Abstract

PFAAs are a family of synthetic, fluorinated carbon chain chemicals which are widely used in the manufacture of numerous consumer products. The most widely used and environmentally dispersed forms are the eight-carbon compounds, also known as C-8s. Within the family of C-8s, perfluorooctanoic acid (PFOA), perfluorooctanosulfonate (PFOS) and ammonium perfluorooctanoate (APFO) are the most abundant. These compounds have surfactant properties (reduces surface tension of liquids) and are essential polymerization aids (helps create chemical chains) used in very small quantities to help make fluoropolymers (chemical chains containing fluorine atoms). PFOS and PFOA are primarily components of larger chemical substances. Although production of PFOS has stopped in the US (37), environmental degradation of larger fluorotelomers and >8 carbon chain PFAAs, in addition to their production for use in a variety of industrial products, yield PFOA. Sources and routes of exposure are just beginning to be understood at this time. For several decades, PFAAs were thought to be environmentally and biologically inert. No regulatory standards were in place until recently. Numerous studies are underway at this time to explore and characterize biological activity of these compounds in both animal models and humans.

The appearance of various cancers, alterations in reproductive and thyroid hormones, immunotoxicity and adverse reproductive outcomes have been reported in animal studies. However, the results vary across studies, largely due to species and gender differences in how the PFAAs are metabolized and/or excreted, as well as marked differences in the half-life of these chemicals in blood (33). In humans, occupational exposures have been linked to bladder and kidney cancers and diabetes(39), while in utero exposures have been linked to reduced weight and size at birth(1,8). This fact sheet provides information about PFAAs, sources of exposures, their effects on puberty, effects in the body, and research studies associating PFAAs with breast cancer. PFAAs are one of several classes of biomarkers being measured and evaluated for health effects in the Breast Cancer and the Environment Research Centers.

What are PFAAs?

PFAAs are a family of synthetic, fluorinated carbon chain compounds which are widely used in the manufacture of numerous consumer products. Chain length may vary from 4 to 14 carbons, in which the carbon atoms are fluorinated. The terminal carbon of the chain contains a charged carboxylate, phosphonate or sulfonate moiety (functional group) (33). Chemical names, formulas, abbreviations and structures of some of the major PFAAs are reported in the literature (15). The most widely detected and environmentally dispersed forms of PFAAs are the eight carbon compounds, also known as C-8s. Within the family of C-8s, perfluorooctanoic acid (PFOA), perfluorooctanosulfonate (PFOS) and ammonium perfluorooctanoate (APFO) are the most prevalent. Higher order chain lengths break down in the environment to form C-8s. C-8s do not biodegrade, nor are they metabolized. EPA has classified C-8s as being environmentally persistent, bioaccumulative toxicants (6,33). PFAAs are found in fish, birds and mammals in North America, Europe, Asia, and Antarctica (33). Sera from all people tested contained some PFAAs (3). In 2002, the 3M Company phased out production of PFOS due to its widespread presence in the environment and its propensity to bioaccumulate in a wide range of wildlife and humans. The amount of this compound in the marketplace has dropped precipitously since then (3M Co., 2003). In contrast, the amount of PFOA produced increased and became one of the most popular PFAAs in commerce. There have been very few studies of the effects of PFOA on human health. Most studies have focused on occupationally exposed male workers and were cross-sectional in design (33). No consistent, confirmed associations have been reported. A large scale community health study, called the C-8 Health Project, was initiated in 2005, as part of a settlement agreement between EPA and Dupont (7). This series of related studies is following approximately 70,000 individuals exposed to PFOA in the Parkersburg, West Virginia area. There are several websites which provide Fact Sheets and updates of PFC research findings (16,17,18). This fact sheet will primarily introduce the two most abundant PFAAs in the global environment, PFOS and PFOA.
What is PFOA?
PFOA, or perfluorooctanoic acid, is a surfactant and an essential polymerization aid used in very small quantities to help make fluoropolymers, which are high performance plastic and synthetic rubber materials. Its chemical formula is C8-H1-F15-O2. The chemical form of PFOA used in fluoropolymer manufacturing is the ammonium salt, known as APFO (C8-H1-F15-O2.H3-N). Within the fluoropolymer industry, APFO is sometimes called C-8, referring to the number of carbon atoms in its molecular structure. In addition to being produced for use in other commercial products, PFOA is also produced as a final degradation product of a variety of precursor perfluorinated chemicals (33).

What is PFOS?
PFOS, the perfluorooctane sulfonate anion, is no longer manufactured globally (37), but is a component of larger chemical substances whose environmental degradation can yield it. Its chemical formula is C8-F17-SO2. Classified as a persistent, bioaccumulative chemical, it is found in most wildlife (33).

Which commercial products contain PFAAs?
These are almost too numerous to list. Because the physical properties of the C-8 PFAAs make them excellent surfactants, they are used in over 200 industrial and consumer applications (33). They are used in the manufacturing of 1) Water or stain-proofing agents, e.g., clothes, carpeting, upholstery, leather, mattresses, footwear, and water-proof outerwear; 2) Grease or water resistant paper packaging materials, e.g., popcorn bags, microwavable meals, and packaging on such foods as chewing gum, candy, donuts, pizza, fast-food; and 3) Miscellaneous products, e.g., fire fighting foam, photography emulsion, specialty fuels, paints, waxes, electroplating materials, and health and beauty products, such as dental floss. PFAAs are also used in the production of trademark materials such as Post It Notes, Teflon, Zonyl (paper coating material), Gor-Tex, and Tyvec. PFOS was used in the production of Scotchgard and Stainmaster. Furthermore, some industries make extensive use of PFAAs. For example, they are used by these industries: film processing, aluminum production, electronics production, refrigeration, pharmaceutical production, and printing (41).

How are humans exposed to PFAAs?
For several decades, PFAAs were thought to be environmentally and biologically inert, so no national regulatory standards were in place. More recently, a number of states, including NJ, NC, and MN, have introduced regulations to limit the level of PFAAs in water. Numerous sources of PFAA exposure have been identified (33). Ingestion and inhalation are the major routes of exposure to these compounds. Consumption of contaminated drinking water is a major source of chronic exposure in certain populations. Inhalation of air emissions around production facilities and resultant contamination of soil and house dust have also been identified as important point sources (4,5,9,33). In fact, the entire Northern hemisphere is contaminated with PFOA and PFOS, which may be due to telomer acid distribution into the atmosphere (34). Contaminated convenience foods form the third major exposure source. Of course, occupational exposures can produce high levels of exposure in a workforce (5,6,7). There are multiple sources of quantitative exposure data available at this time on levels of serum PFAAs in US (3,10). However, few documents provide quantitative data on the levels in the actual products containing the PFAAs. Therefore, the following is largely based on a few studies and scientific inference from other exposure scenarios:

Ingestion

1. Food
PFAAs can inadvertently be added to foods during preparation or packaging for distribution. Many food packaging materials contain residual PFAA, including PFOA, from the manufacturing process. High temperatures can result in the leaching of PFAA from the packing material into the food
product. Examples where such transfer might occur include pizza boxes, french fry boxes or wrappers, microwave popcorn bags, etc (14).

2. Non-stick cookware
PFAAs are used in the application of non-stick coating to cookware. Most PFAAs are removed during the application process, but some residues may remain. Extremely high heat can release PFAAs into the air where they can be inhaled. This is very unlikely to occur during the normal cooking process, since the necessary temperatures would severely burn the food. The safety of cookware coated with fluoropolymer non-stick coatings, e.g. Teflon, has been assessed by regulatory agencies of the United States and many other countries. Non-stick cookware has been approved by the U.S. Food & Drug Administration (FDA) for conventional kitchen use. Governments in other parts of the world have also approved these coatings on cookware and housewares.

3. Soil and Dust
There are seven states currently dealing with environmental PFAA contamination: New Jersey, Virginia, North Carolina, West Virginia, Ohio, Alabama, and Minnesota. The Alabama and Minnesota contamination arose from 3M plant releases and landfills, while the remaining five sites are due to DuPont plant releases or landfills. Air emissions have contaminated surrounding soils and sediment, while runoff has contaminated groundwater and, in some cases, drinking water supplies (5,9,16,18). Contaminated soils, exterior dust and house dust are particularly important sources of exposure for young children due to the likely contamination of their hands and subsequent hand-to-mouth behaviors.

4. Ground Water and Drinking Water
Contaminated drinking water has been responsible for the largest episodes of community exposure (5,7,9,18; median PFOA levels in excess of 300 ng/ml [nanograms per milliliter of blood serum, i.e. parts per billion, or ppb])\(^{\text{(5)}}\), and the greatest publicity to date (9). Levels of PFOA in drinking water can range from less than 0.01 ng/ml, i.e., <LOD (less than the limit of detection), in non-contaminated drinking water supplies to over 7 ppb around some plant sites (5). This contamination led to the largest penalty in the history of the EPA being imposed against DuPont, the industry known to cause the contamination event (15). Currently, several states have imposed their own MCLs for PFOA and many more are underway (18,21). PFOA is under risk assessment review by the EPA and in 2006, the EPA initiated the PFOA Stewardship Program in which the 8 major companies will reduce global emissions and product content of PFOA and related chemicals by 95% by the year 2010 (17).

5. Infant consumption
If drinking water is contaminated with PFAAs, these contaminants can potentially produce unnecessary exposure to infants drinking formula prepared from this water. This is of particular concern given the greater vulnerability of infants to absorption of toxicants and the sensitivity of developing organs to toxic insults. Furthermore, PFOA has been shown to be a developmental toxicant in mouse studies (11, 12, 33). Although there are few reports (20,36), it appears that breast milk is not a major source of PFAA exposure.

6. Toys (painted)
Some paints contain Teflon or have rubberized coatings. Therefore, they are likely to contain some residual PFAAs. Potentially, this could result in exposures if the child chews on the paint. At this time there are no exposure data available.

**How do I know if I have been exposed to PFAAs?**
PFAAs can be measured in blood serum samples using a technique called mass spectrometry (3,19). These tests are very sensitive and can detect concentrations of less than 1 ppb of PFOA. Unfortunately, there are only a few laboratories in the US that can reliably make these measurements; consequently, these tests are currently very expensive, about $300 to $400 each depending on the volume of samples (35). Because of the long half-life (time to eliminate half the
amount) of PFOA and PFOS in the human body, a single measurement cannot be used to determine if the measured level is due to current, ongoing exposures or a prior, episodic exposure, which might have occurred several years earlier.

**How does PFOA work in the human body?**
PFOA is well-absorbed by rats and mice after oral exposure. *Dermal* (skin) absorption has also been reported in the rat, but not in humans (23). In male, but not female rats there is evidence of *enterohepatic circulation* (in bile between the liver and small intestine) (24). PFOA is excreted in both the urine and feces. In animals, there are large species and gender differences in the biological half-life of PFOA, due mainly to differences in *renal* (kidney) clearance (25). Half-life in female rats is only a few hours, while it is several days in the male. There is no difference in half-life in the male and female mouse, estimated at a little over 2 weeks (32). Half-life in humans is estimated to be several years (26). The effects of PFOA in rats include increased *P-450* (hemoprotein enzyme) activity, decreased serum low density lipoproteins and cholesterol, and increased oxidation of fatty acids. These effects lower serum cholesterol and elevate lipids in the liver (22).

**Does PFOA or PFOS exposure influence onset of puberty in girls?**
This is unknown at this time. BCERC’s biology and epidemiology studies are investigating this question. The BCERC epidemiology project entitled “Environmental and Genetic Determinants of Puberty” has measured PFCs in about 80-90 young girls. This small pilot data set will guide future expanded cohort studies. Mouse studies show that PFOA exposure during gestation produces developmental delays and growth retardation (11,12,32), and studies in children demonstrate an inverse relationship of serum PFOA and birth weight (1,8). A single mouse study (32) has assessed pubertal timing and found that low level exposures hasten puberty in males, while no effects on puberty were seen in females until high level exposures were reached. The effects of these compounds in humans are unknown.

**Do PFOS and/or PFOA cross the placenta?**
Yes. Recent studies reveal several different PFAAs present in cord blood, including PFOS and PFOA, in the fetus (1,8).

**Are PFAAs found to be present in breast milk?**
Yes. Karrman et al. studied matched serum and breast milk samples from a group of 12 Swedish women, three months post-partum. They found that the levels of PFOS in breast milk are about 1% of the level found in serum, while PFOA was only infrequently detected (20).

**Are PFAAs endocrine disruptors?**
Yes. According to EPA, an endocrine disrupter is an exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of *homeostasis* (biological stability), reproduction, development and/or behavior (31). PFAAs have been found to adversely affect both prenatal and postnatal development as well as the reproductive system in laboratory animals (11, 12, 29). In a study of adult male rats treated with PFOA, serum *estradiol* (a form of estrogen) was increased, serum testosterone was decreased, and liver *aromatase* (the enzyme responsible for conversion of testosterone to estradiol) activity increased (27).

**Are concentration levels of PFAAs the same in men and women?**
No. Studies have shown that, on average, men have higher serum levels of PFOA than women. The median level in adult men in the US is 6.0 ppb, while it is 4.6 ppb in women (3). There are no significant differences across age groups within the 12 to 60 year range. Currently, there are no national data for children less than 12 years of age.
**Are there in vitro or in vivo studies that have found an association with PFAA exposure and breast cancer risk?**

Yes. A recent study investigated estrogen-like properties of five perfluorinated compounds (30). Using an E-screen assay, they found that several fluorotelomer alcohols have proliferation promotion capacity. However, PFOS and PFOA did not share this hormone-dependent proliferation capacity. Employing the standard MCF-7 human Caucasian breast adenocarcinoma cell assay, they also undertook gene expression analysis of selected estrogen-responsive genes, e.g., TFF1, PRG, ESR1, PDZK1, and ERBB2. Numerous changes were found. White and coworkers also demonstrated in mice a profound effect of prenatal PFOA exposure on the development of the mammary tissue of the offspring (11). The effect was seen with just a 6 day exposure. PFOS is linked with mammary, pancreatic, thyroid, and liver tumors in rats, as well as hyperthyroidism and altered lung development (40). Because of tumor development in a variety of other tissues following lifetime exposure to PFOA in rats, EPA’s Science Advisory Board has classified PFOA as a “likely human carcinogen” (6).

**Are there epidemiological studies that have found an association with PFAA exposure and breast cancer risk?**

Not at this time. The studies to determine the health effects of PFAA exposures in developing children and adults are in their infancy. However, there is a large study currently underway which might provide such information within the next several years. Nearly 70,000 highly-exposed residents of Parkersburg, WV are participating in a long term health study to answer such questions (7).

**What is known about PFAAs from biomonitoring measurements in the National Health and Nutrition Examination Survey (NHANES) or other study Reports?**

Serum samples collected during the NHANES survey were subsequently analyzed for eight different PFAAs, including PFOA and PFOS (3). This study found higher levels in men than women; higher levels in non-Hispanic whites and non-Hispanic blacks than in Mexican-Americans; and no age-related trends between 12-19 year olds and those over age 60. Measurement of PFAAs in sera collected from a separate cohort of 598 children, ages 2 to 12 years old, found a median PFOA level of 5.1 ppb and a 90th percentile of 8.5 ppb (10). Children aged 2-5 years were reported to have higher levels than those aged 6 -10 or 11–15 in Parkersburg WV (5). Lau et al. (33) have summarized available data regarding PFAA serum levels in adult men and women and children in both the US and other countries.

**Has the federal government made recommendations for PFOA or PFOS exposure limits to protect human health?**

EPA

EPA has yet to set a national maximum contaminant level (MCL) for PFOA or PFOS in drinking water. However, EPA has set an interim drinking water MCL in Parkersburg, WV, which was initially 150 ppb, but reduced to 0.5 ppb in 2006 (7). In March 2007, the Minnesota Department of Health established maximum safe drinking water limits of 0.5 ppb and 0.3 ppb for PFOA and PFOS, respectively (18). In April 2007, New Jersey set a preliminary health-based lifetime exposure limit which translates to an MCL of 0.04ppb (21). In January 2006, the EPA initiated a PFOA stewardship program with eight major producers to reduce emissions and product content by 95% no later than 2010 and to eliminate these chemicals from emissions and products by 2015 (38).
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For more information on the Breast Cancer and the Environment Research Centers, go to http://www.bcerc.org.
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