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Cumulative health risk assessment of 17 perfluoroalkylated and polyfluoroalkylated substances (PFASs) in the Swedish population

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ABSTRACT

Humans are simultaneously exposed to a multitude of chemicals. Human health risk assessment of chemicals is, however, normally performed on single substances, which may underestimate the total risk, thus bringing a need for reliable methods to assess the risk of combined exposure to multiple chemicals. Per- and polyfluoroalkylated substances (PFASs) is a large group of chemicals that has emerged as global environmental contaminants. In the Swedish population, 17 PFASs have been measured, of which the vast majority lacks human health risk assessment information. The objective of this study was to for the first time perform a cumulative health risk assessment of the 17 PFASs measured in the Swedish population, individually and in combination, using the Hazard Index (HI) approach. Swedish biomonitoring data (blood/serum concentrations of PFASs) were used and two study populations identified: 1) the general population exposed indirectly via the environment and 2) occupationally exposed professional ski waxers. Hazard data used were publicly available toxicity data for hepatotoxicity and reproductive toxicity as well as other more sensitive toxic effects. The results showed that PFASs concentrations were in the low ng/ml serum range in the general population, reaching high ng/ml and low μg/ml serum concentrations in the occupationally exposed. For those congeners lacking toxicity data with regard to hepatotoxicity and reproductive toxicity read-across extrapolations was performed. Other effects at lower dose levels were observed for some well-studied congeners. The risk characterization showed no concern for hepatotoxicity or reproductive toxicity in the general population except in a subpopulation eating PFOS-contaminated fish, illustrating that high local exposure may be of concern. For the occupationally exposed there was concern for hepatotoxicity by PFOA and all congeners in combination as well as for reproductive toxicity by all congeners in combination, thus a need for reduced exposure was identified. Concern for immunotoxicity by PFOS and for disrupted mammary gland development by PFOA was identified in both study populations as well as a need of additional toxicological data for many PFAS congeners with respect to all assessed endpoints.

1. Introduction

As a result of human activity a large number of chemicals have been and are being released into the biosphere. Our knowledge about possible impacts on human health and the environment is inadequate for many individual chemicals and, in particular, for chemical mixtures.

Human health risk assessment of chemicals normally considers the effects of single substances in isolation. However, compounds in a mixture may work together and produce an effect larger than by the individual components themselves and, hence, assessing single chemicals may underestimate the total risk (Backhaus and Faust, 2012; Kortenkamp et al., 2009; Silva et al., 2002). During the last decade the area of mixture toxicology has developed with multi-component mixtures being more commonly tested (Kortenkamp et al., 2009). However, due to the large number of chemical compounds used and the infinite number of possible mixtures it is practically impossible to experimentally test for more than a very limited set of all possible chemical combinations (Backhaus et al., 2010). Therefore, there is a need for reliable methods to assess the risk from combined exposure to multiple chemicals via all relevant routes and pathways, defined as *cumulative risk assessment* (WHO, 2009).

A number of methods have been developed to predict the toxicity and risk of mixtures based on their chemical composition and knowledge of the toxicities of the mixture components. Most of these methods are based on the concepts of Concentration Addition (CA) and Independent Action (IA) (Backhaus et al., 2010). CA assumes that the individual components act via a similar mode of action, only differing in their relative potency to elicit a toxic effect (Backhaus et al., 2010), whereas IA, assumes that the individual components act independently of each other (Backhaus et al., 2010). Both concepts assume that no interactions occur between the mixture components (SCHER, 2011). Examples of cumulative risk assessment

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methods include the Hazard Index (HI), Point of Departure Index (PODI), Combined Margin of Exposure Index (MOE_T), Toxic Unit Summation (TUS) and Relative Potency Factors/Toxic Equivalency Factors (RPF/TEF) (Boobis, 2009; Kortenkamp et al., 2009; Sarigiannis and Hansen, 2012; SCHER, 2011; U.S. EPA, 1986). The Hazard Index (HI) is defined as the sum of the respective Hazard Quotients (HQs) for individual mixture components, calculated as the ratio between exposure (e.g. daily intake) and a reference dose (RfD, e.g. tolerable daily intake (TDI)) and has been put forward as the preferred approach when extensive mechanistic information of the mixture components is not available (SCHER, 2011; U.S. EPA, 1989). The HI does not predict the overall health effect of the mixture, but provide a measure of the total risk based on the individual risk of each component. Thus, the HI can be used also for identification of the largest contributors to the risk (Sarigiannis and Hansen, 2012).

Perfluoroalkylated and polyfluoroalkylated substances (PFASs) belong to a large class of highly fluorinated organic chemicals of anthropogenic origin that has been used since the 1950s as components of and precursors for surfactants and surface protectors in industrial and consumer applications (3M Company, 1999). Characteristic for these chemicals is an extreme resistance towards chemical and biological degradation and a number of PFASs are also bioaccumulative and toxic (reviewed in Lau et al., 2007). During the last decade, PFASs have emerged as global environmental contaminants with widespread presence in humans and the environment.

Different PFASs show a relatively comparable toxicological profile, where repeated-dose studies in rodents and monkeys point out the liver as a target organ (reviewed in Lau et al., 2007) and with hepatotoxicity being a sensitive endpoint (ECHA, 2011) manifested as e.g. hepatocellular hypertrophy, vacuolation, pigmentation and necrosis as well as increased liver weight. Further, PFASs cause reproductive toxicity following *in utero* exposure, demonstrated as e.g. reduced fetal/perinatal/neonatal body weight and viability as well as reduced pup body-weight gain and litter loss in the dams (reviewed in Lau et al., 2007). In addition, other toxic effects on body weight, lipid metabolism and thyroid hormone levels as well as immunotoxicity, impaired mammary gland development and developmental neurotoxicity have been observed for several congeners (DeWitt et al., 2012; Johansson et al., 2008; Lau et al., 2004, 2007; Viberg et al., 2012; White et al., 2007). The mode of action of PFASs has not yet been clarified (Lau, 2012a). For perfluorooctanoic acid (PFOA), mechanistic studies using knockout (KO) mice for the peroxisome proliferator activated receptor alpha (PPARα) have demonstrated that some effects (complete litter loss and liver weight increase in dams and pups) seem to be independent of PPARα expression (Abbott et al., 2007). Other effects, such as increased postnatal pup mortality, reduction in pup body weight and postnatal growth and development (delayed eye opening) have indicated interference/contribution of PPARα for the toxicity of PFOA but not for the analogous compound perfluorooctane sulfonate (PFOS) (Abbott et al., 2009). With regard to hepatotoxicity, hepatocellular hypertrophy, vacuolation and increased liver weight seems independent of PPARα based on studies in PPARα KO mice, at least for PFOA and PFOS (Abbott et al., 2007; Rosen et al., 2010; Wolf et al., 2008a; Yang et al., 2002), whereas hepatocellular proliferation appear to be PPARα-dependent (Wolf et al., 2008a).

Diet, particularly fish and seafood, has been proposed as a major exposure route to several PFASs for the general population (Haug et al., 2010) as well as household dust (Haug et al., 2011). Occupationally exposed individuals are highly exposed, most likely through inhalation of PFASs-containing aerosols and dust (ATSDR, 2009; Vestergren and Cousins, 2009). In Sweden, professional ski waxers have been shown to have the highest serum concentrations of PFASs (Nilsson et al., 2010). As a measure of human exposure, serum concentrations of PFASs are commonly used and a 1:1 ratio for serum to plasma concentrations and a 2:1 ratio for serum/plasma to whole blood concentrations has been shown for several PFASs congeners (Ehresman et al., 2007) enabling easy comparison between these matrices.

PFASs have been highlighted as a group of compounds of concern for human health. Health risk assessments have, however, only been performed for perfluorobutane sulfonate (PFBS), PFOS, perfluorobutanoate (PFBA) and PFOA (Specified in Supplemental Tables 2–4), of which PFOS and PFOA are the most studied. In addition, no cumulative assessment of PFASs have yet been performed. The aim of this study is therefore, for the first time, to perform a cumulative health risk assessment of 17 PFASs based on Swedish biomonitoring data and publicly available toxicity data using the HI approach.

2. Materials and methods

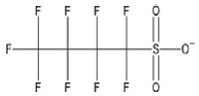
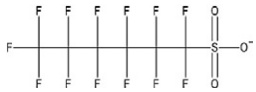
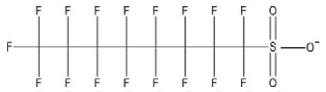
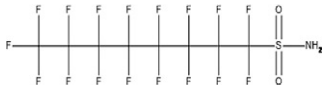
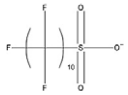
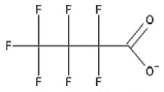
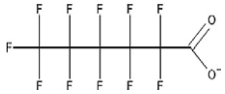
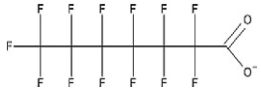
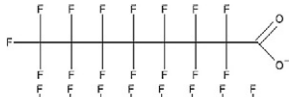
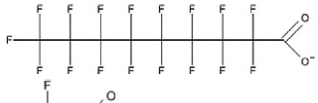
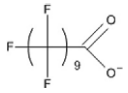
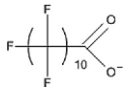
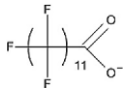
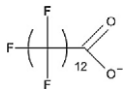
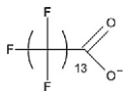
2.1. Exposure assessment

Biomonitoring data (blood/serum concentrations) of all PFAS congeners measured in the Swedish population were used for the evaluation of PFASs exposure. External (oral/inhalation/dermal) exposures were not included. The exposure data were collected from reports within the Swedish Health-Related Monitoring Programme (HÄMI), other national reports and scientific publications. Exposure data included in the assessment were derived from snapshot studies or temporal studies with sampling 2006 or later, earlier samplings were considered out-of-date. In total, six studies were found that fulfilled these criteria (Supplemental Table 1) and, based on these, two population groups were identified: 1) individuals exposed indirectly via the environment, i.e. the general population; and 2) occupationally exposed professional ski waxers. Based on the low number of individuals in the studies ($n = 9–80$ for individuals exposed indirectly via the environment and $n = 8$ for the occupationally exposed) the highest PFASs concentrations in samples from the selected key studies were used. Congeners that were present at concentrations under the limit of detection (LOD) were treated as being <LOD. To enable comparisons between blood and serum/plasma concentrations, whole-blood concentrations were converted into serum/plasma concentrations using a 1:2 whole blood:serum/plasma ratio as shown by Ehresman et al. (2007). For a full list of the compounds evaluated, their CAS-number and chemical structure see Table 1. The date for the last literature search for exposure data was 2013-01-15.

2.2. Hazard assessment

The toxicological endpoints evaluated were hepatotoxicity (hepatocellular hypertrophy, hepatocellular vacuolation, increased liver weight and liver-to-body ratio) and reproductive toxicity (reduced fetal/perinatal/neonatal viability, reduced body weight/body weight gain and litter loss in the dams). In addition, other endpoints, if observed at a lower dose level than hepatotoxicity and reproductive toxicity, were included. Points of departure (PODs) were PFASs serum/plasma concentrations at the respective No-Observed-Adverse-Effect-Levels (NOAELs), Lowest-Observed-Adverse-Effect-Levels (LOAELs) or Benchmark doses (BMDs). The toxicological data and key studies/critical effects were collected from already existing hazard- and/or risk assessments where the studies selected therein have been given preference, for different reasons, over other studies available in these reports. The hazard- and risk assessment were also supplemented with additional published relevant data from literature searches in PubMed, i.e., studies on hepatotoxicity or reproductive toxicity published subsequently to the hazard/risk assessment reports and studies showing other effects with lower effect concentrations than for hepatotoxicity and reproductive toxicity. The date for the last literature search of hazard data was 2013-02-01. In total, 17 relevant hazard- or risk assessment reports and 29 additional (as defined above) scientific publications were found (Supplemental Tables 2–4). Congeners that lacked toxicological information

Table 1
PFAS congeners included in the assessment and their acronyms, CAS-number and chemical structure.

Acronym	Substance name	CAS-number	Structure
PFBS	Perfluorobutane sulfonate	29420-49-3 (potassium salt) 75-22-4 (acid)	
PFHxS	Perfluorohexane sulfonate	3871-99-6 (potassium salt) 355-46-4 (acid)	
PFOS	Perfluorooctane sulfonate	2795-39-3 (potassium salt) 1763-23-1 (acid)	
PFOSA	Perfluorooctane sulfonamide	754-91-6	
PFDS	Perfluorodecane sulfonate	67906-42-7 (ammonium salt) 335-77-3 (acid)	
PFBA	Perfluorobutanoic acid	375-22-4 (acid)	
PFPeA	Perfluoropentanoic acid	2706-90-3 (acid)	
PFHxA	Perfluorohexanoic acid	307-24-4 (acid)	
PFHpA	Perfluoroheptanoic acid	375-85-9 (acid)	
PFOA	Perfluorooctanoic acid	335-67-1 (acid) 335-95-5 (sodium salt) 3825-26-1 (ammonium salt)	
PFNA	Perfluorononanoic acid	375-95-1 (acid)	
PFDA	Perfluorodecanoic acid	335-76-2 (acid)	
PFUnDA	Perfluoroundecanoic acid	2058-94-8 (acid)	
PFDoDA	Perfluorododecanoic acid	307-55-1 (acid)	
PFTrDA	Perfluorotridecanoic acid	72629-94-8 (acid)	
PFTeDA	Perfluorotetradecanoic acid	376-06-7 (acid)	
6:2 FTS	1,1,2,2-Tetrahydro perfluorooctane sulfonate	27619-97-2 (acid)	

for hepatotoxicity (n = 7/17) and reproductive toxicity (n = 9/17) and/or corresponding internal dose measurements (n = 12/17) were subject to read-across extrapolation to the closest most potent congener for the respective endpoint. The read-across was performed on an equivalent molar basis. No extrapolations from external doses to internal dose were made. From the PODs, RfDs were derived by the use of appropriate assessment factors (AFs): RfD = POD/AFs. In accordance with the European Union's chemicals legislation REACH guidelines (ECHA, 2010) the following AFs were applied:

Table 2
Summary of Swedish human serum/plasma biomonitoring data on perfluoroalkylated and polyfluoroalkylated substances (PFASs) from key studies in the general population and occupationally exposed professional ski waxers Selected concentrations represent the highest concentrations at the latest time-point in a temporal study or from a sample in a snapshot study. All selected samples were taken during 2006 and 2010.

Congener	General population		Occupationally exposed	
	Serum concentration (ng/ml)	Reference	Serum concentration (ng/ml)	Reference
PFBS	0.10	Glynn et al. (2012)	N.A.[c]	Glynn et al. (2012)
PFHxS	8.0	Glynn et al. (2012)	8.6	Nilsson et al. (2010)
PFOS	27.5/204[a]	Jönsson et al. (2009)	54	Nilsson et al. (2010)
PFOSA	<0.040	Glynn et al. (2012)	N.A.[c]	Glynn et al. (2012)
PFDS	0.025	Glynn et al. (2012)	N.A.[c]	Glynn et al. (2012)
PFBA	N.A.	–	2.2	Nilsson et al. (2010)
PFPeA	N.A.	–	0.28	Nilsson et al. (2010)
PFHxA	<0.22[b]	Ericson et al. (2008)	24	Nilsson et al. (2010)
PFHpA	<0.24[b]	Ericson et al. (2008)	40	Nilsson et al. (2010)
PFOA	5.2	Jönsson et al. (2009)	1070	Nilsson et al. (2010)
PFNA	2.6	Jönsson et al. (2010)	326	Nilsson et al. (2010)
PFDA	0.70[b]	Ericson et al. (2008)	48	Nilsson et al. (2010)
PFUnDA	0.83	Jönsson et al. (2010)	5.6	Nilsson et al. (2010)
PFDoDA	<0.1	Glynn et al. (2012)	N.A[c]	Glynn et al. (2012)
PFTrDA	<0.15	Glynn et al. (2012)	N.A[c]	Glynn et al. (2012)
PFTeDA	<0.25	Glynn et al. (2012)	N.A[c]	Glynn et al. (2012)
6:2 FTS	<3.6[b]	Ericson et al. (2008)	N.A[c]	Ericson et al. (2008)

N.A. = Not analyzed.
[a] Highly exposed subpopulation (Hovgard et al., 2009).
[b] Concentration converted from whole-blood to serum using a whole blood:serum/plasma ratio of 2 as shown by Ehresman et al. (2007).
[c] Due to lack of exposure data the same value as for the general population will be used in the risk characterization.

- Exposure duration: For extrapolation of subchronic to chronic as well as subacute to chronic exposure for hepatotoxicity an AF of 2 was used. This rather low AF is motivated by a rapid onset of hepatotoxicity and a limited aggravation with time. For other effects, AFs of 3 and 6 were applied for subchronic to chronic and subacute to chronic exposure, respectively.
- PODs: For extrapolations from LOAEL to NOAEL in studies where no NOAEL could be established an AF of 3 was used.
- Interspecies differences: For extrapolations of data from animals to humans with regard to differences in toxicodynamics an AF of 2.5 was applied. No AF for toxicokinetic differences between animals and humans was considered needed since internal doses were directly compared.
- Intraspecies differences: For differences in sensitivity among humans the AFs 10 and 5 were applied for the general population and workers, respectively.
- Read-across extrapolations: For extrapolations from shorter to longer congeners an AF of 3 were used, based on differences in potency. Shorter congeners are generally being more rapidly excreted than their longer homologues and are thus generally less potent. No AF was used for read-across from a longer to a shorter congener.

Table 3
Summary of points of departure for hepatotoxicity and reproductive toxicity. Doses represent NOAELs if not stated otherwise. For congeners lacking data, read-across extrapolation from the closest most conservative congener on a molar basis has been performed. Original congener-specific data is marked in bold.

Congener	Point of departure (POD)			
	Hepatotoxicity		Reproductive toxicity	
	External dose (mg/kg bw/day)	Internal dose (μg/ml serum)	External dose (mg/kg bw/day)	Internal dose (μg/ml serum)
PFBS	**100**	67[a]	**300**	>45[a]
PFHxS	**1.0**	**89**	**>10.0**	**>60**
PFOS	**0.025**	**4.04**	**0.1**	**4.9**
PFOSA	0.024[b]	4.03[b]	0.1[b]	4.9[b]
PFDS	0.029[b]	4.85[b]	0.1[b]	5.9[b]
PFBA	**6.0**	**14**	**175**	**4.4**
PFPeA	0.04[c]	4.5[c]	0.55[c]	10.0[c]
PFHxA	**20**	5.4[c]	**100**	11.9[c]
PFHpA	**20**	6.2[c]	0.76[c]	13.8[c]
PFOA	**0.06**	**7.1**	**0.86**[d]	**15.7**[d]
PFNA	**0.83**[e]	**28.5**	**0.83**	**8.9**
PFDA	**1.2**	31.6[f]	**3.0**	9.9[f]
PFUnDA	1.01[f]	34.6[f]	1.01[f]	10.8[f]
PFDoDA	**0.02**[c]	37.7[f]	1.10[f]	11.8[f]
PFTriDA	1.19[f]	40.8[f]	1.19[f]	12.7[f]
PFTeDA	1.28[f]	43.9[f]	1.28[f]	13.7[f]
6:2 FTS	0.020[b]	3.45[b]	0.085[b]	4.2[b]

[a] Read-across on a molar basis from PFHxS.
[b] Read-across on a molar basis from PFOS.
[c] Read-across on a molar basis from PFOA.
[d] BMDL/BMCL.
[e] LOAEL.
[f] Read across on a molar basis from PFNA.

2.3. Risk characterization of exposure to individual and combined PFASs congeners

Hazard Quotients (HQs) were derived for all individual congeners by comparing their respective RfDs (POD/AFs; see Section 2.2) with the exposure to evaluate whether the exposure level is tolerable or not: HQ = Exp/RfD, where a ratio of <1 indicates a tolerable exposure

Table 4
Summary of points of departure for PFAS congeners and effects observed at a lower effect concentration than for hepatotoxicity and reproductive toxicity.

Congener	Effect	External dose (mg/kg bw/day, μg/l)	Internal dose (μg/ml serum)
PFBS	Hematology (↓ hemoglobin and hematocrit)	60[a]	N.A.[b]
PFHxS	Hematology (↓ hemoglobin)	0.3[a,c]	44[c]
PFOS	Immunotoxicity (↓ IgM response)	0.000166[a]	0.0178
PFBA	↓ Serum cholesterol	3.0[a]	N.A.[b]
PFOA	Mammary gland development	0.005[c,d]	0.021[c]
	↑ Adult body weight, serum leptin and insulin	0.01[a,c]	N.A.[b]
6:2 FTS[e]	Nephrotoxicity	15[a]	N.A.[b]

N.A. = Not available.
[a] mg/kg bw/day.
[b] Will not be used in the risk characterization based on the lack of serum concentration.
[c] LOAEL.
[d] μg/l water.
[e] No effect level for hepatotoxicity or reproductive toxicity identified.

Table 5
Reference doses (RfDs) for hepatotoxicity and reproductive toxicity in individuals exposed indirectly via the environment (Ind. Exp.) and in occupationally exposed individuals (Occ. Exp.). The RfDs were derived from the use of assessment factors (AFs) to the point of departure (POD) for the respective effects. Original congener-specific data is marked in bold.

Congener	Liver toxicity					Reproductive toxicity				
	POD (ng/ml serum)	Overall AF		RfD (ng/ml serum)		POD (ng/ml serum)	Overall AF		RfD (ng/ml serum)	
		Ind. Exp.	Occ. Exp.	Ind. Exp.	Occ. Exp.		Ind. Exp.	Occ. Exp.	Ind. Exp.	Occ. Exp.
PFBS	66,754	50	75	1335	2670	>45,000	25	12.5	>1800	>3600
PFHxS	**89,000**	50	25	**1780**	**3560**	**>60,000**	25	12.5	**>2400**	**>4800**
PFOS	**4040**	25	12.5	**162**	**323**	**4900**	25	12.5	**196**	**392**
PFOSA	4032	25	12.5	161	323	4890	25	12.5	196	391
PFDS	4848	75	37.5	65	130	5880	75	37.5	78	157
PFBA	**14,000**	N.I.	25	N.I.	**560**	**4400**	N.I.	12.5	N.I.	**352**
PFPeA	4528	N.I.	25	N.I.	181	10,012	N.I.	12.5	N.I.	801
PFHxA	5385	50	25	108	215	11,908	25	12.5	476	953
PFHpA	6242	50	25	125	250	13,804	25	12.5	552	1104
PFOA	**7100**	50	25	**142**	**284**	**15,700**	25	12.5	**628**	**1256**
PFNA	**28,500**	150	75	**190**	**380**	**8900**	25	12.5	**356**	**712**
PFDA	31,571	450	225	70	140	9859	75	37.5	263	514
PFUnDA	34,642	450	225	77	154	10,818	75	37.5	144	288
PFDoDA	37,713	450	225	84	168	11,777	75	37.5	157	314
PFTrDA	40,784	450	225	91	181	12,736	75	37.5	170	340
PFTeDA	43,855	450	225	97	195	13,695	75	37.5	183	365
6:2 FTS	3451	25	12.5	138	276	4185	25	12.5	167	335

N.I. = Not included due to lack of exposure data.

level and a ratio of >1 indicates a non-tolerable exposure level. In addition, a cumulative risk characterization was performed for all the congeners combined by the derivation of Hazard Indexes (U.S. EPA, 1989) for hepatotoxicity and reproductive toxicity: HI = $\sum$HQs. Toxicological data for other endpoints were only available for a few individual PFAS congeners and it is unclear whether other PFASs exert these effects, thus a HI could not be derived for these endpoints.

3. Results

3.1. Exposure assessment

3.1.1. Indirect exposure via the environment

In total five Swedish PFASs biomonitoring studies on the general population with blood samples drawn during or after 2006 were identified and evaluated (Supplemental Table 1). Three of these were snapshot studies and two were temporal trend studies, with sample numbers of 9–80. In these studies PFAS congeners were detected at low ng/ml serum concentrations or were <LOD. In one of the studies, PFOS was found at higher ng/ml concentrations in a small population eating PFOS-contaminated fish from a lake receiving run-offs from a nearby airport where PFOS-containing aqueous film-forming foams (AFFFs) have been used (Hovgard et al., 2009). The serum concentrations for the respective PFAS congeners that are used in the risk characterization for the general population are summarized in Table 2.

3.1.2. Occupational exposure

One study on occupational exposure to PFASs in Sweden was identified and evaluated (Nilsson et al., 2010, Supplemental Table 1). The study, performed during 2007–2008 on occupationally exposed Swedish and international professional ski waxers (n = 8) showed that the serum concentrations of some PFAS congeners were significantly higher than in the general population, e.g. PFNA and PFOA being approximately 125 and 200 times higher, respectively, reaching high ng/ml and low μg/ml concentrations in serum (Supplemental Table 1). The serum concentrations for the respective PFAS congeners that are used in the risk characterization for the occupationally exposed ski waxers are summarized in Table 2.

3.2. Evaluation of hazard/risk assessments and toxicological data

From the literature search on hazard/risk assessments and toxicological data in total 17 relevant hazard- or risk assessment reports and 29 additional scientific publications on hepatotoxicity and reproductive toxicity published subsequently to the hazard- or risk assessment reports or with other more sensitive effects were found (Supplemental Tables 2–4). The different PFAS congeners displayed qualitatively similar toxicological profiles with hepatotoxicity and reproductive toxicity being common toxic effects. Hepatotoxicity was in the evaluated reports/studies manifested as hepatocellular hypertrophy, increased absolute and/or relative liver weight and/or hepatocellular vacuolation at lower doses (Supplemental Table 2) and as more adverse effects such as necrosis at higher doses, as shown for PFOS, PFOA and perfluorodecanoic acid (PFDA) (ATSDR, 2009; Butenhoff et al., 2012; Yahia et al., 2010). Reproductive toxicity was demonstrated as reduced fetal/perinatal/neonatal body weight and viability and reduced pup body weight gain or litter loss in the dams (Supplemental Table 3). Toxicological data for hepatotoxicity and reproductive toxicity were available for 10 and 8 congeners, respectively (Table 3), and corresponding internal serum concentration data were available for 5 of the 17 congeners for hepatotoxicity and reproductive toxicity, respectively (Table 3). Thus, data for 12 congeners had to be extrapolated using read-across (Table 3). The PODs ranged between 4 and 89 μg/ml serum for

Table 6
Derived reference doses (RfDs) for effects observed at lower doses than hepatotoxicity and reproductive toxicity in indirectly exposed (Ind. Exp.) and occupationally exposed individuals (Occ. Exp.). The RfDs were derived from the use of assessment factors (AFs) to the point of departure (POD) for the respective effects.

Congener	Effect	POD (ng/ml serum)	Overall AF		RfD (ng/ml serum)	
			Ind. Exp.	Occ. Exp.	Ind. Exp.	Occ. Exp.
PFHxS	Hematology	44,000	450	225	98	196
PFOS	Immunotoxicity	17.8	150	75	0.12	0.24
PFOA	Mammary gland development	21.3	75	37.5	0.28	0.57

Table 7
Individual Hazard Quotients (HQs) and Hazard Indexes (HIs) for hepatotoxicity and reproductive toxicity in individuals exposed indirectly via the environment, derived from comparison of the exposure with the reference dose (RfD), and whether there is an associated concern or not.

Congener	Exposure (ng/ml serum)	Hepatotoxicity					Reproductive toxicity				
		RfD (ng/ml serum)	HQ[a]	% of HI	Concern?		Reference dose (ng/ml serum)	HQ[a]	% of HI	Concern?	
					Yes	No				Yes	No
PFBS	0.108	1335	0.000081	0.03		√	>2400	<0.000060	<0.03		√
PFHxS	8.50	1780	0.0048	1.8		√	>2400	<0.0035	<1.9		√
PFOS	27.5/(204)[b]	162	0.17/(1.26)[b]	64.0	(√)	√	196	0.14/(1.0)	76.2	(√)	√
PFOSA	<0.040	161	<0.00025	<0.09		√	196	<0.0002	<0.11		√
PFDS	0.035	65	0.00054	0.2		√	65	0.0004	0.24		√
PFHxA	<0.22	108	0.0020	0.8		√	628	0.00046	<0.25		√
PFHpA	0.135	125	0.0011	0.4		√	628	0.00024	0.13		√
PFOA	5.24	142	0.037	13.8		√	628	0.0083	4.5		√
PFNA	2.6	190	0.014	5.1		√	356	0.0073	4.0		√
PFDA	0.70	70	0.010	3.8		√	119	0.0053	2.9		√
PFUnDA	0.83	77	0.011	4.1		√	119	0.0058	3.3		√
PFDoDA	<0.03	84	<0.00036	<0.1		√	119	<0.00019	<0.10		√
PFTrDA	<0.15	91	<0.0017	<0.6		√	119	<0.00088	<0.48		√
PFTeDA	<0.04	97	<0.00041	<0.15		√	119	<0.00022	<0.12		√
6:2 FTS	<1.82	138	<0.013	<5.0		√	196	<0.011	<5.9		√
HI[c]			0.25–0.27 (1.3–1.4)[b]		(√)	√		0.17–0.18 (1.1)[b]		(√)	√

N.A. = Not available/not applicable.
[a] HQ = Exposure/RfD, ratio < 1 = no concern, ratio >1 = concern.
[b] Highly exposed population.
[c] HI = ΣHQs.

hepatotoxicity and between 4 and >60 μg/ml for reproductive toxicity (Table 3). For other endpoints with lower effect levels than hepatotoxicity and reproductive toxicity, data were available for 6 congeners of which 3 had corresponding internal serum concentrations that could be used for risk characterization (perfluorohexane sulfonate (PFHxS), PFOS and PFOA) (Table 4). In particular, PFOS and PFOA were associated with PODs for effects on the immune system and mammary gland development at very low serum concentrations (~0.02 μg/ml serum).

For individuals exposed indirectly via the environment, the derived RfDs for hepatotoxicity and reproductive toxicity ranged between 65 and 1780 ng/ml serum and between 78 and >2400 ng/ml serum, respectively (Table 5). For other more sensitive endpoints, the RfDs ranged between 0.12 and 98 ng/ml (Table 6). As the AF for intraspecies variation in workers is half that for the general population the RfDs for the occupationally exposed were 2-fold higher than for the general population for all endpoints (Tables 5 and 6). For a detailed description of the AFs used for the respective congeners for the general population and the occupationally exposed, respectively, see Supplemental Tables 5–7.

3.3. Characterization of risk to human health

3.3.1. Indirect exposure via the environment

The result of the risk characterization showed that for hepatotoxicity and reproductive toxicity all HQs were ≤1, i.e. indicating no cause for concern for individuals exposed indirectly via the environment to individual PFAS congeners (Table 7). For hepatotoxicity, the HI for all congeners combined was in the order of 0.25. Thus, all congeners combined are not expected to give any cause for concern for hepatotoxicity. HQs were highest for PFOS and PFOA, 0.17 and 0.037, respectively, contributing in total with 64% and 14% to the HI. For reproductive toxicity, the HI was in the order of 0.17; hence, all congeners combined are not expected to give any cause for concern. The main contributor to the HI was PFOS contributing with 76%.

One subpopulation that had the highest exposure to PFOS through the consumption of PFOS-contaminated fish also showed the highest HQs, 1.3 and 1.0 for hepatotoxicity and reproductive toxicity, respectively (Table 7), indicating a cause for concern for these endpoints. Consequently, the HIs for hepatotoxicity and reproductive toxicity for that particular subpopulation were in the range of 1.1–<1.4.

For other more sensitive effects, very high HQs in the general population were obtained (Table 9). For immunotoxicity (reduced antigen response) by PFOS a HQ of 228 was derived and for disrupted mammary gland development in offspring by PFOA a HQ of 19 was derived, indicating a concern for these endpoints.

3.3.2. Occupational exposure

In the occupationally exposed, a concern for hepatotoxicity based on the concentrations of PFOA was identified, with a HQ of 3.8 (Table 8). The concentration of PFNA was close to being of concern with a HQ of 0.86. The HI was 5.5, resulting in a concern for hepatotoxicity for all congeners combined, with PFOA being the main contributor (69%). For reproductive toxicity, no concern was identified for any congener, although the concentration of PFOA was close to being of concern with a HQ of 0.85. For all congeners combined a concern for reproductive toxicity was identified based on a HI of 1.7 (Table 8). PFOA and PFNA were the main contributors with 49% and 27%, respectively.

For other more sensitive effects, immunotoxicity by PFOS and disrupted mammary gland development by PFOA, very high HQs were obtained, 228 and 1884, respectively (Table 9), indicating concern for these endpoints.

4. Discussion

This is the first attempt to perform a cumulative health risk assessment of PFASs. For this risk assessment, the HI approach was selected. This method is the primary and mostly used regulatory approach for risk assessment of mixtures of toxicologically similar chemicals (Mumtaz, 1995; U.S. EPA, 2000) and has been put forward as a preferred approach when mechanistic information on mixture components is lacking (SCHER, 2011). Therefore, this method can be applied to mixtures of similarly as well as dissimilarly acting compounds (EFSA, 2007) and it has been used for other cumulative assessments of structurally similar substances, such as phthalates (Benson, 2009; Pan et al., 2011; Soeborg et al., 2012), and for structurally dissimilar substances, such as a mixture of anti-androgenic compounds (Kortenkamp and Faust, 2010). The HI method, derived from the toxicological concept of Concentration Addition, assumes additivity of the different mixture components and that they differ only in their relative potency (Backhaus et al., 2010; U.S. EPA, 2000). The HI method was

Table 8
Individual Hazard Quotients (HQs) and Hazard Index (HIs) for hepatotoxicity and reproductive toxicity in occupationally exposed individuals, derived from comparison of the exposure with the reference dose (RfD), and whether there is an associated concern or not.

Congener	Exposure (ng/ml serum)	Hepatotoxicity					Reproductive toxicity				
		RfD (ng/ml serum)	Hazard Quotient[a]	% of HI	Concern?		HI (ng/ml serum)	HQ[a]	% of Hazard Index	Concern?	
					Yes	No				Yes	No
PFBS	5.6	3560	0.002	0.04		√	>4800	<0.0016	<0.09		√
PFHxS	8.6	3560	0.002	0.04		√	>4800	<0.0018	<0.1		√
PFOS	54	323	0.17	3.1		√	392	0.14	8.0		√
PFOSA	<0.040	323	<0.00012	<0.002		√	392	<0.00010	<0.006		√
PFDS	0.035	108	0.00027	0.005		√	131	0.00022	0.013		√
PFBA	2.2	560	0.0039	0.07		√	352	0.0063	0.36		√
PFPeA	0.28	284	0.0015	0.03		√	1256	0.00035	0.02		√
PFHxA	24	284	0.11	2.0		√	1256	0.025	1.5		√
PFHpA	40	284	0.16	2.9		√	1256	0.036	2.1		√
PFOA	1070	284	3.8	69.0	√		1256	0.85	49.3		√
PFNA	326	380	0.86	15.7		√	712	0.46	26.5		√
PFDA	48	127	0.34	6.3		√	237	0.18	10.6		√
PFUnDA	5.6	127	0.036	0.67		√	237	0.019	1.1		√
PFDoDA	<0.03	127	<0.00018	<0.003		√	237	<0.000096	<0.006		√
PFTrDA	<0.15	127	<0.00082	<0.015		√	237	<0.00044	<0.03		√
PFTeDA	<0.04	127	<0.00021	<0.004		√	237	<0.00011	<0.006		√
6:2 FTS	<1.82	323	<0.0066	<0.12		√	392	<0.0054	<0.32		√
HI[b]			5.5		√			1.7		√	

[a] HQ = Exposure/RfD, ratio < 1 = no concern, ratio >1 = concern.
[b] HI = ΣHQs.

Table 9
Individual Hazard Quotients (HQs) for other endpoints in individuals exposed indirectly via the environment and in occupationally exposed individuals, derived from comparison of the exposure with the reference dose (RfD), and whether there is an associated concern or not.

Congener	Effect	Indirect exposure					Occupational exposure				
		Exposure (ng/ml serum)	RfD (ng/ml serum)	HQ[a]	Concern?		Exposure (ng/ml serum)	RfD (ng/ml serum)	HQ[a]	Concern?	
					Yes	No				Yes	No
PFHxS	Hematology	8.6	98	0.08		√	8.6	196	0.04		√
PFOS	Immunotoxicity	27.5	0.12	229	√		54	0.24	228	√	
PFOA	Mammary gland development	5.2	0.28	18	√		1070	0.57	1884	√	

[a] HQ = Exposure/RfD, ratio < 1 = no concern, ratio > 1 = concern.

considered well suited for cumulative risk assessment of the 17 PFASs addressed herein given their structural similarities differing primarily in their chain lengths, i.e. being between 4 and 14 carbons long and containing either a sulfonate or a carboxylate group. Indeed, a few studies on binary mixtures of PFASs in vitro have indicated additivity (Carr et al., 2013; Hu and Hu, 2009). Also, the mode- and mechanism of action for PFASs has yet not been clarified (Lau, 2012a) which further motivates the use of this method.

4.1. Exposure assessment

The exposure assessment showed that the different PFAS congeners were present in the general Swedish population at low ng/ml serum concentrations. These levels are comparable to other western countries, such as the Unites States (Kato et al., 2011; Olsen et al., 2012) and Germany (Schröter-Kermani et al., in press). In one subpopulation that had consumed PFOS-contaminated fish, PFOS was found at higher ng/ml concentrations, in line with the proposal of food, particularly fish, being a major source of exposure to this compound (Haug et al., 2010; Vestergren et al., 2012). The lake was situated in the vicinity of an airport where PFAS-containing AFFFs has been used, illustrating that high unintentional exposures may occur next to point-sources such as airports, PFASs production sites (Emmett et al., 2006), fire-fighting training areas (Weiss et al., 2012) and agriculture run-offs (Hölzer et al., 2008). In general, airports have been identified as point-sources for PFAS in Sweden (Hovgard et al., 2009; Woldegiorgis et al., 2010) as well as in other countries (Awad et al., 2011; De Solla et al., 2012; Moody et al., 2003; Nunes et al., 2011).

PFOS has for long been the dominant PFAS congener in human serum in western countries (Glynn et al., 2012; Haug et al., 2009; Kato et al., 2011), however it now shows a decreasing trend together with PFOA in the Swedish population (Glynn et al., 2012), consistent with observations in other western countries (Haug et al., 2009; Kato et al., 2011; Olsen et al., 2012; Schröter-Kermani et al., in press). This is likely due to the phase-out of PFOS-related production in 2002 by the major manufacturer (3M Company, 2003) and by the ongoing phase-out of PFOA by some manufacturers (U.S. EPA, 2013). In contrast, the concentrations of PFBS, PFHxS, PFNA, PFDA and PFUnDA in serum shows an increase and the latest measurements showed that the concentrations of PFHxS in the city of Uppsala exceeded that of PFOS (Glynn et al., 2012). The increase in PFBS is likely due to that it has been introduced as a replacement chemical for the six- and eight carbon analogs (Ehresman et al., 2007), however the reason for the increase of PFHxS serum levels in Uppsala, different to the trend observed in other western countries (Olsen et al., 2012; Schröter-Kermani et al., in press), is not clearly established, but could be due to the presence of PFHxS in this city's municipal water (Glynn, 2012). The increasing concentrations of the long-chain carboxylates PFNA, PFDA and PFUnDA in the Swedish population, consistent with results from studies in other countries (Haug et al., 2009; Kato et al., 2011) could be due to a shift in use towards perfluorocarboxylates with longer carbon chains or from degradation of long-chain fluorotelomers (Ellis et al., 2004).

In the occupationally exposed professional ski-waxers, the serum concentrations of some PFASs, such as PFOA and PFNA, were significantly higher than in the general population. This is likely due to that perfluorinated carboxylates are constituents of certain gliding waxes (Freberg et al., 2010), for which also a correlation between serum concentrations and the number of working years have been found (Nilsson et al., 2010). This is in agreement with the proposal of inhalation of indoor air being a significant exposure route for e.g. PFOA in occupational settings (Vestergren and Cousins, 2009). In contrast, the serum concentrations of perfluorinated sulfonates were unaffected by the wax exposure indicating other sources of exposure for these congeners (Nilsson et al., 2010).

In the exposure assessment, internal doses (serum/plasma concentrations of PFASs) as opposed to external exposure measurements

were used. The advantage of this approach is that these internal concentrations represent an integrated measure of exposure for the respective PFAS congeners, irrespective of the source, e.g. precursor molecules that can be metabolized to e.g. PFOS and PFOA. Also, using serum concentrations facilitates kinetic extrapolations from animals to humans and exclude the need to use a corresponding AF for kinetic differences. This direct comparison of internal doses can be justified for the majority of the congeners by their long half-lives of PFASs in humans and animals (reviewed in Lau, 2012a) though some, primarily short-chain PFAS, may possess half-lives in the magnitude of hours in laboratory animals.

4.2. Hazard assessment

The hazard assessment showed that the PFAS congeners were relatively similar with regard to their hepatotoxic and reproductive toxic effect levels based on internal doses. The available data also indicated that the potency of the congeners was related to the carbon chain length. Long-chain PFASs, i.e. carboxylates with ≥ 7 perfluorinated carbons and sulfonates with ≥ 6 perfluorinated carbons, were generally more potent than the short-chain PFASs. This is in accordance with previous findings by e.g. Kudo et al. (2000), Kudo and Kawashima (2003), and Kudo et al. (2006) showing that hepatotoxicity is dependent on the hepatic concentration of the congener and not on the structure of the congener itself, and that difference in potency between congeners likely is due, to some extent, to kinetic differences with the short-chain congeners being more rapidly excreted than the long-chain congeners (Lau et al., 2007). Whether this is similar also for reproductive toxicity has not been shown, but it is plausible.

Toxicological data with corresponding internal dose measurements were available for 5 of the 17 congeners for hepatotoxicity and reproductive toxicity; thus data for 12 congeners had to be extrapolated. This was done by a read-across approach from the closest most conservative congener, i.e. the congener with a longer carbon chain. For some congeners (e.g. PFDA) extrapolation from a shorter chain congener was performed which may underestimate its potency, due to the kinetic differences, and was therefore compensated for with an extra AF. Overall, given the structural similarities between the PFAS congeners, we consider this approach fairly robust.

For PFBS, PFHxS, PFOS, PFBA and PFOA, endpoints with lower effect levels than hepatotoxicity and reproductive toxicity were identified. In particular, PFOS and PFOA affected the immune system and mammary gland development at very low doses, with serum concentrations at their respective LOAELs of 92 and 21 ng/ml, which is in the range of or even below current human exposure levels. In fact, a true NOAEL for the effects on mammary gland development has not yet been identified (reviewed in Post et al., 2012). This effect has so far only been reported for PFOA and could thus not be used in a cumulative assessment. Similar studies on other congeners are therefore warranted. Immunotoxicity have been observed for a number of other PFASs in addition to PFOS, e.g. PFOA, PFNA and the PFOS-precursor and insecticide sulfluramide (reviewed in DeWitt et al., 2012; Lau, 2012a). Generally, the immunotoxic effects have been observed at higher doses than those reported herein, thus further research on the effects of PFASs on immune functions at low doses is warranted (Lau, 2012a). Also, exposure of mice to a low dose of PFOA, 0.01 mg/kg bw/day (LOAEL) during gestation has been shown to induce overweight and affect metabolic hormone levels in adult life (Hines et al., 2009; Supplemental Table 4). Although no serum concentrations of PFOA were measured in that study, another similar study (Macon et al., 2011) using the same dose showed serum PFOA concentrations in the offspring between 0.017 and 0.285 ng/ml. Thus, more research also on this effect reflecting possible alterations in developmental metabolic programming is warranted (Lau, 2012a). In addition, exposure of immature female mice to the same dose of PFOA, 0.01 mg/kg bw/day, was shown to produce histopathologic changes in the reproductive tract (Dixon et al., 2012; Supplemental Table 4).

4.3. Risk characterization

The result of the risk characterization showed no concern for hepatotoxicity or reproductive toxicity in individuals exposed indirectly via the environment at current exposure levels, neither for congeners assessed individually nor combined. The serum concentrations can, according to risk assessment principles, be considered well below those that would cause any concern for these endpoints. However, the risk characterization showed that higher PFAS-levels of concern can be reached at sites with high accidental PFASs exposure, in this case in the vicinity of an airport. This scenario is based on eating locally contaminated fish, but could potentially also be valid for scenarios where people are drinking well-water contaminated with PFASs from airports.

For the occupationally exposed professional ski waxers, a cause for concern according to risk assessment principles was obtained for hepatotoxicity based on single and cumulative PFASs exposure and for reproductive toxicity based on cumulative PFASs exposure. Humans appear to be less sensitive than rodents to PFAS-induced hepatotoxicity. PFAS production workers have displayed serum concentrations of PFOS and PFOA of up to 10,000 and 12,700 ng/ml, approximately 200 and 10 times higher than the average population, respectively, without any changes in those biomarkers of hepatotoxicity that were measured (Olsen et al., 2003). However, the hepatotoxicity in rodents may also be viewed upon as biomarker of general PFAS toxicity, since other effects on e.g. lipid metabolism occur at similar dose-levels. Regarding reproductive toxicity, some epidemiological studies on the general population have found associations between e.g. serum concentrations of PFASs and developmental effects such as decreased birth weight (Apelberg et al., 2007; Fei et al., 2007; Washino et al., 2009) whereas other on general and highly exposed populations have not (Grice et al., 2007; Nolan et al., 2009, 2010; Savitz et al., 2012a, b).

Concern for immunotoxicity and disrupted mammary gland development was identified for both individuals exposed via the environment and for the occupationally exposed. Since these effects occur in animals at levels below current human exposure, high HQs were derived. A number of substances, such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), atrazine and nonylphenol have in animal studies been shown to affect mammary gland development (reviewed in Fenton, 2006), though more data are warranted in order to translate these effects in rodents to humans (Fenton et al., 2012). For immunotoxicity, limited epidemiological data are available (DeWitt et al., 2012). Grandjean et al. (2012) reported an association between increasing serum concentrations of PFASs and decreased antibody response following vaccination of children, and Granum et al. (2013) also reported correlations between increasing prenatal exposure to PFHxS, PFOS, PFOA and PFNA and decreased antibody response following vaccination of children.

4.4. Uncertainty analysis

In this assessment, there are some data gaps and uncertainties. The major ones are related to the hazard assessment where the majority of the congeners lacked toxicological data, requiring read-across extrapolations. Hence, the toxicity data may not be fully accurate for all congeners. The hepatotoxic and reproductive toxic effects can, however, be considered fairly well-established effects following PFASs exposure, observed for 10 and 8 of the 17 congeners assessed herein, respectively, and at relatively similar internal serum concentrations. Thus, we consider this read-across approach fairly robust and the most suitable method today to perform a cumulative assessment of PFASs. The other more sensitive effects than hepatotoxicity and reproductive toxicity were only studied for some congeners and could therefore not be reliably extrapolated to other congeners and assessed

cumulatively. The relatively limited amount of data available for these endpoints also adds uncertainty with regard to their effect levels.

In addition, it should be kept in mind that the congeners assessed herein represent only those that have been measured in the Swedish population. Other classes, such as polyfluoroalkyl phosphoric acid esters (PAPs) that are used in food contact materials and that more recently have been discovered in human serum (D'Eon et al., 2009; Lee and Mabury, 2011), are not included. However, assuming that serum PAPs concentrations would be in the same range in the Swedish population as in the U.S., low ng/ml to low pg/ml (Lee and Mabury, 2011), they would not significantly affect the overall outcome of this assessment.

The human relevance of the endpoints investigated herein is not clearly established; in particular as the mode and mechanisms of action for PFAS remain unclear. PFASs are known to activate certain nuclear receptors, in particular PPARα (Vanden Heuvel et al., 2006; Wolf et al., 2008b, 2012), a regulator of lipid metabolism (Berger and Moller, 2002) that, when activated, induce peroxisome proliferation leading to hepatocellular hypertrophy and increased liver weight (Holden and Tugwood, 1999) in e.g. rodents (Maronpot et al., 2010) and monkeys (Hoivik et al., 2004). The human PPARα receptor is expressed to a lower extent than in rodents and appears to be less sensitive to the effects of PFASs (Albrecht et al., 2013; reviewed in Klaunig et al., 2003; Wolf et al., 2008b, 2012). However, although PFASs bind PPARα and induce effects similar to peroxisome proliferators, PFOS and PFOA have been shown to cause hepatotoxicity also via PPARα-independent mechanisms (Rosen et al., 2010; Wolf et al., 2008a; Yang et al., 2002). Further, PFOS have been shown to induce hepatic effects in rodents and non-human primates without affecting markers for peroxisome proliferation (reviewed in Lau et al., 2007) suggesting involvement of other mechanisms of action. Reproductive/developmental toxicity studies with PFOA in mice have shown that some effects (complete litter loss and liver weight increase in dams and pups) seem independent of PPARα expression (Abbott et al., 2007) whereas other effects, such as increased postnatal pup mortality, reduction in pup body weight and postnatal growth and development (delayed eye opening), indicate interference/contribution of PPARα, though also other mechanisms may contribute (Abbott et al., 2007). For PFNA, however, postnatal pup mortality, reduced pup body weight and postnatal growth and development (delayed eye opening) in mice indicate interference/contribution of PPARα (Wolf et al., 2010). In contrast, the neonatal mortality in mice following in utero exposure to PFOS was shown to be independent of PPARα (Abbott et al., 2009), indicating that PFOS acts via non-PPARα-related mechanisms in this regard. Indeed, PFASs have been shown to activate multiple receptors other than PPARα, such as PPAR β and γ as well as the xenoreceptors constitutive androstane receptor (CAR) and the pregnane X-receptor (PXR) (Bjork et al., 2011; Elcombe et al., 2010, 2012), adding more complexity into the mechanisms of action of PFAS. Human and mouse PXR and CAR have been shown to respond similarly with regard to hepatocellular hypertrophy and increased liver weight following exposure to e.g. phenobarbital and chlordane (Ross et al., 2010), and it cannot be excluded that the response could be similar also for PFASs. In addition, other mechanisms of action of PFASs have been proposed, such as oxidative stress, effects on other cell-signaling pathways, epigenetic changes, interference with cell communication and alterations in mitochondrial bioenergetics (reviewed in Lau, 2012a, b). Thus, since the mechanism of action of PFASs has not yet been clarified, and there has not been evidence presented that would rule out these effects from occurring in humans, it is reasonable to consider the endpoints assessed herein to be of human relevance.

Overall, this assessment should be looked upon as conservative. Based on the limited sample sizes in the exposure data, the upper range of PFAS concentrations in human serum were used. Thus, the risk estimate based on these exposure levels might be slightly overestimated. In addition, the HI method, which is a relatively simple method to apply, is also likely to overestimate the risk and is therefore useful primarily in lower tier assessments (Boobis, 2009; Meek et al., 2011). However, we consider it applicable and the most suitable approach for assessing PFASs. As opposed to the PODI, MOE_T, TUS and RPF/TEF approaches, the advantage of the HI method is that it takes into account uncertainties of the data for every individual component in the form of AFs. In this case, it allowed the use of read-across extrapolations that could be compensated for by assessment factors. The RPF/TEF concepts are recommended to be used when the mechanism of actions is known (U.S. EPA, 1989), and the TEF approach has been suggested to be avoided for PFASs due to their unknown mechanism of action and possible species differences in response (Peters and Gonzalez, 2011).

5. Conclusion

In conclusion, this first attempt of a cumulative health risk assessment of a large number of PFASs present in the Swedish population showed no concern for hepatotoxicity and reproductive toxicity in the general population, but that high local exposures may be of concern. For the occupationally exposed a need to reduce the exposure was identified. In addition, a concern for other effects such as immunotoxicity and effects on mammary gland development was identified for PFOS and PFOA. A need of additional toxicological data for many PFAS congeners with respect to hepatotoxicity and reproductive toxicity as well as for other toxic effects was recognized.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2013.05.009.

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