Perfluorinated compounds: occurrence and risk profile

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Abstract

Perfluorinated compounds (PFCs) such as perfluoro-octane sulphonate (PFOS) and perfluorooctanoic acid (PFOA) are emerging environmental pollutants, arising mainly from their use as surface treatment chemicals, polymerization aids and surfactants. They are ubiquitous, persistent and bioaccumulative in the environment. Perfluorinated compounds are being proposed as a new class of POPs. Although tests in rodents have demonstrated numerous negative effects of PFCs, it is unclear if exposure to perfluorinated compounds may affect human health. This review provides an overview of the recent toxicology and toxicokinetics, monitoring data now available for the environment, wildlife, and humans and attempts to explain the mechanisms of action of PFCs.

REVIEW ARTICLE

Abbreviations

BAF - bioaccumulation factor
BMF - biomagnification factor
CAR - constitutive androsteron receptor
CYP 450 - (CYP2B2, CYP3A4, CYP4A1) cytochrome P450
DPPC - dipalmitoylphosphatidylcholine
FTCA - fluorotelomer carboxylic acid
FTOH - fluorotelomer alcohol
GJIC - gap junctional intercellular communication
HPT axis - hypothalamic-pituitary-thyroid axis
L-FABP - liver fatty acids binding protein
N-MeFOSE - N-methyl perfluorooctanesulphonamidoethanol
N-EtFOSE - N-ethyl perfluorooctanesulphonamidoethanol
PFAAs - perfluoroalkyl acids
PFBA - perfluorobutanoic acid
PFBS - perfluorobutane sulphonate
PFCAs - perfluorocarboxylates
PFC - perfluorinated compound
PFDeA - perfluorodecanoic acid
PFHxS - perfluorohexane sulphonate
PFNA - perfluorononanoate
PFOA - perfluorooctanoic acid or perfluorooctanoate
PFOS - perfluorooctane sulphonate
PFOSA - perfluorooctanesulphonamide
PFSAs - perfluoroalkyl sulphonate acids
PFS - perfluoroalkyl substances
POP - persistent organic pollutant
PPAR-α - peroxisome proliferator-activated receptor-α
PPAR-β/δ - peroxisome proliferator-activated receptor-β/δ
PPAR-γ - peroxisome proliferator-activated receptor-γ
T3 - triiodothyronine
T4 - thyroxine
TSH - thyroid-stimulating hormone

INTRODUCTION

Perfluorinated compounds (PFCs) also called polyfluoroalkyl substances (PFSs), are a family of fully fluorinated hydrocarbons consisting of a carbon backbone with 4–14 carbons in length and a functional moiety, mainly carboxylate, sulphonate, or phosphonate.

Carbon-fluorine bonds are among the strongest and fully fluorinated hydrocarbons are stable in the atmosphere and at high temperatures of 150 °C, nonflammable, not readily degraded by strong acids, alkalis, or oxidizing agents, and not subject to photolysis (Lau *et al.*, 2007). Perfluoroalkyl acids (PFAAs), one branch of perfluoroalkyl compounds including perfluorocarboxylate acids (PFCAs) and perfluorosulphonate acids (PFSAs) (Figure 1), may be decomposed by zero-valent iron in subcritical water, which is hot water at 350 °C with sufficient pressure to maintain a liquid phase (Hori *et al.*, 2006) or by irradiation and use of persulphate (Chen & Zhang, 2006). The stability of perfluorinated chemicals renders them essentially nonbiodegradable and persistent in the environment (Key *et al.* 1997; 1998; Prescher *et al.*, 1985).

Two widely known PFAAs, perfluorooctanoic acid (PFOA) and perfluorooctane sulphonate (PFOS) (Figure 1), which each contain an eight-carbon backbone, are synthesized for their unique physico-chemical nature and are incidental final degradation products of related anthropogenic compounds. Perfluorooctane sulphonate and perfluorooctanoate can be released from perfluorinated compounds by biotic and/or metabolic decomposition (Midasch *et al.*, 2007). In contrast to other lipophilic fluorocarbons, PFOS and PFOA have an affinity for protein molecules in biota. Naturally occurring fluorinated organic compounds are rare (Lau *et al.*, 2007).

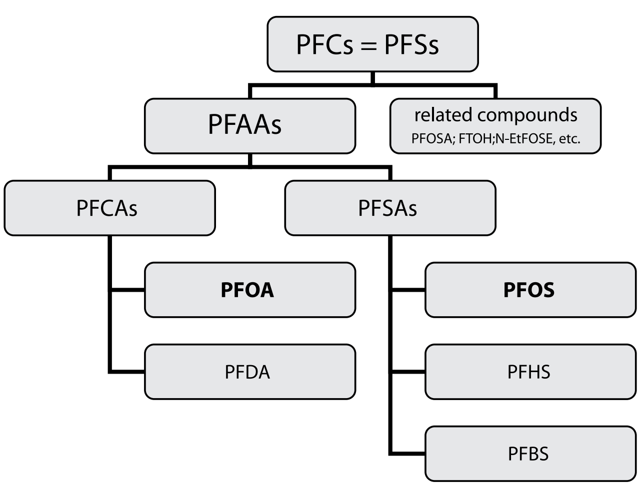

Figure 1. A simple chart showing relationships between chemical compounds referred to in this review.

Two manufacturing processes are used to synthesize PFSs (Houde *et al.*, 2006): (1) Electrochemical fluorination involving the replacement of the hydrogen atoms of a hydrocarbon using fluorine in the presence of an electrochemical current. Perfluorooctane-sulphonyl fluoride based products, which were used to create perfluoroalkyl sulphonamido alcohols, are performed by this process. Perfluoroalkyl sulphonamido alcohols are known to be degraded to perfluoroalkyl sulphonate acids (PFSAs) via biotransformation processes and through abiotic oxidation. For example, perfluorooctane sulphonate may arise from the release of perfluorooctylsulphonamides into the environment. (2) The second important process for manufacture of PFS is telomerization which involves a reaction of pentafluoroiodo-ethane with tetrafluoroethylene oligomers to yield a mixture of perfluoroalkyl iodides. These fluorotelomer iodides are then used to make a variety of telomer products, including fluorotelomer alcohols (FTOHs). FTOHs are transformed in the atmosphere and metabolically in animals and microorganisms, to fluorotelomer carboxylic acids (FTCAs) and perfluorocarboxylates (PFCAs, e.g., perfluorooctanoid acids, PFOA) (Houde *et al.*, 2006).

The physical properties of PFAAs render these chemicals ideal surfactants (Kissa, 2001). PFOS and PFOA are found in over 200 applications including soil- and stain-repellents, coatings for clothing fabrics, leather, upholstery, and carpets, paper coatings, electroplating, photographic emulsifiers, aviation hydraulic fluids, firefighting foams, paints, adhesives, waxes, polishes, pharmaceuticals and insecticides. PFOA is also used as an emulsifier in the production of polytetrafluoroethylene as well as other fluoropolymers and fluoroelastomers.

PFAAs have been in use only in the past half-century, and until recently were considered biologically inactive. Exposure to PFSs has increased over the past 15 to 25 years. Olsen *et al.* (2005) showed that PFOS, PFOA, and PFHxS concentrations were significantly greater in human serum collected in 1989 compared to serum collected in 1974. The production and use of PFOS plateau at the end of the 1980s was estimated at 3,500 t annually. In 2002, the major manufacturer of PFOS, phased out the production of this chemical. Prevedouros *et al.* (2006) reported that PFAAs production is primarily in Japan and that 14 of the world´s 33 fluoropolymer production sites are in eastern Asia. Because our understanding of the environmental fate of PFCs is only in its infancy, additional studies are needed. The aims of this review are to provide recent data on monitoring, and the evaluation of negative effects of perfluorinated chemicals, mainly PFOS and PFOA.

MONITORING STUDIES

The widespread use of PFOA and PFOS in consumer and industrial products, has led to their appearance as global contaminants of the environment. It is widely recognized that PFSAs and PFCAs are persistent and have been measured in water, fish, birds and mammals, including humans worldwide. The collection of internationally representative samples and application of standardized analytical methods is necessary for comparing and interpreting PFAA concentrations in biological matrices worldwide. Surface sea waters, coastal waters, river waters, fresh water, drinking water, rain waters from an urban centre, air, sludge, soils, sediments, and ice caps are all the matrices, in which PFS have been detected (Saito *et al.*, 2004; So *et al.*, 2004). In addition PFOA, PFOS and PFHxS have been detected from dust samples in Canadian homes averaging about 400 ppb (Shoeib *et al.* 2005). The levels of PFOA measured in the environment, were in the parts per trillion (ppt) range, with higher levels ranging from parts per billion (ppb) to parts per million (ppm) detected only rarely.

Several sources, such as discharge of industrial and municipal wastewater, fire-fighting operations at military bases and airports may be responsible for the elevated exposure to PFSs in urban areas. Nevertheless, the detection of these perfluorochemicals in remote regions of the world is unexpected. PFOS, PFOA and other PFAAs have been detected in low concentrations in high Arctic ice caps and the mid-Pacific.

Two hypotheses have been proposed to explain the fate and transport of PFOS, PFOA and other PFAAS around the world (Prevedouros *et al.*, 2006).

Long range transport by oceanic currents (Yamashita *et al.*, 2005). This is supported by the presence of PFAAs in the surface water of the Atlantic and Pacific Oceans, with PFOA being the major PFAA detected there.

Atmospheric transport and transformation of precursor chemicals (Ellis *et al.*, 2003; Stock *et al.*, 2004; D´Eon *et al.*, 2006; Martin *et al.*, 2006; Young *et al.*, 2007). Particulates containing PFOA have been detected in the atmosphere. Two PFOS precursors, *N*-ethyl-perfluorooctane-sulphonamido ethanol (N-EtFOSE) and *N*-methyl-perfluorooctane-sulphonamido ethanol have been measured in the air in Canada (Martin *et al.*, 2002). These PFAAs, emitted from a production site, were transported by wind to the nearby well fields or to the remote regions, deposited onto the surface soils, and then migrated downward with precipitation into the underlying aquifer (Furdui *et al.*, 2007). The volatility of PFOA and PFOS is nominal, that of their precursors and derivatives is high at normal temperature (Stock *et al.*, 2004). Due to their ubiquitous occurrence, persistence and bioaccumulation, they are found in the blood of many animal species and the general human population worldwide.

Marine and freshwater ecosystems

Food web analyses have shown that PFCAs and PFSAs can bioaccumulate and biomagnify in marine and freshwater ecosystems and observations infer their presence in the deep sea food web (Fujii *et al.*, 2007). The route of PFOS transport to the deep oceans is not clear, but may be through sedimentation with sinking particles. Quantitative determination of PFS in samples of tap water, ground water, river water and waste water has shown that PFOA, PFOS, PFBS and other PFSs are present. Water samples were analyzed by LC-ESI-MS/MS and showed that PFOS is the predominant compound in biota and that PFOA is predominant in environmental matrices (Sethilcumar *et al.*, 2007). This fact is supported by the hypothesis that FTOHs are major products of PFCs synthesis and that PFOS is a biotransformation product of FTOHs.

The focus of this article is on an aquatic ecosystem, because of contamination of the hydrosphere; aquatic ecosystems belong to the most burdened biota. Significant toxicological effects including growth inhibition of aquatic intervertebrates and changes in biodiversity (Sanderson *et al.*, 2004) have been identified. Sethilcumar *et al.* (2007) studied liver samples of market fish from Japan and found PFOS and PFOA in the livers of scad (*Trachurus trachurus*), sand fish (*Scincus scincus*), jack mackerel (*Trachurus symetricus*), rainbow trout (*Oncorhynchus mykiss*) and sardine (*Sardina pilchardus*). Amounts detected were estimated at ng.g^{-1} wet weigh. Predators showed higher levels of PFCs in liver than herbivorous or omnivorous fishes.

Laboratory studies suggest that, in fish, uptake from water via the gills and in the diet are both important routes of accumulation (Martin *et al.*, 2003a, 2003b). Sinclair *et al.* (2005) investigated the distribution of PFS in surface waters and in livers of fish and birds in New York State and they also reported PFOS, the most abundant perfluorinated compound, in all fish and bird samples. Two species of popular sport fish, smallmouth bass (*Micropterus dolomieu*) and largemouth bass (*Micropterus salmoides*) were analyzed. Average concentrations of PFOS in fish were 8,850-fold greater than those of surface water. This study highlights the significance of dietary fish in PFOS accumulation in the food chain. In addition, fish can be a significant source of human dietary exposure to perfluoroalkyl substances. Nonetheless, PFCs accumulate preferentially in the liver rather than in muscle of fish (Giesy & Kannan, 2001), and so potential exposure of humans to PFCs via fish consumption plays a nominal role in the risk assessment. In addition to fish tissues PFSAs and PFCAs were reported in fish eggs, suggesting significant intra-ovarian transfer to offspring, possibly through the compounds binding to egg proteins (Houde *et al.*, 2006). Measurements of PFCAs and PFSAs in bottlenose dolphin tissues have shown that plasma, liver and lungs are among the most contaminated organs, and also were found in milk of bottlenose dolphins, suggesting that maternal transfer occurs during lactation. A similar monitoring study was conducted by Jandova & Hajslova (2006) in Czech rivers Vltava and Labe. Results of their study are demonstrated in Figure 2.

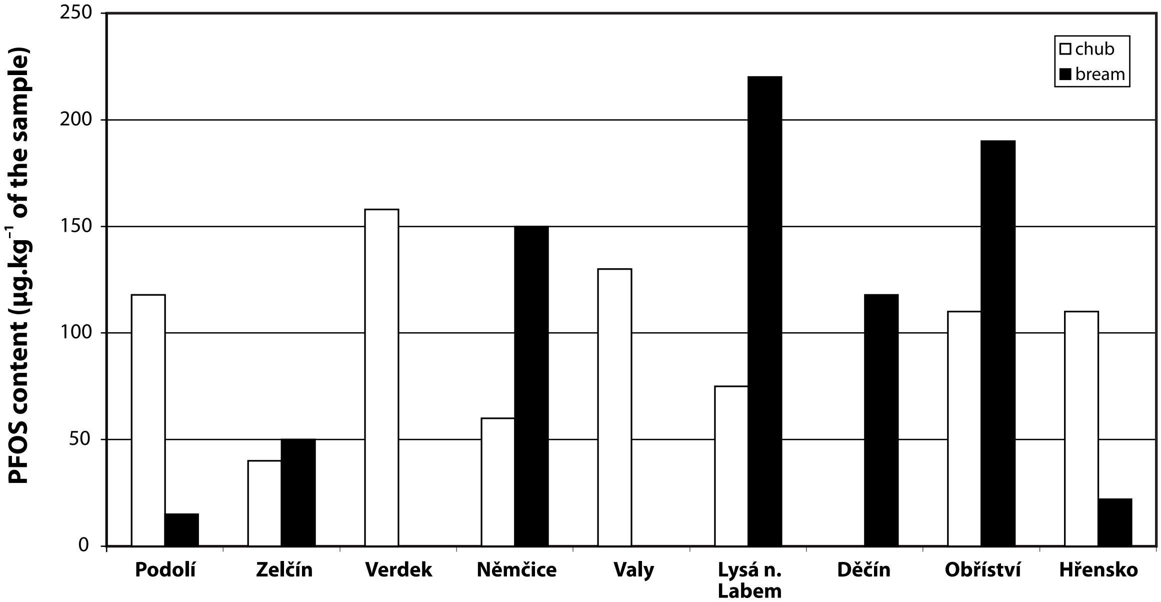

Figure 2. PFOS levels in the livers of chub (*Leuciscus cephalus*) and bream (*Abramis brama*) taken at various locations in Czech rivers Vltava and Labe in 2005, after Jandová *et al*. (2006).

Terrestrial ecosystems

PFS concentrations measured in other animals are in the same range as those detected in fish, with PFOS being the predominant compound in all organisms. PFOS is the compound occurring at the highest concentration, except in some urban or industrial areas where PFOA may have local sources (Houde *et al*., 2005). Generally, PFOS concentration was followed in order by PFOA, perfluorohexane sulphonate (PFHxS), and PFOSA. When analyses of multiple PFAAs are performed, PFOS, PFCAs and PFHxS can bioaccumulate and biomagnify through food webs, reaching elevated concentrations in higher trophic level species.

Biomonitoring data show that PFSs are globally distributed and that biota concentrations are higher when collected close to urbanized/ industrialized regions. Giesy & Kannan (2001) reported the highest concentrations of PFAAs in the livers of piscivorous animals living near industrialized areas. Humans contain greater concentrations than wildlife and have different ratios of PFOS/PFOA. The isomer profile in human blood samples shows a dominance of linear PFCAs. Linear PFCAs are also predominant in polar bear livers (De Silva & Mabury, 2006) suggesting that (i) they are more exposed to linear PFCAs, (ii) linear PFCAs are preferentially absorbed and/or (iii) branched PFCAs isomers are more readily eliminated. Several biomonitoring studies have been conducted in which simultaneous concentrations in organisms and water have been measured in the field, thus enabling field-based bioaccumulation factors (BAFs) to be calculated. Field-based BMFs and BAFs generally increase with increasing perfluoroalkyl chain-length, as observed in laboratory studies (Martin *et al*., 2003a). Numerous factors, such as organism size and unmonitored trophic concentrations, could affect the calculation of BMFs and BAFs, producing many discrepancies. These studies (Martin *et al*., 2003a, 2003b) indicated that animals feeding higher up the food chain had greater PFOS concentrations. Toxicokinetics is not readily clear recently. In some organisms PFC attached to albumin is transported to certain tissues, mainly liver, kidney, lungs, brain and thyroid. Bioaccumulation is due to slow elimination as well as enterohepatic recirculation of PFSs. PFOS has been measured in the brain, suggesting that it can cross the blood-brain barrier as observed in rats (Harada *et al*., 2006a). Transplacental and lactational exposure of neonates to PFCs was determined too (Hinderliter *et al*., 2005). They have been detected in bird eggs, indicating intra-ovum transfer as mentioned above. PFCAs and PFSAs have been measured in dolphin urine which indicates that this may be an important depuration pathway (Fujii *et al*., 2007). The rate of elimination is enhanced with decreasing carbon chain length. The elimination half-life depends on the type of PFS, animal species and in some cases gender of the individual. The half-life of PFOS ranges from 100 days in rats (Johnson *et al*., 1979) to 5.4 years in humans (Olsen *et al*., 2007). PFOA also shows gender differences in elimination; the half-life of PFOA in adult female rats is only 2–4 hours compared to 4–6 days in adult male rats (Kemper, 2003). The elimination is not always faster in females, a converse effect was observed in hamsters and there are no gender differences in mice or rabbits (Hundley *et al*., 2006, Lau *et al*., 2006). The reasons for species and gender differences in elimination of PFOA are not well understood. Elimination is downregulated by testosterone in both female and castrated male rats (Kudo *et al*., 2001, 2002; Vanden Heuvel *et al*., 1992) and upregulated by oestradiol in male rats (Ylinen *et al*., 1989). These differences may be due to the actions of organic anion transporters in the kidney since several transporter proteins are expressed differentially in male and female adult rats (Buist *et al*., 2002; Kudo *et al*., 2002; Buist & Klaassen, 2004). Some of these differences develop during the period of sexual maturation (Buist *et al*., 2002). To date, only one compartment model is used for PFOA and a toxicokinetic model of PFOS has been explored for monkeys (Anderson *et al*., 2006).

The highest concentrations were found in plasma and liver of bottlenose dolphins from the USA and in polar bears. Bottlenose dolphins have a coastal habitat and many are year round residents in areas of human activity and polar bears are food chain apex predators in the Arctic food web. As a consequence, Arctic beluga whales generally have a higher concentration of precursors of PFCs than other animals because they have a lower biotransformation potential toward organohalogens such as polychlorinated biphenyls and flame retardants (Mc Kinney *et al*., 2006).

Human populations

Only few data are available on trends of PFAAs in human populations. Data from The National Health and Nutrition Examination Survey have recently become available and will provide the baseline data from which future trends can be measured in the United States (Calafat *et al*., 2007). PFSs have been detected worldwide in human blood/serum, with PFOS being the most prevalent compound in humans, followed by PFOA (Houde *et al*.,2006). The measurements indicated that some residents of developing countries and remote regions are exposed to PFCs in a manner similar to people inhabiting industrialized and urban areas. The routes of human exposure to PFAAs are currently being investigated and include drinking water, dust in homes (Strynar *et al*., 2008), and food or migration from food packaging and cookware (Moriwaki *et al*., 2003; Begley *et al*., 2005; Kubwabo *et al*., 2005; Powley *et al*., 2005; Shoeib *et al*., 2005; Emmet *et al*., 2006; Falandysz *et al*., 2006; Tittlemier *et al*., 2006, 2007; D´eon and Mabury, 2007;Sinclair *et al*., 2007). However, studies of PFOA released from anti-adhesive cookware did not recover detectable levels of PFOA. Personal care and cleaning products may constitute additional exposure routes.

The effects of ethnicity and sex on PFSs concentrations have been evaluated. Significantly higher liver concentrations of PFOS, PFOA, and PFNA were found in males than females (Harada *et al*., 2006a). In addition concentrations of PFOS and PFOA were higher in more highly educated cohort members. Other studies refer to higher PFS serum concentrations found in American children compared to adults (Houde *et al*., 2007). Different activity (e.g., playing on carpeted floors) and exposure patterns of children may explain the discrepancy. Workers exposed occupationally have serum levels of both PFOA and PFOS approximately one order of magnitude higher than those reported for the general population.

Various researchers have reported their results for PFAAs in whole blood, plasma and serum. Most of these studies assumed a 1:1 ratio between serum and plasma concentrations and have converted whole blood measurements to serum by doubling whole blood concentrations (Kannan *et al*., 2004; Kuklenyik *et al*., 2004). Other studies have reported different results and so resolution of this issue will require additional work. Fujii *et al*. (2007) collected data on PFOS and PFOA in human blood samples from various countries (Table 1).

TOXICOLOGICAL STUDIES

In general, no consistent association between serum fluorochemical levels and adverse health effects has been observed. It is noteworthy that these data are preliminary, cross-sectional, based on small sample sizes, and are derived from different matrices (plasma vs. serum) (Olsen *et al*., 2006, 2007a). Studies examining PFC toxicity have focused on hepatotoxicity, developmental toxicity, immunotoxicity, hormonal effects and neurotoxicity.

Hepatotoxicity

PFOS and PFOA are associated with liver enlargement in rodents and nonhuman primates (Pastoor *et al*., 1987). A 2-year bioassay of PFOS in Sprague–Dowley rats showed an increase of hepatocellular adenomas at a high dietary dose of 20 $mg.kg^{-1}$(3M Company, 2002; Seacat *et al*., 2003). All perfluorinated compounds induced hepatomegaly and peroxisomal β-oxidase activity. The peroxisome proliferator-activated receptors (PPARs), including PPARα, PPARβ/δ, and PPARγ, are a family of transcription factors belonging to the steroid receptor superfamily (Zhang *et al*., 2007). The peroxisome proliferator-activated receptor-alpha (PPAR-α) is involved in the control of lipid metabolism and transport. Activation of PPAR-α has been shown to upregulate adipose differentiation-related protein which is responsible for the formation of lipid droplets in many cell types (Yang *et al*., 2006). Agonism of PPAR-α has been suggested to be involved in tumour (primarily liver) induction in the rodents. The transactivation of PPARγ and PPARβ/δ was at a much lower level. The process of carcinogenesis is one of the most interesting and significant issues for researchers in different fields of medicine (Lewinsky & Wojciechowska, 2007). The key events in the PPAR-α-agonist mode of action for

Table1. Ranges of PFOS blood concentrations (ng.ml^{-1}) from humans in various countries, (after Fujii *et al*. (2007))

Location	Tissue	Number of sample	Mean [ng.ml^{-1}]	PFOS range [ng.ml^{-1}]	Reference
USA	serum	175	49.5	<1.3–164	Olsen *et al*., 2003
Columbia	whole blood	56	8.2	4.6–14	Kannan *et al*., 2004
Brazil	whole blood	27	12.1	4.3–35	Kannan *et al*., 2004
Italy	serum	50	4.3	<1–0.3	Kannan *et al*., 2004
Poland	whole blood	25	44.3	16–116	Kannan *et al*., 2004
India	serum	45	2.0	<1–3.1	Kannan *et al*., 2004
Malaysia	whole blood	23	12.4	6.2–18.8	Kannan *et al*., 2004
Korea	whole blood	50	21.1	3.0–92	Kannan *et al*., 2004
Japan	serum	38	17.1	4.1–40.3	Kannan *et al*., 2004
Sweden	whole blood	66	18.2	1.7–37	Kannan *et al*., 2004
Belgium	plasma	20	NR	4.5–27	Kannan *et al*., 2004
Australia	serum	40	18.2	12.7–29.5	Kärrman *et al*., 2007
China	whole blood	85	NR	10.6–142	Yeung *et al*., 2006
Germany	plasma	356	NR	2.1–55	Midasch *et al*., 2007

Note:
NR, not reported; Whole blood converted to serum measurements (multiplied by a factor of 2).

rodent liver toxicity and hepatocarcinogenesis have been described, and include activation of PPAR-α followed by altered expression of genes involved in peroxisome proliferation, cell cycle control, and apoptosis (Klaunig *et al*., 2003). An *in vitro* study (Luebker *et al*., 2002) has shown that PFOS and PFOA interfere with the binding of fatty acids, or other endogenous ligands, to rat liver acids binding protein (L-FABP). It was suggested that displacement of endogenous ligands from L-FABP may be one mechanism by which PFOS and PFOA induce peroxisome proliferation (Luebker *et al*., 2002).

PFOA also possesses the properties of a mixed type enzyme-inducing agent and marked inductions of CYP2B2, CYP3A4, and CYP4A1 liver microsomes have been observed (Elcombe *et al*., 2007). Cytochrome P450 (CYP 450) is a family of detoxification enzymes. Perturbation of their activity and function is grave and may be associated with carcinogenesis. PFOA interacts with multiple members of the nuclear hormone superfamily, particularly PPAR-α, constitutive androsterone receptor (CAR), and pregnane X receptor (Elcombe *et al*., 2007).

Another effect which may play a role in carcinogenesis is loss of gap junctional intercellular communication (GJIC) (Trosko & Rush, 1998). GJIC is a process by which cells exchange ions, second messages, and other small molecules. In multicellular organisms, GJIC is important in the maintenance of tissue homeostasis and is involved in normal growth, development, and differentiation. PFOS and related compounds also inhibit GJIC *in vitro* and this effect is dependent on the length of the fluorinated carbon chain. However, inhibition of GJIC is a widespread phenomenon. In these studies, its effect was neither species- nor tissue-specific and was generally reversible. Hence, the pathophysiological significance of GJIC inhibition, with regard to the carcinogenic potential of PFOS and PFOA, is currently unclear.

Developmental toxicity

In animal studies PFOS and PFOA induced tumours and developmental toxic effects. The teratological findings of PFOS and N-EtFOSE in rat, mouse and rabbit are generally unremarkable when maternal toxicity is taken into consideration (Case *et al*., 2001; Thibodeaux *et al*., 2003; Luebker *et al*., 2005). Prenatal exposure to PFOS produced fetal weight reduction, cleft palate, delayed ossification of bone and cardiac abnormalities. These pathological changes were seen primarily at the highest dietary doses of 10 mg.kg^{-1} daily during pregnancy. Significant reduction of maternal weight gain was also noted. When rats exposed to PFOS were allowed to give birth, newborns became pale, inactive and moribund within 60 min. Survival improved with lower PFOS exposure, so that in the lowest dose treatment, the neonates were born alive and active. Development of the pups was also hindered, as significant delays in eye-opening, pinna unfolding, surface righting and air righting were noted (Midasch *et al*., 2007). The critical period of exposure is late gestational or perinatal because the neonatal mortality requires PFOS exposure of pregnant rats after day 19 of gestation. These results suggest that organ systems developing late in gestation may be a target for PFOS insult.

Grasty *et al*. (2003, 2005) described significant histological and morphogenetic differences between control and PFOS-treated lungs in the newborns, suggesting that PFOS might inhibit or delay perinatal lung development. Grasty *et al.* (2005) examined the mixing behaviour of dipalmitoylphosphatidylcholine (DPPC), a major component of pulmonary surfactant, with PFOS by differential scanning calorimetry and fluorescence anisotropy. They found that PFOS had a strong tendency to partition into lipid bilayers (Matyszewska *et al.*, 2007). Such PFOS-DPPC physical interactions might interfere with the normal physiological function of pulmonary surfactant. The same result with PFOA provided further support for this hypothesis (Xie *et al.*, 2007). PFOA exposure during gestation also causes developmental toxic effects. A two-generation toxicity study with PFOA showed that parental (P) and F_1 generation male rats suffered decreased body weight along with increased liver and kidney weights at all doses. In contrast, female rats did not show similar changes and no reproductive endpoints were affected by PFOA treatment in either generation.

Since PFOA is a PPAR-α agonist, several studies have examined the potential role of this pathway on mammary gland development and function (Kärrman *et al.*, 2007). PFOA-exposed female pups displayed stunted mammary gland epithelial branching and growth at 10 to 20 days postpartum with no progression of duct epithelial growth evident over this period. Few changes in β-casein and α-lactalbumin following exposure to PFOA were also noted. A PPAR-α signal is required for PFOA induced postnatal lethality, and that expression of one copy of the gene is sufficient for this effect (Rosen *et al.*, 2007). As more information of PFAAs in human populations becomes available, results from animal studies can readily be extrapolated to evaluate the potential human health risks.

Immunotoxicity

The immunotoxic potential of PFOA was examined in the mouse (Yang *et al.*, 2006), where exposure to PFOA led to thymic and splenic atrophy. The numbers of thymocytes and splenocytes significantly decreased >90% and >50%, respectively, by PFOA treatment. Inhibition of cell proliferation as well as suppression of inflammatory response was observed. The response of T- and B-cell activation was attenuated by the fluorochemical. This suggested that PFOA is immunotoxic and its exposure may augment the IgE response to environmental allergens. The immunomodulating action of PFOA appeared to be mediated by the PPAR-α signaling pathway. Wan & Badr (2006) have suggested that hepatocyte-specific retinoid X receptor-alpha plays a role in the anti-inflammatory response to PFOA. The effect on spleen and thymus weights are fully reversible; return to normal weights occurs within 5 to 10 days, respectively, after withdrawal of PFOA from the diet, in contrast to the more persistent effect on liver weight and hepatic peroxisome proliferation.

Hormonal effects

A single dose of PFDA significantly reduced T4 and T3, lowered body temperature, and depressed heart rate in rats. PFDA decreases serum levels of thyroid hormones by reducing the responsiveness of the hypothalamic-pituitary-thyroid (HPT) axis and by displacing circulating hormone from their plasma protein binding sites. Depression of serum T4 and T3 was shown in PFOS-exposed rats (adults, pregnant adults, and neonates), although a corresponding elevation of TSH through feedback stimulation of the HPT axis was absent (Lau *et al.*, 2003; Seacat *et al.*, 2003; Thibodeaux *et al.*, 2003; Luebker *et al.*, 2005;).

In addition to thyroid hormone disruption, changes in sex steroid biosynthesis by PFAA have been reported. Administration of PFOA to adult male rats for 14 days led to a decrease in serum and testicular testosterone and an increase in serum oestradiol levels. The latter was likely associated with increased hormone synthesis in the liver through induction of hepatic aromatase. Furthermore, these hormonal alterations have been implicated in the induction of Leydig cell adenomas seen in rats chronically exposed to PFOA. Preliminary results thus indicated that these PFAAs might be weak xenoestrogens in the environment.

Neurotoxicity

Although PFOS was primarily concentrated in the liver and blood, substantially higher concentrations of PFOS were detected in the neonatal rat brain (Lau *et al.*, 2006). The effects of PFOS on calcium currents have raised concerns that it may have toxicological effects on the central nervous system. Some studies (Harada *et al*, 2006b) in isolated guinea-pig ventricular myocytes and Purkinje cells of *Xenopus laevis* were performed. It has been shown that PFOS altered the activation and inactivation of ionic current (I_{Ca}, I_{Na}, I_K and I_{HCN1}) in the hyperpolarized direction (Wang *et al.*, 2007). These effects appeared to be consistent among different ionic channels and types of cells. Therefore, it was considered that the shifts in the inactivation/activation were due to changes in the surface potential of the cell membrane. PFOS also reduced the firing rate, hyperpolarized the resting membrane potential and decreased action potential frequency (Harada *et al.*, 2006b). This study demonstrated that PFOS has a general inhibitory effect on action potentials *in vitro*, however, the possible toxic effects on the central nervous system *in vivo* remain to be investigated.

CONCLUSION

Recently there has been a great deal of progress in understanding of the distribution and adverse effects of PFAAs in the environment, wildlife, and humans. However, there remain many questions. Although monitoring studies have clearly shown the presence of PFAAs worldwide, the sources and pathways of exposure are unknown. In addition, more standardized analytical methods are needed to understand the effects and temporal trends in exposure. In some cases, wide ranges of values have been reported and on the other hand the sample sizes reported have been small. It is impossible to determine whether this variability is due to matrix effects or due to different laboratory methods, so confidence in existing data is low. Since data quality improvement was needed in the analysis of perfluorinated compounds, the first worldwide study was conducted (Martin *et al*., 2004; Van Leeuwen *et al*., 2006). The participants included 38 laboratories from 13 countries, and each laboratory analyzed 13 PFAAs in three environmental and two human samples. There was approximately 65% concordance between laboratories for PFOS and PFOA in human blood and plasma; but other PFAAs did not fare as well. A second inter-laboratory study is currently underway. Additional work is needed to determine and elucidate other facts in this broad issue. There have also been significant advances in descriptive toxicology for a variety of PFAAs as well as studies of the potential mode of action for some of the toxicological responses. In addition, further research is needed to understand the potential long-term consequences and explore the possible mode of action of these compounds. A leading question for research today, which has major implications for the future, is whether the environmental burden of PFSs is associated with environmental and/or human risk. If the environmental burden of PFSAs and PFCAs is the result of (i) emissions of nonpolymerized residual precursors, or (ii) release of PFSAs and PFCAs from multiple direct applications in aqueous fire-fighting foams or as processing aids, then it can be reasonably hypothesised that a phase-out of, or improvements in, process technology should lead to levelling off, or slow decrease, in the environmental burden of PFSAs and PFCAs. Although the production of PFOS by its major manufacturer was phased out at the end of 2002, replacement PFAA chemicals (such as PFOA and perfluorobutane sulphonate, PFBS) are filling the demand in the consumer and industrial markets. It is anticipated that other PFAA products will be developed to fill the commercial void. If PFCs production and use is not managed, and continues or increases, then levels in the environment including in humans and animals will probably rise.

Consequently, PFOS and 96 PFOS-related substances were proposed as a POP candidate by Sweden in 2005. Recently PFOS has been undergoing risk management evaluation. Similarly, the U .S. Environmental Protection Agency initiated the PFOA Stewardship Program to work toward eliminating emissions and product content of these chemicals by 2015 (U.S EPA, 2006).

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