REVIEW ARTICLE

Occurrence and Toxicology Aspects of Perfluorooctane Sulfonate (PFOS) and Perfluorooctanoic Acid (PFOA) in the Environment and Food: A Review

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ABSTRACT

Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are two perfluorinated chemicals that have recently become international concerns. These compounds are ubiquitously bioaccumulated in the environment and food chain for a long period due to their high chemical and biological stability. PFOS and PFOA are currently being transmitted via the aquatic medium, posing a concern not only to the aquatic ecosystem but also to human and animal health. Evidence of PFOS and PFOA-based toxicity has been associated with hepatoxicity, immunotoxicity, developmental toxicity, endocrine disruptor, and cancer. PFOS and PFOA are primarly absorbed into the animal and human body through ingestion and bioaccumulate in the plasma, liver, and kidney. PFOS and PFOA are difficult to degrade, and as a result, they are frequently excreted in urine in their unchanged form. Methods for detecting PFOS and PFOA at trace levels in environmental and food matrices have been improved over time, resulting in their detection in a variety of environmental and food matrices. Nowadays, PFOS and PFOS have been identified as potential hazards and are included as novel persistent organic pollutants (POPs) in the Stockholm Convention, however their use in some countries such as Malaysia is unregulated. Although PFOS and PFOA have been widely explored in the environment and in food, and toxicological effects in some animals have been identified, human studies warrant further investigation.

Keywords: PFOS, PFOA, Toxicology, Environment, Food

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INTRODUCTION

Perfluorinated compounds (PFCs), often widely referred to as perfluoroalkyl and polyfluoroalkyl, are a group of chemicals of significant importance for industrial and consumer applications. These complex heterogeneous compound groups have been in use for more than 60 years since they were first developed in the 1950s (1). They are used as surfactants and protective coatings for cooking utensils, upholstery, water resistant fabrics and fire-fighting foams (2). Structurally, PFCs are organic compounds with a carbon backbone surrounded by fluorine, indicating their resistance to heat and acid that cause chemical degradation (Fig. 1). Meanhwile, its long-lasting properties and usefulness as surfactants and polymers are due to its stable fluorine-carbon bonds as well as its hydrophobic and lipophobic properties (3). Perfluorinated chemicals are generally classified into 42 families and sub-families, with a total of several hundred compounds. These compounds are known as either "long chain" or "short chain" perfluorinated compounds depending on the length of the carbon chain. The long chain is more of concern due to its accumulative tendency (4).

Perfluoroalkylcarboxylicacids(PFCAs)andperfluoroalkyl sulfonic acids (PFSAs) are the two main classes of long chain PFCs in which PFCAs are compounds with eight or more carbons and a functional group of carboxylic

acids at the end. Perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and pentafluorobenzoic acid (PFBA) are only a few examples of PFCAs (5). In the other hand, PFSAs are sulphonic acid compounds containing six or more carbons such as perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS) and perfluorobutane sulfonate (PFBS) (6). Compared to PFCA with the same length of fluorinated carbon chain, PFSA is shown to be more bioaccumulative and the two most relevant and commonly discussed PFCA and PFSA subclass members are perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) (Fig. 1) (7).

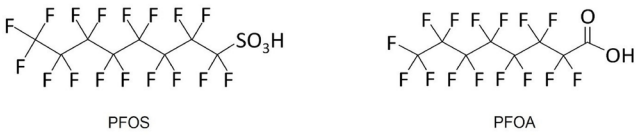

Figure 1: Chemical structure of perfluorooctane sulfonate (PFOS) and Perfluorooctanoic acid (PFOA) [adapted from Smith et al. (60)]

The diverse uses of PFC containing products have led to a widespread environmental and food presence of PFOS and PFOA. Both compounds have previously been described in water, soil, indoor air, house dust, food products, fish, avian eggs and in human blood serum (8-12). This has raised health concerns such as cardiovascular disease, immunodeficiency disorders and cancer due to their toxicity and bioaccumulative characteristics which meets the criteria for defining persistent organic pollutants (POPs) (13). Malaysia has yet to ratify the Stockholm Convention, which identified PFOS and PFOA as new POPs and called for global restrictions on them. Despite the fact that several studies, both globally and locally, have proven scientific evidence of the wide distribution and harmful effects of these substances, we have yet to see any proactive efforts done in Malaysia to regulate PFOS and PFOA (9, 14, 15). This review will gather scientific data on PFOS and PFOA in order to demonstrate their availability in the environment and food matrices. It also intends to investigate the hazardous effects and toxicological aspect of the chemicals. We updated the current method for detecting PFOS and PFOA in a variety of matrices as the presence of the compound at low concentrations may be harmful. This review attempts to provide more toxicological arguments in support of the necessity for regulatory action, notably in Malaysia.

PFOS AND PFOA FATE IN THE ENVIRONMENT

The presence of PFOS and PFOA in tissues of different wildlife species has caused initial concern and interest in the presence of PFCs in the environment (16). These organic perflourinated compounds are widely distributed because of their water-soluble nature, low to moderate soil and sediment sorption, and resistance to biological and chemical degradation (17). PFCs are believed to be majorly present in aquatic environments, and previous studies has projected that the ocean would be the ultimate repository of PFCs (18). Knowledge of transport, bioaccumulation, biomagnification and degradation pathways are therefore important in the assessment of the fate of PFOS and PFOA in the environment.

The global transport of perfluorinated compounds is aided by the use of water bodies (19). PFCs are transported by ocean water as a result of a combination of PFC discharges to surface waters, atmospheric loading, surface water precursor discharge, and PFC precursor transformation (20). Furthermore, the degree to which perfluorinated compounds sorb to sediment and soil during transportation influences their mobility in water (17). PFCs can also be transported through the atmosphere. These compounds have been reported to be capable of long-distance atmospheric transport (21). A study conducted by Liu et al (22), demonstrated the detection of PFCs in the atmosphere of Shenzhen, China with PFOS and PFOA as the major components. The study also discovered that long-distance pollution transport from the region's southeastern coastal area was the source of PFCs in the Shenzhen atmosphere.

Biomagnification of PFCs in food webs, especially involving long-chain types, has been identified by various field studies (23). A direct link between the length of the carbon chain and the bioaccumulation of PFCs has been identified. Martin et al (24) found that as the length of the perfluoroalkyl chain increased, both bioaccumulation factors (BAFs) and bioconcentration factors (BCFs) increased in rainbow trout (*Oncorhyncus mykiss*). Perfluoroalkyl sulfonates have higher BCFs and BAFs than corresponding carboxylates with the same perfluoroalkyl chain length. This indicated that, in addition to chain length, the acid functional group plays a role in bioaccumulation. Biomagnification can be measured using the biomagnification factor (BMF) or the trophic magnification factor (TMF). A BMF value greater than one (BMF>1) indicates that the substance between prey and predator has been biomagnified. The TMF indicates whether a chemical has the ability to biomagnify in food webs (TMF>1). A review of several marine and freshwater studies by Houde et al (25) found that most of the BMFs and TMFs for PFCs were reportedly greater than 1. To date, more progress is being made to better understand the fundamentals of perfluorinated compound bioaccumulation in the environment.

In Malaysia, PFOS and PFOA were studied in Langat River, an important drinking water source in Selangor, the most developed state in the country (26). The concentrations of PFOS and PFOA were found higher when comparing to other rivers in the developed countries such as Tennessee River (US) and Yodo River, Japan (27, 28). The presence of PFOS and PFOA in the river has been related to adverse pollution in water

bodies caused by the industrialization process.

PFOS AND PFOA IN FOODS

Apart from occupational hazards, people are exposed to perfluorinated compounds through consumption of contaminated food and water and major exposure was confirmed to be mostly from the dietary route (29). These are much of a concern, considering the potential of perfluorinated compounds to bioaccumulate in the food chain. In 2008, a tolerable daily intake of 150 ng/kg for PFOS, 1500 ng/kg for PFOA was established by the European Food Safety Authority (European Food Safety Authority, 2008). Many studies on food have been performed, and the results of PFOA and PFOS in foods are summarised in Table I.

Table I: Detection of PFOS and PFOA in food products

Source of food	Sample type	Type of perfluorinated compounds	Measured concentration	Location	Reference
Fish	Blood	PFOS	1 to 834 ng mL^{-1}	Tokyo bay; Osaka bay; Lake Biwa, Japan	(61)
	Liver	PFOS	3 to 7900 ng g^{-1}		
	Blood	PFOS	Up to 29,600 ng g^{-1}	Mississippi River, USA	(17)
	Liver	PFOS	Up to 6,350 ng g^{-1}		
	Muscle	PFOS	<0.03 to 79.9 ng g^{-1}	Pearl River Delta, South China	(15)
	Muscle	PFOS	0.04 to 211 ng g^{-1}	Lake Maggiore, Italy	(16)
Meat and related products	Beef products	PFOS	0.5 to 2.7 ng g^{-1}	Canada	(18)
		PFOA	<0.4 to 2.6 ng g^{-1}		
	Pork products	PFOS	Mean: 0.045 ng g^{-1}	Catalonia, Spain	(62)
		PFOA	Mean: <0.053 ng g^{-1}		
	Pig (liver)	PFOS	0.094 to 11.30 ng g^{-1}	Beijing, China	(19)
		PFOA	0.034 to 1.790 ng g^{-1}		
	Beef cattle (muscle)	PFOS	Mean: 1.1 ± 0.1 µg g^{-1}	North Dakota, USA	(21)
	Beef cattle (liver)	PFOS	Mean: 17.9 ± 2.3 µg g^{-1}		
Dairy products	Milk, cheese	Total PFCs	Mean: <1 ng g^{-1}	United Kingdom.	(63)
	Cheese	PFOS	Mean: 12 pg g^{-1}	Oslo, Norway	(26)
		PFOA	Mean: 13 pg g^{-1}		
	Milk	PFOS	Mean: 7 pg g^{-1}		
		PFOA	Mean: 4.7 pg g^{-1}		
	Milk	PFOS	<5 to 695 pg g^{-1}	Beijing; Tianjin; Wuhan, China	(19)
		PFOA	<18 to 178 pg g^{-1}		
	Yoghurt	PFOS	<5 to 32 pg g^{-1}		
		PFOA	<18 to 229 pg g^{-1}		
	Milk	PFOS	Mean: 10 pg g^{-1}	Netherlands	(23)
		PFOA	Mean: 1 pg g^{-1}		
	Cheese	PFOS	Mean: <85 pg g^{-1}		
		PFOA	Mean: <19 pg g^{-1}		
	Milk	PFOS	Up to 36.3 ± 9.1 µg L^{-1}	Germany	(22)
	Full cream milk	PFOS	0 to 31 ng/L	Italy	(24)
Other food types	Cereals	PFOS	Mean: <0.70 µg kg^{-1}	Italy	(30)
		PFOA	Mean: <0.50 µg kg^{-1}		
	Tea	PFOS	Mean: 0.030 ng/L	Oslo, Norway	(26)
		PFOA	Mean: 9.5 ng/L		
	Vegetables and fruits	PFOA	Mean: 0.001 ng g^{-1}	Busan, Korea	(29)
	Vegetables	PFOS	Mean: 0.022 ng g^{-1}	Catalonia, Spain	(20)
		PFOA	Mean: <0.027 ng g^{-1}		
	Flour	PFOS	Mean: <9 pg g^{-1}	Netherland	(23)
		PFOA	Mean: 17 pg g^{-1}		
	Chicken eggs	PFOS	45.0 to 86.9 ng g^{-1}	China	(27)
	Chicken eggs	PFOS	<0.5 to 24.8 ng g^{-1}	Netherlands	(28)
		PFOA	<0.5 to 2.7 ng g^{-1}		
	Chicken eggs	PFOS	<0.50 to 0.64 ng g^{-1}	Malaysia	(64)
		PFOA	<0.10 ng g^{-1}		
	Duck eggs	PFOS	<0.50 ng g^{-1}	Malaysia	(64)
		PFOA	<0.10 ng g^{-1}		
	Quail eggs	PFOS	<0.50 to 0.69 ng g^{-1}	Malaysia	(64)
		PFOA	<0.10 ng g-1		

Fish are known in consumers as a major food source for perfluorinated compounds. Different studies have shown the bioaccumulation ability of PFOS and PFOA in fish (30, 31). PFOS was found to be dominant PFCs in fish samples with concentrations ranging from <1 ng/g (w/w) to >100 ng/g (w/w) depending on location (32). The highest concentrations of PFOS in fish were found in samples collected from the Mississippi River where the PFOS concentration in the blood sample of white bass was found to be 29,600 ng/g and the PFOS concentration in the liver of a small oral bass was up to 6,350 ng/g (33). The findings reveal that the concentration of PFOS was correlated to PFOS in water, as the PFOS level was considerably high in the sampling area. The distribution to the tissue of perfluorinated compounds in fish was also high in liver compared to muscles suggesting that PFCs were highly binding to the liver fatty-acid (30).

Animal meat, particularly ruminants, has been reported to contain a substantial concentration of perfluorinated compounds after fish (34). The environmental exposure of agricultural animals to contaminated food, water or air results in the presence of PFCs in meat and related products. According to Tittlemier et al (35), PFCs in meat products were relatively high compared to all food products analysed in their study, where PFOS and PFOA were frequently detected in meat, similar to findings from other studies of farm animals in Beijing (36), Spain (37) and USA (38).

Several studies have been conducted on the bioaccumulation of perfluorinated compounds in dairy products (39-41). The presence of perfluorinated compounds in agricultural products, such as milk, indicated the transfer of contaminants from the feed to ruminant tissue and excretion. A study by Kowalczyk et al (39), revealed a high concentration of PFOS (24.2 ± 9.0 µg/L), compared to other PFCs, in the studied cow's milk samples. Several dairy products purchased from markets in China were also analysed for exposure to PFCs from a dietary source. The findings suggested a mean total PFC concentration of 178 pg/g (wet weight) in milk, 98 pg/g (dry weight) in milk powder and 42 pg/g in yoghurt (wet weight) (42). Another study by Haug et al (43) indicated that milk and dairy products contributed to 16% of the total PFOS daily intake and 14.5% of the total PFOA daily intake. Therefore, milk and dairy sources may potentially contribute to dietary PFCs exposure in human, after fish and meat.

Due to the ubiquitous nature of perfluorinated compounds, studies in food has been on expansion, involving various types of foods. Studies on chicken egg, done in China (44), Netherlands and Greece (45), indicated presence of predominantly PFOS in the egg yolk, in the range of <0.5 ng/g (w/w) up to >100 ng/g (w/w). The exposure of PFCs in chicken eggs are mostly contributed to the feeding habits, especially by the free foraging chicken. PFCs contamination was also reported in vegetables, such as potato, carrot, lettuce, at a relatively lower concentration. Heo et al (46) reported in his study that food with high moisture contents such as vegetables, fruits, and beverages, often contain short-chain PFCs (such as PFBA and perfluoropentanoic acid, PFPeA), compared to food with low moisture contents. Other types of food included in studies of PFCs are processed foods (baked beans, canned tuna), fruit jams, beverages, cereals, breads and oil (40, 43, 46, 47).

The occurrence of PFOS and PFOA in food in Malaysia was also investigated in the egg yolks, and it was discovered that PFOS was more prevalent than PFOA in the screened yolk samples, with concentrations ranging from 0.50 ng/g to 1.01 ng/g (48). However, when compared to prior studies in the Netherlands and Greece, the PFOS concentration was lower (45). The contamination of PFCs in poultry eggs is predominantly attributed to these farmed animals' exposure with the external environment, primarily by consumption of contaminated soil, water, or feed.

TOXICOKINETICS OF PFOS AND PFOA

Human exposure to PFCs mainly occurs via ingestion of contaminated foods or water (dietary uptake) where the source of contamination in foods may come from the production processes and/or contact with PFCs-coated cookwares (14). PFOS and PFOA are also easily absorbed after oral exposure by the gastrointestinal tract (15). Apart from oral exposure, inhalation, or dermal contact with PFC-containing dust, or aerosols, can also lead to the absorption of PFOS and PFOA (49). Nevertheless, dermal exposure are less significant than ingestion and inhalation (50).

PFOS and PFOA have a low affinity to lipids, are very water soluble and preferably bound to proteins. The distribution and accumulation of PFOS and PFOA occurs primarily in plasma, liver and kidneys (51). It was suggested by Jones et al that the PFOS molecule's physicochemical structure causes either the sulphonic acid group or the hydrophobic alkyl chain to interact with serum proteins, with PFOS primarily binding to serum albumin at a 1:1 stoichiometric ratio (52). The chain length and acid head group of PFCs have a significant impact on their binding affinity and preference for binding sites. These chemicals bind to serum albumin with the same binding site and affinity as fatty acids (53). In mammals, both PFOS and PFOA are recalcitrant towards metabolism. PFCs are resistant to catabolism and phase II conjugation in general, and they are poorly excreted in humans. Only the precursors, such as FTOH, have been confirmed to undergo perfluorinated compound metabolism. Studies have shown the formation of PFCAs from metabolism of telomer-based precursors where the alcohol groups are oxidised to form fluorotelomer aldehyldes, which are then oxidised to saturated fluorotelomer compounds like FTCA

(fluorotelomer saturated carboxylate) (54). Martin et al (55) demonstrated that FTOHs can be metabolized to perfluorinated carboxylic acids of various chain lengths, suggesting an explanation for the presence of long chain PFCs in human blood. In addition, both PFOS and PFOA are shown to have the capability to cross the placental barrier. According to a pilot study conducted by Midasch et al (56), PFOS concentrations decreased by a factor of 0.41 to 0.80 from maternal to cord plasma, but PFOA concentrations were higher in the placenta than in maternal plasma (ratio of cord plasma : maternal concentration range from 0.91 to 1.95). Nevertheless, the findings revealed that PFOS and PFOA would cross the placental barrier, potentially causing harm to neonatal development.

Urinary excretion is an essential mechanism for the removal of PFCs from the body (57). Both PFOS and PFOA are excreted in urine and faeces, without undergoing biotransformation due to the carbon-fluorine stability and high electronegativity of the perfluorinated alkyl chains (57). Urinary excretion is a fraction of the systemically ingested oral dose of toxicants excreted by the urine, while faecal excretion is a systemically absorbed toxicant found in the digestive tract as well as a portion of non-absorbed toxicants (58). A study in elimination rates of PFOA in male and female cynomolgus monkeys after oral and intravenous dosing showed urinary elimination half life of approximately 20 to 30 days (59). Seacat (60) reported a half-life of approximately 200 days for PFOS in male and female cynomolgus monkeys following daily oral dosing over six months. Due to the long half-life, it takes several months to years for PFOS and PFOA to be completely removed from the body of the mammal.

It should be noted that the absorption, distribution, metabolism, and excretion of PFOS and PFOA should be approached with caution. Individuals, species, and other underlying variables such as age, weight, and genetic make-up can all influence toxicokinetic profiles (61).

TOXICITY OF PFOS AND PFOA

Since PFCs are persistent and bioaccumulative, they are likely to have health implications to animal and human. The presence of PFCs in human sample was earlier discovered by Taves (62) in the late 1960s, when he found fluoride in blood samples that are partially bound to organic compounds of unknown structure. Subsequent studies in the 1970s reported higher than normal organic fluorine levels in the blood of flurochemical industrial workers, indicating the effects of exposure of perflurochemicals (63). However, apparent studies on perfluorinated compounds began in the 2000s, as PFCs were widely found in the environment and human blood samples (64). Laboratory animal studies and epidemiological research on human population had demonstrated affiliation between the exposure to certain PFCs to a wide range of adverse health effects (65).

Body and organ weight changes

A study of the subchronic toxicity of PFOS potassium salt in cynomolgus monkeys found that the monkeys given an oral dose of 0.75 mg/kg/day for 182 days lost a significant amount of their initial body weight and both female and male cynomolgus monkeys had significantly higher liver-to-body weight ratios (60). A study by Cui, Liao (66) showed a sharp loss of body weight in the Sprague-Dawley rats given the high exposure of PFOS at 20 mg/kg. Nonetheless, the results on body weight effects of PFCs differs between animals and human. In human, Liu, Dhana (67) discovered the effect of PFCs causing interference with human weight regulation, which may lead to obesity. They discovered that the greater the PFC concentrations in the blood, the greater was the weight regained after the initial weight loss. The findings were also complemented by a slower regression of the metabolic resting rate (RMR) defined as the amount of energy burned when the body was in a state of rest.

Hepatic toxicity

The potential for hepatic toxicity from exposure to PFCs was found in laboratory animal studies. Histopathological observation in the Sprague Dawley rats of exposure to PFOS and PFOA revealed cytoplasmic vacuolation, focal or flake-like necrosis and hypertrophy in the livers of each treated group (66). In the study, high dose exposure was associated with hepatic focal haemorrhage, erythrocytic transudation, and focal hepatocytic degeneration accompanied by inflammatory cell infiltration. Liver toxicity described by hepatocellular adenomas, hepatocellular hypertrophy and bile duct hyperplasia was observed in two mice strains (CD-1 and 129/Sv) exposed to gestational PFOA for 18 months (68). PPAR-ш (peroxious proliferator activated receptor-alpha) pathway and mitochondrial disruption were the proposed mechanism of action for PFOA-induced hepatic toxicity in rodents (68). However, these mechanisms have yet to be fully characterised and may be implausible for human liver toxicity.

Serum lipid level

Studies on occupationally exposed workers indicated positive association between the serum level of PFOS and PFOA, with serum lipid level, such as cholesterol (69, 70). A study by Sakr et al (71) on DuPont workers, had observed a positive correlation between serum PFOA and total cholesterol, low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL). Dyslipidemia (abnormal blood lipids) has been shown in general population to be related to environmental exposures to PFCs (69). Since dyslipidemia is strongly associated to an increased risk of cardiovascular disease, exposure to PFCs is likely to result in cardiovascular complications. In the findings of animals, however, there was a disparity between exposure to PFCs and serum lipid where in

a 5 mg/kg PFOS study, a decreased levels of serum cholesterol, high density of lipoprotein (HDL) and low density of lipoprotein (LDL), but a higher level of serum triglyceride were reported (72). The release of ventral fat and high serum albumin is proposed as factors that cause the triglyceride level to rise. The dissimilar response of the PPAR-α between the two species were suggested as the result of the opposite findings between human and animal studies (73). In addition to other regulations on physiological processes such as wound healing, reproduction and carcinogenesis, PPAR-α demonstrated an important role in lipid homesotasis (73).

Immunotoxicity

Both PFOS and PFOA have been reported for prompt immunomodulation in laboratory animal models where alteration of immunity is mostly associated with suppression of the antibody response, as demonstrated by Peden-Adams et al (74). In the study, humoral immunity was described as the most sensitive immune endpoint, and the suppression of antibody production suggested that cellular or molecular targets for humoral immunity suppression are attributed to alterations in B-cells or antigen presenting cells (APCs) (75). Data on immunotoxicity in humans is limited, but some studies have suggested that PFC exposure has immunosuppressive effects in humans, particularly in early life (76).

Other health effects

Cancer risks have been demonstrated in both *in vitro* and animal studies after exposure to PFCs (77, 78). Long-chain PFCs are possible carcinogens that can cause pathological effects by causing oxidative stress. An *in vitro* study using the human hepatoma cell line HepG2 found that when the culture was treated with several PFCs, the generation of reactive oxygen species (ROS) increased where an uncontrolled increase in ROS may cause DNA damage, implying that PFCs may be cytotoxic and genotoxic in humans (79). In addition, PFC serum levels are also associated with reproductive dysfunction, including infertility and poor semen quality in human populations (80).

DETECTION OF PFOS AND PFOA IN ENVIRONMENTAL AND FOOD MATRICES

The demand for the analysis of perfluorinated compounds in the environmental and biological medium has increased. The existence of these compounds in various phases and the complexity of biological matrices, particularly in biota, make determining their presence and distribution difficult (81). Pre-analytical preparation is important to ensure that all external sources of contamination can be eliminated. This is particularly true during the preparation of samples in the laboratory, where the ubiquitous presence of PFCs in laboratory materials and equipment would be a concern. Therefore, the use of any TeflonTM or other fluoropolymer containing materials must be avoided in the analysis of PFCs. Research in this area has changed tremendously since perfluorinated compounds were first identified in human blood serums using nuclear magnetic resonance (NMR) (82). Researchers have faced many analysis difficulties in the past as well as problems in sample extraction and preparation techniques due to the comparatively low levels of PFC in the most samples, the lack of pure authentic standards and internal standards. The use of a highly sensitive device, such as liquid chromatography tandem mass spectrometry (LC-MS/MS), has allowed the measurement up to a low pg/mL (ppt) of these compounds and has benefited greatly the research in this field (48). Moreover, the ultra-high-performance liquid chromatography (UHPLC) allows for rapid separation and high-resolutions analyses, thus allowing for better separation of PFCs in complicated samples, such as food matrices (83). As compared to gas chromatography mass spectrometry (GCMS) analysis, LC-MS/MS analysis does not include any derivatization measures, resulting in a simpler and faster analytical workout. Furthermore, using a mass spectrometric detector to detect precursor and product ion transitions provides precise confirmation of the target compounds' identity. However, developing and performing studies of these persistent compounds remains difficult. Poor recoveries, inter-laboratory variations, matrix complexity, and structural isomers in biological samples are just a few of the challenges raised (84). The presence of interference components such as lipids, proteins, organic matter, and pigments in biota and food analysis can result in ion suppression of target compounds, which would have a major impact on the sensitivity of the analysis. Furthermore, PFC extraction and sample preparation are typically time-consuming and expensive, as most laboratories must use comprehensive cleaning procedures, such as solid phase extraction (SPE), to achieve high target compound recovery (85).

The widespread occurrence and health hazards of perfluorinated compounds are key factors that lead to the intensive development of analytical methods for the biomonitoring of these compounds in different matrices. Recent advances in chromatographic techniques have given rise to new innovations, such as ultra-performance convergence chromatography (UPC2), which offers lower detection limits, narrower peak width and shorter acquisition time (81). Compared to other mass analyzers, the use of a high-resolution time-of-flight (TOF) mass spectrometer may also be considered due to a distinguished satisfactory system combining high selectivity and optimum sensitivity in trace analysis (86). In addition, many researchers have opted for analytical techniques using a green chemistry approach to minimise the environmental burden of PFC research (87). Green chemistry approach includes the use of the micro-solid phase extraction method (μ-SPE), which reduces the solvent amount used, simplifies the extraction process and can be applied to different complex matrices

such as biological tissues, food products and aqueous samples The fast and high analytical throughput can also be provided by simple techniques such as direct injection and protein precipitation. Other approaches in green analytics include the use of FUSLE, solid-liquid dispersion (dSPE) and turbulent flow chromatogram (TFC). The analytical methods for PFOA and PFOS detection are tabulated in Table II.

CONCLUSION

Both PFOS and PFOA are emerging contaminants which posed various challenges to the environment and human health. Our review shows that both of these compounds are widely distributed in the ecosystem, due to the persistent and bio-accumulative characteristics, as well as their capability of being transported to great distance. Their recalcitrant nature towards human metabolism resulted in disruption of endocrine and immune system, changes of body weight, and suspected carcinogenicity, as demonstrated by many *in vitro* and animal studies. It was learnt that between various exposure pathways, dietary intake was the main contributor among others. The consumption of fish and seafoods are postulated to be a significant dietary source, nevertheless, the presence of these compounds in other food materials such as eggs, meat and dairy products should not be neglected. Given the current condition, analytical approaches particularly involving the detection of these compounds have evolved from time to time. The development of new and green clean-up techniques, such as micro-solid phase extraction (μ-SPE), have aided researchers in analyzing these compounds within various complex matrices. In addition, the application of advanced instrumentation such as time-of-flight (TOF) mass spectrometer and ultra-performance convergence chromatography (UPC2) had contributed much to the increased sensitivity and resolution of the analysis. However, despite all the advancement, considerable knowledge gap such as issues involving variation of distribution and toxicity in animals and human still exist, thus, focus and concern in respective research areas are required. Further studies should also emphasize more on epidemiological and trend monitoring studies, in order to evaluate the consequences of these contaminants towards human and the entire ecosystem. Considering the potential hazard and inclusion of PFOS and PFOA as new POPs in the Stockhlom Convention, the use of both chemicals should be regulated in the country. In the case of Malaysia, there are just a few studies to support the reinforcement for PFOS and PFOA regulation, and the involvement of various stakeholders would be required in the future.

ACKNOWLEDGEMENT

The authors would like to thank Universiti Sains Malaysia for the funding to facilitate this study (USM short-term

Table II: Analytical methods for analysis of PFOS and PFOA

Sample type	Instrument used	Sample preparation technique	Analyte	Limit of Quantitation	Reference
Biological, environmental and food samples	Ultra-high performance liquid chromatography tandem mass spectrometry (UHPLC–MS/MS)	Automated on-line solid phase extraction	PFOS	50 ng L^{-1}	(65)
			PFOA	10 ng L^{-1}	
Marine organisms	Liquid chromatography-time of flight-mass spectrometry (LC-TOF-MS)	Solid phase extraction (SPE)	PFOS	0.1 ng g^{-1}	(66)
			PFOA	1 ng g^{-1}	
Fish fillet homogenates	Liquid chromatography tandem mass spectrometry	Simple protein precipitation	PFOS	0.51 ng g^{-1}	(4)
			PFOA	0.25 ng g^{-1}	
Sewage sludge	Ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UHPLC/Q-ToF-MS)	Focused ultrasound solid-liquid extraction (FUSLE)	PFOS	0.30 ng g^{-1}	(67)
			PFOA	0.60 ng g^{-1}	
Fish fillet	Liquid chromatography tandem mass spectrometry	Micro-solid solid phase extraction	PFOA	6.16 ng g^{-1}	(68)
Human serum	Liquid chromatography tandem mass spectrometry	Liquid-liquid extraction	PFOS, PFOA	0.03 μg L^{-1}	(7)
Chicken egg (yolk and albumen)	Liquid chromatography tandem mass spectrometry	Solid phase extraction (SPE)	PFOS, PFOA	0.5 ng g^{-1}	(69)
Chicken egg, duck egg and quail egg (yolk)	Liquid chromatography tandem mass spectrometry	Simple protein precipitation	PFOS	0.1 ng g^{-1}	(64)
			PFOA	0.02 ng g^{-1}	
Cereal		Solid phase extraction (SPE)	PFOS	0.70 μg kg^{-1}	(30)
			PFOA	0.50 μg kg^{-1}	
Rain and river water	Ultra performance convergence chromatography tandem mass spectrometry (UPC^2-MS/MS)	Solid phase extraction (SPE)	PFOS, PFOA	0.2 ng mL^{-1}	(70)
Tap water	Liquid chromatography tandem mass spectrometry	Dispersive liquid–liquid microextraction (DLLME)	PFOS	0.9 ng L^{-1}	(71)

grant/304/CIPPT/6315287).

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