



Potential human health effects of perfluorinated chemicals (PFCs)

Glenys Webster¹

Summary

- Perfluorinated chemicals (PFCs), including perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA), are stain, water and grease repellent chemicals found in a wide range of consumer products.
- Almost everyone has detectable levels of PFOS, PFOA, and other PFCs in their blood.
- Although levels of PFOS and PFOA in human serum have declined in the US and Europe over the past decade, levels of PFNA (perfluorononanoic acid, the nine carbon version of PFOA) have increased. Serum PFOS levels have also increased exponentially in some areas of China over the past few years, likely reflecting increased PFOS production in China.
- PFCs have been linked to many health effects in animal studies, but often at higher exposure levels than are found in people.
- Few human health studies of PFCs have been conducted in the **general population**. To date, associations have been found between PFOS or PFOA levels in the general population and reduced female fertility and sperm quality, reduced birth weight, attention

deficit hyperactivity disorder (ADHD), increased total and non-HDL (bad) cholesterol levels, and changes in thyroid hormone levels. Some results are inconsistent across studies and further work is needed to confirm these initial findings.

- In a **highly exposed community** living near a chemical plant, PFOS and PFOA have been associated with pre-eclampsia (pregnancy-induced hypertension), birth defects (PFOA only), and increased uric acid levels – a marker of heart disease.
- Occupationally-exposed workers may have increased risk of prostate and bladder cancer.
- The production of PFOS, PFOA, and some of their precursors is being phased out in many parts of the world, but PFOS production has increased dramatically in China since 2003. Many other PFCs and precursors remain in commercial use worldwide.
- Humans are exposed to many chemicals in addition to PFCs. The long-term health effects of multiple, low-level exposures are poorly understood.
- Chemical exposures to the developing fetus, infants, and children are the greatest concern; these periods are the most sensitive stages of human development.

evidence
review

¹ School of Environmental Health, University of British Columbia

Introduction

This document summarizes current knowledge about the human health effects of perfluorinated compounds (PFCs), including perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA), the most prevalent PFCs found in human serum. Background information on these chemicals, current PFC regulations, and recommendations for reducing exposure are also presented. This information will be useful for students, researchers, policy-makers, and the general public wanting to understand the current state of human health knowledge about these highly persistent and ubiquitous compounds.

What are PFCs?

PFCs are a group of man-made chemicals used in a wide range of applications as stain, grease, and water repellents. PFCs are found in fast food packaging, paper plates, stain-resistant carpets, carpet cleaning solutions, windshield washing fluid and fire-fighting foam, as well as in some adhesives, cosmetics, pharmaceuticals, electronics, cleaning products, polishes and waxes, insecticides, and paints.^{1,2} PFOA is also used in the manufacture of non-stick cookware (e.g., Teflon) and waterproof fabrics (e.g., Gore-tex). The extreme stability of PFCs makes them ideal for many industrial uses but also means they break down very slowly in the environment and in people. Human half-lives are approximately 5.4 years for PFOS and 3.8 years for PFOA.³ Because of their widespread use and persistence, nearly everyone in the general population now has detectable levels of PFCs in their blood.^{4,6}

The two main groups of PFCs are the perfluorinated carboxylic acids (PFCAs), including PFOA or C8, and PFNA or C9, and the perfluorinated sulfonates, including PFOS and perfluorohexane sulfonate (PFHxS), among others. PFOS and PFOA (Figure 1) are the most widely studied PFCs, and are found at the highest levels in humans.⁴ Because many precursor chemicals degrade to PFOS or PFOA, tracking the sources of these chemicals in the environment and in people is especially challenging.

Levels of PFCs in people

PFOS and PFOA have been detected in a wide range of human tissues, including blood serum,⁵ umbilical cord blood,^{7,8} liver tissue,^{9,10} seminal fluid,¹¹ and

breast milk.^{10,12-16} Because they cross the placenta, the developing fetus is exposed to these chemicals *in utero*. Exposures to the fetus, infants, and children are of the greatest concern as these are the most sensitive stages of human development.

Table 1 summarizes the serum PFC levels measured in select studies from around the world. In the general population, PFOS and PFOA concentrations have decreased since the early 2000s in North America and parts of Europe, likely in response to reduced production of these chemicals (see below). However, serum levels of PFNA have nearly doubled over the same time period in the US (Table 1). In China, PFOS levels have increased exponentially since the early 2000s,¹⁷ mirroring the sudden increase in Chinese PFOS production starting in 2003.¹⁸ In 2004, median PFOS levels in Shenyang China were approximately seven times higher than those found in the US general population during the same time period (Table 1).^{19,20}

PFC concentrations tend to be higher in men than in women and vary somewhat with age, although inconsistently across studies.²⁰⁻²² Recent US studies found lower levels of several PFCs in Mexican Americans compared to Non-Hispanic blacks or Non-Hispanic whites, whose levels were similar.^{4,20} These differences may reflect different diets or different patterns of contact with PFC-containing products across cultures.

How do PFCs get into people?

The sources of human exposure to PFCs are not fully understood, but dietary intake is thought to be an important route of exposure.²³ Food can become contaminated directly from food packaging coated with grease and water repellent coatings (e.g., fast food containers, microwave popcorn bags)²⁴ or by bioaccumulation into animal or plant-based foods.²³ Other routes of exposure include indoor air,^{25,26} drinking water,²⁷ dust,²⁸ and contact with PFC-containing consumer products.²⁹ Among consumer products, pre-treated carpeting, professional carpet-care liquids, treated floor waxes, stone, tile, and wood sealants, and treated home textile products and upholstery are thought to be the most important sources of PFOA in typical American homes.²⁹ Exposures may occur directly by touching consumer products followed by hand to mouth contact, or indirectly by ingesting indoor dust.²⁹ Nonstick cookware is thought to be a minor source of PFOA to people,^{24,30} but microwave popcorn bags and other

fast food packaging may be important exposure sources of PFOA and its precursors (e.g., fluorotelomer alcohols).²⁴ For people living in communities close to PFOA chemical plants, contaminated drinking water is thought to be the main route of exposure.^{21, 22, 31}



PFOS and PFOA are easily absorbed through the gut, are poorly eliminated, and are not metabolized. Unlike most persistent chemicals, they bind to proteins rather than fats (lipids) and are distributed mainly to the blood serum, kidney, and liver.³² Several PFCs have been measured in human umbilical cord blood, indicating that they can cross the placenta.^{33, 34} Exposure to the fetus is of particular concern, as fetal life is the most sensitive stage of human development.

What are the potential health effects of PFCs?

Animal studies

In animals, PFCs have been linked to a wide range of health effects, including liver toxicity (e.g., enlarged livers^{35, 36} and liver cancer³⁷), increased neonatal and adult mortality,^{35, 36} decreased body weight,^{35, 36} developmental delays,³⁶ behavioural changes,³⁸ abnormal mammary gland development,³⁹ immune system effects, lower testosterone⁴⁰ and cholesterol levels,³⁵ changes in estrogen levels,³⁵ and decreased thyroid hormones which are essential for normal growth and development.^{35, 36} Extrapolating these results to humans is difficult partly because of differences in how quickly PFOS and PFOA are cleared from the body (half-lives of days for rats versus years for humans) and partly because certain modes of PFC action (e.g., peroxisome proliferation) are also thought to be less relevant in humans than in rodents.^{24, 32} Although the mechanisms of PFC toxicity

are not fully understood, PFOS and PFOA have both been shown to alter fatty acid metabolism, lipid transport, cholesterol synthesis, proteasome activation and proteolysis, cell communication, and inflammation processes in rodent studies.³²

Human studies

Birth Outcomes, Pregnancy Outcomes, and Developmental Effects

Several studies in the US, Japan, and Denmark have found links between PFOS and PFOA levels in umbilical cord blood and lower birth weight, but the findings have not always been consistent across studies.^{7, 41, 42} Small reductions in ponderal index (a ratio of infant mass to height) and head circumference has also been found in US newborns.⁷ In Denmark, no association was found between maternal PFOS and PFOA levels and an infant's Apgar score at birth or with developmental milestones at 6 and 18 months.⁴³ However, higher odds of attention deficit hyperactivity disorder (ADHD) was recently found in 12 to 15-year-old American children with higher levels of PFOS, PFOA, PFHxS, and PFNA in their blood.⁴⁴ In a highly exposed West Virginia population living near a fluoropolymer chemical plant, serum PFOS and PFOA exposures were weakly associated with self-reported pre-eclampsia (high blood pressure during pregnancy) and birth defects (PFOA only) (Table 1).⁴⁵

Fertility

Two recent studies suggest that PFCs may reduce human fertility. In Danish women, higher PFOS and PFOA levels were associated with a longer time to pregnancy, and with having irregular menstrual cycles.⁴⁶ Young Danish men with high combined PFOS and PFOA levels also had half the number of normal sperm compared to men with lower levels. Participants of both studies had PFC levels similar to those found in the US population⁴⁷ (Table 1).

Effects on thyroid hormones

Few studies have examined the effects of PFCs on thyroid hormone levels in humans; existing results are somewhat inconsistent and difficult to interpret. Thyroid disruption is of particular concern during pregnancy because thyroid hormones play a critical role in fetal brain development.⁴⁸ 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 (TSH) or free thyroxine (fT4), but the sample size was extremely

small (n=15 mother-infant pairs).³⁴ PFOS was negatively associated with TSH, total triiodothyronine (TT3) and thyroid binding globulin (TBG) in Canadian Inuit adults,⁴⁹ whereas a positive trend was found with fT4. A similar increase in fT4 (although non-significant) was also found with increased levels of PFDA and PFUnDA (the 10 and 11 carbon versions of PFOA) in New York state sport fisherman.⁴⁸ However, the opposite pattern (higher TT3 and lower fT4) has been found in workers highly exposed to PFOA.⁵⁰ No effect of PFOA on TSH was seen in a highly exposed community living near a PFC facility,⁵¹ but this study failed to consider potentially important confounders. More work is required to understand the potential effect of PFCs on human thyroid hormones, especially during pregnancy.

Increased cholesterol

Several studies have found positive trends between PFCs in human blood and total and non-HDL (*bad*) cholesterol. Similar patterns have been found in the general US population,⁵² in community residents exposed to high levels of PFOA in drinking water,⁵³ and in workers in PFC manufacturing facilities.⁵⁴

Immune system effects

Immune responses to PFCs have not been studied in humans. In mice, PFOA has been shown to reduce the production of lymphocytes (immune system cells) by both the spleen and the thymus⁵⁵ and to suppress humoral immune response (immunity mediated by antibodies secreted by B cells). This may decrease the body's ability to respond to bacterial invasion and infection.⁵⁶ PFOA exposure may also enhance the immune response to environmental allergens, increasing the severity of allergies.⁵⁷

Uric acid

Three cross-sectional studies have found modest positive associations between PFOA or PFOS and increased uric acid, a risk factor for hypertension.^{54, 58, 59}

Cancer

Increased rates of bladder cancer have been found in workers in a PFOS manufacturing facility, but this result was based on only three cases.⁶⁰ Another study in PFOA-exposed workers found an association between the length of employment (a surrogate for exposure) and prostate cancer.⁶¹ In 2005, the U.S. EPA's Science Advisory Board recommended that PFOA be classified as a likely human carcinogen.^{62, 63}

What is being done?

Regulation of PFOS and related chemicals

PFOS has never been manufactured in Canada, but has historically been imported either as raw chemicals or already incorporated into products or chemical formulations.⁶⁴ In 2000, the 3M company (the primary international manufacturer of PFOS) began a voluntary phase-out of PFOS production, completed by 2003.⁶⁵ A ban on most uses of PFOS was imposed in the US in 2000⁶⁶ and in the European Union in 2008.⁶⁷ Canada banned the manufacture, sale, and importation of PFOS as well as PFOS-containing products in 2006, with exceptions for existing stocks of PFOS-containing fire-fighting foams and for uses in the metal plating, semiconductor, and photographic industries.^{66, 68} In January 2009, PFOS and its salts were added to the Virtual Elimination List under the Canadian Environmental Protection Act (CEPA 1999).⁶⁴ In May 2009, PFOS and its salts were also added to Annex B of the Stockholm Convention on persistent organic pollutants. However, Annex B only imposes *restrictions* on chemical uses and exemptions were granted for all of the major historic uses: photo-imaging, fire-fighting foams, insect baits, metal plating, and surface treatment of leather, apparel, textiles, upholstery, paper, and packaging.⁶⁹

In contrast to many other regions around the world, China dramatically increased the production of PFOS and its precursors in 2003.¹⁸ Sixty-six PFOS-related chemicals are currently registered in the *Inventory of Existing Chemical Substances in China*,¹⁸ with approximately half of Chinese production exported to Europe, Japan, and Brazil.⁷⁰

Regulation of PFOA and its precursors

In 2004, Canada imposed a 2-year ban on four fluorinated telomer alcohols known to transform to PFOA and other long chain PFCAs in the environment.⁶⁶ A permanent ban on the manufacture, sale, and importation of these telomer alcohols was proposed two years later. However, because products already containing these chemicals may still be imported into Canada, exposures to PFOA are likely to continue.⁶⁶ In February 2006, US regulators reached a voluntary agreement with eight companies to reduce emissions of PFOA from their facilities and

consumer products by 95% by 2010, and work toward eliminating sources of PFOA by no later than 2015.⁷¹ Progress towards the initial 2010 goal has been unclear and concerns have been raised about the safety of *shorter chain* PFCs that are being used as replacements in some applications.⁷²

Evidence gaps

The study of PFC health effects in humans is still in its infancy. Uncertainties remain about:

- the main sources and pathways of human exposure;
- human health effects at population exposure levels, especially for exposures in the womb, in infancy, and in childhood;
- understanding how quickly PFCs (other than PFOS and PFOA) are cleared from the human body;
- the mechanisms of PFC action in humans;
- the relative importance of direct exposures to PFOS and PFOA versus exposures to their precursors; this distinction is important as many precursor chemicals remain commercially available;
- the safety of replacement chemicals, including “shorter chain” PFCs;
- best practices for reducing PFC levels in homes and in the body.

How to reduce exposures to PFCs

Few data exist on how to best reduce exposures to PFCs. The following recommendations are based on common sense, given current knowledge about possible PFC exposure sources to humans:

- Wash your hands before you eat to reduce ingestion of PFCs on your hands from contact with consumer products and dust.

- Reduce consuming fast foods and packaged foods (e.g., microwave popcorn, takeout french fries, takeout pizza, TV dinners), especially foods that are heated in their packaging.
- Avoid fluorinated stain repellent treatments on new carpets and furniture and decline fluorinated stain repellent treatments during carpet and furniture cleaning; request a non-fluorine based alternative.
- Avoid stain or dirt-repellent clothing and clothing bearing a Teflon label.
- Avoid personal care products and cosmetics with *fluoro* or *perfluoro* on the ingredients list (e.g., in lotions, pressed powders, nail polish, and shaving cream).
- Reduce exposure to indoor dust as much as possible; dust with a wet cloth and use a vacuum cleaner with a HEPA filter, if possible.

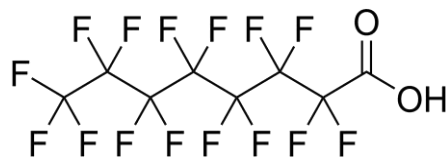
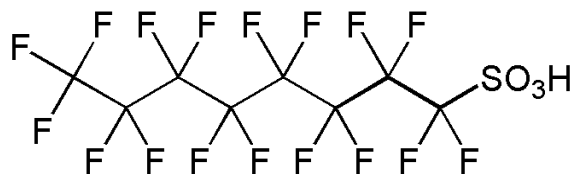


Figure 1 Chemical structure of perfluorooctane sulfonate (PFOS, top) and perfluorooctanoic acid (PFOA, bottom), the two PFCs found at the highest levels in human serum.

Table 1 Median serum levels of PFCs (ng/mL or parts per billion) in a selection of recent human studies

Population	Year of Sample Collection	N	PFOS	PFOA	PFHxS	PFNA	Health Effect Associated with Increasing PFC Levels	Reference
1. General population studies								
USA population (≥12yrs) [†]	99-00	1,562	30.2	5.1	2.1	0.6	-	4
USA population (≥12yrs) [†]	03-04	2,094	21.1	4.0	1.9	1.0	-	20
USA adults (20-80 yrs) [†]	03-04	860	21.0	3.9	1.8	1.0	PFOS, PFOA, PFNA: ↑ Total and non-HDL ("bad") cholesterol. PFHxS: ↓ Total and non-HDL cholesterol. No effect on body size or insulin resistance.	52
Danish women attempting pregnancy	96-02 [†]	1,240	33.7	5.3	-	-	PFOS and PFOA: increased time to pregnancy, irregular menstrual cycle.	46
Danish young men (median age = 19 yrs)	2003	105	24.5	4.9	6.6	0.4	High versus low combined PFOS and PFOA: Reduced sperm quality.	47
Canadian Inuit adults ^{**}	2004	623	18.3 [†]	-	-	-	PFOS: Changes in thyroid hormone levels (↓TSH, ↓TT3, ↓TBG, ↑fT4). ^{††}	49
Canadian pregnant women (Hamilton, ON)	04-05	101	16.6	2.1	1.8	0.7	-	8
Canadian pregnant women (Vancouver, BC)	07-08	152	4.8	1.7	1.0	0.6	Thyroid hormone results not yet available.	73
Chinese adult volunteers (Shenyang)	2004	6	140.2	1.0	3.8	0.8	-	19
males								
males		4	139.0	0.7	1.4	0.6		
2. Studies in a highly exposed community living near a Dupont fluoropolymer plant								
Pregnant women (Parkersburg, West Virginia USA)	00-06	5,262 (PFOS) 1,845 (PFOA)	13.6	21.2	-	-	PFOS and PFOA: ↑ pre-eclampsia; no association with miscarriage or preterm birth; PFOS only: ↓ birthweight; PFOA >90 th percentile: ↑ birth defects.	45
Adults >18 yrs (Parkersburg, West Virginia USA)	05-06	46,292	19.6	26.6	-	-	PFOS or PFOA: ↑ total, LDL and non-HDL cholesterol; no association with HDL cholesterol; PFOA only: ↑ triglycerides;	53
Adults >20 yrs (Parkersburg, West Virginia USA)	05-06	54,951	20.2	27.9	-	-	PFOS and PFOA: ↑ uric acid. ^{†††}	59

Notes: Studies are grouped into two levels of exposure: **1.** the general population; **2.** a highly exposed community living near a chemical plant in West Virginia. Studies are further grouped by country and listed in approximate chronological order for the year of serum collection. PFOS = perfluorooctane sulfonate, PFOA = perfluorooctanoic acid (C8), PFHxS = perfluorohexane sulfonate. PFNA = perfluorononanoic acid (C9); '-' indicates that the data were not measured or were not reported.

* Data from the 1999-2000 and 2003-2004 National Health and Nutrition Examination Surveys (NHANES)

** PFCs measured in blood plasma rather than serum.

*** Subset of data from this study. PFC concentrations in whole blood were multiplied by 2 to convert to serum concentrations. Data from supplemental information.¹⁹

† Geometric mean rather than median.

†† TSH = thyroid stimulating hormone; TT3 = total triiodothyronine (T3); TBG = Thyroid binding globulin; fT4 = free thyroxine (T4).

††† Uric acid is a risk factor for hypertension and possibly for cardiovascular disease, stroke, diabetes, and metabolic syndrome.⁵⁹

Acknowledgements

We would like to thank Patti Dods, Tim Foggin, and Mark Payne for their valuable input and review of the draft document. Glenys Webster acknowledges support of the University of British Columbia Bridge Program.

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This document was produced by the National Collaborating Centre for Environmental Health at the British Columbia Centre for Disease Control in October 2010.

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Production of this document has been made possible through a financial contribution from the Public Health Agency of Canada.

ISBN 978-1-926933-03-0

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400 East Tower
555 W 12th Avenue
Vancouver, BC V5Z 3X7

Tel.: 604-707-2445
Fax: 604-707-2444
contact@ncceh.ca



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