Neurotoxic Effects of Perfluoroalkylated Compounds: Mechanisms of Action and Environmental Relevance

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Abstract Perfluoroalkylated compounds (PFCs) are used in fire-fighting foams, treatment of clothes, carpets and leather products, and as lubricants, pesticides, in paints and medicine. Recent developments in chemical analysis have revealed that fluorinated compounds have become ubiquitously spread are regarded as potential threats to the environment. Due to the carbon-fluorine bond, which has a very high bond strength, these chemicals are extremely persistent towards degradation and some PFCs have a potential for bioaccumulation in organisms. Of particular concern has been the developmental toxicity of PFOS and PFOA, which has been manifested in rodent studies as high mortality of prenatally exposed newborn rats and mice within 24 hours after delivery. The nervous system appears to be one of the most sensitive targets of environmental contaminants. The serious developmental effects of PFCs have lead to the upcoming of studies that have investigated neurotoxic effects of these substances. In this review the major findings of the neurotoxicity of the main PFCs and their suggested mechanisms of action are presented. The neurotoxic effects are discussed in light of other toxic effects of PFCs to indicate the significance of PFCs as neurotoxicants. The main findings are that PFCs may induce neurobehavioral effects, particularly in developmentally exposed animals. The effects are, however, subtle and inconclusive and are often induced at concentrations where other toxic effects also are expected. Mechanistic studies have shown that PFCs may affect the thyroid system, influence the calcium homeostasis, protein kinase C, synaptic plasticity and cellular differentiation. Compared to other environmental toxicants the human blood levels of PFCs are high and of particular concern is that susceptible groups may be exposed to a cocktail of substances that in combination reach harmful concentrations.

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Introduction

Environmental contaminants have been of major concerns since the discovery of their presence in environmental samples in the late 1960s. Since then, measures have been taken to reduce spread of man-made chemicals and there has been an increased awareness of emerging contaminants. Perfluoroalkylated compounds (PFCs), such as perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA), have the last decade received particular attention as emerging environmental pollutants. Large volumes of fluorinated organic compounds are used as surfactants in fire-fighting foams, treatment of paper, clothes, carpets and leather products. In addition, they are used as lubricants, pesticides, paints and as surfactants in pharmaceutical pills. PFCs, such as perfluorinated cyclic alkylamines, are even used as blood substitutes (Golovanov and Tsygankova, 2001; Kissa, 2001; Lowe 1999). Several of the PFCs have been used for over 50 years, and the presence of fluorine in human blood was reported as early as 1968 (Traves, 1968). Only recently this group of substances has been regarded as a potential threat to the environment. Due to the carbon-fluorine bond, which has a very high bond strength, these chemicals are extremely persistent towards degradation. Recent developments in chemical analysis, especially in LC-MS techniques, have revealed that several fluorinated compounds have become ubiquitously spread in the environment (Lau et al., 2007). It has also been discovered that some PFCs has a potential for bioaccumulation in organisms (Conder et al., 2008; Haukås et al., 2007; Martin et al., 2004), which has raised concerns about their harmful effects. Considerable amounts of PFOS and PFOA have been detected in animals from the Arctic, such as in polar bears, birds and marine mammals (Bossi et al., 2005; Haukås et al., 2007; Smithwick et al., 2005ab; Verreault et al, 2005). The major manufacturer of PFC derivates, 3M, has ceased their production of PFOS and

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PFOA and replaced these with shorter chain PFCs (Lehmler, 2005; Renner, 2001). These are less subjected to bioaccumulation (Renner, 2001), since bioaccumulation of PFCs is a function of carbon length (Conder et al., 2008). In industrial countries, such as in Europe, North-America and Japan, the levels of PFCs in biota and human samples are now slowly decreasing making the general population in these areas less susceptible to potential harmful exposure (e.g. Donaldson et al., 2010; Hardell et al., 2010; Hart et al., 2008; Haug et al., 2009; Kato et al., 2011; Olsen et al., 2005; Sundström et al., 2011; Zushi et al., 2010). Similar trends are also observed for other pollutants, such as the polychlorinated biphenyls (PCBs) and the brominated flame retardants (BFRs). In certain developing countries, however, the situation is more complex and use of different hazardous pollutants are extensive, probably due to increased industrialization, less control on use and waste handling of the industrial chemicals, and of economical matters (e.g. Athanasiadou et al., 2008; Carvalho 2006; Minh et al., 2006; Suk et al., 2003; Weber et a., 2011; Zamir et al., 2008).

Of particular concern has been the developmental toxicity of PFOS and PFOA, which has been manifested in rodent studies as high mortality of prenatally exposed newborn rats and mice within 24 hours after delivery. In a study by Lau et al (2003) pregnant Sprague-Dawley rats and CD-1 mice were given 1-20 mg/kg PFOS/day from gestational day (GD) 2 to GD 20 and GD 1 to GD 17 respectively. At high doses (10 mg/kg/day) an increase was observed in the prevalence of birth defects, such as cleft palate, anasarca, ventricular septal defects and enlargement of the right atrium. The neonates showed a reduction in both free and bound serum thyroxine(T4) (all groups) and experienced a delay in eye opening (2 mg/kg/day). Even more concerning was the observation that 50% of the newborn rats and mice died within 24 hours when prenatally exposed to 3 and 10 mg/kg/day respectively. In

another study by Luebker et al. (2005a) it was shown that maternal exposure to 1.6 mg PFOS/kg/day during pregnancy is a critical dose leading to approximately 50% mortality among prenatally exposed rat pups within 4 days after delivery. Similar developmental effects have been observed in rodents after exposure to PFOA and N-ethyl perfluorooctane sulfonamidoethanol (N-EtFOSE), but not with perfluorobutane sulfonate (PFBS) and perfluorohexane sulfonate (PFHxS) (Lau et al., 2004 and references therein).

The serious developmental effects of PFCs have initiated research on the neurotoxic effects of these substances. The nervous system appears to be one of the most sensitive targets of environmental contaminants, which have been suspected as possible causative agents for an increased prevalence of attention deficit hyperactivity disorder (ADHD) and susceptibility of dementia disorders, such as Parkinson's disease (e.g. Barkley, 1998; Brown et al., 2005; Hardell et al., 2002; Hoffman et al., 2010; Lai et al. 2002; Rice 2000; Schettler, 2001). In addition, it has been hypothesized that environmental contaminants can affect cognitive functions, such as learning and behavior, and motor skills (For reviews e.g. Grandjean and Landrian, 2006; Mariussen and Fonnum, 2006). Exposure to harmful agents during the early development is regarded as a particular critical period, since some substances are shown to mimic hormones, such as the thyroid hormones (TH), which are essential for nervous development (e.g. Porterfield, 1994). In this review, the major findings of the neurotoxicity of the main PFCs and their suggested mechanisms of action are summarized. First, a short overview of the main groups of PFCs is presented, followed by an overview of the levels of PFCs found in brain tissues from human and wild-life compared with the levels found in the blood and the liver. The environmental levels of PFCs are then compared with uptake characteristics in

animals exposed in the laboratory in order to enlighten differences to real-life exposure. Then, the reported neurotoxic effects, including neurobehavioral effects, neurochemical and neuroendocrine targets of different PFCs will be presented. In the last section the significance of PFCs as neurotoxcants is discussed in light of other potential harmful effects that are reported, in addition to future needs for additional research. For a general overview of the toxicology of PFC, the reviews by Lau et al., (2004, 2007) and Kennedy et al., (2004) are recommended.

Perfluoroalkylated compounds (PFCs)

The most environmentally relevant PFCs can be divided in three major groups (de Voogt, 2006; Lehmler, 2005), which include the perfluoroalkyl sulfonates and sulfonamides; the perfluorinated carboxylic acids; and the fluorotelomer alcohols and fluorotelomer sulfonates (Fig 1)). The perfluoroalkyl sulfonates and sulfonamides, and the perfluorinated carboxylic acids are fully fluorinated in the hydrophobic tail, whereas the fluorotelomers contain non-fluorinated sites, typically methylene groups, near the head group. It is primarily the area tied to the head group that is subjected to degradation in the environment. It has for example been shown that the fluorotelomers can be metabolized into carboxylic acids (Fasano et al., 2006; Hagen et al., 1981; Kudo et al., 2005; Martin et al., 2005). The perfluoroalkyl sulfonates and sulfonamides include the perfluorooctane sulfonic acids (PFOS) salts and sulfonamide derivates of PFOS, such as perfluorooctane sulfonamide (PFOSA) and the alkylated perfluorooctane sulfonamidoethanol (PFOSE). The PFOS derivates are prepared by electrochemical fluorination of octansulfonyl fluoride and are used as fire fighting foams, pesticides and as surface coatings in textiles and paper products (Kissa, 2001; Lehmler, 2005). The major perfluorinated carboxylic acid is perfluoroctanoic acid

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(PFOA), which is used in the aid of manufacturing polytetrafluoroethylene (PTFE) and polyvinylidine fluoride (Lehmler, 2005). PFOA is also used as a fire extinguisher agent, as an insulator and as a surfactant in textiles (Kissa, 2001). The PFCs is a diverse group of chemicals and for additional readings about use, manufacture and structural features of PFCs see e.g. Kissa, (2001) and Lehmler (2005).

Uptake and accumulation of PFCs in the brain

The PFCs differ from other halogenated environmental pollutants, such as the PCBs and BFRs, in that they primarily accumulate in protein rich tissues, such as in the liver and blood. Blood analyses of PFOS, PFOA, PFHxS and PFNA, show concentrations that are higher than for the PCBs and dichlorodiphenyltrichloroethane (DDT), even in background areas (Hopf et al., 2009; Kannan et a., 2004; Weschler, 2009; White et al., 2011). The background levels in serum of sum PCBs in US citizens are less than 5 ng/ml (Hopf et al., 2009; Weschler et al., 2009). In occupationally exposed workers it has been found blood levels of approximately 300 ng/ml and 2000 ng/ml of PFOS and PFOA respectively (Ehresman et al., 2007). It is not the scope of this review to present a detailed overview of levels and trends of PFCs, which recently have been presented by Butt et al., (2010) and Lau et al., (2007). It is, however, of interest to compare the brain levels of the contaminants with the level found in other tissues in order to evaluate compound specific organ partitions and discover potential vulnerable groups.

Usually, the blood and liver are analyzed for PFCs, and only few studies have analyzed on brain tissue. An overview of the levels found in brain tissue, compared with serum and liver levels is presented in Table 1. The dominating compound found in the environment as well as in brain tissue is PFOS, which probably reflects both its

historical use, persistence to environmental degradation and ability to biomagnify (e.g. Lau et al., 2007). The level of PFOS is a factor of 10 to 100 higher than the sum of the other PFCs that have been identified in brain tissue. The levels of PFCs in human wildlife are clearly regional specific with the highest concentrations found in marine animals near industrialized areas (ref Table 1, van de Vijver, et al., 2007; Verrault, et al., 2005). Only one study has analyzed human brain tissue finding 1.3 and 0.5 ng/g wet weight of PFOS and PFOA in brain respectively, 5.1 and 3.0 ng/g in blood and 13.6 and 3.1 ng/g in the liver (Maestri et al., 2006). These concentrations of PFOS and PFOA are similar to what is found in brains of different wild-life species as shown in Table 1. The levels in brain are, in general, lower than in liver tissue and serum, indicating that most PFCs have limited access to cross the blood brain barrier (BBB). One study, performed by Harada et al., (2007), analyzed PFOS and PFOA in human cerebrospinal fluid (CSF), blood and bile to compare the partition characteristics between the different compartments. The median serum level was 18.4 and 2.6 ng/ml wet weight of PFOS and PFOA, respectively. The median levels in CSF were 0.06 and 0.1 ng/ml of PFOS and PFOA indicating that only a small portion of the analyzed PFCs pass the BBB. Some exceptions from this rule are apparent, indicating that PFUnDA, PFDoDA, PFDoDA, PFTriDA and PFOSA have similar partitions between the tissues (Table 1).

Several studies have evaluated tissue distribution of PFCs in animals after *in vivo* exposure (Table 2). Austin et al., (2003) exposed rats intraperitoneally with 1 or 10 mg PFOS/kg body weight daily for 14 days, which corresponds to cumulative doses of 14 and 140 mg/kg body weight respectively. Accumulated levels in the brains were approximately 300 and 6000 ng/g wet weight respectively.

Table 1) Levels of PFCs in brain, serum/blood and liver from environmental samples.

Species	Compound	Location	Year of collection	Brain levels (ng/g w.w.)	Serum levels (ng/ml)	Liver levels (ng/g w.w.)	References
Harbor seal	PFOS	German Bight	2007	99 ± 49	349 ± 370	1017 ± 536	Ahrens et al. (2009)
Pelicans	PFOS	Cartagena Bay, Colombia	2004	3.5		36.7	Oliveiro-Verbel et al (2006)
Red-throated divers	PFOS	German Baltic Sea	2004	40 ± 12	73 ± 26	182 ± 62	Rubarth et al. (2011)
Harbor seal	PFOA	German Bight	2007	0.06 ± 0.1	0.62 ± 0.58	0.70 ± 0.59	Ahrens et al. (2009)
Red-throated divers	PFOA	German Baltic Sea	2004	0.4 ± 0.2	1.0	1.0 ± 0.3	Rubarth et al. (2011)
Pelicans	PFOSA	Cartagena Bay, Colombia	2004	1.3		<1	Oliveiro-Verbel et al (2006)
Red-throated divers	PFOSA	German Baltic Sea	2004	12 ± 7.4	21 ± 17	18 ± 3.8	Rubarth et al. (2011)
Harbor seal	PFOSA	German Bight	2007	0.14 ± 0.14	5.06 ± 1.23	1.55 ± 0.69	Ahrens et al. (2009)
Red-throated divers	PFHxS*	German Baltic Sea	2004	1.0 ± 0.4	4.4 ± 2.5	2.7 ± 0.7	Rubarth et al. (2011)
Harbor seal	PFHxS	German Bight	2007	1.58 ± 1.0	3.16 ± 1.08	6.9 ± 4.03	Ahrens et al. (2009)
Red-throated divers	PFHpS	German Baltic Sea	2004	0.4 ± 0.2	0.8	1.7	Rubarth et al. (2011)
Harbor seal	PFHpS	German Bight	2007	0.66 ± 0.45	0.66 ± 0.66	2.27 ± 2,29	Ahrens et al. (2009)
Red-throated divers	PFDS	German Baltic Sea	2004	0.5 ± 0.1	0.2	0.4	Rubarth et al. (2011)
Harbor seal	PFDS	German Bight	2007	0.04 ± 0.08	0.12 ± 0.13	0.53 ± 0.38	Ahrens et al. (2009)
Red-throated divers	PFNA	German Baltic Sea	2004	0.8 ± 0.3	2.0 ± 0.7	3.5 ± 1.3	Rubarth et al. (2011)
Harbor seal	PFNA	German Bight	2007	1.2 ± 0.5	3.93 ± 2.08	15.3 ± 5.75	Ahrens et al. (2009)
Red-throated divers	PFDA	German Baltic Sea	2004	0.4 ± 0.4	0.4 ± 0.08	1.0 ± 0.5	Rubarth et al. (2011)
Harbor seal	PFDA	German Bight	2007	1.55 ± 0.47	4.38 ± 2.35	15.2 ± 4.49	Ahrens et al. (2009)

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Table 1) Levels of PFCs in brain, serum/blood and liver from environmental samples (continues)

Species	Compound	Location	Year of collection	Brain levels (ng/g w.w.)	Serum levels (ng/ml)	Liver levels (ng/g w.w.)	References
Harbor seal	PFUnDA	German Bight	2007	1.06 ± 0.16	1.71 ± 0.84	5.26 ± 1.59	Ahrens et al. (2009)
Red-throated divers	PFDoDA	German Baltic Sea	2004	3.2 ± 1.4	1.1 ± 0.3	1.7 ± 0.7	Rubarth et al. (2011)
Harbor seal	PFDoDA	German Bight	2007	0.51 ± 0.36	0.47 ± 0.24	1.47 ± 0.49	Ahrens et al. (2009)
Red-throated divers	PFTriDA	German Baltic Sea	2004	8.6 ± 3.4	1.8 ± 0.4	3.1 ± 1.0	Rubarth et al. (2011)
Harbor seal	PFTriDA	German Bight	2007	0.73 ± 0.55	0.76 ± 0.34	1.53 ± 0.55	Ahrens et al. (2009)
Harbor seal	PFTeDA	German Bight	2007	0.1 ± 0.12	0.08 ± 0.06	0.22 ± 0.16	Ahrens et al. (2009)
Human tissue	PFOS	Italy		1.3	5.1	13.6	Maestri et al. (2006)
Human tissue	PFOA	Italy		0.5	3.0	3.1	Maestri et al. (2006)

*PFHxS = perfluorohexane sulfonate; PFHpS = Perfluoroheptane sulfonate; PFDS = perfluoro-1-decanesulfonate; PFNA = Perfluorononanoic acid; PFDA = perfluorodecanoic acid; PFUnDA = perfluoroundecanoic acid; PFDoDA = perfluorododecanoic acid; PFTriDA = perfluorotridecanoic acid; PFTeDA = perfluorotetradecanoic acid

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An interesting observation was the proportional higher levels of PFOS in the brains of the high dose group. The serum to brain, and liver to brain proportion were approximately 36 and 92, respectively, in the low dose group and 8 and 17 in the high dose group. Similar observations have been reported by Chang et al., (2009) and Cui et al., (2009). The higher concentrations in the brains of the high dose groups may indicate an increase in the permeability of the BBB to the compound. A recent study by Wang et al., (2011) may strengthen this view; it was showed that PFOS at relatively high concentrations *in vitro* induces disassembly of endothelial tight junctions, via the phosphatidylinositol-3 kinase/Akt-pathway, increasing the permeability of PFOS. Several studies have, however, shown that PFCs are accumulated in highest concentrations in the liver, indicating a preferential accumulation in this organ, which may be due to high affinity to proteins (Jones et al., 2003; Luebker et al., 2002; Vanden Heuvel, 1992; Ylinen and Auriola, 1990; Ylinen et al., 1989). The higher concentration in the brains of the high dose groups may therefore indicate a saturation kinetic of which a larger portion of the PFCs are available for uptake in the brain with increasing exposure concentrations. Only one study have compared concentrations of PFCs between the adult and juvenile brain showing a higher relative concentration of PFOS in brain of the rat fetuses compared with the brains from the dams and juveniles with a factor of approximately 10 (Chang et al., 2009; Table 2). The concentrations in serum and livers differed less between the groups indicating that the BBB of the fetus has increased permeability of PFOS. Only a couple of studies have compared uptake kinetics in brain between different PFCs. The studies by Cui et al (2009) and Onishchenko et al., (2011) showed that PFOS is accumulated in rat and mice brain in higher concentrations than PFOA (Table 2), which probably is due to a higher elimination rate of PFOA.

Neurobehavioral effects of PFCs

Most studies have been performed with PFOS and PFOA on rats and mice, which indicate that the most pronounced effect, are delays on neuromotor development on prenatally exposed animals. Animals exposed as adults appear less sensitive (Table 3). In an early and much refereed carcinogenicity study by Siblinski et al., (1983), female and male rats were exposed to 30 and 300 ppm PFOA in the diet for two years. These figures corresponded to daily doses of 1.5 and 15 mg/kg/day respectively. Among the tested female rats it was observed a dose related increase in ataxia (3.1, 18 and 23% respectively), which is characterized by loss of coordination. The effect was primarily observed among the moribund rats and not observed in the male rats even though it has been shown that female rats excrete PFOA, PFNA and PFDA faster than the males (Butenhoff et al., 2004a; Ohmori et al., 2003; Tatum-Gibbs et al., 2011; Vanden Heuvel et al., 1991ab) and therefore probably had a higher body burden. As discussed by Butenhoff et al., (2005) similar symptoms have not been reported in other studies with PFOA, even at higher doses (Butenhoff et al, 2005 and references therein), and the observed ataxia was therefore probably not treatment related.

One study measured functional observational battery (FOB) parameters (for detection of functional deficits) and motor activity of adult rats exposed to perfluorohexane sulfonate (PFHxS) (0.3, 1, 3 and 10 mg/kg/day for 40-50 days) and did not report any effects (Butenhoff et al., 2009a). Butenhoff et al., (2011) exposed adult rats to ammonium perfluorobutyrate (PFBA) for 28 and 90 days (Table 3) finding no effects on hearing, static rightning, grip strenght or motor activity. A delayed bilateral pupillary reflex in the 150 mg/kg group was observed. In the same study adult rats were exposed to 30 mg/kg/day for 28 days finding, according to the

authors, a slight, but not significant, decrease in motor activity as measured in FOB. In a e study by Lau et al., (2003) developmentally exposed rats (3 mg PFOS/kg/day from GD)2 to 21) were tested at postnatal day (PND) 21 in the T-maze, which is used to study spatial learning and memory. They tested on both female and male rats finding no differences in the performance between PFOS exposed pups and the controls. Similar were observed by Luebker et al (2005b) who tested maternally exposed rat pups at PND 24 for learning,

Table 2) Concentrations of PFCs in brain, liver and serum in laboratory exposed animals.

Species	Compound	Dose and exposure	Cumulative dose	Brain levels (µg/g w.w.)	Serum levels (µg/ml)	Liver levels (µg/g w.w.)	References
Spraque Dawley rats (female)	K^+PFOS	Intraperitoneally exposure to 1 mg/kg BW for 14 days	14 mg/kg BW	0.29	10.5	26.6	Austin et al. (2003)
Spraque Dawley rats (female)	K^+PFOS	Intraperitoneally exposure to 10 mg/kg BW for 14 days	140 mg/kg BW	5.7	45.5	97.4	Austin et al. 2003
Wistar rats (male)	Na^+PFOA	Intravenous exposure to 0.041 mg/kg BW	0.041 mg/kg BW	0.003 ± 0.001	0.25 ± 0.02	0.56 ± 0.09	Kudo et al. (2007)
Wistar rats (male)	Na^+PFOA	Intravenous exposure to 16.56 mg/kg BW	16.56 mg/kg BW	1.38 ± 0.7	105 ± 4.2	87 ± 12	Kudo et al. (2007)
Spraque Dawley rats (male)	PFOA	Peroral exposure to 5 and 20 mg/kg/day for 28 days	140 and 560 mg/kg BW	10.5 ± 9.8; 7.2 ± 6.03	39.2 ± 14.4; 58.8 ± 17.6	218 ± 21; 196 ± 10	Cui et al. (2009)
Spraque Dawley rats (male)	K^+PFOS	Peroral exposure to 5 and 20 mg/kg/day for 28 days	140 and 560 mg/kg BW	13.6 ± 1.0; 146 ± 34	72 ± 25.7; n.a	345 ± 40; 648 ± 17	Cui et al. (2009)
Spraque Dawley rats (dams, GD20)	K^+PFOS	Peroral exposure to 0.1, 0.3 and 1.0 mg/kg GD 0 to GD 20	Maternal dose: 2.0 mg/kg; 4.0 mg/kg; 20 mg/kg	0.15 ± 0.01; 0.37 ± 0.04; 1.0 ± 0.08	1.7 ± 0.07; 6.2 ± 0.9; 26.6 ± 3.9	8.3 ± 0.3; 21.7 ± 0.7; 48.9 ± 72.7	Chang et al. (2009)
Spraque Dawley rats (fetus, GD20)	K^+PFOS	Maternal peroral exposure to 0.1, 0.3 and 1.0 mg/kg GD 0 to GD 20	Maternal dose: 2.0 mg/kg; 4.0 mg/kg; 20 mg/kg	1.2 ± 0.07; 3.1 ± 0.2; 13.0 ± 1.1	3.9 ± 0.001; 10.4 ± 0.3; 31.4 ± 1.0	3.2 ± 0.2; 5.8 ± 0.2; 20 ± 2.0	Chang et al. (2009)
Spraque Dawley rats (male pups, PND21)	K^+PFOS	Maternal peroral exposure to 0.1, 0.3 and 1.0 mg/kg GD 0 to PND 21	Maternal dose: 4.2 mg/kg; 8.4 mg/kg; 42 mg/kg	0.22 ± 0.01; 0.65 ± 0.05; 2.6 ± 0.2	1.7 ± 0.08; 5.0 ± 0.1; 18.6 ± 1.0	5.9 ± 0.6; 14.8 ± 0.8; 44.9 ± 2.6	Chang et al. (2009)
Spraque Dawley rats (female pups PND21)	K^+PFOS	Maternal peroral exposure to 0.1, 0.3 and 1.0 mg/kg GD 0 to PND 21	Maternal dose: 4.2 mg/kg; 8.4 mg/kg; 42 mg/kg	0.23 ± 0.01; 0.74 ± 0.04; 2.7 ± 0.2	1.8 ± 0.08; 5.2 ± 0.1; 18.0 ± 0.7	5.2 ± 0.2; 13.6 ± 0.3; 41.2 ± 2.3	Chang et al. (2009)

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Table 2) Concentrations of PFCs in brain, liver and serum in laboratory exposed animals (*continues*)

Species	Compound	Dose and exposure	Cumulative dose	Brain levels (µg/g w.w.)	Serum levels (µg/ml)	Liver levels (µg/g w.w.)	References
Adult male Spraque Dawley rats	*n*-PFOS	Peroral exposure to 0.27 mg/kg	0.27 mg/kg	0.037	0.3	4.2	Benskin et al. (2009)
Adult male Spraque Dawley rats	*n*-PFHxS	Peroral exposure to 30 µg/kg	30 µg/kg	0.0004	0.1	0.0017	Benskin et al. (2009)
Adult male Spraque Dawley rats	PFNA	Peroral exposure to 0.39 mg/kg	0.39 mg/kg	0.02	0.92	5.0	Benskin et al. (2009)
Adult male Spraque Dawley rats	*n*-PFOA	Peroral exposure to 0.4 mg/kg	0.4 mg/kg	0.03	1.17	2.82	Benskin et al. (2009)
KM mice (female)	PFOS	One subcutaneous injection at PND 7, 14, 21, 28 and 38	50 mg/kg	50 (PND 7), 45, 45, 20, 30 (PND 35)	90 (PND 7), 95, 80, 80, 95 (PND 35)	200 (PND 7), 29 400, 420, 500 (PND 35)	Liu et al. (2009)
KM mice (female)	PFOS	One subcutaneous injection at PND 7, 14, 21, 28 and 38	50 mg/kg	45 (PND 7), 40, 40, 40, 20 (PND 35)	80 (PND 7), 95, 90, 95, 90 (PND 35)	210 (PND 7), 28 420, 400, 520 (PND 35)	Liu et al. (2009)
CD-1 mice	PFOA	Maternal peroral exposure to 0.3, 1.0 and 3.0 mg/kg GD 1 to GD 17	Maternal dose: 5.1 mg/kg; 17 mg/kg; 51 mg/kg	PND 7 female: 150 ± 26; 479 ± 41; 1594 ± 162	PND 7 female: 4980 ± 218; 11026 ± 915; 207000 ± 3900	PND 7 female 2078 ± 90; 8134 ± 740; 16700 ± 749	Macon et al. (2011)
CD-1 mice	PFOA	Maternal peroral exposure to 0.3, 1.0 and 3.0 mg/kg GD 1 to GD 17	Maternal dose: 5.1 mg/kg; 17 mg/kg; 51 mg/kg	PND 84 female: < lOQ	PND 84 female: 16 ±5; 71 ± 8; 125	PND 84 female: 43 ± 12; 55 ± 12; 235 ± 79	Macon et al. (2011)
CD-1 mice	PFOA	Maternal peroral exposure to 0.3, 1.0 and 3.0 mg/kg GD 1 to GD 17	Maternal dose: 5.1 mg/kg; 17 mg/kg; 51 mg/kg	PND 7 male: 188 ± 48; 412; 1256 ± 305	PND 7 male: 5940; 11600; 27050 ± 1550	PND 7 male: 2600 ± 490; 6490; 17450 ± 450	Macon et al. (2011)

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Table 2) Concentrations of PFCs in brain, liver and serum in laboratory exposed animals (*continues*)

Species	Compound	Dose and exposure	Cumulative dose	Brain levels (µg/g w.w.)	Serum levels (µg/ml)	Liver levels (µg/g w.w.)	References
CD-1 mice	PFOA	Maternal peroral exposure to 0.3, 1.0 and 3.0 mg/kg GD 1 to GD 17	Maternal dose: 5.1 mg/kg; 17 mg/kg; 51 mg/kg	PND 84 male: < lOQ	PND 84 male: 39; 29; nd	PND 84 male: 83; 172 ± 97; 421 ± 29	Macon et al. (2011)
C57BL/6/Bkl mice (neonatal pups)	K^+PFOS	Exposure by food to 0.3 mg/kg GD1 to GD21	Maternal dose: 6 mg/kg	3.1 ± 0.3		11.8 ± 1.5	Onishchenko et al. (2011)
C57BL/6/Bkl mice (neonatal pups)	PFOA	Exposure by food to 0.3 mg/kg GD 1 to GD 21	Maternal dose: 6 mg/kg	0.7 ± 0.1		16.3 ± 4.1	Onishchenko et al. (2011)
Spraque Dawley rats (neonatal pups)	K^+PFOS	Maternal peroral exposure to 0.1, 0.6 and 2.0 mg/kg/day GD 2 to GD 21	Maternal dose: 1.9 mg/kg; 11.4 mg/kg; 38 mg/kg	PND 0: 0.4 ± 0.1; 5.2 ± 1.6; 13.4 ± 3.9	PND 0: 1.5 ± 0.4; 24.6 ± 3.0; 45.7 ± 4.8		Zeng et al. (2011)
Spraque Dawley rats (neonatal pups)	K^+PFOS	Maternal peroral exposure to 0.1, 0.6 and 2.0 mg/kg/day GD 2 to GD 21	Maternal dose: 1.9 mg/kg; 11.4 mg/kg; 38 mg/kg	PND 21: 0.06 ± 0.04; 1.0 ± 0.6; 3.7 ± 1.0	PND 21: 0.4 ± 0.1; 1.9 ± 0.4; 4.3 ± 1.7		Zeng et al. (2011)

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Table 3) Summary of neurobehavioral studies of PFCs

Species	Compound	Dose and exposure	Effects	References
Neonatal Sprague-Dawley rats	K^+PFOS	Maternal oral exposure to 3 mg/kg, from GD 2 to GD 21	No effect in the T-maze delayed alternation test at PND 21	Lau et al. (2003)
Neonatal NMRI male mice	K^+PFOS	Single oral exposure to 0.75 and 11.3 mg/kg at PND 10	Effects on spontaneous behavior (locomotion, rearing and total activity) and habituation (lack of habituation) in 2- and 4 month old mice in the high dose group. No effects on the elevated plus maze	Johansson et al. (2008)
Neonatal NMRI male mice	PFOA	Single oral exposure to 0.58 and 8.7 mg/kg at PND 10	Effects on spontaneous behavior (locomotion, rearing and total activity) and habituation (lack of habituation) in 2- and 4 month old mice in all the groups. No effects on the elevated plus maze	Johansson et al. (2008)
Neonatal NMRI male mice	PFDA	Single oral exposure to 0.72 and 10.8 mg/kg at PND 10	No behavioral effects observed	Johansson et al. (2008)
Neonatal Crl:CD (SD) rats	K^+PFOS	Maternal oral exposure to 0.1, 0.3 and 1.0 mg/kg, from GD 0 to PND 20	Male offspring from 1.0 mg/kg group, displayed increased motor activity and reduced habituation at PND 17, but not on PND 13, 21 and 61	Butenhoff et al. (2009b)
Adult CDI male mice	K^+PFOS	Exposure by gavage to 3 and 6 mg/kg/day for four weeks	Small, but not dose-related, effects on activity in open-field tests and on retention tests	Fuentes et al. (2007a)
Offspring of exposed CDI-mice	K^+PFOS	Maternal oral exposure to 6 mg/kg/day GD 12 to 18. Half of the exposed animals were attributed to restraint stress	Three months after birth, the group prenatally exposed to PFOS showed delayed neuromotor maturation and the males showed decrease in numbers of falls in the rotarod. Restrain stress appeared to counteract the effects of PFOS	Fuentes et al. (2007b)
Offspring of exposed CDI-mice	K^+PFOS	Maternal oral exposure to 6 mg/kg/day GD 12 to 18. Half of the exposed animals were attributed to restraint stress	Three months after birth, the group prenatally exposed to PFOS and restraint stress showed reduced mobility in the open-field test and female offspring travelled longer distances than control mice in the water maze during acquisition	Fuentes et al. (2007c)

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Table 3) Summary of neurobehavioral studies of PFCs (*continues*)

Species	Compound	Dose and exposure	Effects	References
Offspring of exposed CDI-mice	K^+PFOS	Maternal oral exposure to 6 mg/kg/day from GD 12 to 18. Half of the exposed animals were attributed to restraint stress	Three months after birth, the group prenatally exposed to PFOS spent more time in the center of the open-field device. Stress counteracted the effect. No effects on activity in the open-field	Ribes et al. (2010)
Neonatal Crl:CD (SD) rats	K^+PFOS	Maternal oral exposure to 0.1, 0.4, 1.6 and 2 mg/kg/day, 42 days prior to mating to lactation day 20	Offspring from 1.6 mg/kg group, displayed delay in surface and air righting. No behavioral effect on offspring in the passive avoidance device and the water maze at PND 24 and PND 70 respectively	Luebker et al. (2005)
Cobb I chicken broiler strain	K^+PFOS	Fertilized chicken eggs injected on embryonic day 0 to 5 mg/kg or 10 mg/kg	Reduced imprinting performance at hatching day 1	Pinkas et al. (2010)
Cobb I chicken broiler strain	PFOA	Fertilized chicken eggs injected on embryonic day 0 to 5 mg/kg or 10 mg/kg	Reduced imprinting performance at hatching day 1	Pinkas et al. (2010)
Adult Crl:CD (SD) rats	PFHxS	Oral exposure to 0.3, 1, 3 and 10 mg/kg for 40-50 days	No effects in the functional observational battery or motor activity	Butenhoff et al. (2009a)
Adult Sprague Dawley ratt	PFBA	Oral exposure to 0, 6, 30 and 150 mg/kg/day for 28 days	No effects in hearing, static rightning, grip strength or motor activity. Delayed bilateral pupillary reflex in the 150 mg/kg group	Butenhoff et al. (2011)
Adult Sprague Dawley ratt	PFBA	Oral exposure to 0, 1.2, 6 and 30 mg/kg/day for 90 days	No effects in hearing, static rightning, grip strength or motor activity. Slight delay in pupillary reflex in the 30 mg/kg group	Butenhoff et al., (2011)
Adult Sprague Dawley ratt	NH_4^+PFOA	Oral exposure to 30 mg/kg/day for 28 days	Slight, but not significant, decrease in motor activity	Butenhoff et al.(2011)

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short-term retention and memory in a passive avoidance device, and at PND 70 for learning and memory in the water maze with no effects. The most profound effect linked to neuromotor development was a delay in surface and air righting at PND 2 in the 1.6 mg PFOS/kg/day group. This exposure group also experienced high mortality. Butenhoff et al., (2009b) examined neurotoxic endpoints in gestational and lactational exposed neonatal rats finding increased motor activity and reduced habituation on PND 17 in the high dose group, which were exposed through their mothers to 1 mg PFOS /kg/day. No effects on these parameters were observed on PND 13, 21 or 61. In addition Butenhoff et al., (2009b) tested the rats in a FOB and for acoustic startle response (hearing sensitivity) finding no significant effects.

Eriksson and his colleagues expose mice prenatally at specific time points, and observe that the animals are especially vulnerable to exposure of environmental contaminants at the period of high neuronal growth, the so-called brain growth sprout (BGS), which is critical periods of brain development (Eriksson, 1997). In rodents BGS is the first 2-4 weeks after birth, whereas in humans it begins during the third trimester of pregnancy and continues throughout the first 2 years of life. Typically, mice are exposed to one single dose of a contaminant at PND 10. After 2 and 4 months the mice are tested for effects on spontaneous behavior (locomotion, rearing and total activity) and habituation. Habituation is a kind of adaptive behavior that is classified as non-associative learning. In addition, they test the response of exposed mice to nicotine in order to study developmental effects on the cholinergic system. Recently, Johansson et al (2008) exposed mice to single doses of PFOS (0.75 and 11.3 mg/kg), PFOA (0.58 and 8.7 mg/kg) and perfluorodecanoic acid (PFDA, 0.78 and 10.8 mg/kg) at PND 10. Effects on spontaneous behavior and habituation were observed in the mice exposed to the high doses of PFOS and PFOA after 2 and 4 months. Apparently, PFOA showed a dose dependent effect, where the low dose group showed a small, but

significant effect on spontaneous behavior. After the 4 month test, the animals were administered one dose of nicotine (80 μg nicotine/kg, subcutaneous administered) and subjected to analysis on spontaneous behavior. The PFOS and PFOA exposed animals showed a hypoactive response to the nicotine compared to the control animals that responded with hyperactivity indicating that the cholinergic system had been influenced. Previously Eriksson has performed similar experiments on mice exposed to environmental contaminants such as the PCBs, the BFRs pentabromo diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCD) and dichlorodiphenyl trichloroethane (DDT) finding similar effects. The concentrations used to induce effects have varied. The chlorinated pesticide DDT (Eriksson et al., 1992) and the coplanar PCB 77 and 126 (Eriksson et al., 1991; Eriksson and Fredriksson 1998) were shown to induce effects at approximately 0.5 mg/kg, the noncoplanar PCBs 52 and 28 were shown to induce effects at approximately 4 mg/kg (Eriksson and Fredriksson, 1996), whereas the BFRs BDE-99, -209 and HBCD were shown to induce effects at 8 mg/kg, 20 mg/kg and 13.5 mg/kg respectively (Eriksson et al., 2002; 2006; Viberg et al., 2003). The potencies of PFOS and PFOA to induce neurobehavioral effects with Erikssons model are therefore similar to the noncoplanar PCBs and the lower molecular weight PBDEs.

In a series of studies, pregnant mice have been exposed to stress, by subjecting the animals to restraint and PFOS in order to evaluate behavioral effects on the offspring (Fuentes et al., 2006, 2007ab; Ribes et al., 2010). The rationale for the studies was to evaluate if stress and PFOS exposure could influence behavioral development on the offspring. The mothers were exposed to 3 and 6 mg/kg/day from GD 12 to 18. Half of the exposed animals were subjected to restraint stress and the offspring were examined for neuromotor and reflex maturation immediately after birth, followed by an examination in a battery of behavioral tests after 3 months, such as the open-field test, the water maze test and the rotarod test. In general, prenatally PFOS exposed mice appeared to show a temporarily delay in neuromotor

development, such as reduced response time on the righting reflex, diminished resistance to backward pull, and reduced climb ability and forelimb strength. Maternal exposure to stress appeared to counteract the PFOS induced effects on the offspring. In the behavioral tests of the 3 months old mice, the results were more complicated indicating that restraint stress on the mothers had a larger impact on the offspring than PFOS itself. In the stress induced animals the vertical activity, measured as number of rearings in the open field, increased; the distance travelled in the open-field decreased; and male animals had a temporarily increase in number of falls in the rotarod. Male offspring exposed to PFOS only, had a temporarily decreased numbers of falls in the rotarod. Otherwise, only minor effects were observed on the PFOS exposed animals, but PFOS tended to counteract the effects of stress indicating some sort of interaction. An interaction between stress and PFOS was also indicated during the acquisition period in the water maze, showing that female mice in particular, travelled longer distances than control mice, indicating effects on spatial learning and memory. Fuentes et al., (2007c) also exposed adult mice to 3 and 6 mg PFOS/kg/day for four weeks followed by evaluation for motor and sensory function by a FOB, general activity and exploratory behavior in an open-field, and learning and memory in the water maze. No significant effects were found indicating that adult animals are less sensitive than the prenatally exposed animals.

Neurochemical targets of PFCs

The behavioral effects of PFC exposure, implicating negative impact on memory, learning, and motor functions, may involve structural changes in brain or affect neuronal plasticity as a result from effects on several neurochemical targets. Neonatal exposure of PFOS and PFOA at specific time points, at the period of high neuronal growth, was shown to induce behaviour effects in adult mice (Johansson et al., 2008). The exposure appeared to involve an effect on the development of the cholinergic system. In a later study Johansson et al., (2009) exposed

mice for one single dose of PFOS (11.3 mg/kg) and PFOA (8.7 mg/kg). One day after exposure the animals had increased levels of the proteins CaMKII, GAP-43, synaptophysin and Tau, which are involved in neuronal growth and synaptogenesis. The effects were particularly pronounced in brain tissue from hippocampus and it was postulated that cellular processes, such as development of synaptic plasticity and long-term potentiation (LTP), can be affected by the exposure. In a recent study by Zeng et al., (2011a) rat dams were exposed from GD2 to GD21 for 0.1, 0.6 and 2.0 mg PFOS/kg/day. At PND 0 and 21 they analyzed synaptophysin and synapsin in hippocampus finding a reduction in the levels. In cortex they found an increase in the levels of synaptophysin and a decrease in the levels of synapsin. These findings both contrast and confirm the observations made by Johansson et al., (2009) making it difficult to interpret the significance of the findings. Nevertheless, these studies indicate that PFOS might influence synaptic plasticity and development, and future research should focus on comparative studies with established neurotoxicants as positive controls.

In a study by Pinkas et al., (2010) it was shown that chicks exposed prenatally to PFOS and PFOA had impaired imprinting behaviour. The eggs were exposed once at incubation day 0 for 5 and 10 mg/kg. In both exposure groups there were high mortality; between 30 and 50% of the eggs did not develop embryos. After the behavioural testing at hatching day 1 the brains were removed and the levels of three protein kinase C (PKC) isoforms (PKC -α, -β, -γ) were analysed in the left intermedial part of the hyperstriatum ventrale (IMHV). In the PFOS exposed birds it was found an overall reduction in cytosolic PKC, whereas PFOA induced an overall increase in cytosolic PKC. No effects on membrane bound PKC were found. According to the authors, translocation of cytosolic PKC to the membrane is required for imprinting and plays a role in the transfer of cholinergic input involved in learning and memory. Different PKC isoforms have previously been postulated as possible targets

following both adult and developmental exposure to halogenated aromatic hydrocarbons, such as the PCBs (Kodavanti et al., 1994, 1998; Yang et al., 2003).

Relatively few studies have assessed the *in vitro* neurotoxicity of PFCs. Harada et al., (2005) showed that 30 μM of PFOS has a complex modulating effect on ion currents in rat cerebellar Purkinje cell towards a hyperpolarized state involving voltage gated Ca^{2+}, Na^{+} and K^{+} channels. Liao et al., (2008) showed that PFOS increased Ca^{2+} currents recorded in the CA1 region of hippocampal slices and in cultured hippocampal neurons. In addition, it was shown that PFOS inhibits neurite growth and synaptogenesis in cultured neurons. The effects could be blocked by the L-type voltage gated Ca^{2+} channel blocker nifedipine indicating that PFOS facilitate influx of calcium. The effect was further shown to increase with the carbon chain length of the tail moiety of the PFCs, and that the effects of the carboxylated compounds were less pronounced than the sulfonates (Liao et al., 2009a). In another study, Liao et al., (2009b) also showed that PFOS increases K^{+} currents at doses over 10 μM towards a hyperpolarized direction without affecting Na^{+} currents in hippocampal neurons. In addition it was showed that a low concentration of PFOS (1 μM) increases inward glutamate currents whereas higher concentrations of PFOS (10 and 100 μM) dose-dependently reduce the inward glutamate currents. Liu et al., (2011a) searched to elucidate in more detail the mechanisms of the PFOS and PFOA induced disturbance of Ca^{2+}-homeostasis in hippocampal neurons. PFOS was shown to induce elevated intracellular concentrations of Ca^{2+} at 30 μM whereas PFOA induced a small increase at 100 μM. The increase in Ca^{2+} appeared to be of both extracellular and intracellular origin involving voltage gated Ca^{2+} channels, ryanodine receptors and inositol phosphate-3 (IP_3)-receptors. The disturbance of the Ca^{2+}-homeostasis was followed by an increase in oxidative stress, as measured with DCF, and an increased expression of calcineurin , which is a Ca^{2+} activated protein phosphatase.

Slotkin et al., (2008) investigated developmental effects of PFOSA, PFOS, PFOA and PFBS on undifferentiated PC12 cells *in vitro*. They showed that, particularly PFOSA, but also PFOS promote differentiation of the PC12 cell into the cholinergic phenotype at the expense of the dopaminergic phenotype. At the highest concentration, the effect of PFOSA switched and promoted differentiation into the dopaminergic phenotype. No mechanisms for the effects were postulated, but it was suggested that the induction of oxidative stress could be a factor. PFOSA induced lipid peroxidation and was also the most cytotoxic compound. The findings that several PFCs may disturb the Ca^{2+}-homeostasis may implicate induction of oxidative stress due to activation of several signalling pathways such as the PKC (Kodavanti et al. 1994), the phospholipase 2 (PLA2) (Kodavanti and Derr-Yellin 2002), the nitric oxide synthase (NOS) (Kang et al. 2002) and the glutamate receptors (Gafni et al. 2004; Mariussen et al. 2002).

Cytotoxicity and oxidative stress may also be induced as a consequence of inflammatory responses, such as immune responses. Zeng et al (2011b) showed that prenatally exposed rats had increased inflammatory responses in brain as shown by increased levels of the astrocyte markers fibrillary acidic protein and S100 Ca^{2+}-binding protein B in hippocampus and cortex. In addition they found increased mRNA levels of the proinflammatory cytokines interleukin 1β, tumor necrosis factor α, AP-1, NF-kappa-B and CREB. PFOS and PFOA have previously been shown to enhance inflammatory responses of macrophages to lipopolysaccharide (LPS) in mice (Qazi et al., 2009) and may be implicated in elevated stress responses, such as oxidative stress.

Neuroendocrine targets of PFCs

A major concern in environmental toxicology has been the possible interaction of environmental toxicants with neuroendocrine targets. Sex steroids and the TH system appear

particular vulnerable to environmental toxicants especially during early development (for reviews Colborn 2004; Crisp *et al.* 1998; Parent et al., 2011; Porterfield 1994; Zoeller *et al.* 2002), although it is hypothesized that animals have a certain tolerance for exogenous substances that mimic the action of hormones (Nilsson, 2000). TH is crucial for brain development and TH deficiency during gestation causes cretinism, with severe cognitive and/or mental disorders in the offspring (Koibuchi and Chin 2000; Oppenheimer and Schwartz 1997). Haddow et al., (1999) showed that children of mothers with high levels of thyroid stimulating hormones (THS) and low T4 in plasma during pregnancy averaged 4-7 points lower on IQ scores. An environmental toxicant may influence the synthesis of thyroid hormones, interact with TH transport proteins or receptors, or induce the hepatic uridine diphosphate glucuronosyltransferase (UGT), which increases the elimination of thyroxin (Barter and Klaassen, 1994; Beetstra et al., 1991; Brouwer, 1989, 1990, 1991; Brouwer et al., 1998; Collins and Capen, 1980, Morse et al., 1996; McKinney et al. 1987; Rickenbacher *et al.* 1986).

PFDA was early shown to reduce serum T4 levels in rats exposed to one intraperitoneal dose (75 mg/kg). The T4 level remained depressed throughout the 8 day study (Langley and Pilcher, 1985). It was later showed that PFDA displaces T4 from rat albumin (Gutshall et al., 1989). The main carrier proteins of TH in mammals are the thyroxin-binding globuline (TBG), albumine and transthyretin (TTR) (Schussler, 2000). Weiss et al., (2009) investigated the potencies of different PFCs to compete with T4 for binding to TTR. They found that the binding potencies decrease in the order PFHxS>PFOA/PFOS>PFHpA>L-PFOSi>PFNA. The binding potencies ranged 12.5-50 times less than the natural ligand T4. Several others PFCs were, in addition, tested displaying much less affinity to TTR

In vivo studies on animals exposed to PFCs have shown inconclusive results on the TH levels. Butenhoff et al., (2011) exposed adult rats to PFBA for 28 and 90 days (Table 3). There

was a dose-dependent decrease in both free and bound T4 in PFBA exposed male rats, but no effect on THS was observed. In the same study rats were exposed to one dose PFOA (30 mg/kg/day) for 28 days finding reduced free and total T4 in addition to reduced TSH level in male and reduced T4 in females. In Cynomolgus monkeys, exposed daily for 6 month to PFOA (3, 10 and 20/30 mg/kg/day), no significant effect on thyroid status was found (Butenhoff et al., 2002). The general view has, however, been that PFCs induce a reduction in TH levels, particularly the T4 levels, resembling a state of hypothyroidism (for review Lau et al., 2007; Yu et al., 2009). These reports were recently challenged by Chang et al., (2007) who claimed that the reported PFC-induced TH reduction in blood could be artifactual due to methodological interferences. The observed reduction in TH level after PFCs exposure has, in addition, not been associated with an expected compensatory increase in the levels of TSH. Chang et al., (2007) exposed female rats to three daily doses of PFOS (5 mg/kg) and analyzed serum concentrations of TSH and T4 24 h after the last dose. By comparing three different methods for T4 analysis it was showed that two of the methods indicated a more than 50% decrease in both total and free T4, whereas a third method, regarded as the reference method, showed no effect. The TSH level was unaffected. Chang et al., (2008) then exposed rats to one single dose of 15 mg PFOS/kg showing a transiently increase in free T4 and a decrease in TSH levels within 6 hours. The effect was followed by an increase in mRNA transcript of UGT1, which is the enzyme responsible for elimination of T4, and a concomitant decrease in total T4 and T3, probably due to increased elimination. The increased elimination was connected to the ability of PFOS to displace thyroxin from protein binding and it was concluded that that there was no evidence that PFOS induces a hypothyroid state in rats or alter the function of hypothalamic-pituarity-thyroid axis.

The thyroid hormone levels in plasma from wild-life animals have been used as biomarkers for exposure to environmental contaminants (e.g. Jenssen, 2006). In two recent

studies it was shown a positive relationship between total T4 (Nøst et al., 2012) and total T3 (Braune et al., 2011) and PFCs (PFHpS, PFOS, PFNA, PFCA) in arctic seabirds. This effect contradict *in vivo* experiments of which a reduction or no-effect on the TH-level is expected. The significance of these findings is unknown and may be a species specific effect or could reflect the high affinity of PFCs to proteins in liver and plasma. The TH and contaminants levels in serum/blood are usually expressed volumetrically, as mol/l or ng/l. Due to the high affinity of PFCs to proteins both TH and PFC-levels should in addition be expressed as per unit protein to take into account differences in the plasma fluid volumes per unit proteins between individuals.

Epidemiological studies have shown a possible association between hypothyroidism, measured as reduced levels of TH in blood plasma or self -reported diagnosed thyroid disease, and serum concentration of PFOS or PFOA in US adult populations (Knox et al., 2011; Melzer et al., 2010). However, as reviewed by White et al., (2011) there are even more studies that do not find clear evidences of such interactions, even in occupationally exposed workers (Grice et al., 2007; Olsen et al., 2003) and further work is needed to add more weight of evidence for this plausible relationship.

PFCs and their relevance for neurotoxic effects

PFOS and PFOA have previously been subjected to extensive risk assessments. Most of the studies that have showed neurobehavioral effects are on prenatally or neonatally animals exposed to doses that have caused other serious effects, such as increased mortality, reduced growth and maturation, and birth defects. These effects may lead to the assumption that other toxicological endpoints are of higher importance. The observed neurobehavioral effects also appear subtle and inconclusive. Lau et al., (2003) estimated a $BMDL_5$, which is the lower 95% confidence limit of the benchmark dose (BMD) for a 5% response, at 0.58 mg

PFOS/kg/day based on survival of rodents to postnatal day 8, which corresponded to a neonatal serum concentration of about 16 μg/ml (Lau et al., 2007). The dams had been orally exposed daily from gestational day 2 to 21. The effect of PFOA on rodent is clearly species dependent and dependent on their ability to eliminate the compound. Pregnant CD-1 mice were exposed by gavage to PFOA daily from GD1 to GD17 (1, 3, 5, 10, 20 or 40 mg/kg/day) (Lau et al., 2006). Shortly after delivery approximately 25% of the pups in 5 the mg/kg/day group died, whereas only 25% of the pups in 10- and 20 mg/kg dose groups survived. The observation was reported to be similar to the developmental effects as previously observed for PFOS. A $BMDL_5$ for neonatal survival at 1.09 mg/kg was estimated corresponding to a maternal serum concentration of approximately 19 μg/ml (Olsen et al., 2009). Lau et al., (2006) also estimated a $BMDL_5$ for effects on limb phalange ossification (bone tissue formation) and neonatal body weight at an exposure concentration of approximately 0.6 and 0.8 mg PFOA/kg/day respectively, corresponding to a serum concentration at term of approximately 13-15 μg/ml (Olsen et al., 2009). Seacat et al., 2002, exposed Cynomolgus monkeys to PFOS to 0.03, 0.15 and 0.75 mg/kg/day (5.46, 27.3 and 136.5 mg cumulative dose) for 182 days and the no adverse effect level (NOAEL) was associated with the 0.15 mg/kg/day group which had a serum concentration of 82.6 ± 25.2 and 66.8 ± 10.8 μg/ml PFOS in males and female respectively. In a similar study by Seacat et al., (2003) on rats the NOAEL was associated with a serum concentration of 44 and 64 μg/ml PFOS in males and female respectively. Whereas the blood serum concentrations in laboratory exposed animals are at the levels of μg/ml, the background levels in human and wild-life are at the levels of ng/ml indicating a relatively high margin of safety of approximately 1000 or more. In occupationally exposed workers it has, however, been measured serum PFOA levels of 2 μg/ml (Ehresman et al., 2007), which according to the risk assessment made by Butenhoff et al., (2004a) is only a factor of approximately 10 below their estimated serum concentration of

PFOA which may affect liver weight in Cynomolgus monkeys and a factor of approximately 50 below the concentrations that may induce serious teratogenic effects in mice, such as increased pup mortality (Lau et al., 2006).

For the general adult population the background figures of PFCs are probably of less neurotoxicological concern. No animal studies have yet shown that adult exposure to PFCs may be able to induce neurotoxic effects, even at doses that can be characterized as high. Exposure during development, especially during the fetal and post fetal period, appears, however, to be a critical period and it is plausible that developmental exposure to PFCs may have effects on the nervous system. The central nervous system is protected by the BBB, which limit the transport of both endogenous and exogenous compounds into the brain (e.g. Staddon and Rubin, 1996). The BBB is functional very early in the development (Ek et al., 2012). There has been a general view that the BBB is not fully developed at birth and that larger amounts of the chemicals therefore may reach the brains of the fetus or the newborn. The evidences for this view is weak (Ek et al., 2012), but it has been shown that breast-feeding infants may be exposed to higher concentrations of lipophilic compounds per unit body mass compared to adult (e.g. Patandin et al., 1999). PFCs are also shown to be transferred from mother to the fetus (Chang et al., 2009; Liu et al., 2011b). The infant brain may therefore be exposed to relatively higher concentrations of contaminants than the adult brain. Exposure to toxicants is probably also of special concern during critical periods of the brain development (Eriksson and Talts, 2000).

Most studies on PFCs, including neurobehavioral studies, are performed on rats and mice, which may have implication for the extrapolation of PFCs as potential neurotoxicants or endocrine disruptors to other species. Perhaps the most profound effect of PFCs on rats and mice is as peroxisome proliferators through activation of the peroxisome profilator activated receptor (PPAR) and several of the effects of PFCs can be attributed to PPAR activation. This

receptor belongs to the steroid/thyroid/retinoid superfamily of nuclear receptors, and is involved in the regulation of carbohydrate - and lipid-metabolism as well as in cell-regulation (Suga, 2004). Characteristics for peroxisome proliferators are hepatomegaly, proliferation of smooth endoplasmatic reticulum and peroxisomes in association with enzyme induction, and inhibition of mitochondrial beta-oxidation. Biochemical characteristics are decrease in serum lipids, such as triglycerides and cholesterol and induction of CYP4A. PARP inducers are recognized as non-genotoxic carcinogens, or tumour promoters. The significance of PPAR activation in humans and mammals other than rodents, however, is uncertain (Fidaleo, 2009). Recently, use of rats and mice models in risk assessment of PFCs in humans was questioned (Bjørk and Wallace, 2009). They showed that PFCs-induced PPAR activation in rats could not be extrapolated to humans. As commented by Rosen et al., (2009) rodent studies of PFCs may overestimate risk. There are effects of PFCs that are shown independent of PPAR activation, even in rats and mice. Future studies should, therefore, focus on PPAR independent effects, and identify the relation between PPAR activation and different toxicological end points, for example with use of PPAR knock-out mice or preparations from other animal species, which are less sensitive for PPAR activation. There are for example a cross-talk between TH and PPAR activation (Lu and Cheng, 2010).

Another important factor which may increase the relevance of PFCs as neurotoxicants is the cocktail effect. Several organohalogen compounds and heavy metals are established as neurotoxicants and the hypothesis that they may interact has caused some concerns. Interactions between chemicals are defined as a deviation from an expected additive outcome. Additivity can be defined as the obtained effect if two doses of the same chemical are mixed (Sühnel, 1990). There are very few reports, however, that have shown interactions between pollutants, but there are reasons to believe that they may act additive. Additivity is an important property of environmental contaminants and should be considered in risk

assessments. A typical blood concentration of 5 ng/ml PFOS in humans resembles a molar blood concentration of 10 nM, which is a factor of approximately 10 lower and 10 higher than the total blood level of T4 and T3 of respectively (Calvo et al., 2002; Schussler, 2000). In occupationally exposed workers it has been found levels of approximately 300 and 2000 ng/ml of PFOS and PFOA respectively (Ehresman et al., 2007), which corresponds to approximately 0.6 and 4.8 μM respectively in serum. 50 ng/g lead and 5 ng/g MeHg in blood (Weschler, 2009) correspond to approximately 240 nM and 23 nM respectively. In polar bear the sum PCB levels in blood can reach an approximate concentration of 100 nM (Villanger et al., 2011). A background concentration of 5 ng/g wet weight of PCB in blood corresponds to approximately 15 nM (based on a MW of the Aroclor 1254 mixture of 324). Particularly, under circumstances of fasting and of which lipid soluble components can be mobilized from lipid tissue to blood (Bustnes et al., 2010; Henriksen et al., 1998), it is plausible that the toxicants in combination may reach concentrations that can be harmful for neuroendocrine development, or on other neurochemical or toxicological parameters. A large part of the accumulated toxicants in blood are probably immobilized on carrier proteins, such as albumin. There will, however, be some kind of steady state between active (toxic) and inactive (non-toxic) substance and more research should focus on toxicokinetic parameters, such as partition between free and bound substance in addition to the cocktail effect.

Concluding remarks

The last decade, the use of PFOS and PFOA has been reduced, and recent monitoring studies have shown a reduction in the body-burden of these compounds, both in human and wild-life. PFOS and PFOA have been replaced by other PFCs in consumer products and apparently these compounds are less prone to environmental accumulation and are less toxic. Still, however, the background blood levels in humans are relatively high due to their high affinity

to protein rich tissue. Susceptible groups such as children and occupationally exposed workers may be exposed to concentrations with decreased margins of safety. PFOS and PFOA have been subjected to extensive risk assessment and the reported neurotoxicological effects appear to be subtle and inconclusive, even in developmentally exposed animals. There are, however, species specific differences in the toxicity of PFCs and more studies should focus on PPAR independent effects by using models which are less sensitive for PPAR activation. The studies should be followed by the elucidation of the modes of action. It is of particular concern that susceptible groups may be exposed to a cocktail of substances that in combination reach harmful concentrations. The nervous system is regarded as particular vulnerable, especially during development and thorough risk assessment studies should be performed on defined mixtures of environmental contaminants to elucidate potential interactions between the substances. The models to be used should enable comparison with previous studies performed on single substances, such as performed by Eriksson et al (2006) who claimed interactions between PCB 52 and PBDE 99 on neurotoxicological parameters such as spontaneous behavior. To avoid misinterpretations of the data and to reduce the number of experiments, recognized models to identify deviations from a predictive additive effect should be used, such as the Löewe model of additivity and the Bliss model of independent action (Greco et al., 1992) or by statistical design as performed by Lundstedt-Enkel et al., (2010). Finally, more studies should also focus on toxicokinetic parameters such the partition between free and bound substance and organ specific accumulation to identify effective doses and critical targets.

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Figure legend

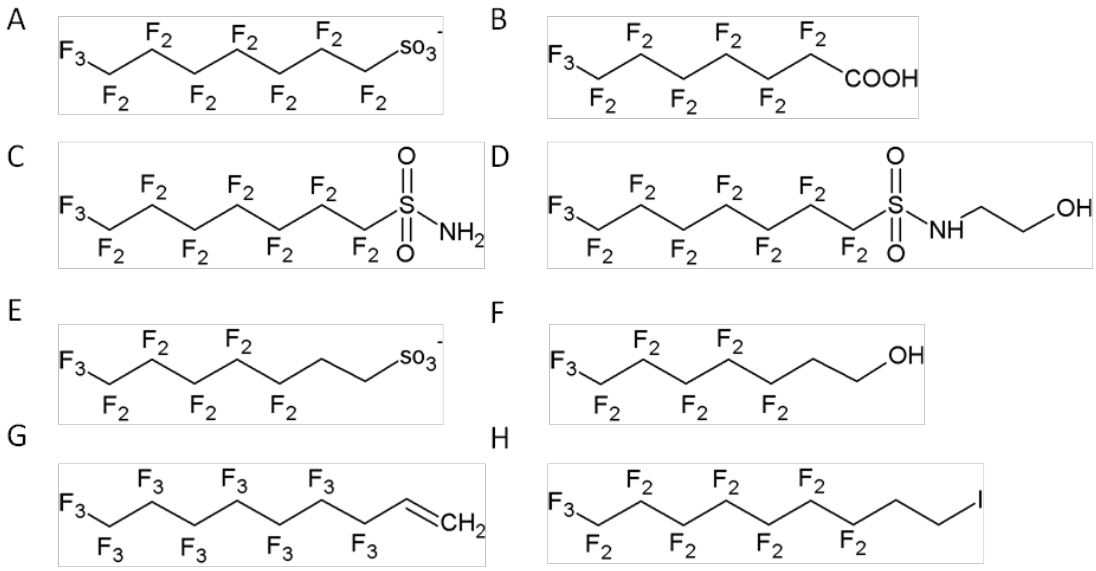

Fig. 1 (A) Perfluorooctanesulfonate (PFOS), (B),), perfluorooctanoic acid (PFOA), (C) Perfluorooctanesulfonamide (PFOSA), (D) perfluorooctane sulfonamidoethanol (PFOSE), (E) Fluorotelomersulfonates (FTS), (F) fluorotelomer alcohol (FTOH), (G) Fluorotelomer olefin (Ftolefin), (H) fluorotelomer jodid (FTjodid)

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