Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env.Pharmacol. Life Sci., Vol 4 [7] June 2015: 183-191

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD
Global Impact Factor 0.533
Universal Impact Factor 0.9804

REVIEW ARTICLE

Impacts of Perfluorinated Compounds on Human Health

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ABSTRACT

Perfluorinated compounds (PFCs) have received worldwide attention in recent years. PFCs are organofluorine chemical compound. Several PFCs are being used as surfactants, surface protectors, popular for the non-stick cookware, stain-repellant and aqueous film-forming foams from the past five decades. PFCs are proposed as a new class of POP (Persistent organic pollutant), PFOA (Perfluorooctanoic acid), PFOS (Perfluorooctanesulfonate), and other typical PFCs are generally considered as reference substances. PFCs can be detected almost ubiquitously in water, different kinds of foodstuffs, fish, birds, as well as in human breast milk, blood and umbilical cord blood. Available data have provided evidence that PFCs are involved in the etiology of a variety of disorders including diabetes, cerebrovascular disease, neurotoxicity, immune deficiency and cancer. Recently, public concern has been focused on the effects of PFCs on humans. Efforts are needed to develop systematic studies and to investigate the mechanisms of action of PFCs in order to fully understand their effects on humans and wildlife.

Keywords: *Perfluorinated compounds, persistent organic pollutant, sources, health effects, PFOA, PFOS*

Received 02.03.2015 Revised 14.03.2015 Accepted 04.04.2015

INTRODUCTION

There are thousands of POP chemicals, often coming from certain series or families of chemicals. PFCs belong to the group of POPs, and there are different PFCs differing from each other by the level of the fluorine atom and substitution position. A huge expansion in industry and technology has taken place in the last century, leading to the development of numerous chemicals with properties favorable for specific purposes. Such chemicals are often present in consumer products including PFCs and the derivatives such as perfluorinated sulfonates (PFSAs), perfluorocarboxylic acids (PFCAs), perfluorinated telomere alcohols (FTOH), perfluorinated sulfonamides (FOSA) and perfluorinated phosphonic acid (PFPAs).The common characteristic of PFCs are the fully fluorinated alkyl chain of varying length and hydrophilic end group. PFCs molecules gain their properties from two basic parts, water-soluble head and nonpolar fluorinated tail. The Physico chemical properties of PFCs presented in table 1, indicates the large differences that exist between the water solubility and vapor pressure for the individual PFOS and PFOA substances. It should be noted that they are low in vapor pressure, highly soluble in water, and persistent in the environment (1). PFOA is sparingly volatile (3.3×10^{-4} pa) and moderately water soluble (1080 mg/L), and PFOS is completely water soluble (>20 mg/L). The hydrophilic and oleophilic nature of the PFCs is slightly different from other hydrocarbon surfactants, and they have peculiar physiochemical properties in the environment.

Based on the properties, these compounds are used in variety of industrial applications. For example in plastics and rubber industry (emulsifying agent for polymerization and latex stabilizer purposes), petroleum industry (wetting agent for oil well treatment), textile and leather industries (wetting agent for drying , printing work), paint and pigment industries (leveling agent for floor waxes, adjuvant for waxes to improve oil and water repellency), photolithography and semiconductors (surface-active qualities are exploited), photographic industry (anti-static and cleaning purpose), chromium plating (mist suppressant), fire fighting form (wetting agent for fire-fighting agent in forest), floor polishes, pharmaceutical industries (2). After five decades of their production, the 3M Company, the major producer phased out PFOS and some of its derivatives in 2002 due to their toxicity, persistence, bioaccumulation and global distribution. Also, the European Union (EU) banned most uses of PFOS and

related compounds as from the summer 2008. A further goal is to work toward eliminating emissions and product content of these chemicals by 2015 (3).

Chemicals containing the fluorinated chain are commercially manufactured by two major processes, namely electrochemical fluorination (ECF) and electrochemical telomerization (ECT) developed by Simons and his co-workers in 1944 (4). In electrochemical fluorination organic raw material (e.g., Octane sulphonyl fluoride) undergoes electrolysis process; at the end of the process, the entire hydrogen atom will be replaced by fluorine atoms. The free radical nature of the process leads to carbon chain rearrangements, resulting in a mixture of linear and branched chain products. The major historic manufacturer is now making alternative products using the ECF process based on perfluorobutane and perfluorosulfonyl compound. The ECF process yields straight or branched chains of fluorinated compounds with odd and even number of carbon atoms, but in ECT process exclusively generates linear products with an even number of carbon atoms (5).

As a result of human manufacture and use, PFCs are released to the environment by various ways (I) Industry (example: used in fabric treatment) (II) During production (example: treatment process) (III) During product use (example: fabric wear, wash, etc.) (IV) During product disposal (example: fabric disposal) (V) Incorporation into final products (lim *et al*., 2011). Fluorinated surfactants usually reach the environment either through their release into rivers or via wastewater discharge into receiving waters. Predominately however; they are adsorbed onto sewage sludge. The use of sludge for the land treatment or its disposal on dump sites leads to the remobilization of these compounds. Their polarity and mobility in water and soil allow them to reach the sea or ground water in unaffected conditions. The sources of human exposure to PFCs are not fully understood, but dietary intake (contaminated foodstuffs or drinking water) is thought to be an important route of exposure (6). In general, food might be polluted with PFCs compound. Further, it can migrate from food packaging (e.g., fast food containers, microwave popcorn bags) and nonstick cookware (e.g., fluorotelomer alcohols), which thus represents the sources of exposure from food or by accumulation into animal/plant based products. However other routes include house dust, indoor air and personal care products . People living in an industrialized area have been examined for the presence of PFOA, PFOS, and the results suggested that PFCs chemical plants is thought to be the main route of exposure of PFCs. As a consequence, these compounds have been shown to be distributed globally mainly to the blood serum. Several PFCs have been measured in human umbilical cord blood, indicating that they can cross the placenta. Exposure to the fetus is of particular concern, as fetal life is the most sensitive stage of human development. Due to their lipophilic properties, they can easily bioaccumulate in a variety of cells, tissues and blood (Figure 1) (7).

PFCs IN HUMANS BLOOD SAMPLES

Numerous field studies, designed to provide basic scientific information related to the occurrence of PFCs in the human tissues including blood serum, liver tissues, umbilical cord blood, and breast milk. Because of the widespread environmental occurrence of PFOA and PFOS, along with their ability to cross the placental barrier (Gutzkow *et al*., 2012), exposure of the developing human fetus to these compounds is inevitable. Exposures to the fetus, infants, and children are of the greatest concern as these are the most sensitive stages of human development. Table 2 summarizes the serum PFCs levels measured from around the world. Kannan *et al*, examined 473 blood/ plasma/serum samples from people of various countries. Of the four PFCs measured (PFOS, PFHxS, PFOA, FOSA), PFOS was quantitatively the dominant component in blood. The highest PFOS concentrations were detected in samples from the USA and Poland (> 30 μg/L). In Korea, Belgium, Malaysia, Brazil, Italy, and Colombia, blood PFOS concentrations were in the range 3 to 29 μg/L. The lowest PFOS concentrations were measured in samples from India (< 3 μg/L). In this study, the PFOA concentrations were lower than the values for PFOS, except in India and Korea. The joint occurrence of the four PFCs varied according to the country of origin of the samples. This suggests differences in the exposure pattern in the individual countries (16). Recently during 2000 to 2010, background level of PFOA and PFOS have been declining in the Western world, where the percentage decline in geometric mean concentrations from 2000 to 2010 was reported to be 76% for PFOS and 48% for PFOA (18). This study suggested that the initial decline in PFOA was the result of its phase out by 3M. Subsequently, in 2006 the U.S. EPA agency implanted a 1020/2015 PFOA stewardship program with fluorinated compounds manufacturing companies. Lee and maburry have shown a family of fluorotelomer based phosphate surfactants, the polyfluoroalkyl phosphate diesters, were lower in serum samples collected in 2009 than in earlier years (2005, 2005 and 2008). The concentrations of PFCs vary in different countries. These differences may reflect different diets or different patterns of contact with PFCs containing products across cultures. The half-lives of PFOA and PFOS in human serum have been estimated to be 3.8 years and 5.4 years, respectively (Table 3).

Thus exposure to PFCs is ubiquitous and unavoidable and there is growing concern that living in an PFCs contaminated world may be contributing to adverse health trends, such as neurotoxicity, immune

deficiency, because of growing evidence that a number of PFCs can produce varied effects (19), as described below.

Potential health effects of PFCs

Extensive studies have shown possible associations between exposure to environmental pollutions and an increased risk of certain abnormalities and diseases, both in humans and animals. High doses of PFCs are toxic, relatively low concentration of them are present in the environment and have been reported to cause alteration in the organism. In addition to toxic effects, they are able to interfere with thyroid function, reproductive toxicity (20), development toxicity (7), development of arthritis (21), metabolic dysregulation (22), immuno toxicity (23), neurotoxicity (24) and Carcinogenesis (25). Because these chemicals alter hormone-dependent processes and disrupt endocrine system, they have been classified as endocrine-disrupting chemicals (EDCs). Available data have provided evidence that PFCs are involved in the etiology of a variety of disorders including immune system, thyroid, liver function, and hormones problems (26).

Impacts of PFCs on nervous system

PFCs have received the most attention for their risk for neurotoxicity. It has been demonstrated that chronic exposure to PFCs, such as increases the negative charge density in the cell membrane of Purkinje cells, reduced the membrane potential, leading to hyperpolarization and thus influencing activation and inactivation of the ion channels. This appears to indicate that PFOS has an effect on the action potential in nerve cells, which may result in neurodegenerative disorder. There was a data, that exposure PFOS can have an influence on the neuro endocrine system in rats. They reduce the food intake and body weight, influence on the ovarian cycle, increased corticosterone concentration, and decreasing leptin concentration in serum. In addition, adrenaline concentrations in the paraventricular nucleus of the hypothalamus were elevated (27). PFOS has been reported to inhibit neural stem cell proliferation and to cause neurotoxicity via inhibition of peroxisome proliferator-activated receptors (28). PFCs including PFOS, PFOA, FOSA, and PFBS were found to be depressed DNA production, caused oxidative stress, and reduced the viability of the cells, increases the negative charge density in the cell membrane of Purkinje cells, e.g., nerve cells in the cerebellum of rats (29).Exposure of PFCs to rats, they affect the neurotoxic on the central nerve system via the molecules of the calcium signal pathway (30).Numerous other classes of POPs have been linked to neural degenerations, including PCB, PAH and organophosphate but epidemiological evidence is mostly lacking. Epidemiological studies that focus on the impact of PFCs on the nervous system, their mechanism of action and involvement in neurological pathologies study are needed.

Impacts of PFCs on thyroid hormone

Thyroid hormones are involved in numerous physiological processes as regulators of metabolism, cardiac function, bone remodeling and mental status. Thus, maintenance of normal thyroid function is essential for psychological function. However, thyroid hormones are of special importance in fetal development, as development of the brain is dependent on normal levels of thyroid hormones. Absence of thyroid hormones reduces neuronal growth and differentiation in the cerebral cortex, hippocampus, and cerebellum (31). PFCs exposure has also been found to alter hormone levels (e.g. thyroid hormone, estrogen, and testosterone) and hormone-responsive genes in mammalian and aquatic species. Langley and Pilcher also reported the effect of PFCs on thyroid hormones. From this study, rats that had received a dose of perfluorodecanoic acid (PFDA) were found to have significantly reduced thyroxin (T4) and T5 concentrations, lower body temperature, and a slower heartbeat than control animals. Treatment with T4 was not able to reverse the hypothermia. Other studies on rats also showed that PFOS exposure resulted in a reduction of T4and triiodothyronine (T3) in serum (32). Perinatal exposure to PFOS also reduced serum levels of T4, both in pregnant dams and offspring.

There is, however, no increase in thyroid stimulating hormone (TSH), a hormone that enhances formation of T4 and T3. There is evidence that PFOS, similarly to PFDA, displaces the thyroid hormone from its binding protein as it circulates in the blood. The association between PFCs and human thyroid function has been reported elsewhere. Among the US general adult population, greater concentrations of PFOA and PFOS were also associated with current thyroid disease (33). A positive association was detected between perfluorotridecanoic acid in maternal blood serum and T3 and T4 of fetal cord blood serum (34). However the direction of association between PFCs and thyroid hormones in human blood serum was not always consistent. While no significant associations were observed between the concentrations of six PFCs with free thyroxin or TSH among New York State Angler Cohort Study participants (35), blood PFOS concentrations were negatively associated with TSH and positively associated with fT4 in a study with an Inuit population of Nunavik from the Canadian Arctic (36). The only study of thyroid hormones during pregnancy found no effect of PFOS or PFOA levels in maternal or cord serum on fetal thyroid stimulating

hormone or free thyroxin (37). Recently Coperchini *et al*., evaluate the effect of the in vitro exposure to PFOA and PFOS on thyroid cell proliferation and viability. These studies were investigated using rat thyroid line-5 (FRTL-5) cells. FRTL-5 cell cultured in the presence of PFOA and PFOS concentration up to 104nM does not changes in their viability and proliferation rate, while at a concentration of 105 nM of either PFCs, significant inhibition of cell proliferation, mainly due to increased cell deaths, was found (38). In summary, experimental evidence suggests strongly that perfluorinated compounds are capable of disrupting thyroid hormone metabolism, but human studies are still needed.

Figure 1 : sources and health effectes of perfluorianted comounds

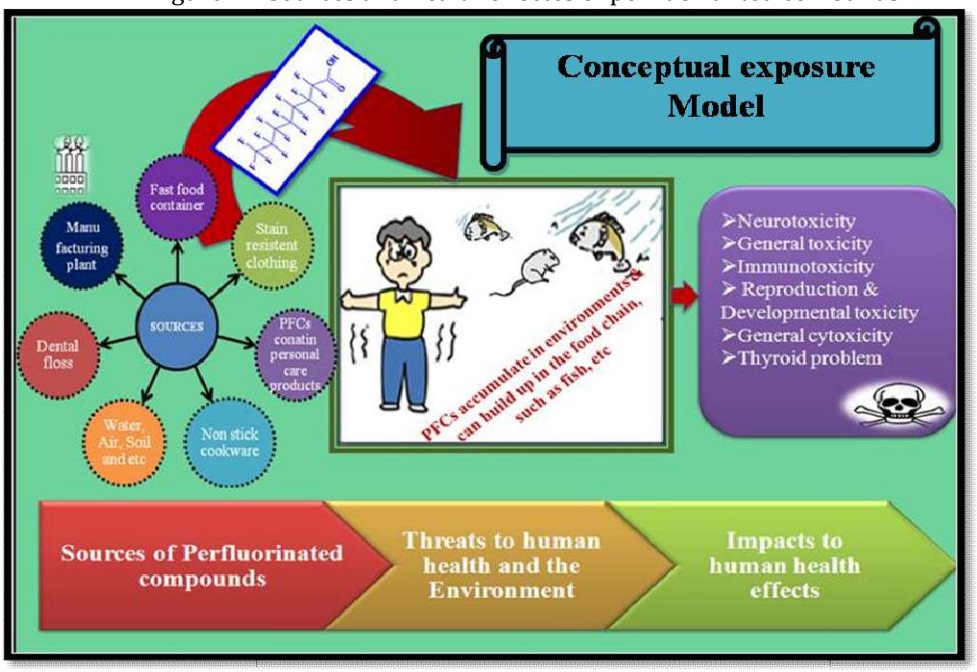


Table 1. Physico-chemical properties of PFCs

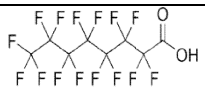
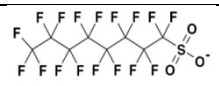
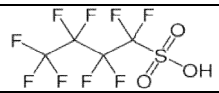
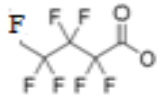
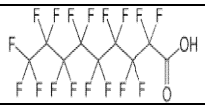
Name	Acronym	Structure	Molecular formula	Melting point	Vapor pressure	Solubility in pure water	Pka
Perfluoroctanoic acid	PFOA		$C_8F_{17}COO^-$	45˚C to 50˚C	10mmHg at 25˚C	3.4 g/L	2.5
Perfluoroctane Sulfonate	PFOS		$C_8F_{17}SO^-$	≥400˚C	-	570 mg/L	NA
Perfluoro sulfonate	PFBS		$C_4F_9SO_3$	NA	0.29 mm Hg at 20˚C	Dispersible in all proportion	NA
Fluorotelomer alcohols	FTOH		$F(CF_2)_nCH_2CH_2HO$	NA	-	-	-
Perfluorobutanoate	PFB		$F(CF_2)_3CO_2^-$	NA	0.29 mm Hg at 20˚C	Dispersible in all proportions	NA
Perfluorooctanoate	PFO		$F(CF_2)_7CO^-$	55˚C	10 mm Hg at 25°C 128 mm Hg at 59˚C	3.4 g/L	NA
Perfluorononanoic acid	PFNA		$C_9HF_{17}O_2$	59˚C to 62˚C	-	9.5g/	~ 0

Table 1. Levels of PFOS and PFOA in human blood/ Plasma from various countries

Country	**No. samples**	**Sample type**	**PFOS (**ng/mL**)**	**PFOA (**ng/mL**)**	**Reference**
USA	65	Serum	6.7 to 81.5	BDL	(9)
America	31	Blood serum	< 6.1 to 58.3	3.1	(10)
Japan	10	Whole blood	2 to14	-	(11)
China	85	Blood sample	79.2	-	(12)
Sweden	66	Whole blood	1.7to37	BDL	(13)
Denmark	1399	Blood plasma	6.4to106.7	<1.0 to 41.5	(14)
Poland	15	Blood	4.6 to 6.7	1.3 to 5.2	(15)
Italy	50	Serum	4.3	3	(16)
India	45	Serum	< 1 to 3.1	< 3 to 3.5	(16)
Spain	48	Plasma	0.8 to16.2	0.8 to 3.1	(16)
Canada	23	plasma	36.9	2.2	(17)

Table 2. Half-life of different PFCs

Compound	**half – life**	**Species**
Perfluoroctane sulfonate	8.5 years	Human
Perfluorooctanic acid	1to3.5 years	Human
Perfluorooctane sulfonates	89 days	Rat
Perfluorooctane sulfonates	180 days	Monkey
Perfluorohexane sulfonic acid	7.3 years	Human
Perfluorohexane sulfonate	8.5 years	Human

Impacts of PFCs on immune system

Many cell subsets of the immune system undergo extensive proliferation when stimulated. At high concentration, PFOA and PFOS have been found to increase the rate of lymphocytes apoptosis in the thymus and decrease the body weight. In the mice, exposures to PFOA (0.02%) for 7 to 10 days led to a loss of body weight and reduce the mass of the thymus and the spleen. Thymus and spleen cells were reduced by more than 90% and by approximately 50%, respectively, probably as a result of inhibition of cell proliferation. The immature CD4+ and CD8+ populations of the thymus cells were most noticeably reduced. The T and B cells were affected in the spleen. An increase in liver weight and peroxisome proliferation occurred in a similar time course as the thymus and the spleen atrophy (39). Xie *et al*., also observed a dramatic decrease in adipose tissue after exposure to PFOA, which reflected a loss of fat from the adipocytes (40). In addition, Fairley *et al*., examined the effects of PFOA dermal exposure on the hypersensitivity response to ovalbumin in mice and demonstrated increased IgE when PFOA and ovalbumin were co administered. Ovalbumin specific airway hyper reactivity was increased significantly in these animals with an increased pleiotropic cell response characterized by eosinophilia and mucin production. These results suggested that PFOA exposure may also enhance the immune response to environmental allergens, increasing the severity of allergies (41). There is also evidence from animal studies that PFOA can suppress inflammatory responses which is similar to the effects of other peroxisome proliferator-activated receptor agonists. Moreover recent studies have shown that PFOS affects antibody production in mice at levels found in the general human population. Peden *et al*., reported that serum concentrations of PFOS associated with the lowest observed effect for suppression of humoral immunity (42). Additionally, PFOS exposure suppressed immunity to influenza infection in mice without altering body or lymphoid organ weights, resulting in significant increases in emaciation and mortality (43). Potential effects on immune system development were studied by Grandjean *et al*., reported decreased antibody responses to childhood diphtheria vaccinations in association with prenatal PFOA and PFOS exposures (44). The data, supports the antibody production is an endpoint sensitive to modulation by PFCs. Hence, additional studies to correlate the immunotoxicity responses of PFCs with body burden of the chemical and to account for the uncoordinated processes responsible for the immunotoxicity, hypolipidemic, and hepatotoxicity effects of PFCs are warranted.

Effects on reproductive performance

Human studies have suggested the associations between exposures to PFCs compounds to altered reproductive functions; the direct effect of PFCs on female fertility has been scarcely studied. Moreover,

the biological mechanisms by which exposure to PFCs interferes with fertility are unknown. It was postulated that by interrupting the hypothalamic pituitary ovarian regulation, the PFCs may cause irregular menstrual cycles and delayed ovulatio Studies of adult male rats showed that PFOA exposure may cause reduced testosterone levels and increased estradiol levels (45), and a study on sexually mature mice indicated that PFOS exposure might affect testicular signalling, causing reduced serum testosterone and decreases in epididymal sperm counts. Two cross-sectional studies reported negative associations of PFOS, or high PFOA and PFOS combined, with the proportion of morphologically normal spermatozoa in adult men (46). Furthermore, in a study of men attending an *in vitro* fertilization clinic, Raymer *et al*, reported that luteinizing hormone (LH) and free testosterone were significantly positively correlated with plasma PFOA, although PFOA was not associated with semen characteristics (47). Vested *et al* suggested that *in utero* exposure to PFOA may affect adult human males' semen quality and reproductive hormones level (48). Rats after exposure to PFOS or PFOA lead to adult Leydig cell (ALC) hyperplasia and eventually Leydig cell adenomas, and decreased testosterone production (45).Very recent study reported the effects of PFDA and PFTrDA on sex and expression of mRNA of selected genes in hypothalamic pituitary gonad (HPG) axis are studied after 120 d exposure of zebrafish. The results of this study showed that long-term exposure (120 days) to PFDA or PFTrDA could modulate sex steroid hormone production and related gene transcription of the HPG axis in a sex-dependent manner (49).

In a study reported by Lau *et al*., all pups were born alive and active; however, in the high-dose group (10 mg/kg), newborns became pale, inactive, and moribund within 1 h. These pups died soon afterward. At 5 mg/kg PFOS, the neonates became moribund but survived for 8–12 h. However, over 95% of these offspring did not survive the first day of postnatal life and only a few pups reached puberty. Survival improved with lower PFOS exposure. The first week of postnatal life was also critical to the long-term survival of the neonates, as no mortality was detected thereafter (50). Das *et al*., reported PFOS and PFOA, PFNA at 5mg/kg or lower doses produced hepatomegaly in the pregnant mice, but did not affect the number of implantations, fetal viability, or fetal weight. Mouse pups were born alive and postnatal survival in the 1 and 3mg/kg PFNA groups was not different from that in controls. In contrast, although most of the pups were also born alive in the 5mg/kg PFNA group, 80% of these neonates died in the first 10 days of life. The pattern of PFNA-induced neonatal death differed somewhat from those elicited by PFOS or PFOA. A majority of the PFNA-exposed pups survived a few days longer after birth than those exposed to PFOS or PFOA, which typically died within the first 2 days of postnatal life (51).

Uric acid, Lipids

Uric acid is a natural product of purine metabolism and has both oxidant and antioxidant properties. There is considerable epidemiologic evidence that elevated uric acid is a risk factor for hypertension (52).Three cross-sectional studies have found modest positive associations between PFOA or PFOS and increased uric acid, a risk factor for hypertension (26; 53). Several studies have found positive trends between PFCs in human blood and total and cholesterol. Similar patterns have been found in the US population (54), in community residents exposed to high levels of PFOA in drinking water, and in workers in PFC manufacturing facilities (55).

Cancer

Increased rats of bladder cancer have been found in worker in a PFOS manufacturing facility, but this result was based on only three cases (56). Another study in exposed workers found an association between the length of employment and prostate cancer (57). The US EPA has proposed PFOA to be classified as a rodent carcinogen with relevance to humans (3). Breast cancer (BC) is the most common cancer for women in the world. Animal data suggest that pancreatic, testicular, liver, and perhaps breast cancer is related to PFOA exposure (58). An association between PFAS serum levels and the risk of BC was reported for the first time in a small case–control study from Greenland (25), and it was found that the genetic polymorphisms in CYP1A1 (Val) and CYP17 (A1) may increase the BC risk among Inuit women, and that the risk increases with higher serum levels of PFOS and PFOA (59). Recently Jorgensen *et al*., estimate the association between concentrations of PFAS determined during pregnancy, and the risk of BC. The results were, Weak positive and negative insignificant associations were found between BC risk and levels of perfluorooctane sulfonamide (PFOSA) and Perfluorohexanesulfonate (PFHxS), respectively. Grouped into quintile, the BC cases had a significant positive association with PFOSA at the highest quintiles and a negatively association for PFHxS. Sensitivity analyses excluding uncertain cases caused stronger data for PFOSA and weaker for PFHxS. No further significant associations were observed. This study does not provide convincing evidence for a causal link between PFAS exposures and premenopausal BC risks 10–15 years later (60).

CONCLUSION

A variety of different groups of perfluorinated chemical that have found a wide use in industrial products and in a vast area of consumer products, including protective coatings (for paper, carpets, textiles, and leather) lubricants, paint, cosmetics, surfactants, and fire-fighting foams. These compounds, which are persistent in the environment, bioaccumulative and can cause toxicity, have been detected almost ubiquitously in the environment. The available literature points to a strong link between the presence of PFCs in the environment and an increase in disorders. Limited data also support the involvement of nuclear receptors in the association of neurological disorders with PFCs. There is substantial evidence that PFCs have adverse effects on thyroid function. Experimental animal and in vitro studies have indicated possible mechanisms of action for perfluorinated chemicals, but evidence from mammalian and human studies is often sparse. Efforts are needed to develop systematic epidemiological studies and investigate the mechanism of action of PFCs to fully understand their effects on wildlife and humans.

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CITATION OF THIS ARTICLE

Sunantha G and Namasivayam V. Impacts of Perfluorinated Compounds on Human Health. Bull. Env. Pharmacol. Life Sci., Vol 4 [7] June 2015: 183-191