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Serum concentrations of perfluorinated alkyl substances in farmers living in areas affected by water contamination in the Veneto Region (Northern Italy)

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ABSTRACT

Human exposure to per- and polyfluorinated alkyl substances (PFASs) is a major public health concern because in the last decades several cases of overexposure of people to PFASs, in particular through contaminated water, occurred worldwide. In 2013–2017 a PFAS drinking water contamination was discovered and investigated in northern Italy (Veneto region) and high PFAS serum levels were detected in exposed people. 629 subjects were enrolled: 257 residing in municipalities in the areas under impact, 250 residing in municipalities in areas at presumed background exposure and 122 farmers living in contaminated rural areas producing and consuming own livestock and vegetables and frequently using well water. The highest PFAS serum concentrations (median PFOA concentrations 40 ng/g) were found in the subgroup of farmers. The main factors influencing PFAS serum levels of farmers were residence area and the related extent of drinking water contamination, gender, years of residence in the municipalities, well water consumption and consumption of own produced food. PFOA serum concentrations in farmers residing in the areas of the Veneto region impacted by PFAS contamination are among the highest found worldwide.

1. Introduction

Per- and polyfluorinated alkyl substances (PFASs) are persistent amphiphilic compounds with peculiar chemical and physical properties that have made them suitable for various industrial and commercial applications. Since 1950 they have been widely produced and used and for decades they entered the environment, diffused in water, soil, biota and also entered the food web. Currently humans worldwide are exposed to PFASs and interest in these contaminants has been growing, with particular regard to toxicity, human exposure and implications for public health.

Although an increasing number of papers have been published in the last years, the knowledge of the overall toxicological profile of PFASs is still affected by many uncertainties, even for the most studied ones, PFOS and PFOA. In experimental animal toxicity studies, the liver was a target organ for PFOS and PFOA in rodents and both have developmental neurotoxicity potential (EFSA, 2018). However, animal studies are not fully relevant, due to the differences in PFAS toxicokinetic between rodents and humans; on the other hand, epidemiological studies are sometimes inconsistent (Health Council of the Netherlands, 2013; Bundesgesundheitsbl, 2016; US EPA, 2016a; US EPA, 2016b; ATSDR, 2018; EFSA, 2018; Health Canada, 2018a, 2018b). A number of human epidemiological studies provide strong support in a weight of evidence approach for causal associations between exposure to PFOS and PFOA and increased serum levels of cholesterol in adults and support for a causal association between exposure to PFOA and increased serum levels of the liver enzyme alanine transferase (EFSA, 2018). The association between PFOS exposure and the decrease in antibody response at vaccination in children was considered by European Food Safety Authority (EFSA) as likely to be causal (EFSA, 2018), while for other pathologic findings related to the impairment of human immune system the causal relationship with PFAS exposure is still under discussion (Chang et al, 2016; EFSA, 2018).

In the general population diet is the principal source of PFAS exposure, including drinking water (ATSDR, 2018; EFSA, 2012, 2018; Hu et al., 2016; Hurley et al., 2016). Drinking water exposure is a major

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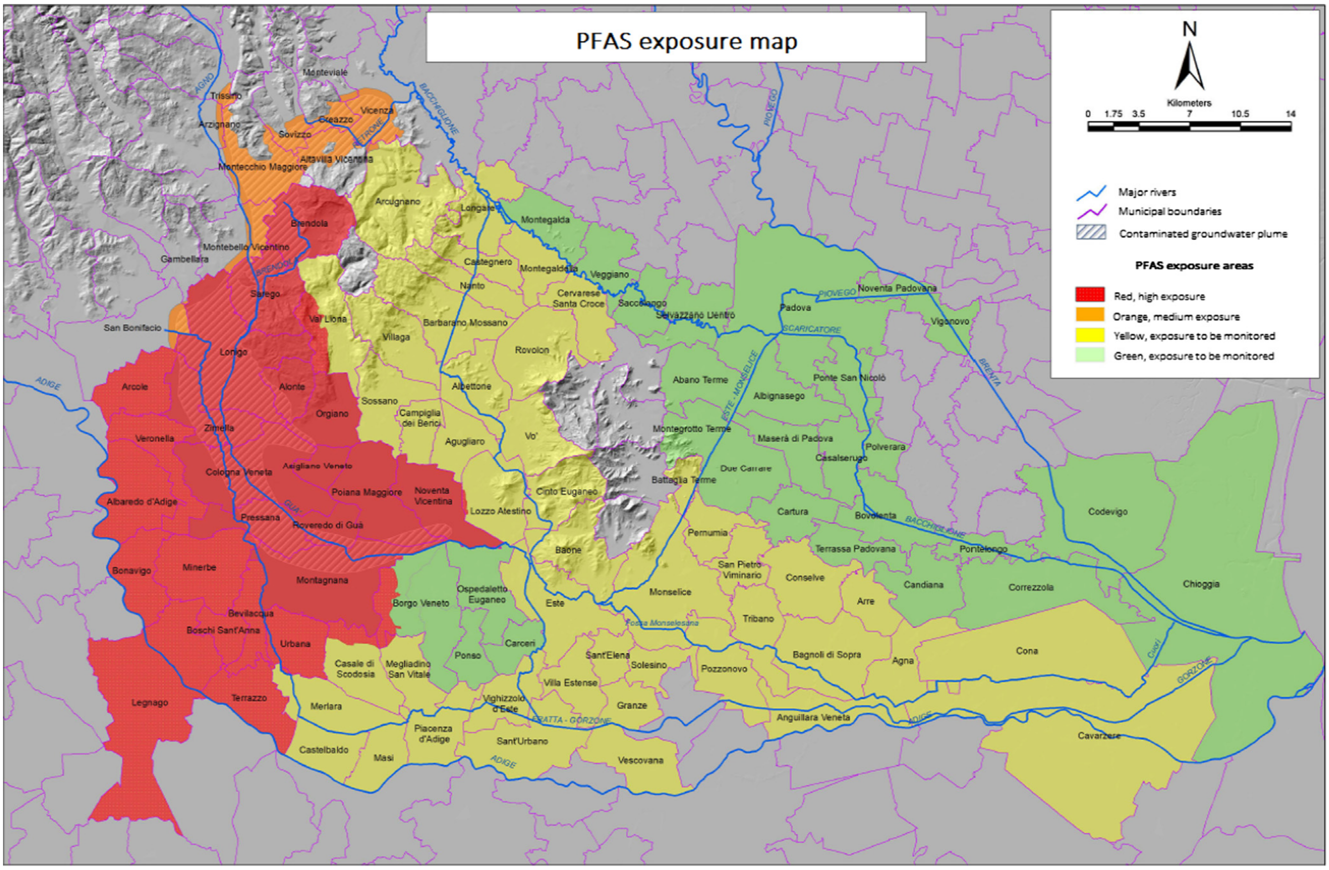

Fig. 1. PFAS exposure map (adapted from Regione del Veneto, 2017): the red area (maximum exposure area) comprises the municipalities where water contamination involved public drinking water, private wells water, surface water and groundwater; the orange area comprises the municipalities where PFAS contamination was detected in private wells water, surface water and groundwater while aqueducts were connected to clean water supplies; the yellow and green areas comprise municipalities only slightly impacted by PFASs, where a monitoring programme was set up to better understand the extent of exposure.

public health concern because in the last decades several cases of overexposure of people to PFASs through contaminated water occurred worldwide (Emmett et al., 2006; Hoffman et al., 2011; Hölzer et al., 2008; Jakobsson et al., 2014; Steenland et al., 2009; Vieira et al., 2008; Ingelido et al., 2018). Indeed, the extensive production and use of PFASs, in combination with their persistency and relatively high water solubility, has resulted in a widespread contamination of the aquatic environment that occasionally also involved drinking water.

We have previously described (Ingelido et al., 2018) an episode of PFAS water contamination discovered in May 2013 in some areas of the Veneto Region (northern Italy), mainly associated with the activity of an industrial plant located in the area (WHO, 2017), which produced PFASs by electrochemical fluorination for decades. After the discovery of the contamination, the Environmental Protection Agency of the Veneto Region started to analyze PFASs in surface water, groundwater and drinking water (Regione del Veneto, 2015) and, together with other regional authorities, to take a series of technical measures to limit human exposure to PFASs (WHO, 2017). In particular, in July 2013 the water-service companies installed activated carbon filters in the treatment plants of the public drinking water distribution system. After the filter installation PFAS concentrations in public drinking water of the red area decreased considerably (PFOA decreased from about 0.32 to 0.22 µg/L, and PFOS from about 0.018 to 0.005 µg/L (Istituto Superiore di Sanità and Regione del Veneto, 2017). In autumn, private wells were mapped and most of the single municipalities were legally authorized to oblige citizens to assess PFAS levels in their private wells, and to not use well water in case of PFAS contamination. The Italian National Institute for Health (Istituto Superiore di Sanità, ISS) provided scientific support to the Veneto Region on dealing with the PFAS contamination to limit population health risk. As part of these supporting activities the ISS designed and conducted a human biomonitoring study in collaboration with the Region and the Local Health Units (Unità Locali Socio-sanitarie, ULSSs) to assess the actual exposure to PFASs of citizens. The main part of the study involved 507 subjects from the general population and the study aims were to define the extent of exposure to PFASs of people living in the contaminated areas with respect to a control group of subjects living in neighboring areas not affected by water contamination and to identify the main factors associated with PFAS serum concentrations, exploring also the possibility of a potential association with the presence of a polymorphic renal transporter. PFASs are indeed good substrates of organic anion transporters (OATs) and organic anion-transporting polypeptides (OATPs) in the luminal and basolateral membranes of renal tubular epithelial cells, which are responsible for active transport in secretion and resorption (Andersen et al., 2008; Harada et al., 2005). The transporters are under hormonal control, show differences in expression levels and activity between species and genders and are also polymorphic, possibly resulting in interindividual difference in the elimination rate of substances (Seithel et al, 2008).

Beside the enrollment of subjects from the general population (consisting of 257 subjects residing in the impacted areas and 250 residing in presumed background exposure areas), whose results have already been published (Ingelido et al., 2018), a group of farmers was also included. This latter subgroup consisted of individuals living in contaminated rural areas considered at higher risk to be over-exposed to PFASs since producing and consuming own livestock and vegetables, as confirmed by results presented in this paper.

Table 1
Characteristics of the study participants (exposed and not exposed subjects data are from Ingelido et al., 2018).

	Exposed farmers n (%)	Exposed (general population) n (%)	Not exposed (general population) n (%)
Gender			
Females	58 (48)	130 (51)	123 (49)
Males	64 (52)	127 (49)	127 (51)
Age (years)			
20–29	39 (32)	80 (31)	79 (32)
30–39	39 (32)	85 (33)	82 (33)
40–51	44 (36)	92 (36)	89 (36)
Body Mass Index (kg/m^2)			
Underweight	5 (4)	12 (5)	10 (4)
Normal	74 (61)	169 (66)	153 (61)
Overweight	35 (29)	60 (23)	68 (27)
Obese	8 (6)	16 (6)	19 (8)
Residence area			
Urban	8 (7)	128 (50)	78 (31)
Suburban	70 (57)	70 (27)	131 (52)
Rural	44 (36)	58 (23)	41 (16)
Grow and consume own fruits/vegetables			
Yes	114 (93)	103 (40)	117 (47)
No	8 (7)	151 (59)	132 (53)
Raise and consume own animals			
Yes	75 (61)	21 (8)	55 (22)
No	47 (39)	233 (91)	192 (77)
Drink tap water			
Yes	36 (30)	142 (55)	92 (37)
No	86 (70)	115 (45)	158 (63)
Drink well water			
Yes	36 (30)	6 (2)	87 (35)
No	86 (70)	251 (98)	163 (65)
Use of water to water fruits/vegetables			
Tap water	20 (16)	61 (24)	21 (8)
Well water	87 (71)	27 (10)	93 (37)
Surface water (rivers, lakes…)	5 (4)		
Use of water to water animals			
Tap water	15 (13)	12 (5)	10 (4)
Well water	60 (49)	7 (3)	46 (18)

2. Materials and methods

2.1. Study design

The entire biomonitoring study involved 629 subjects (507 from general population and a subgroup of 122 farmers) residing in selected areas of the Veneto Region, affected and not affected by PFAS water contamination. Affected areas, defined by the regional authorities on the basis of the match between the results of this biomonitoring study and those of the tests carried out on water, are described in Fig. 1. In the figure, the PFAS contaminated groundwater plume is showed, together with information on the exposure of people residing near the plume (WHO, 2017; Regione del Veneto, 2018). Highly exposed subjects resided in the red area, characterized by PFAS contamination of public drinking water, well water, surface water and groundwater; moderately exposed subjects resided in the orange area, where only well water, surface water and groundwater were affected by pollution and no contamination of the public drinking water had been identified (WHO, 2017). Although yellow and green areas were only slightly impacted by PFAS pollution, a monitoring programme was set up to assess exposure of subjects living in these areas. The 507 subjects from general population comprised 257 residing in municipalities in the red and orange areas (Fig. 1) impacted by water contamination (identified with "E" for "Exposed" in the paper), and 250 residing in municipalities in areas at presumed background exposure (identified with "NE" for "Not Exposed"), as previously described (Ingelido et al., 2018).

The 122 farmers (identified with "EF" for "Exposed Farmers") lived in 17 municipalities in the red and orange areas, comprising all the (seven) municipalities of residence of the E group. The 17 municipalities were under the territorial competence of five different ULSSs of the Veneto Region: ULSSs 5, 6, 17, 21, 22 (at sampling time, lately ULSS classification was modified). Water pollution and people exposure were not homogenous in the five ULSSs: ULSS 6 was in the orange area while the other ULSSs were in the red area.

Participants were selected in each area and stratified by gender and age (age classes: 20–29, 30–39, and 40–51 years). Each subject had resided in an area for at least 10 years. The additional selection criteria for EF were to produce fruits or vegetables and/or to raise farm animals.

The genetic analysis was focused on the OATP1A2*3 allelic variant. The transporter is expressed in the human kidney at the apical membrane of the distal nephron (Lee et al., 2005; Roth et al., 2012). It corresponds to the rat transporter Oatp1a1, which is expressed on the apical membrane of the proximal tubule cells, where it has been shown to transport PFOA from the urine back into the proximal tubule cells facilitating renal reabsorption (Weaver et al., 2010). OATP1A2 was shown in vitro not to be directly involved in the cellular uptake of perfluorocarboxylates (Yang et al., 2010; Han et al., 2012). However, the studied Single Nucleotide Polymorphism (SNP) has been shown to have an altered activity with some substrates, when compared to the wild type (Gong and Kim, 2013), likely due to a change in the affinity for the substrates: this could occur also for PFASs, thus recognized as in vivo substrates.

In this paper only results of the analysis of serum samples of the 122 EF are described, data from the other two groups (E and NE), reported in Ingelido et al. 2018, were only considered as reference groups.

2.2. Sampling and analysis

The study was approved by the local ethical committees. Written informed consent was obtained from each participant.

Sampling was performed by ULSSs 5, 6, 17, 21 and 22 personnel between July 2015 and January 2017. Participants were randomly chosen from ULSS registers on the basis of selection criteria and eligible individuals were asked to take part in the study.

A blood sample of about 5 mL was withdrawn from each participant; 1 additional mL of blood was collected to genotype the population for a polymorphic allele coding for the renal transporter OATP1A2, with the aim of investigating if a particular genetic trait could be able to influence internal exposure.

A questionnaire was administered by interview to all study participants; self-reported information were about anthropometric and socio-demographic characteristics, lifestyle, drinking-water consumption, diet (with specific focus on consumption of own produced food), and water use in agricultural and breeding practices.

Analyses were carried out at ISS: 9 perfluorocarboxylic acids (PFBA, PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUdA, and PFDoA) and 3 perfluorosulfonates (PFBS, PFHxS, and PFOS) were determined in serum samples. About 250 μL of serum were spiked with labelled internal standards, mixed with acetonitrile, centrifuged and reduced to 300 μL for instrumental analysis (Ingelido et al., 2018). Instrumental analysis was carried out by HPLC (Waters Alliance 2695, Waters Corporation, Milford, MA, USA) interfaced with a triple quadrupole mass spectrometer (Micromass QuattromicroTM API, Waters Corporation, Milford, MA, USA). The laboratory is accredited for the analysis of POPs according to ISO/IEC 17025 and participate in the intercomparison exercise organized by the Institut National de Santé Publique du Québec, Centre de Toxicologie du Québec (Canada), and has met the performance acceptability criteria for PFASs in human serum. The limits of quantification ranged from 0.01 to 0.5 ng/g. Genotyping of

Table 2
Descriptive statistics of PFAS serum concentrations (ng/g) assessed in exposed farmers, exposed and not exposed subjects (exposed and not exposed subject's data are from Ingelido et al., 2018).

Exposed farmers	N	Minimum	P_5	P_{25}	Median	Geometric mean	Mean	P_{75}	P_{95}	Maximum
PFHpA	122	0.015	0.024	0.039	0.062	0.073	0.12	0.12	0.36	1.4
PFOA	122	0.036	3.0	12	40	40	110	160	500	720
PFNA	122	0.049	0.19	0.37	0.56	0.55	0.68	0.92	1.5	2.3
PFDA	122	0.072	0.12	0.26	0.43	0.42	0.54	0.72	1.3	2.1
PFUdA	122	0.027	0.069	0.13	0.24	0.22	0.27	0.38	0.63	0.80
PFHxS	122	0.090	0.58	2.1	4.5	5.3	12	15	49	71
PFOS	122	1.6	3.3	5.5	12	12	17	23	46	66
Exposed	N	Minimum	P_5	P_{25}	Median	Geometric Mean	Mean	P_{75}	P_{95}	Maximum
PFHpA	257	0.011	0.016	0.030	0.050	0.054	0.075	0.10	0.21	0.42
PFOA	257	0.70	2.2	4.9	14	19	61	87	250	750
PFNA	257	0.046	0.22	0.40	0.61	0.58	0.70	0.88	1.5	2.5
PFDA	257	0.042	0.094	0.22	0.33	0.32	0.40	0.51	0.86	2.0
PFUdA	257	0.012	0.037	0.093	0.16	0.16	0.22	0.30	0.56	1.0
PFHxS	257	0.090	0.20	1.2	3.0	2.8	5.5	6.9	21	43
PFOS	257	0.93	2.7	5.5	8.7	8.9	12	15	29	70
Not exposed	N	Minimum	P_5	P_{25}	Median	Geometric Mean	Mean	P_{75}	P_{95}	Maximum
PFHpA	250	0.010	0.010	0.016	0.032	0.033	0.048	0.066	0.13	0.26
PFOA	250	0.32	0.57	1.1	1.6	1.6	1.9	2.2	3.9	28
PFNA	250	0.039	0.23	0.41	0.58	0.57	0.68	0.80	1.3	7.7
PFDA	250	0.026	0.12	0.24	0.32	0.33	0.41	0.49	0.97	3.1
PFUdA	250	0.010	0.010	0.11	0.18	0.16	0.24	0.30	0.62	1.4
PFHxS	250	0.029	0.18	1.4	2.5	1.9	2.8	4.0	6.0	9.1
PFOS	250	0.56	2.1	3.9	5.8	6.2	8.3	9.3	21	120

rs11568563, a SNP present in OATP1A2/SLCO1A2 gene, known to be functional determining a change in the activity toward different substrates, was performed as previously described (Ingelido et al., 2018). No checks were carried out for other variants, since the number of enrolled individuals was not high enough to give statistical power to the study, considering the frequency of the mutated allele.

2.3. Statistical analysis

Data distribution was tested by the Shapiro-Wilk W test for normality; as variables were not normally or log-normally distributed (with the only exception of PFOS), non-parametric statistics was applied. Analyses were carried out using Statistica 8.0 (StatSoft Inc. Tulsa, OK, USA). Mann–Whitney and Kruskal-Wallis tests and the Spearman correlation were used to investigate the statistical significance of the differences in PFAS serum concentrations between groups and the correlations between PFAS concentrations and variables from the questionnaires.

Data below the limit of quantification (LOQ) were included as LOQ/$\sqrt{2}$ in performing statistical analysis. Only median values are reported in the text for all the 12 PFASs analyzed; all the other statistical analyses were applied only to the PFASs determined in more than half of the samples (PFHpA, PFOA, PFNA, PFDA, PFUdA, PFHxS and PFOS).

The $\chi 2$ test was applied to investigate if observed and expected genotype frequencies of OATP1A2/SLCO1A2 locus were in Hardy-Weinberg equilibrium. A $p < 0.05$ was considered to be statistically significant.

3. Results and discussion

3.1. Characteristics of the study participants

Characteristics of the study participants are shown in Table 1. Subjects' sex and age were well balanced, and in accordance with the study design. Body mass index (BMI) distribution was in line with data reported for the Italian population (ISTAT, 2008). Characteristics of the EF subjects were very similar to those of individuals enrolled within the general population (E and NE). The exceptions were, as expected and requested on purpose by the study design, the residence area and consumption of own products (both of vegetal and animal origin) and well water, both higher in the EF group. Nearly all the EF participants (93%) lived in rural or suburban areas, and grew and consumed own fruits or vegetables; in addition, about 61% of them raised and consumed their own animals. Water from wells was the most frequent source of water for watering fruits, vegetables and animals. A significant percentage of subjects declared to consume bottled water, reflecting people's recent concern for water PFAS pollution in the area, although the use of tap or well water for drinking cannot be excluded and it can be expected to have occurred in the past.

3.2. PFAS serum concentrations

Most frequently detected PFASs in serum samples were PFOA, PFNA, PFDA, PFHxS and PFOS (> LOQ in more than 90% of the samples) followed by PFUdA (77%) and PFHpA (54%). PFOA was found at the highest concentration (Table 2). All the other PFASs were above their respective LOQ in less than 35% of the samples. Their median serum concentrations in EF group were: PFBA 0.076 ng/g, PFPeA 0.064 ng/g, PFHxA 0.061 ng/g, PFDoA 0.16 ng/g, PFBS 0.13 ng/g.

As to the relative contribution of the different PFASs in EF, PFOA was detected at relatively highest levels, accounting for about 68% of the total PFAS concentration. A similar PFAS distribution was found in serum samples of E subjects, while in NE subjects the greatest relative contribution to PFAS concentration derived from PFOS (56% of the total) and 14% only from PFOA. PFOS and PFOA relative concentration measured in NE subjects (PFOS ≫ PFOA) was very similar to the one most frequently observed in Italian general population exposed to background levels of environmental contamination (Ingelido et al., 2010; De Felip et al., 2015). The PFAS distribution observed in E subjects (PFOA ≫ PFOS) was interpreted as determined by the over exposure to contaminated water and as a consequence, although the exposure scenarios in EF was more complex, drinking water seems to be still the predominant source of exposure compared to dietary exposure in contaminated areas.

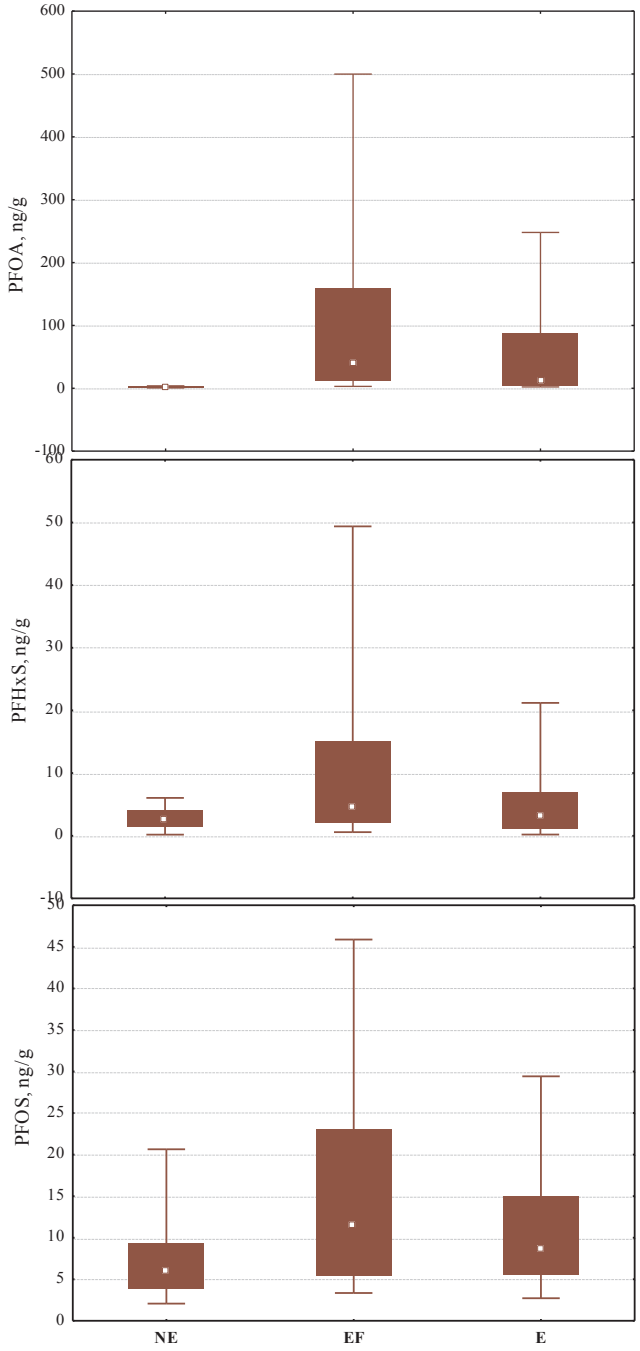

Fig. 2. PFOA, PFHxS and PFOS serum concentrations (ng/g) in exposed (E) and not exposed (NE) subjects from the general population, and in exposed farmers (EF) of the Veneto Region. Whiskers: 5th and 95th percentiles; box: 25th and 75th percentiles; middle point: median.

A strong positive correlation ($p < 0.05$) was observed among different analytes, with the exception of PFNA (not significantly correlated with PFHpA and PFUdA) and PFUdA (significantly correlated only with PFDA). The observed correlation is suggestive of a common and prevalent source of environmental contamination for most of PFASs found in human serum, that could have been released from the source as such, or derive from common precursors.

Data distributions were right skewed for all the substances analyzed, in particular for PFHxS (P_{95} value more than 10 times higher than the median) and PFOA (P_{95} value more than 12 times higher than the median).

The concentrations of the most frequently detected PFASs were generally higher in EF group than in E and NE groups (Fig. 2), with PFOA showing the highest median concentration: it was almost three times higher than in E group (14 ng/g) and 25 times higher than in NE group (1.6 ng/g). On the whole, PFAS serum levels in EF subjects were significantly higher (Mann-Whitney test, $p < 0.05$) than in NE and E subjects from general population for all the considered PFASs with the only exception of PFNA (Table 3). This finding confirmed the hypothesis that exposure to sources other than the direct consumption of public contaminated drinking water contributed to enhance PFAS internal dose in the study areas because E and EF municipalities were supplied by the same aqueduct. Indeed, the exposure scenario characterizing the EF subjects is more complex than subjects from the general population with the same kind of drinking water consumption (E subjects). It is very likely that additional PFAS exposure is attributable to a more diffused consumption and use of non-public drinking water (in particular well water), and to the use of well water and groundwater to water vegetables and raise animals for own consumption at least during the 10 years residing in a rural environment, which was one of the study inclusion criteria.

This observation is supported by results previously described in NE group, where highest PFAS serum concentrations related with years of residence in the areas as well as with growing own vegetables and raising own livestock (Ingelido et al., 2018), and suggest a possible diffusion of the contamination to other environmental media also in geographical areas adjacent to those directly affected by drinking water contamination.

3.3. Correlation between PFAS serum levels and characteristics of the study participants

Results of Spearman correlation, Mann-Whitney and Kruskal-Wallis tests to assess the associations between PFAS serum levels and EF characteristics are reported in Table 3.

Gender related differences in serum concentrations were observed for most PFASs (males showed serum concentrations significantly higher than females); in particular, PFOA and PFHxS median concentrations in males (respectively 110 and 12 ng/g) were about 5 times higher than in females (respectively 20 and 2.6 ng/g) and PFOS concentrations about 3 times higher (20 ng/g in males and 6.9 in females). This variability in PFAS concentrations between men and women was also found in the E group (Ingelido et al., 2018) and in other studies (Bartolomé et al., 2017; Calafat et al., 2007a, 2007b; Góralczyk et al., 2015; Siebenaler et al., 2017; Steenland et al., 2009). The reasons for this difference in humans are not yet fully explained. Although females have specific elimination routes such as menstrual loss or breastfeeding, it has been also hypothesized a greater efficiency in the renal elimination of PFASs (the expression of the involved OATP is under sexual hormone control (Wong et al., 2014)), in analogy to what was observed in rats (Worley and Fisher, 2015), but this hypothesis has not yet been experimentally confirmed (Bartell et al., 2010; Seals et al., 2011). In addition, although women had mostly shorter PFAS half-lives compared with men, the differences in half-lives are marked for some PFASs and modest for others (Bartell et al., 2010; Li et al., 2017) and elimination pathways seemed to be not only sex specific but also substance specific (Li et al., 2017). This observation is supported by results described in this study, where women who breastfeed showed lower PFAS concentrations, significantly lower for PFOA ($p = 0.049$) and PFHxS ($p = 0.032$).

Age influence on PFAS serum concentration was limited to PFOS for which a direct significant correlation with age was detected as previously reported (Hsu et al., 2013). No correlation with age was observed when the general population living in the area was considered (E and NE) (Ingelido et al., 2018); however, with this parameter a wide range of possible results (positive, negative, partial or no correlation) has been reported so far (Ji et al., 2012; Lindh et al., 2012; Fromme et al., 2007; Zeng et al., 2015; Frisbee et al., 2009).

Table 3
Characteristics of exposed farmers (EF) and relationship with PFAS serum concentrations. Significant p values ($p < 0.05$) are shown in bold.

	PFHpA	PFOA	PFNA	PFDA	PFUdA	PFHxS	PFOS
Spearman correlation	R (p) [a]	R (p)	R (p)	R (p)	R (p)	R (p)	R (p)
Age (years)	**−0.25 (0.0052)**	0.043 (0.63)	−0.028 (0.76)	0.084 (0.36)	0.16 (0.070)	0.090 (0.32)	**0.21 (0.018)**
Body Mass Index (kg/m^2)	0.0036 (0.97)	**0.21 (0.022)**	0.060 (0.51)	0.059 (0.52)	0.082 (0.37)	**0.28 (0.0021)**	**0.25 (0.0053)**
Residence in the municipalities (years)	−0.061 (0.50)	**0.21 (0.023)**	0.082 (0.37)	0.090 (0.32)	**0.19 (0.039)**	**0.31 (< 0.001)**	**0.40 (< 0.001)**
Mann-Whitney test	p [b]	p	p	p	p	p	p
EF *vs* NE serum concentrations	**≪0.001**	**≪0.001**	0.93	**0.0011**	**0.013**	**≪0.001**	**≪0.001**
EF *vs* E serum concentrations	**0.0087**	**≪0.001**	0.46	**≪0.001**	**≪0.001**	**≪0.001**	**0.0032**
Gender (male/female)	**0.023**	**≪0.001**	**0.0051**	**0.026**	0.93	**≪0.001**	**≪0.001**
Tap water consumption (yes/no)	0.12	0.48	1.00	0.15	0.68	0.73	0.83
Well water consumption (yes/no)	0.18	0.055	**0.034**	0.077	0.44	**0.042**	**0.0030**
Raise and consume own livestock (yes/no)	0.65	0.28	0.052	**0.0039**	0.24	0.23	**0.012**
Food origin (retailer level/own production) [c]							
Beef	0.20	**≪0.001**	**0.034**	**≪0.001**	0.84	**0.0025**	**≪0.001**
Chicken	0.76	0.062	**≪0.001**	**≪0.001**	0.97	**0.043**	**≪0.001**
Eggs	0.56	0.58	**0.0047**	**0.0025**	0.59	0.31	**0.048**
Legumes	0.73	0.062	**0.039**	0.10	0.61	**0.041**	**0.020**
Vine	0.70	0.21	0.11	**0.044**	0.65	0.23	**0.010**
Kruskal-Wallis test							
ULSSs	**≪0.001**	**≪0.001**	**0.034**	**0.005**	0.079	**≪0.001**	**≪0.001**

[a] Spearman's R correlation coefficient (p value)
[b] p value for Mann-Whitney and Kruskal-Wallis test for differences between groups
[c] Some food items (milk, cheese, lamb, fish, vegetable oil) were not tested for differences because of the very small percentage (< 20%) of subjects in one of the tested categories. Only tested food items are shown in the table.

All the considered PFAS concentrations showed an increasing trend with increasing BMI, but the correlation reached the statistical significance for PFOA, PFHxS and PFOS only and seems to be influenced by sex: serum PFAS concentrations of females inversely (but not significantly) correlated with BMI and in males a direct correlation is significant for PFHxS and PFOS only. Since PFAS bioaccumulation is not related to body fat, these results are not surprising; due to the relevance of binding to both plasma and liver protein (especially albumin), gender differences in protein relative content could be one of the possible explanation.

Most PFAS concentrations, particularly PFOA, PFUdA, PFHxS and PFOS levels directly correlated with years of residence in the municipalities. This correlation supported the hypothesis of a years-long exposure of the local population, which started long before the discovery of water contamination in 2013.

In the EF group, subjects from different ULSSs showed significantly different serum concentrations (Kruskal-Wallis test $p < 0.05$) for all the considered PFASs with the exception of PFUdA (Table 3). PFOA, PFHxS and PFOS concentrations in EF, E and NE subjects from different ULSSs are showed in Fig. 3. The highest serum concentrations in EF subjects were observed mostly in ULSS 5 (N = 59, PFOA median concentration 160 ng/g) and the lowest in ULSS 6 (N = 22, PFOA median concentration 7.2 ng/g). In ULSSs 17, 20 and 21 intermediate levels were detected: PFOA median concentrations were respectively 57, 27, 36 ng/g. Very similar results were already observed in the E group of general population (Ingelido et al., 2018), reflecting the differences in water pollution in the five ULSSs, with individuals in ULSS 6 being exposed only to sources other than the public drinking water consumption (WHO, 2017). This difference reinforced the hypothesis that the predominant source of PFAS exposure in the Veneto Region is consumption of contaminated public drinking water.

Subjects who declared to raise and consume their own livestock showed higher serum concentrations of all the analyzed PFASs (of PFDA, PFOS and to a minor extend, $p = 0.052$, PFNA significantly higher) than subjects that did not consume own food of animal origin. The difference in consumption of own produced vegetables was not investigated because of the limited number (n = 8) of subjects who declared not to produce/consume own fruits or vegetables.

Going down into details, we compared the serum PFAS concentration in farmers consuming own produced food versus farmers consuming food from the retailer level for the single food categories, namely: beef, chicken, eggs, legumes, vine. In relation to these food items, all PFAS serum levels were higher (in some cases significantly) in farmers that consumed own produced food (Table 3), mostly for PFNA, PFDA, PFHxS and PFOS and to a minor extend for PFOA. This finding supported the hypothesis that watering vegetables and animals with contaminated well water and groundwater contributed to increase farmers' exposure trough food consumption. For some other food categories (e.g. milk, cheese, lamb, fish, vegetable oil) it was not possible to carry out this analysis, because of the very small percentage (< 20%) of subjects in one of the tested categories. Our results are supported by available data on contamination of locally produced food, gathered in a recent Report published by the ISS Department of Food Safety, Nutrition and Veterinary Public Health (Istituto Superiore di Sanità, 2019): it was possible to estimate from these data that consumption of local products from local farms (in particular eggs, and beef) gives a significant contribution to overall exposure although water consumption (mainly well water) represents the predominant source of exposure. Because of such prevailing contribution of water, and because the amounts of food eaten were quantified on the basis of self-reported data in a questionnaire, the contribution to serum concentrations associated to local food consumption could not be adequately characterized, this representing a limitation of the study.

According to the questionnaire answers, tap water and well water consumption was very limited (only 36% of subjects declared to drink tap and/or well water, Table 1); no significant correlation was found between PFAS serum levels and tap water consumption while PFNA, PFHxS and PFOS (and to a minor extent PFOA, $p = 0.055$ and PFDA, $p = 0.077$) concentrations positively and significantly correlated with well water consumption (Table 3).

The relative contribution of the different PFASs in EF subgroups stratified by tap water consumption, well water consumption and own produced food consumption is very similar (characterized by PFOA at relatively highest levels) and almost the same observed in the entire EF group, confirming drinking water as the predominant source of exposure compared to dietary exposure in contaminated areas also for

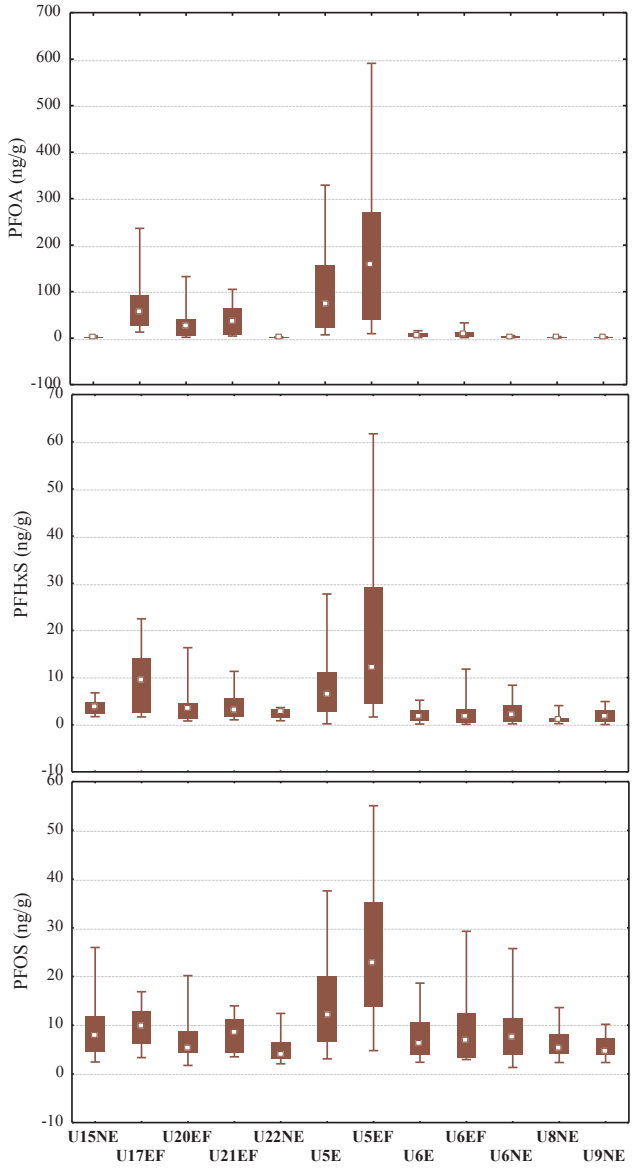

Fig. 3. PFOA, PFHxS and PFOS serum concentrations (ng/g) in exposed (E) and not exposed (NE) subjects from the general population, and in exposed farmers (EF) from the ULSSs (U) of the Veneto Region. Whiskers: 5th and 95th percentiles; box: 25th and 75th percentiles; middle point: median.

subjects consuming their own animal products.

The highest PFOA concentration (720 ng/g) was observed in a 44 years old man, which was the only subject with serum concentrations of 5 PFASs (PFHpA, PFOA, PFDA, PFHxS, PFOS) above their respective P_{95} values. This subject has all the main determinants of exposure detected in the study: he is a male, born and resident in ULSS 5, he drank tap water and consumed own fruits, vegetables and animals grown and raised with local water.

3.4. Correlation between PFAS serum levels and genetic features of the study participants

Regarding the genetic analysis aimed to find a possible relationship between the OATP1A2*3 allelic variant and the blood levels of PFASs, results indicated that the Hardy Weinberg equilibrium was respected (p = 0.22) in the population recruited for the project, indicating that the selection was not biased. The allelic frequencies (w = 0.97 and m = 0.044) were comparable with those reported in the general population (w = 0.95 and m = 0.050) (Ingelido et al., 2018) and in the literature (Bosó et al., 2014; Laitinen and Niemi, 2011). The Chi Square test (χ^2) indicated that there was no significant differences in the allelic distribution among the different groups in the overall study (EF, E, and NE) (χ^2 = 0.86p = 0.35). The correlation between PFAS serum concentrations and the differences in genotype distribution could not be investigated in the EF subgroup, due to the limited number of subjects with at least one mutant allele (only 5 w/m individuals), not adequate to allow the performance of a reliable statistical analysis.

However, results obtained in the general population showed that there are no relationships between the OATP1A2*3 allelic variant and the blood levels of PFASs, suggesting that this polymorphism is not able to alter PFAS elimination in a way capable to change the blood levels in the carrier individual (Ingelido et al., 2018). Including the EF within the E group did not change the overall results.

3.5. Comparison with results of other biomonitoring studies on populations exposed to contaminated drinking water

Several human biomonitoring studies were conducted all over the word in communities affected by PFAS contaminated drinking water (ATSDR, 2013; Brede et al., 2010; Frisbee et al., 2009; Gyllenhammar et al., 2015; Kari et al., 2009; Li et al., 2017) that experienced an increased exposure similar to E and EF subjects of this study, resulting in PFAS serum concentrations higher than concentrations observed in general population. Serum concentrations of PFOA, PFOS, and PFHxS (the most frequently analyzed substances) from this study have been found mostly comparable with concentrations in people exposed to contaminated drinking water in other countries (Fig. 4), with the exception of PFHxS and PFOS data from Sweden 2014–2016 (Li et al., 2017) that are consistently higher than the others. The relative occurrence of these three different PFASs in serum samples is very different in the considered studies, probably depending on the origin of the contamination. In our study PFOA, considered as a suitable marker for drinking water contamination as the major source, was detected at relatively higher levels and indeed PFOA serum concentrations in EF group are the highest observed in studies reporting other cases of water contamination.

4. Conclusions

Serum concentrations of most of the analyzed PFASs in exposed farmers were higher than those measured in exposed subjects from general population and consistently higher than those measured in not exposed subjects. These results showed that environmental exposure sources other than contaminated public drinking water consumption also played a role in determining PFAS internal dose of subjects residing in contaminated areas of the Veneto Region. Indeed, although the consumption of contaminated public drinking water was the predominant source of exposure, private well water and local food consumption contributed to increase PFAS concentrations in the EF group.

The main factors influencing PFAS serum levels of farmers were residence area (ULSS) and the related extent of drinking water contamination, gender, years of residence in the municipalities, well water consumption and consumption of own produced food.

PFOA serum concentrations in farmers residing in the areas of the Veneto Region impacted by PFAS contamination are among the highest found worldwide, in particular for the most contaminated subgroup (subjects from ULSS 5).

Comparing levels detected in the EF with the derived health-related guidance values (HBM I values) for PFOA and PFOS in blood plasma (2 and 5 ng/mL, respectively (Apel et al., 2017; Bundesgesundheitsbl, 2016)), it is evident that the great majority of the enrolled EF (97% for PFOA and 79% for PFOS) exceeded the limits. Also in the other two groups included in our study (E and NE) a high percentage of subjects showed PFOA and PFOS concentrations above these limits (Ingelido

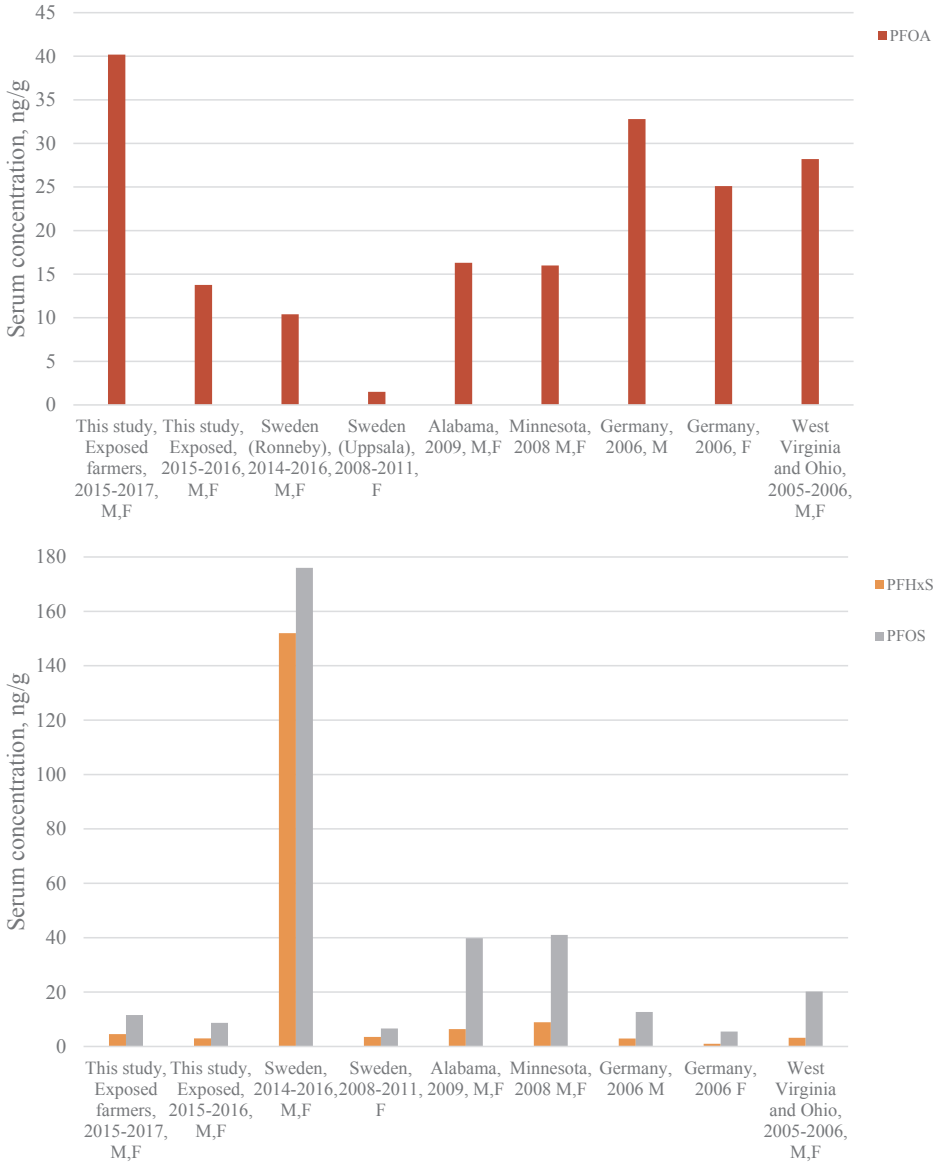

Fig. 4. PFOA, PFHxS and PFOS serum concentrations (medians, ng/g) found in this study and in other studies of populations exposed to contaminated water (data from ATSDR, 2013; Brede et al., 2010; Frisbee et al., 2009; Gyllenhammar et al., 2015; Kari et al., 2009; Li et al., 2017). For Alabama (ATSDR 2013) geometric means are reported.

et al., 2018). Exposure to PFASs of people living in (and near) the contaminated areas of the Veneto Region is expected to decline following the actions taken by the local authorities to remove PFASs from the public water supplies. Nevertheless, other contamination sources (e.g. well water, groundwater, local food) are more difficult to take under control and it is important to continue efforts to reduce the level of PFASs in the local environment, and to follow-up the residing population both looking at the possible health effect and the internal dose. Particular attention must be taken in most exposed subgroups that, even after prompt end of exposure from public water, could experience, in a life-course perspective, an overexposure due to residual environmental contamination.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Andersen, M.E., Butenhoff, J.L., Chang, S.C., Farrar, D.G., Kennedy, Lau, C., Olsen, G.W.,

Seed, J., Wallace, K.B., 2008. Perfluoroalkyl acids and related chemistries— toxicokinetics and modes of action. Toxicol. Sci. 102, 3–14.
Apel, P., Angerer, J., Wilhelm, M., Kolossa-Gehring, M., 2017. New HBM values for emerging substances, inventory of reference and HBM values in force, and working principles of the German Human Biomonitoring Commission. Int. J. Hyg. Environ. Health 220, 152–166.
ATSDR, 2013. Health Consultation. Exposure Investigation. Perfluorochemical Serum Sampling in the Vicinity of Decatur, Alabama, Morgan, Lawrence and Limestone Counties. Available at: < https://www.atsdr.cdc.gov/hac/pha/Decatur/Perfluorochemical_Serum%20Sampling.pdf > .
ATSDR, 2018. Toxicological Profile For Perfluoroalkyls. Available at: < https://www.atsdr.cdc.gov/toxprofiles/TP.asp?id=1117&tid=237 > .
Bartell, S.M., Calafat, A.M., Lyu, C., Kato, K., Steenland, K., 2010. Rate of decline in serum PFOA concentrations after granular activated carbon filtration at two public water systems in Ohio and West Virginia. Environ. Health Perspect. 118, 222–228.
Bartolomé, M., Gallego-Picó, A., Cutanda, F., Huetos, O., Esteban, M., Pérez-Gómez, B., Castaño, A., 2017. Perfluorinated alkyl substances in Spanish adults: geographical distribution and determinants of exposure. Sci. Total Environ. 603–604, 352–360.
Bosó, V., Herrero, M.J., Buso, E., Galán, J., Almenar, L., Sánchez-Lázaro, I., Sánchez-Plumed, J., Bea, S., Prieto, M., García, M., Pastor, A., Sole, A., Poveda, J.L., Aliño, S.F., 2014. Genotype and allele frequencies of drug-metabolizing enzymes and drug transporter genes affecting immunosuppressants in the Spanish white population. Ther. Drug Monit. 36, 159–168.
Brede, E., Wilhelm, M., Göen, T., Müller, J., Rauchfuss, K., Kraft, M., Holzer, J., 2010. Two-year follow-up biomonitoring pilot study of residents' and controls' PFC plasma levels after PFOA reduction in public water system in Arnsberg, Germany. Int. J. Hyg. Environ. Health 213, 217–223.
Bundesgesundheitsbl, 2016. HBM I values for perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) in blood plasma statement of the German human biomonitoring commission (HBM Commission). Available at: http://dx.doi.org/10.1007/s00103-016-2437-1.
Calafat, A.M., Kuklenyik, Z., Reidy, J.A., Caudill, S.P., Tully, J.S., Needham, L.L., 2007a. Serum concentrations of 11 polyfluoroalkyl compounds in the US population: data from the National Health and Nutrition Examination Survey (NHANES). Environ Sci Technol 41, 2237–2242.
Calafat, A.M., Wong, L.Y., Kuklenyik, Z., Reidy, J.A., Needham, L.L., 2007b. Polyfluoroalkyl chemicals in the U.S. population: data from the National Health and Nutrition Examination Survey (NHANES) 2003–2004 and comparisons with NHANES 1999–2000. Environ Health Perspect 115, 1596–1602.
Chang, E.T., Adami, H-O., Boffetta, P., Wedner, H. J., Mandel, J.S., 2016. A critical review of perfluorooctanoate and perfluorooctanesulfonate exposure and immunological health conditions in humans. Crit Rev Toxicol. 46, 279–331.
EFSA, 2012. Perfluoroalkylated substances in food: occurrence and dietary exposure. EFSA J. 10, 2743. Available at: < https://www.efsa.europa.eu/it/efsajournal/pub/2743 > .
EFSA, 2018. Scientific Opinion on the risk to human health related to the presence of perfluooctane sulfonic acid and perfluooctanic acid in food. EFSA Journal, 16(12): 5194. Available at: < https://www.efsa.europa.eu/en/efsajournal/pub/5194 > .
De Felip, E., Abballe, A., Albano, F.L., Battista, T., Carraro, V., Conversano, M., Franchini, S., Giambanco, L., Iacovella, N., Ingelido, A.M., Maiorana, A., Maneschi, F., Marra, V., Mercurio, A., Nale, R., Nucci, B., Panella, V., Pirola, F., Porpora, M.G., Procopio, E., Suma, N., Valentini, S., Valsenti, L., Vecchiè, V., 2015. Current exposure of Italian women of reproductive age to PFOS and PFOA: a human biomonitoring study. Chemosphere 137, 1–8.
Emmett, E.A., Zhang, H., Shofer, F.S., Freeman, D., Rodway, N.V., Desai, C., Shaw, L.M., 2006. Community exposure to perfluorooctanoate: relationships between serum levels and certain health parameters. J. Occup. Environ. Med. 48, 771–779.
Frisbee, S.J., Brooks, P., Maher, A., Flensborg, P., Arnold, S., Fletcher, T., Steenland, K., Shankar, A., Knox, S.S., Pollard, C., Halverson, J.A., Vieira, V.M., Jin, C., Leyden, K.M., Ducatman, A.M., 2009. The C8 health project: design, methods, and participants. Environ. Health Perspect. 117, 1873–1882.
Fromme, H., Midasch, O., Twardella, D., Angerer, J., Boehmer, S., Liebl, B., 2007. Occurrence of perfluorinated substances in an adult German population in southern Bavaria. Int. Arch. Occup. Environ. Health 80, 313–319.
Góralczyk, K., Pachocki, K.A., Hernik, A., Struciński, P., Czaja, K., Lindh, C.H., Jönsson, Bo A.G., Lenters, V., Korcz, W., Minorczyk, M., Matuszak, M., Ludwicki, J.K., 2015. Perfluorinated chemicals in blood serum of inhabitants in central Poland in relation to gender and age. Sci. Tot. Environ. 532, 548–555.
Gyllenhammar, I., Berger, U., Sundström, M., McCleaf, P., Eurén, K., Eriksson, S., Ahlgren, S., Lignell, S., Aune, a., Kotova, N., Glynn, A., 2015. Influence of contaminated drinking water on perfluoroalkyl acid levels in human serum – a case study from Uppsala, Sweden. Environ. Res. 140, 673–683.
Gong, I.Y., Kim, R.B., 2013. Impact of genetic variation in OATP transporters to drug disposition and response. Drug Metab. Pharmacokinet. 28, 4–18.
Han, X., Nabb, D.L., Russell, M.H., Kennedy, G.L., Rickard, R.W., 2012. Renal elimination of perfluorocarboxylates (PFCAs). Chem. Res. Toxicol. 25, 35–46.
Harada, K., Inoue, K., Morikawa, A., Yoshinaga, T., Saito, N., Koizumi, A., 2005. Renal clearance of perfluorooctane sulfonate and perfluorooctanoate in humans and their species-specific excretion. Environ. Res. 99, 253–261.
Health Canada, 2016a. Perfluorooctane Sulfonate in Drinking Water. Available at: < https://www.canada.ca/en/health-canada/programs/consultation-perfluorooctane-sulfonate-pfos-in-drinking-water/document.html > .
Health Canada, 2016b. Perfluorooctanoic Acid in Drinking Water. Available at: < https://www.canada.ca/en/health-canada/programs/consultation-perfluorooctanoic-acid-pfoa-in-drinking-water/document.html > .
Health Council of the Netherlands, 2013. Perfluorooctanoic acid and its salts. In: Evaluation of the Carcinogenicity and Genotoxicity, Publication no. 2013/32. Available at: < https://www.gezondheidsraad.nl/sites/default/files/201332Perfluorooctanoic_acid_and_its_salts.pdf > .
Hoffman, K., Webster, T.F., Bartell, S.M., Weisskopf, M.G., Fletcher, T., Vieira, V.M., 2011. Private drinking water wells as a source of exposure to perfluorooctanoic acid (PFOA) in communities surrounding a fluoropolymer production facility. Environ. Health Perspect. 119, 92–97.
Hölzer, J., Midasch, O., Rauchfuss, K., Kraft, M., Reupert, R., Angerer, J., Kleeschulte, P., Marschall, N., Wilhelm, M., 2008. Biomonitoring of perfluorinated compounds in children and adults exposed to perfluorooctanoate-contaminated drinking water. Environ. Health Perspect. 116, 651–657.
Hsu, J.Y., Hsu, J.F., Ho, H.H., Chiang, C.F., Liao, P.C., 2013. Background levels of persistent organic pollutants in humans from Taiwan: perfluorooctane sulfonate and perfluorooctanoic acid. Chemosphere 93, 532–537.
Hu, X.C., Andrews, D.Q., Lindstrom, A.B., Bruton, T.A., Schaider, L.A., Grandjean, P., Lohmann, R., Carignan, C.C., Blum, A., Balan, S.A., Higgins, C.P., Sunderland, E.M., 2016. Detection of poly- and perfluoroalkyl substances (PFASs) in US drinking water linked to industrial sites, military fire training areas, and wastewater treatment plants. Environ. Sci. Technol. Lett. 3, 344–350.
Hurley, S., Houtz, E., Goldberg, D., Wang, M., Park, J.S., Nelson, D.O., Reynolds, P., 2016. Preliminary associations between the detection of perfluoroalkyl acids (PFAAs) in drinking water and serum concentrations in a sample of California women. Environ. Sci. Technol. Lett. 3, 264–269.
Ingelido, A.M., Marra, V., Abballe, A., Valentini, S., Iacovella, N., Barbieri, P.G., Porpora, M.G., di Domenico, A., De Felip, E., 2010. Perfluorooctanesulfonate and perfluorooctanoic acid exposures of the Italian general population. Chemosphere 80, 1125–1130.
Ingelido, A.M., Abballe, A., Gemma, S., Dellatte, E., Iacovella, N., De Angelis, G., Zampaglioni, F., Marra, V., Miniero, R., Valentini, S., Russo, F., Vazzoler, M., Testai, E., De Felip, E., 2018. Biomonitoring of perfluorinated compounds in adults exposed to contaminated drinking water in the Veneto Region, Italy. Environ. Int. 110, 149–159.
Istituto Superiore di Sanità and Regione del Veneto, 2017. PFAS nella filiera idro-potabile in alcune provincie del Veneto. Available at: < https://www.regione.veneto.it/web/sanita/informazione-e-comunicazione > .
Istituto Superiore di Sanità, 2019. Dipartimento di Sicurezza Alimentare, Nutrizione e Sanità Pubblica Veterinaria. Contaminazione da sostanze perfluoroalchiliche in veneto -Valutazione dell'esposizione alimentare e caratterizzazione del rischio. Relazione Finale. Available at: < https://rdv.box.com/s/le1x47b1jgzpfvnzsb446e8ku2fgij1y > .
ISTAT, 2008. Annuario Statistico Italiano 2008. Istituto Nazionale di Statistica, Roma. Available at: < https://www.istat.it/it/archivio/obesit%C3%A0 > .
Jakobsson, K., Kronholm Diab, K., Lindh, C., Persson, B., Jönsson, B., 2014. Exponering för perfluorerade ämnen (PFAS) i dricksvatten i Ronneby kommun.
Ji, K., Kim, S., Kho, Y., Paek, D., Sakong, J., Ha, J., et al., 2012. Serum concentrations of major perfluorinated compounds among the general population in Korea: dietary sources and potential impact on thyroid hormones. Environ. Int. 45, 78–85.
Kari, A., Johnson, J., Williams, A., Huset, C., 2009. East metro PFC biomonitoring pilot project. Technical Report, July 21, 2009. Available at: < http://www.health.state.mn.us/divs/hpcd/tracking/biomonitoring/projects/pfcfinalrpt2009.pdf > .
Laitinen, A., Niemi, M., 2011. Frequencies of single-nucleotide polymorphisms of SLCO1A2, SLCO1B3 and SLCO2B1 genes in a Finnish population. Basic Clin. Pharmacol. Toxicol. 108, 9–13.
Lee, W., Glaeser, H., Smith, L.H., Roberts, R.L., Moeckel, G.W., Gervasini, G., Leake, B.F., Kim, R.B., 2005. Polymorphisms in human organic anion-transporting polypeptide 1A2 (OATP1A2): implications for altered drug disposition and central nervous system drug entry. J. Biol. Chem. 280, 9610–9617.
Li, Y., Fletcher, T., Mucs, D., Scott, K., Lindh, C.H., Tallving, P., Jakobsson, K., 2017. Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. Occup. Environ. Med. 75, 46–51.
Lindh, C.H., Rylander, L., Toft, G., Axmon, A., Rignell-Hydbom, A., Giwercman, A., Pedersen, H.S., Góalczyk, K., Ludwicki, J.K., Zvyezday, V., Vermeulen, R., Lenters, V., Heederik, D., Bonde, J.P., Jönsson, B.A.G., 2012. Blood serum concentrations of perfluorinated compounds in men from Greenlandic Inuit and European populations. Chemosphere 88, 1269–1275.
Regione del Veneto, 2015. Acqua Potabile in Veneto. Modello di Azione Integrata. Available at: < http://repository.regione.veneto.it/public/0f871628d0f0f0d08a4c37c31ab5e73d.php?lang=it&dl=true > .
Regione del Veneto, 2017. Contaminazione da sostanze perfluoroalchiliche (PFAS). Available at: < http://repository.regione.veneto.it/public/c8bd0b54945daea3d01f92267c106e5f.php?lang=it&dl=true > .
Regione del Veneto, 2018. Bollettino Ufficiale Regione del Veneto n.97S del 25 settembre 2018. Deliberazione del consiglio regionale n. 108 del 1 agosto 2018 Relazione finale, in esecuzione del mandato conferito alla Commissione d'inchiesta per le acque inquinate del Veneto in relazione alla contaminazione di sostanze perfluoroalchiliche (PFAS). Available at: < https://bur.regione.veneto.it/BurvServices/Pubblica/DettaglioDcr.aspx?id=377223 > .
Roth, M., Obaidat, A., Hagenbuch, B., 2012. OATPs, OATs and OCTs: the organic anion and cation transporters of the SLCO and SLC22A gene superfamilies. Br. J. Pharmacol. 165, 1260–1287.
Seals, R., Bartell, S.M., Steenland, K., 2011. Accumulation and clearance of perfluorooctanoic acid (PFOA) in current and former residents of an exposed community. Environ. Health Perspect. 119, 119–124.
Seithel, A., Glaeser, H., Fromm, M.F., König, J., 2008. The functional consequences of genetic variations in transporter genes encoding human organic anion-transporting polypeptide family members. Expert Opin. Drug. Metab. Toxicol. 4, 51–64.

Siebenaler, R., Cameron, R., Butt, C.M., Hoffman, K., Higgins, C.P., Stapleton, H.M., 2017. Serum perfluoroalkyl acids (PFAAs) and associations with behavioral attributes. Chemosphere 184, 687–693.

Steenland, K., Jin, C., MacNeil, J., Lally, C., Ducatman, A., Vieira, V., Fletcher, T., 2009. Predictors of PFOA levels in a community surrounding a chemical plant. Environ. Health Perspect. 117, 1083–1088.

US EPA, 2016a. Drinking water health advisory for perfluorooctanoic acid (PFOA). Available at: < https://www.epa.gov/sites/production/files/2016-05/documents/pfoa_health_advisory_final_508.pdf > .

US EPA, 2016b. Drinking water health advisory for perfluorooctane sulfonate (PFOS). Available at: < https://www.epa.gov/sites/production/files/2016-05/documents/pfos_health_advisory_final_508.pdf > .

Vieira, V., Webster, T., Bartell, S., Steenland, K., Savitz, D., Fletcher, T., 2008. PFOA community health studies: exposure via drinking water contaminated by a Teflon manufacturing facility. Organohalogen Compd. 70, 730–732.

Weaver, Y.M., Ehresman, D.J., Butenhoff, J.L., Hagenbuch, B., 2010. Roles of rat renal organic anion transporters in transporting perfluorinated carboxylates with different chain lengths. Toxicol. Sci. 113, 305–314.

WHO, 2017. Keeping Our Water Clean: The Case of Water Contamination In the Veneto Region, Italy. Available at: < www.euro.who.int/_data/assets/pdf_file/0019/341074/pfas-report-20170606-h1330-print-isbn.pdf > .

Yang, C.H., Glover, K.P., Han, X., 2010. Characterization of cellular uptake of perfluorooctanoate via organic anion-transporting polypeptide 1A2, organic anion transporter 4, and urate transporter 1 for their potential roles in mediating human renal reabsorption of perfluorocarboxylates. Toxicol. Sci. 117, 294–302.

Wong, F., MacLeod, M., Mueller, J.F., Cousins, I.T., 2014. Enhanced elimination of perfluorooctane sulfonic acid by menstruating women: evidence from population-based pharmacokinetic modeling environ. Sci. Technol. 48, 8807–8814.

Worley, R., Fisher, J., 2015. Application of physiologically-based pharmacokinetic modeling to explore the role of kidney transporters in renal reabsorption of perfluorooctanoic acid in the rat. Toxicol. Appl. Pharmacol. 289, 428–441.

Zeng, X.-W., Qian, Z., Vaughn, M., Xian, H., Elder, K., Rodemich, E., Bao, J., Jin, Y.H., Dong, G.H., 2015. Human serum levels of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) in Uyghurs from Sinkiang-Uighur Autonomous Region, China: background levels study. Environ. Sci. Pollut. Res. 22, 4736–4746.