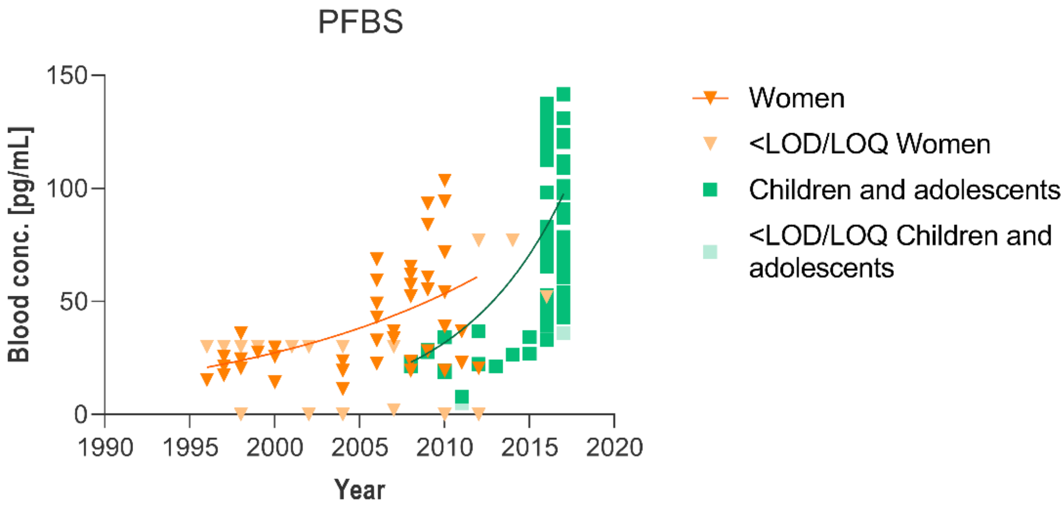

Fig. S1 Time trends of PFBS in women and children and adolescents. Trendlines are added when *p*-value <0.05.

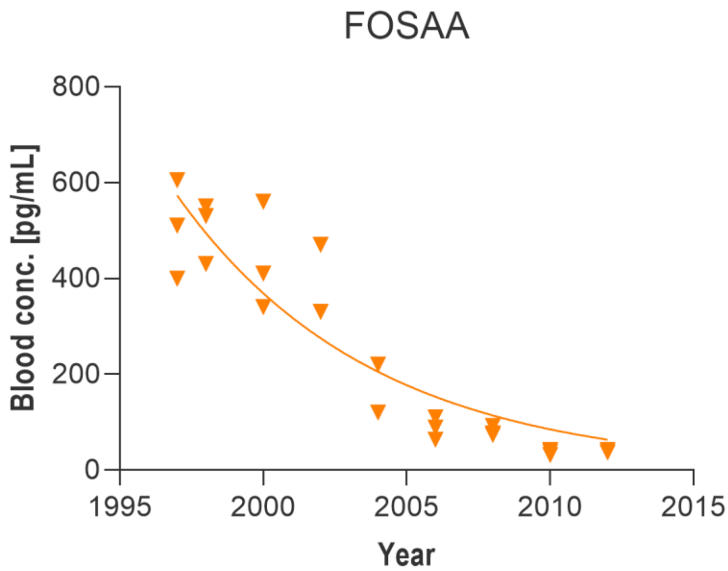

Fig. S2 Time trend of blood concentration of FOSAA in Swedish women. Trendlines are added when *p*-value <0.05.

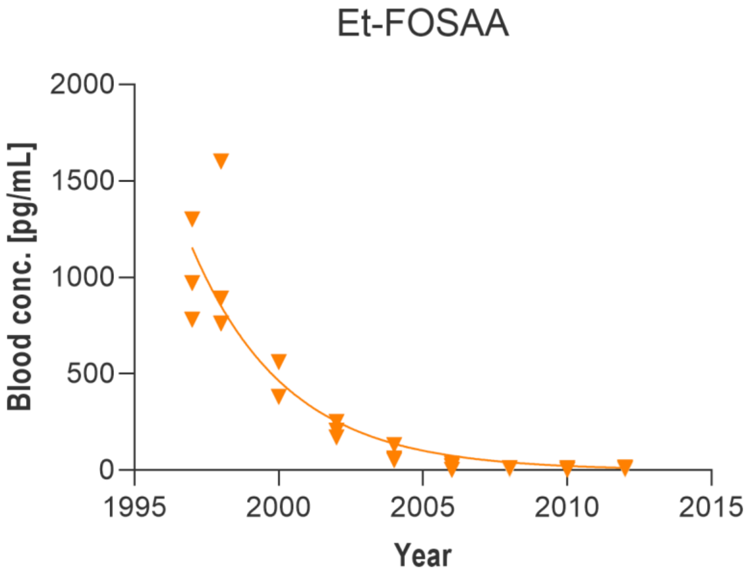

Fig. S3 Time trend of blood concentration of Et-FOSAA in Swedish women. Trendlines are added when *p*-value <0.05.

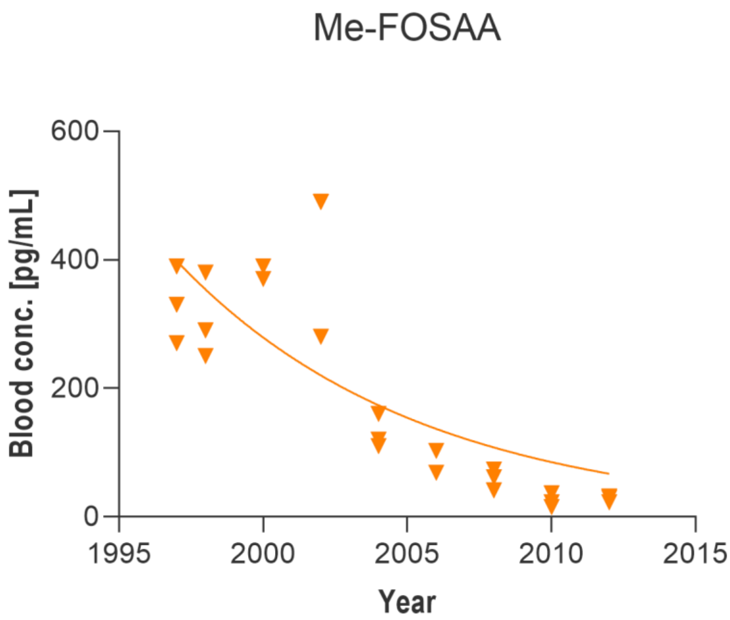

Fig. S4 Time trend of blood concentration of Me-FOSAA in Swedish women. Trendlines are added when *p*-value <0.05.

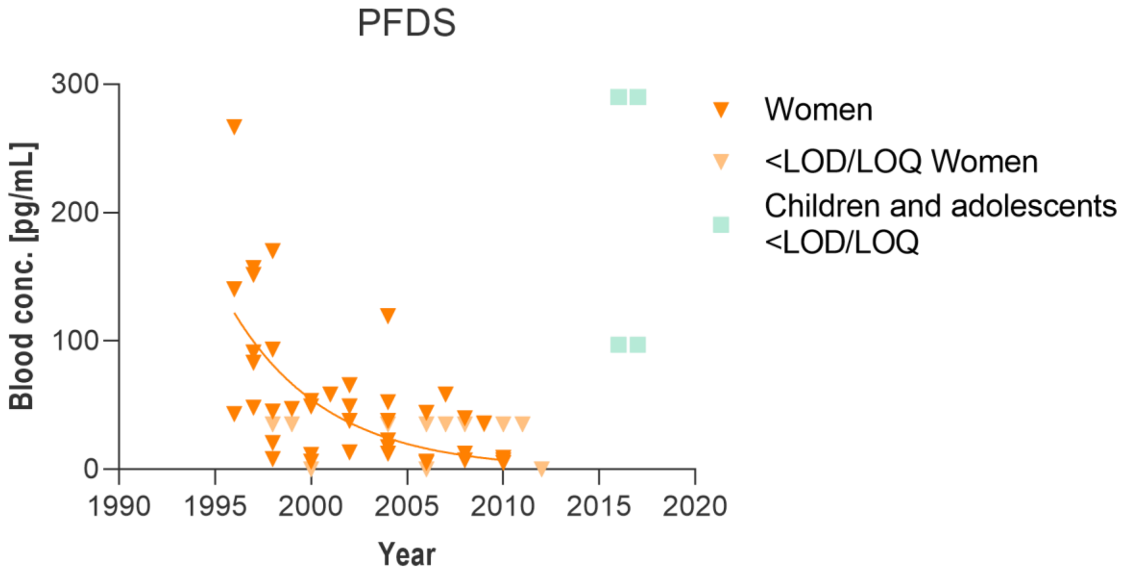

Fig. S5 Time trend of blood concentration of PFDS. Trendlines are added when *p*-value <0.05.

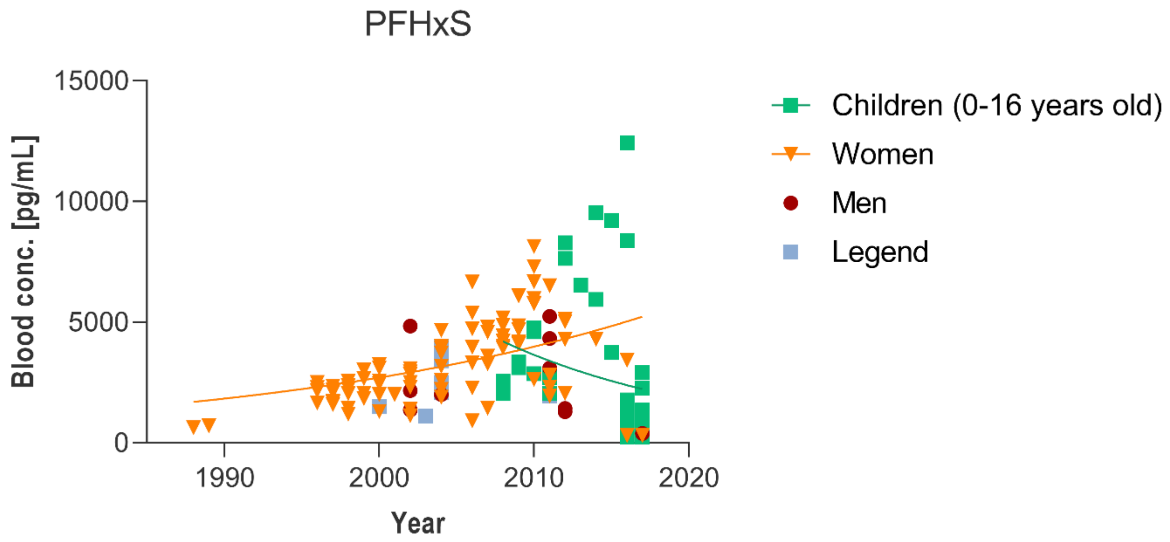

Fig. S6 Time trend of blood concentration of PFHxS, there are two outliers not shown in the graph, two studies in children 2017 (37,000 pg/mL and 57,000 pg/mL). Trendlines are added when *p*-value <0.05.

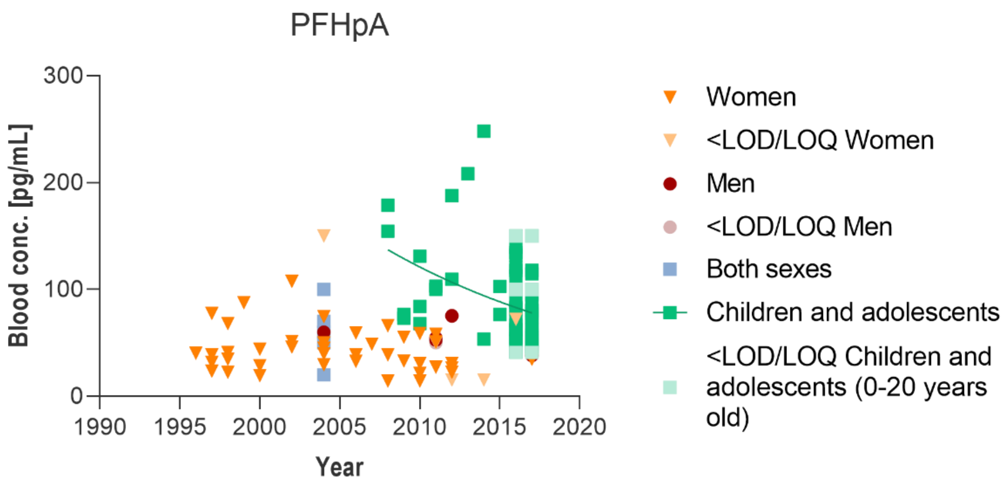

Fig. S7 Time trend of blood concentrations of PFHpA, there is one outlier not shown in the graph, 700 pg/mL from the PIVUS cohort. Trendline is added when *p*-value <0.05.

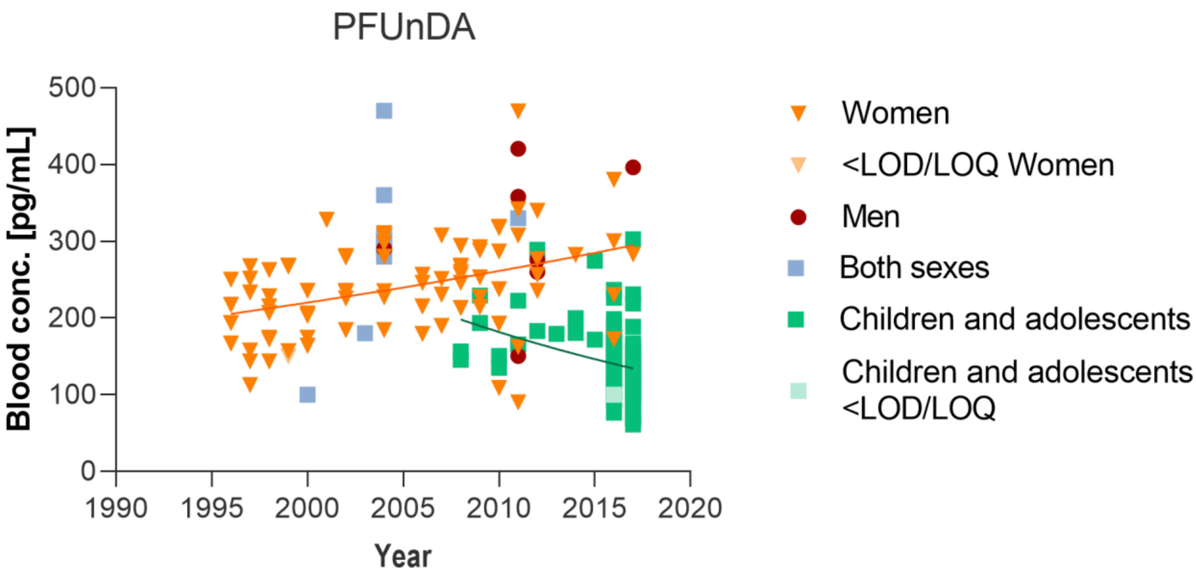

Fig. S8 Time trend of blood concentration of PFUnDA. Trendlines are added when *p*-value <0.05.

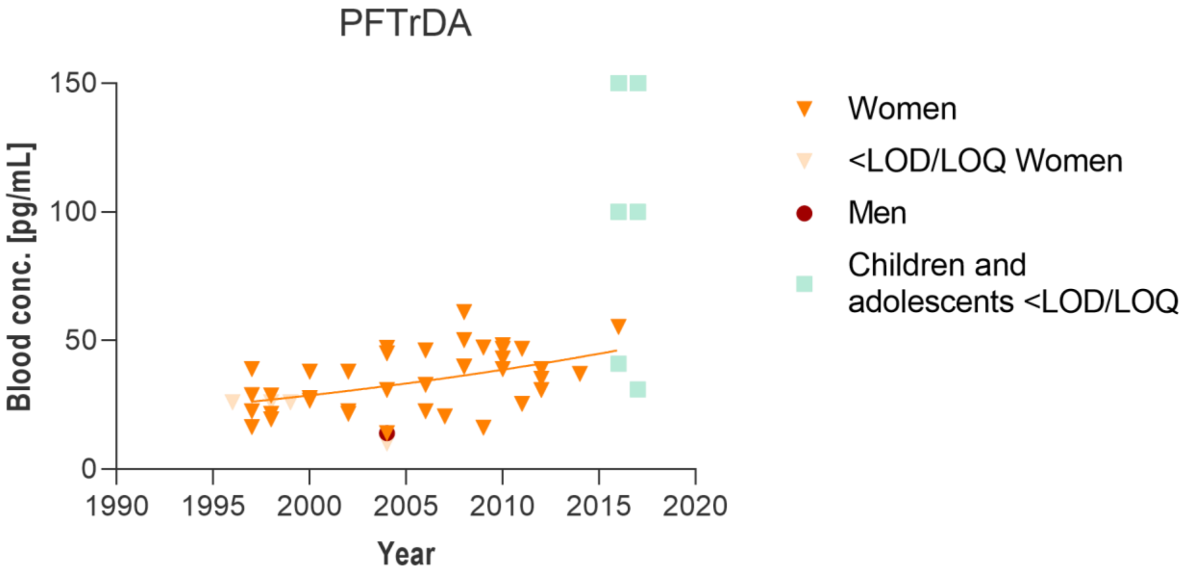

Fig. S9 Time trend of blood concentration of PFTrDA. Trendlines are added when *p*-value <0.05.

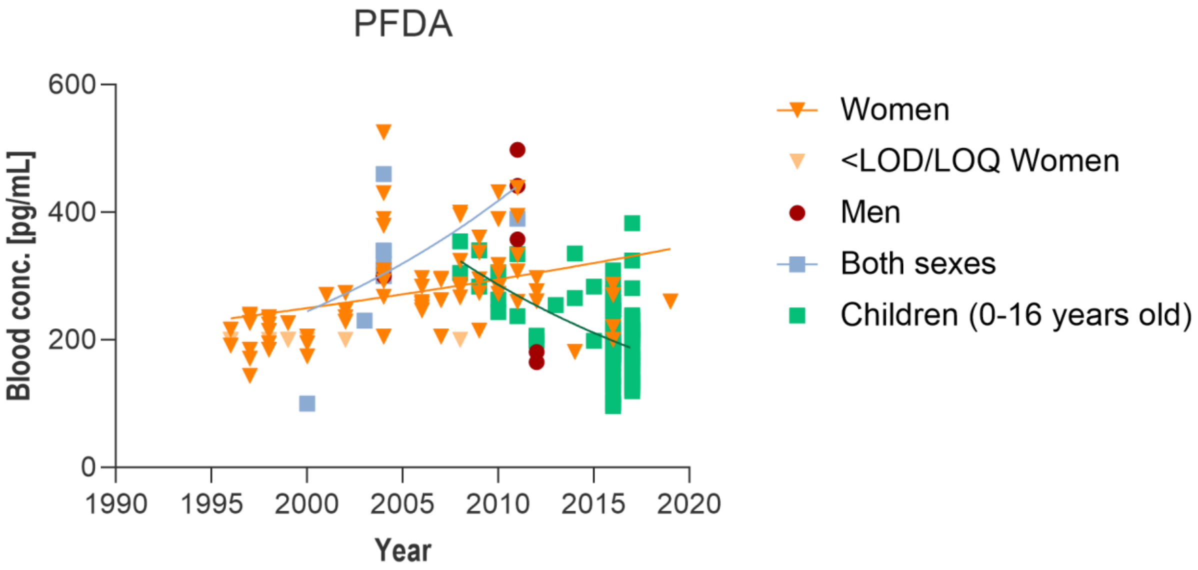

Fig. S10 Time trend of blood concentration of PFDA. Trendlines are added when *p*-value <0.05.

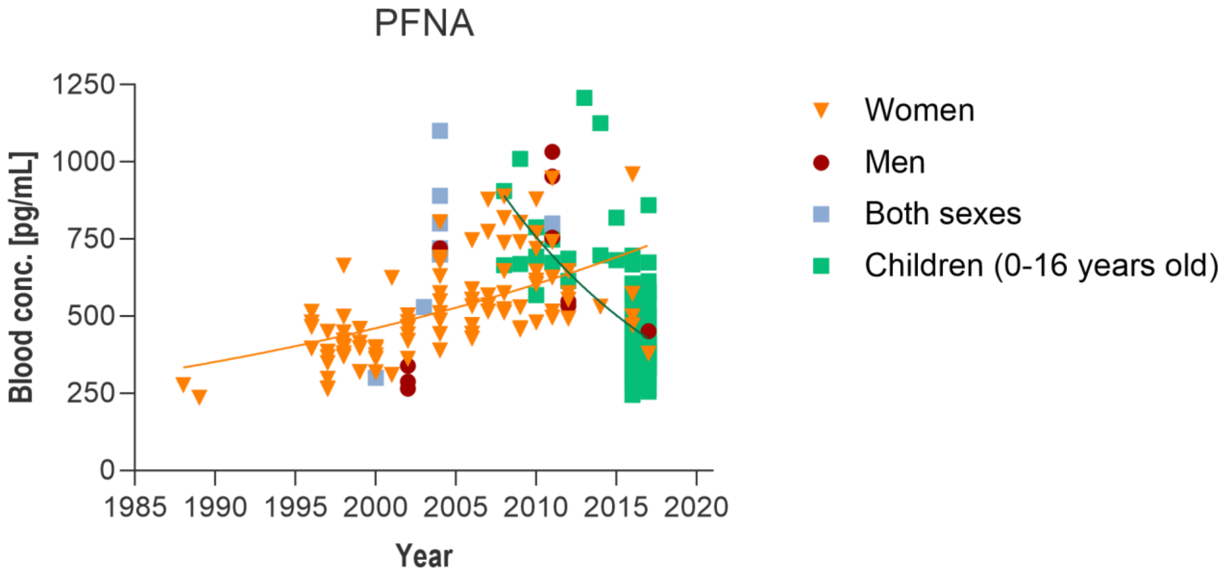

Fig. S11 Time trend of blood concentration of PFNA. Trendlines are added when *P-value* <0.05.

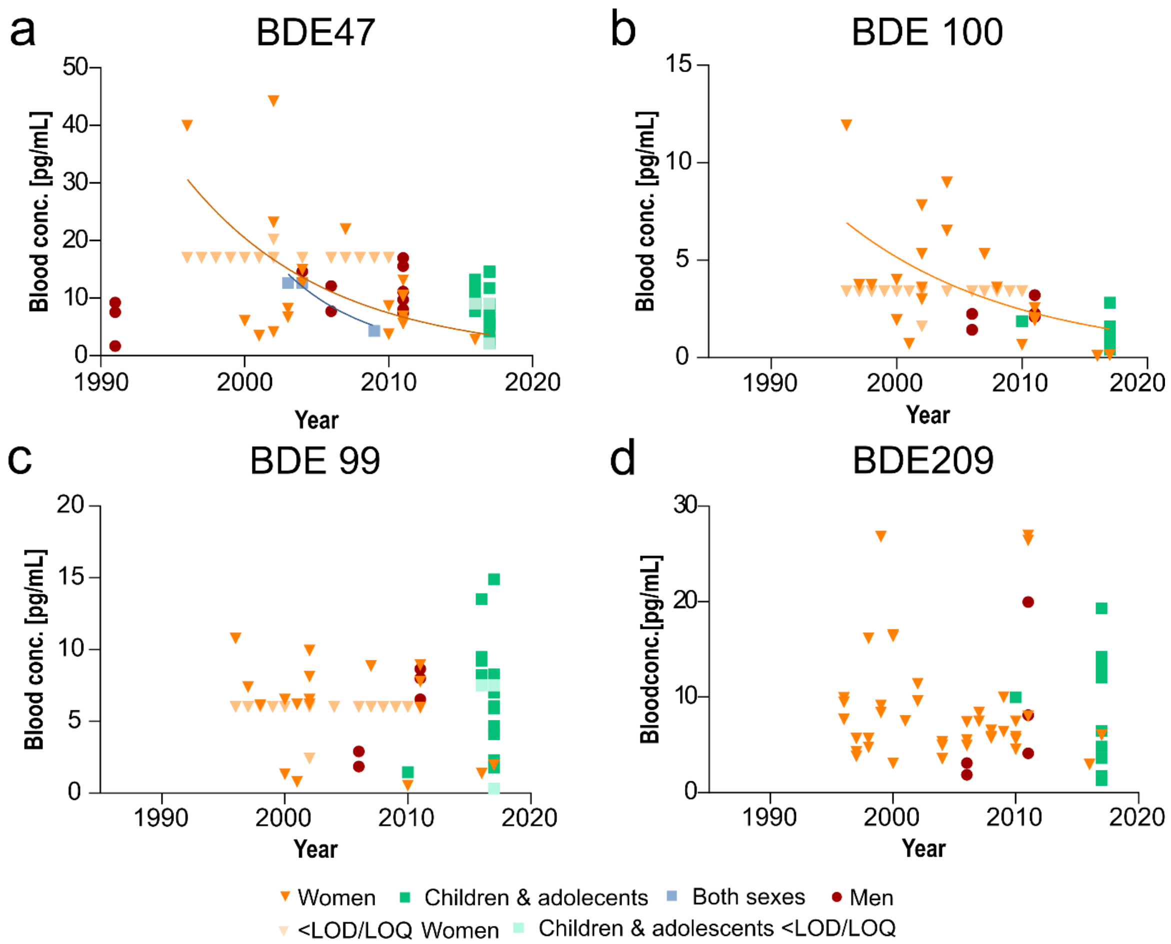

Fig. S12 Time trends of four PBDEs. Trendlines are added when *p*-value <0.05. (a) BDE 47 (b) BDE 100 (c) BDE 153 (d) BDE 209

References

Aylward LL, Hays SM, Gagné M, Nong A , Krishnan K (2010) Biomonitoring equivalents for hexachlorobenzene. Regulatory Toxicology and Pharmacology. https://doi.org/10.1016/j.yrtph.2010.06.003

Aylward LL, Lakind JS , Hays SM (2008) Derivation of biomonitoring equivalent (BE) values for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds: a screening tool for interpretation of biomonitoring data in a risk assessment context. J Toxicol Environ Health A. https://doi.org/10.1080/15287390802361755

German HBM Commission (1997) Stoffmonographie Pentachlorphenol-Referenz- und Human-Biomonitoring-Werte (HBM). Bundesgesundheitsblatt. https://doi.org/10.1007/BF03042913

German HBM Commission (2015) Stoffmonographie für 1,2,5,6,9,10-Hexabromcyclododecan (HBCDD) - HBM-Werte für HBCDD im Fettanteil der Muttermilch oder des Blutplasmas. Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz. https://doi.org/10.1007/s00103-015-2193-7

Hölzer J, Lilienthal H , Schümann M (2021) Human Biomonitoring (HBM)-I values for perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) - Description, derivation and discussion. Regulatory Toxicology and Pharmacology. https://doi.org/10.1016/j.yrtph.2021.104862

Kirman CR, Aylward LL, Hays SM, Krishnan K , Nong A (2011) Biomonitoring Equivalents for DDT/DDE. Regulatory Toxicology and Pharmacology. https://doi.org/10.1016/j.yrtph.2011.03.012

Krishnan K, Adamou T, Aylward LL, Hays SM, Kirman CR , Nong A (2011) Biomonitoring Equivalents for 2,2′,4,4′,5-pentabromodiphenylether (PBDE-99). Regulatory Toxicology and Pharmacology. https://doi.org/10.1016/j.yrtph.2011.03.011

Rauchfuss K, Kraft M , Michael W (2013) Derivation of a health based guidance value for PCB in human blood samples. https://ehp.niehs.nih.gov/doi/abs/10.1289/isee.2013.P-2-13-08. Accessed 12 January 2022

Swedish Environmental Protections Agency (2019) Hälsorelaterad miljöövervakning (HÄMI). https://ki.se/imm/halsorelaterad-miljoovervakning. Accessed 25 October 2019