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Perfluorooctanesulfonate and perfluorooctanoic acid exposures of the Italian general population

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ABSTRACT

The serum concentrations of perfluorooctanesulfonate (PFOS) and perfluorooctanoic acid (PFOA) were determined in 230 subjects of the Italian general population. Participants were enrolled in 2008 in two Italian towns (Brescia, Northern Italy, and Rome, Central Italy) and belonged to the three age ranges: 20–35 years, 36–50 years, and 51–65 years.

PFOS and PFOA were quantified by HPLC interfaced to a mass spectrometer operating in the electrospray negative mode. Data were acquired using multiple reaction monitoring (MRM). The isotope dilution technique was applied throughout.

The median serum concentrations of all participants were 6.31 ng g^{-1} and 3.59 ng g^{-1} for PFOS and PFOA, respectively, and the pertinent 90th percentiles were 12.38 and 6.92.

Men had higher concentrations of PFOS and PFOA than women, regardless of age. The differences were statistically significant in the 20–35 and 36–50 years groups, but not in the 51–65 group.

An increase of PFOS and PFOA serum concentrations with age was observed. The Median test showed a statistically significant difference ($p \ll 0.01$) between the three age groups for both PFOS and PFOA when applied to the entire dataset (males and females). When the test was applied to the groups of males and females separately, a significant difference was observed for females ($p \ll 0.005$) but not for males ($p > 0.1$).

The observed strong correlation between PFOS and PFOA concentrations suggests same or similar exposure routes.

1. Introduction

Perfluorinated chemicals (PFCs) represent a wide family of chemicals, characterized by resistance to heat and acids, high surface activity, both hydro- and lipophilic characteristics. As a consequence of this range of properties, they have been extensively used for more than 50 years in industry as surfactants, lubricants, polymers, and in consumer products as stain repellent coatings for carpets and textiles, and as greaseproof coatings for food packaging (OECD, 2002; EFSA, 2008a).

Their inertness to environmental and biological degradation, susceptibility to long-range atmospheric transport, and ability to bioaccumulate and biomagnify along food chains, have resulted into a widespread contamination (3M, 2000; Giesy and Kannan, 2001), which has prompted regulators to take actions.

In particular the eight carbon chained perfluorooctane sulfonate (PFOS), and perfluorooctanoic acid (PFOA), have drawn considerable scientific and regulatory interest.

PFOS has been widely used *per se* (i.e. as a surfactant in fire fighting foams), and also is the end-stage metabolite of several different fluorinated chemicals used as protective coatings for carpets and textiles, and insecticide formulations (3M, 2003).

PFOA, as its ammonium salt, is mainly used as surfactant in the manufacturing of fluoropolymers, (such as polytetrafluoroethylene, PTFE) used in a wide variety of consumer and industrial applications (OECD, 2007) including non-stick surfaces on cookware (Begley et al., 2005). PFOA may also be a degradation product of small polymers (telomers), used in a range of commercial products including fire fighting foams, stain and grease resistant coatings on carpets, leather, textiles, and paper (Prevedouros et al., 2006).

Both these chemicals have been found to be environmentally persistent and globally present even in remote regions as the

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Arctic, and detected worldwide in biota and humans (Paul et al., 2009). Toxicological studies have demonstrated the adverse health effects of PFOS and PFOA among which hepatotoxicity, developmental toxicity, immunotoxicity, hormonal effects and carcinogenicity (OECD, 2002; Kennedy et al., 2004; US EPA, 2005; Lau et al., 2007; Andersen et al., 2008; EFSA, 2008a).

From a regulatory standpoint, PFOS and PFOA have been shown to fulfil the criteria for persistence, bioaccumulation, potential for long-range environmental transport, and adverse effect to human health, and consequently recently included in the list of persistent organic pollutants (POPs) under the Stockholm Convention (Stockholm Convention on Persistent Organic Pollutants, 2009). The European Union Directive 2006/122/EC of the European Parliament set restrictions on the marketing and use of PFOS for new products in the non-food area that became effective in June 2008. According to the Directive, ongoing risk assessment activities on PFOA should be kept under review (EFSA, 2008a).

There is currently no legislation on PFCs in food or feed within the EU. The EFSA Scientific panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food issued an opinion on the safety of ammonium salt of PFOA as food contact material (EFSA, 2008a), but this has not so far led to regulatory measures.

PFOS and PFOA have been detected globally in human blood, with PFOS being the most prevalent compound. Both substances are persistent in humans because poorly metabolized and excreted. PFOS half-life in serum has been reported to be approximately 5 years, while PFOA half-life has been estimated to be approximately 3.5 years (Olsen et al., 2007).

Human exposure to PFOS and PFOA occurs via a number of routes. Dietary exposure, including consumption of drinking water, has been recognised as possibly the major route (EFSA, 2008a). Food contamination may be of environmental origin and may also result from different production processes and/or cooking, due to contact with treated cookware that can release PFCs. Migration from food packaging, in particular from fast-food packaging (Begley et al., 2005; Tittlemier et al., 2006; Renner, 2007), has also been recognised as a potential source for PFOS-related precursors and PFOA. In addition, exposure may occur *via* dermal contact with personal care and cleaning products, as well as through ingestion and/or inhalation of contaminated dust. House dust in particular has been reported to contribute, together with treated carpeting and treated apparel, some 40% to the overall exposure in some countries (Tittlemeier et al., 2007).

The objective of the present study was to provide biomonitoring data to characterize the extent of exposure to PFCs of groups of the Italian general population residing in different urban locations. This study is part of ongoing activities carried out by the Italian National Institute for Health (Istituto Superiore di Sanità, ISS) with the Italian Ministry for the Environment, Land and Sea to characterise human exposure to POPs in Italy.

2. Materials and methods

2.1. Study participants

Analysis was carried out on blood samples collected in 2008 from 230 subjects residing in Rome, in the Lazio Region, Central Italy (182 subjects), and in Brescia, an industrial town located in the Lombardia Region, Northern Italy (48 subjects). Prior to blood withdrawal, each participant signed an informed consent form.

All enrolled subjects had been residing in the area for at least 15 years. Enrolled women (109 as a total) were nulliparous (71) or had not breast-fed in the last 15 years. The whole age range was 20–65 years. Study participants were distributed in three age groups: 20–35 years (62 subjects, 19 males and 43 females), 36–50 years (94 subjects, 60 males and 34 females), and 51–65 years (74 subjects, 42 males and 32 females).

2.2. Analysis

The analytical method used was adapted from a previously published method (Inoue et al., 2004). An aliquot of about 250 μL of each serum sample was fortified with a mixture of ^{13}C-labelled PFOS and PFOA (internal standards) and allowed to rest overnight at 4 °C. Extraction was performed with acetonitrile by manual shaking in a centrifuge tube. After centrifugation and separation of the two phases, the volume of the acetonitrile phase was reduced in a multiple samples evaporator system and transferred to an autosampler vial to undergo instrumental analysis. Instrumental analysis was carried out by HPLC interfaced to a mass spectrometer operated in the electrospray negative mode. Data were acquired using multiple reaction monitoring (MRM). The isotope dilution technique was applied throughout. Recovery ranges, were 70–110% for the ^{13}C-labelled internal standards. The analysis of blanks and control samples was systematically carried out to check the analytical reliability. The limits of detection for PFOS and PFOA were 0.05 ng g^{-1} and 0.1 ng g^{-1}, respectively.

2.3. Statistical analysis

Non-parametric tests (Median test, Mann–Whitney U test, Spearman test) were used to investigate the possible association of PFOS and PFOA serum concentrations with sex and age of the subjects, and between PFOS and PFOA concentrations (STATISTICA, version 6.0).

3. Results

PFOS and PFOA were detected and quantified in all samples. Serum concentrations of PFOS and PFOA are summarised in Table 1. PFOS concentrations ranged from 0.06 ng g^{-1} to 29.6 ng g^{-1}, PFOA concentrations from 0.22 ng g^{-1} to 51.9 ng g^{-1}. The medians, geometric means, arithmetic means were 6.31, 5.77, 6.86 ng g^{-1} for PFOS and 3.59, 3.32 and 4.15 ng g^{-1} for PFOA, respectively. On the whole, PFOS concentrations were consistently higher than those of PFOA in all age groups.

In order to assess a possible gender-related difference, the Mann–Whitney U test was applied to the entire PFOS and PFOA dataset and to the three age subgroups. For both PFOS and PFOA, significantly higher concentrations were observed in males in the age ranges 36–50 and 51–65 years, as well as in the entire dataset (Table 2). The difference between males and females was not significant in the age range 51–65 years.

The Median test (Table 3) confirmed a statistically significant difference ($p \ll 0.001$) between the three age groups for both PFOS and PFOA concentrations when applied to the entire dataset (males and females). When the test was applied to the two groups of males and females separately, a significant difference between the three age classes was observed for females ($p < 0.005$) but not for males ($p > 0.3$).

Results of the Spearman test applied to PFOS and PFOA concentrations showed a strong correlation between the levels of the two analytes throughout the dataset (Spearman $r = 0.42$, $p \ll 0.01$).

4. Discussion

Concentrations of PFOA and PFOS were higher in males than in females across all age groups.

Table 1
Serum concentrations (ng g^{-1}, whole weight) of perfluorooctane *sulfonate* (PFOS) and perfluorooctanoic *acid* (PFOA) in groups of the Italian general population.[a]

Characteristics of subjects	*N*	Median	Geometric mean	Mean (SD)	Min–max	10th Percentile	25th Percentile	75th Percentile	90th Percentile
PFOS									
All	230	6.31	5.77	6.86 (3.93)	0.06–29.6	2.74	4.18	8.43	12.38
Subgroups									
Males	121	7.21	7.32	8.06 (3.58)	1.24–17.9	4.27	5.62	9.60	14.51
Females	109	4.82	4.43	5.53 (3.89)	0.06–29.6	1.88	2.88	7.10	8.96
Age 20–35	62	4.46	4.05	5.13 (3.4)	0.06–16.4	1.86	2.80	6.54	–[b]
Age 36–50	94	6.67	5.84	6.63 (3.15)	0.71–15.7	2.86	4.35	8.08	10.84
Age 51–65	74	7.25	7.62	8.61 (4.53)	1.24–29.6	4.22	5.77	10.35	–
PFOA									
All	230	3.59	3.32	4.15 (3.79)	0.22–51.9	1.71	2.51	5.08	6.92
Subgroups									
Males	121	4.05	3.64	4.72 (4.80)	0.22–51.9	2.03	2.91	5.93	7.22
Females	109	2.85	3.00	3.52 (2.03)	0.31–9.73	1.56	2.15	4.50	6.90
Age 20–35	62	2.87	2.82	3.34 (1.81)	0.25–9.11	1.56	2.15	4.50	—[b]
Age 36–50	94	3.24	2.85	3.57 (1.95)	0.22–8.10	1.35	2.24	4.75	6.63
Age 51–65	74	4.50	4.61	5.56 (5.87)	1.63–51.9	2.52	3.24	6.61	–

[a] Values rounded off to three figures.
[b] Only percentiles calculated on a sufficient ($N(1-p) \geqslant 8$; EFSA, 2008b) number of subjects (N) are shown.

Table 2
Serum concentrations (ng g^{-1}, whole weight) of perfluorooctane *sulfonate* (PFOS) and perfluorooctanoic *acid* (PFOA) by age and sex in groups of the Italian general population.[a]

Characteristics of subjects	Males				Females				
	N	Median	25th Percentile	75th Percentile	*N*	Median	25th Percentile	75th Percentile	*p* value[b]
PFOS									
All	121	7.21	5.62	9.60	109	4.82	2.88	7.10	$\ll$0.001
Age 20–35	19	6.50	5.20	8.43	43	3.15	2.35	5.50	$\ll$0.001
Age 36–50	60	7.10	5.38	8.60	34	4.55	2.86	7.38	$\ll$0.001
Age 51–65	42	7.97	6.12	12.29	32	7.02	5.08	8.84	0.1[c]
PFOA									
All	121	4.05	2.91	5.93	109	2.85	2.15	4.50	$\ll$0.001
Age 20–35	19	3.64	2.89	5.08	43	2.56	1.88	4.15	0.02
Age 36–50	60	4.04	2.56	5.38	34	2.74	1.96	3.32	$\ll$0.001
Age 51–65	42	4.98	3.34	6.61	32	4.38	2.86	6.75	0.5[c]

[a] Values rounded off to three figures.
[b] Mann–Whitney U test.
[c] Not significant at $p < 0.05$.

Table 3
Serum concentrations (ng g^{-1}, whole weight) of perfluorooctane *sulfonate* (PFOS) and perfluorooctanoic *acid* (PFOA) by sex and age in groups of the Italian general population.[a]

Characteristics of subjects	Age 20–35			Age 36–50			Age 51–65			
	N	Median	25th–75th Percentile	*N*	Median	25th–75th Percentile	*N*	Median	25th–75th Percentile	*p* value[b]
PFOS										
All	62	4.46	2.80–6.54	94	6.67	4.35–8.08	74	7.25	5.77–10.35	$\ll$0.001
Males	19	6.50	5.20–8.43	60	7.10	5.38–8.59	42	7.97	6.12–12.29	0.33[c]
Females	43	3.15	2.35–5.50	34	4.55	2.86–7.38	32	7.02	5.08–8.84	$\ll$0.001
PFOA										
All	62	2.87	2.15–4.50	94	3.24	2.24–4.75	74	4.50	3.24–6.61	$\ll$0.001
Males	19	3.64	2.89–5.08	60	4.04	2.56–5.38	42	4.98	8.34–6.62	0.45[c]
Females	43	2.56	1.88–4.15	34	2.74	1.96–3.32	32	4.38	2.86–6.74	0.003

[a] Values rounded off to three figures.
[b] Median test.
[c] Not significant at $p < 0.05$.

This is in agreement with studies carried out in the USA (Olsen et al., 2003; Calafat et al., 2007), Australia (Toms et al., 2009), China (Yeung et al., 2006), Japan (Harada et al., 2004), and Germany (Midasch et al., 2006; Wilhelma et al., 2009). Although differences in exposure or pharmacokinetics have been proposed to explain gender-related differences, their reasons remain to be elucidated. Lactation and pregnancy, suggested by some authors (Fei et al., 2007; Kärrman et al., 2007; So et al., 2006; Tao et al., 2008) to be partly responsible for the observed gender-related PFOS and PFOA concentrations in human serum, cannot be advocated in this study, since the enrolled women were nulliparous (65%) or had not breast-fed in the last 15 years. The hypothesis of a sex-specific elimination route formulated by Harada and co-workers (Harada et al., 2005), based on the consideration that menstrual bleeding might be an additional route of elimination for females, better matches with our findings. In particular, the loss in significance

Table 4
Concentrations of PFOS-PFOA (ng mL^{-1}) in groups of the general population from European and Non-European countries.

Sampling year	Country	Sample type	PFOS	PFOA	Number and characteristics of donors	Reference
European Countries						
1998–2000	Belgium	Serum	10.4[a] 17.6[a]	2.4[a] 4.3[a]	4 females 16 males	Kannan et al., 2004
2003	Germany	Plasma	13[a]	2.6[a]	11 females, pregnant	Midash et al., 2007
2003–2004	Germany	Plasma	22.3[a] 27.1[a] 19.9[a]	6.8[a] 8.3[a] 5.8[a]	105 adults 51 males 54 females	Midasch et al., 2006
2001	Italy	Serum	3.5[a] 4.2[a]	<3[a] <3[a]	8 females 42 males	Kannan et al., 2004
2010	Italy	Serum	6.3[a] 7.2[a] 4.8[a]	3.6[a] 4.1[a] 2.9[a]	230 adults 121 males 109 females	Present study
n.s	Poland	Blood[b]	10.4–168[c]	2.4–17.4	60 adults	Falandysz et al., 2006
2003	Poland	Blood[b]	67.6[a] 81.8[a]	46.4[a] 36.8[a]	15 females 10 males	Kannan et al., 2004
1997–2000	Sweden	Blood[b]	24.2[a]	5[a]	66 adults	Kärrman et al., 2004
Non-European Countries						
2006–2007	Australia	Blood[b]	30.4[d] 41.4[d] 29.8[d] 49.2[d] 37.2[d]	12.8[d] 13.8[d] 9[d] 13.8[d] 11.8[d]	2420 adults, 84 pools Males (age range 31–45) Females (age range 31–45) Males (age range 46–60) Females (age range 46–60)	Toms et al., 2009
2003	Brazil	blood [b]	16.8[a] 25.4[a]	<40[a] <40[a]	17 females 10 males	Kannan et al., 2004
n.s	Canada	Blood[b]	57.6[d]	6.8[d]	56 adults	Kubwabo et al., 2004
2004–2005	Canada	Serum	16.6[a]	2.13[a]	101 females, pregnant	Monroy et al., 2008
2004	China (Shenyang) China (Nanjing)	Blood[b]	112.6[d] 2.8[d]	4[d] 10[d]	5 adults 10 adults	Yeung et al., 2008
2003	Colombia	Blood [b]	14.6[a] 16.2 [a]	11.2[a] 11.8[a]	25 females 31 males	Kannan et al., 2004
2002	Japan	Serum	18.3[a] 12.4[a]	12.3[a] <6.8[a]	13 females 25 males	Kannan et al., 2004
2003	Japan	Blood[b]	9.8–35.2[c]	<1–4.6[c]	15 females, pregnant	Inoue et al., 2004
2003	Japan (Kyoto) Japan (Miyang)	serum	13.8[e] 28.1[e] 3.5[e] 5.7[e]	7.1[e] 12.4[e] 2.8[e] 3.3[e]	26 females 28 males 23 females 32 males	Harada et al., 2004
2000	India	Serum	2.5[a] 1.3[a]	<3[a] 3.5[a]	11 females 34 males	Kannan et al., 2004
2003	Korea	Blood[b]	22.6[a] 43.4[a]	61.8[a] 53.6[a]	25 females 25 males	Kannan et al., 2004
2004	Malaysia	Blood[b]	15.4[a] 26.2[a]	<20[a] <20[a]	16 males 7 females	Kannan et al., 2004
2000	Michigan, USA	Serum	28.9[a] 26.2[a]	4.4[a] 5.7[a]	46 females 29 males	Kannan et al., 2004
2003	USA (Atlanta)	Serum	53.66[d] 57.97[d]	4.22[d] 2.89[d]	10 females 10 males	Kuklenyik et al., 2004
2002	USA(Kentucky)	Blood[b]	162[a] 144[a]	40[a] 76.2[a]	11 females 19 males	Kannan et al., 2004
2002	USA (NY City)	Plasma	42[a]	25.2[a]	70 adults	Kannan et al., 2004
2000–2001	USA (Seattle)	Blood[b]	60.4[a]	8.4[a]	238 adults	Olsen et al., 2004
1999–2000	USA	Serum	30.4[e]	5.2[e]	1562 adults	Calafat et al., 2007
2000–2001	USA	Blood[b]	71.6[a]	9.4[a]	645 adults	Olsen et al., 2003

[a] Median.
[b] PFOS and PFOA blood concentrations have been adjusted to serum concentrations by multiplying by two (Kannan et al., 2004).
[c] Range.
[d] Mean.
[e] Geometric mean.

of the gender-related difference in PFC concentrations in subjects of age $\geqslant$51 years could be explained with the end of that sex-specific elimination route.

The age-related increase observed in the present study is in agreement with what is observed for PFCs in other studies (Fromme et al., 2007; Toms et al., 2009). Age-dependence of PFC

concentrations is plausible to be related to the persistence and potential for bioaccumulation (Lau et al., 2007) of these chemicals, associated with conditions of constant exposure. The highly significant correlation between age and PFOS and PFOA concentrations observed for the enrolled subjects altogether results to be mostly determined by the group of females. In fact, when the Median test is applied to the two groups of males and females separately, age-dependence of PFOS and PFOA concentrations results to be not statistically significant for males, whereas it is still highly significant for females . This finding is probably associated with the capability of women of age <50 years to better eliminate these chemicals.

The strong correlation observed between PFOS and PFOA concentrations is in line with observations reported in other studies (Calafat et al., 2007; Ericson et al., 2007; Kannan et al., 2004; Wilhelma et al., 2009). Since PFOS cannot convert directly into PFOA, or *vice versa* (Tomy et al., 2004) it may be hypothesized that the observed correlation could be partly due to the uptake of both compounds from common sources or pathways (food and migration from food packaging, drinking water, indoor dust) (EFSA, 2008a).

The PFOS and PFOA serum concentrations measured in humans in different geographical locations are shown in Table 4 (blood concentrations have been adjusted to serum concentrations by multiplying by two (Kannan et al., 2004) and all concentrations expressed in ng mL^{-1}, since serum density is approximately 1 g mL^{-1}). Within the limits affecting comparability, mostly due to differences in study design and analytical techniques, the concentrations measured in the present study result to be among the lowest observed worldwide. The PFOS concentrations detected are comparable with those observed in a group of subjects (50 adult donors, 42 males and eight females) enrolled in the town of Siena, Tuscany, Central Italy, in 2001 (Kannan et al., 2004), although a straight comparison between the two studies is hindered by differences in geographical areas, year of collection, gender distribution and number of individuals. As to PFOA, in contrast to what was found by Kannan and co-workers, we detected this compound in all the samples analysed (detection limit of 0.1 ng g^{-1}).

An interpretation of the comparatively low concentrations observed for Italy is made problematic by the limited knowledge of the contributions from the different pathways of exposure. The modest use in Italy of carpets and fitted carpets, recognised as an important route of exposure for other countries (Tittlemeier et al., 2007; Trudel et al., 2008), might be responsible of a comparatively lower indoor contamination.

Dietary habits (i.e. moderate consumption of fast food items (ISTAT, 2008)), and resulting probable moderate exposure from food packaging, could certainly play a role in determining the low levels observed, but the substantial lack of PFOS and PFOA occurrence data for most foodstuffs makes very difficult to properly identify those food categories and/or dietary habits that could determine the low exposure levels observed. Data on the occurrence of PFOS and PFOA in different food categories would be needed to assess the relative contribution of these to the Italian dietary exposure.

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