UNITED STATES AIR FORCE
SCHOOL OF AEROSPACE
MEDICINE

Detailed Information and Frequently Asked Questions for Bioenvironmental Engineers and Medical Providers on Perfluorinated Compounds (PFC) and Perfluoroalkyl Substances (PFAS) in Drinking Water

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14. ABSTRACT
Perfluoroalkyl substances (PFAS) are a class of synthetic chemicals frequently used for their non-stick properties. They have been used extensively by the Air Force and commercial aviation industries in aqueous film-forming foam (AFFF) for fighting fires involving flammable liquids. Although the manufacture of some varieties of PFAS have been halted in the US, these compounds are highly persistent in the environment and have been found in drinking water in many locations around the globe. Some PFAS have also been linked with possible health effects in humans. This document is intended to aid the bioenvironmental engineers and medical providers of the Air Force in answering several common and uncommon questions that the general public may have regarding these compounds.

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PFOS, PFOA, PFAS, perfluorooctane sulfonate, perfluoroctanoic acid, perfluoroalkyl substances, risk communication, AFFF, perfluorinated compounds, PFC

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1.0 Sources of Information

The information used for compiling the perfluorinated compound (PFC) or perfluoroalkyl substances (PFAS) Frequently Asked Questions (FAQs) in this document are based on two main sources:

1) Readily available materials and references from various Federal Agencies such the U.S. Environmental Protection Agency (EPA), the National Institute of Environmental Health Sciences (NIEHS), the National Toxicology Program, the Agency for Toxic Substances and Disease Registry (ATSDR), and the Centers for Disease Control and Prevention (CDC).
2) Guidance and technical correspondence with the Department of the Navy, Department of the Air Force, Air Force Civil Engineer Center, and Air Force Medical Support Agency.

2.0 Background

2.1 What are PFAS, PFC, PFOS and PFOA?

PFAS (perfluoroalkyl substances) are a class of synthetic or man-made compounds containing approximately 6,000 chemicals formed from carbon chains with fluorine attached to these chains. This C-F bond is the shortest and strongest bond in nature. PFAS is a broad term encompassing both completely and incompletely fluorinated chemicals.

PFC (perfluorinated compounds) are a subset of PFAS containing completely fluorinated compounds, to include PFOS (perfluorooctane sulfonate) and PFOA (perfluorooctanoic acid). PFOA and PFOS have been the most extensively produced and studied of these chemicals.

2.2 What were uses of PFC?

PFC have been used to make carpets, clothing, fabrics for furniture, paper packaging for food and other materials (e.g., cookware) that are resistant to water, grease or stains. They were also used in firefighting foam and in a number of industrial processes. Commercial and consumer products containing PFC were first introduced in the 1950s.

2.3 Why is this a concern for the Air Force?

In 1970, the Air Force began using Aqueous Film Forming Foam (AFFF), a firefighting agent containing PFC, to extinguish petroleum fires and protect people and property. AFFF has also been used for firefighting training and in some aircraft hangar fire suppression systems. PFOS is a component of AFFF and PFOA is a stable end product resulting from the degradation of precursor substances.

Because of their chemical structure, PFC, including PFOS and PFOA, do not easily break down in the environment and can migrate into groundwater drinking water sources. Releases into the environment have occurred by actions such as spills and leaks, training activities, and emergency responses.

2.4 Are PFAS still being produced?

In general, the production of PFOS and PFOA has greatly declined over the past 15 years. For example, the largest U.S. manufacturer of PFOS voluntarily stopped production in 2002. However, other countries still produce PFOS, and it can be imported into the United States in limited quantities. The EPA and major companies in the PFAS industry have also agreed to phase out production of PFOA as well.

As companies have stopped producing PFOS and PFOA, short-chain PFAS have replaced them in many cases. However, the toxicity and environmental impacts of short-chain PFAS have not been thoroughly researched, and more research is needed to demonstrate their potential effects.

2.5 What is the AF doing to assess potential risk to its personnel?

The Air Force is committed to the safety and well-being of its personnel. Drinking water provided at AF installations and locations is currently being sampled by AF/SG personnel to assess risk to on-base consumers. Installations deemed to be at an unacceptable level of risk will be provided alternate sources of drinking water by the AF. The AF also has an ongoing comprehensive assessment and cleanup program to address PFOS and PFOA contamination at its locations.

3.0 Regulatory Framework

3.1 What are the regulatory standards for PFOS and PFOA?

Currently, PFAS are classified as unregulated or “emerging” contaminants, which have no Safe Drinking Water Act (SDWA) regulatory standards or routine water quality testing requirements. PFAS are being studied by the EPA to determine if regulation is needed. On 19 May 2016, the EPA’s Office of Water issued new health advisory levels (HALs) for two PFAS: (1) perfluorooctane sulfonate (PFOS) - Publication EPA 822-R-16-004 and (2) perfluorooctanoic acid (PFOA) – EPA 822-R-16-005.

The EPA HALs are 0.07 parts per billion (ppb) for both PFOS and PFOA, individually or as the sum of the two.

For more information on how EPA manages the unregulated or “emerging” contaminants, refer to: UCMR - https://www.epa.gov/dwucmr/learn-about-unregulated-contaminant-monitoring-rule.

For more information on drinking water health advisories for PFOS and PFOA, refer to: https://www.epa.gov/ground-water-and-drinking-water/drinking-water-health-advisories-pfoa-and-pfos.

3.2 What are health advisory levels?

Health advisory levels (HALs) are not regulatory standards. HALs identify the concentration of a chemical of concern in drinking water at and below which adverse health effects are not anticipated to occur over specific exposure durations (e.g., 1 day, 10 days, a lifetime). The EPA recommends actions to be taken to prevent exposures when concentrations exceed the HAL.

HALs also serve as informal technical guidance to assist federal, state, and local officials, and managers of public or community water systems in protecting public health when emergency spills or other unusual situations occur. A HAL document provides information on the environmental properties, health effects, analytical methodology, and treatment technologies for removing drinking water chemicals of concern. [1] [2]

3.3 How did EPA set the drinking water health advisory levels for PFOS and PFOA?

The EPA set the lifetime HAL value at 0.07 µg/L (ppb) to prevent a variety of adverse developmental effects to fetuses during pregnancy and to infants during breast feeding. Lactating women tend to intake more water than pregnant women and the population in general, so water intake parameters for this sensitive population were used to calculate a lifetime health advisory that would not only be protective of the general population but also the most vulnerable population. EPA recommends that the lifetime HAL for PFOA and PFOS of 0.07 µg/L apply to both short-term (i.e., weeks to months) scenarios during pregnancy and lactation, as well as to lifetime-exposure scenarios.

The lifetime HAL was derived from studies in animals such as rats, mice, and monkeys. In these studies, the PFC values which do not show any effects are selected to be potentially used as references from which advisory levels can be derived. The data are subjected to a number of calculations, including uncertainty factors which compensate for variability in the human population and differences in the ways humans and other animals react to PFAS. Since developmental effects were among the most sensitive endpoints, the final HAL calculations were performed using parameters from pregnant and lactating women as explained above. [1] [2]

3.4 What do parts per billion (ppb) and parts per trillion (ppt) concentrations in drinking water mean in simple terms?

Parts per billion (ppb) and parts per trillion (ppt) are the most commonly used terms to describe very small amounts or trace levels of chemicals of concern in our drinking water.

One ppb is the equivalent of one drop of impurity in 500 barrels of water or 1 cent out of $10 million.

One ppt is the equivalent of one drop of impurity in 20 Olympic-size swimming pools -or- traveling 6 inches out of a 93 million-mile journey toward the sun.

4.0 Exposure and Exposure-Reduction Questions

4.1 What populations are most sensitive to PFAS exposure?

The EPA and ATSDR have identified pregnant and lactating women, women who may become pregnant, and infants as the most sensitive populations due to the possibility of developmental effects associated with PFC exposure. Members of these populations should avoid ingesting water which is at or above the HAL by using bottled water for drinking, preparation and cooking of food, and brushing teeth. [3]

4.2 How do PFAS behave in our body?

Because of their widespread use, most people in the United States have some amount of PFAS in their body. Once the PFAS are in a person's body, it takes several years before those PFAS levels go down by half, even if no more is taken in. [4]

More information is available from both the ATSDR and the U.S. EPA.

Reference ATSDR: http://www.atsdr.cdc.gov/HAC/pha/decatur/Blood%20PFC%20Testing%20and%20Health%20Information.pdf

Reference EPA-PFOS: https://www.epa.gov/sites/production/files/2016-05/documents/pfos_hesd_final_508.pdf

Reference EPA-PFOA: https://www.epa.gov/sites/production/files/2016-05/documents/pfoa_hesd_final_508.pdf

4.3 How are people exposed to PFAS?

PFAS are man-made, so there are no natural sources in the environment. However, higher environmental levels of PFAS can be found near areas where they are manufactured or where products containing PFAS are often used. PFAS can travel long distances, move through soil, seep into groundwater, or be carried through air. Because they are stable chemicals and move so easily in the environment, PFAS have been found in soil, sediment, and water samples far away from where they were made or used. Potential sources of PFAS in the environment may include industrial sources, areas where PFAS are used frequently, and consumer products. Listed below are places where they can be found:

- Public water systems and drinking water wells, soil, and outdoor air near industrial sources or areas with frequent PFAS use.
- Indoor air in spaces that contain carpets, textiles and other consumer products treated with PFAS to resist stains.
- Surface water (lakes, ponds, etc.) and run-off from areas where AFFF is often used, such as military or civilian airfields.
- Locally caught fish from contaminated bodies of water.
- Food items sold in the marketplace.
- Consumer products such as non-stick coatings on cookware, grease-resistant paper used for foods, and stain resistant coatings on carpets, upholstery, and other fabrics.

Consuming contaminated food and water is thought to be the main way people are exposed to PFAS. PFAS have been measured in waterbodies used for drinking water around the world, and PFAS have been found in a variety of commercial food items. However, PFOA and PFOS are no longer used in most of these products. Due to their ability to build up in the body, even small amounts of PFAS consumed regularly can result in measurable levels of PFAS in exposed people. [4]

4.4 How likely are PFOS/PFOA to cause cancer?

Researchers and regulators continue to evaluate the likelihood of PFAS causing cancer. The National Toxicology Program has not made a final definitive statement about the ability of any PFAS to cause cancer. The ATSDR expressed caution in concluding any causal relationship from PFOS/PFOA exposures.

PFOS – The EPA has stated that there is suggestive evidence for carcinogenic potential in PFOS, but the weight of evidence was judged to be too limited to support a quantitative cancer assessment.

PFOA – The EPA has stated that there is suggestive evidence for carcinogenic potential in PFOA, but subsequent quantitative risk assessments have shown that the HAL of 0.07 µg/L is protective against cancer.

Information on cancer studies is listed below in the Additional Information section.

Additional references are available at:

ATSDR - http://www.atsdr.cdc.gov/pfc/health_effects_PFAS.html

EPA - http://www.epa.gov/ground-water-and-drinking-water/drinking-water-health-advisories-pfoa-and-pfos

4.5 Are there PFAS in foods?

Various studies have examined the concentrations of PFAS in different food items available for purchase in the marketplace. Items in which PFAS have been detected include potatoes, canned vegetables, eggs, sugars, preserved foods, beef, fish, milk, and microwave popcorn. PFAS can be transferred to vegetables and other plants from contaminated soil and water, though the uptake, distribution, and storage properties of individual plants can vary. Cattle, poultry, and other animals can be exposed through the consumption of feed contaminated with PFAS or through the ingestion of contaminated drinking water, which in turn can lead to the contamination of food items produced from these animals. In addition, the non-stick coatings on many items used to cook or store food may function as a source of PFAS contamination in prepared foods. [4]

The consumption of fish is thought to be a major pathway for PFAS exposure for both the general population and for people living near PFAS contaminated waters. Typically, elevated concentrations of PFAS in fish are found near areas involved in the production or manufacture of PFAS. Before consuming recreationally caught fish in these areas, please consult local fish and seafood advisories. [4]

4.6 Is it safe to swim in municipal pools or recreational waters?

Currently, there is insufficient information to assess whether recreational exposures to PFAS-contaminated waters are harmful to human health. Many PFAS, including PFOS and PFOA, are essentially non-volatile, such that inhalation while swimming or bathing is not likely to be a major pathway. In the interim, anyone with concerns, including sensitive populations, should consult with their appropriate state agencies. [4]

4.7 Is it safe to do laundry and wash dishes with tap water?

Yes. Doing laundry or washing dishes is not likely to pose a significant exposure to PFAS. [4]

4.8 Is it safe to take a shower or bath?

ATSDR has stated that routine showering or bathing will not likely cause a significant exposure. Studies have shown very limited absorption of PFAS through the skin. Many PFAS, including PFOS and PFOA, are essentially non-volatile, such that inhalation while bathing or showering is not likely to be a major inhalation exposure pathway. [3]

4.9 Are there methods to show whether people have been exposed to PFAS?

Various methods are available for testing if people have been exposed to PFAS. One method, known as biomonitoring, involves measuring how much of a chemical is present in the human body. Levels of a chemical of concern in the body suggest that some level of exposure occurred, but biomonitoring cannot determine which exposure(s) caused the chemical to be present. Moreover, the presence of chemicals in the blood or other body tissue does not automatically mean that harmful health effects will occur. Scientists do not currently know whether and at what common levels of exposure many chemicals of concern, including PFAS, in the blood could lead to harmful effects. [3]

More information on biomonitoring can be found at:

http://www.atsdr.cdc.gov/pfc/additional_resources.html

4.10 Should people concerned about exposures to PFAS get themselves tested?

ATSDR does not advise individuals in general or sensitive populations to be tested for PFAS exposure. Most Americans have serum concentrations of one or more specific PFAS, including PFOS and PFOA. A serum PFAS concentration does not provide diagnostic or treatment information, and cannot predict future health effects. The measurements must be done in specialized laboratories and are expensive. It does not indicate when exposure occurred or the source of the exposure. The only information which can be obtained from serum PFAS are comparisons of serum levels to the general population. [3]

4.11 How do I eliminate PFAS from my body if I have been exposed?

Currently, there are no medical interventions that will remove PFAS from the body. PFAS are removed from the body naturally via the urine. [4]

4.12 Is there treatment for people who have been exposed to PFAS?

ATSDR does not recommend any specific treatments for people who have been exposed to PFAS. [3]

4.13 What can people do to reduce their risk of exposure to PFAS?

PFAS are found in the blood of people and animals all over the world and are present at low levels in a variety of food products and in the environment (air, water, soil, etc.). Therefore, completely preventing exposure to PFAS is unrealistic, and no effective recommendations can be made for entirely reducing individual exposures in the general population. [3]

If the AF deems that a base population is at an unacceptable risk of exposure to PFAS from AF-produced drinking water, then alternative drinking water sources will be provided for drinking, food preparation, cooking, brushing teeth, and any activity that might result in ingestion of water.

For those living off-base near known sources of PFAS contamination, certain steps can be taken to reduce one's risk of exposure to PFAS. For example, numerous states have issued advisories cautioning consumers to either stop or limit eating fish from waters contaminated with PFOS or other PFAS. Check with your state public health and environmental quality departments for any advisories in place in your area to learn the types and local sources of fish that are safe to eat.

A variety of consumer products, including non-stick coatings on cookware and coatings on clothing, carpets, and paper packaging, have contained different types of PFAS in the past. While recent efforts to remove long-chain PFAS from many of these products have reduced the likelihood of exposure to long-chain PFAS, exposure to short-chain PFAS may still be possible through modern consumer products.

Contact CDC/ATSDR for updated information on this topic at 1-800-CDC-INFO. Contact the Consumer Product Safety Commission at 1-800-638-2772 for questions or concerns about products used in the home.

4.14 I drank the water, will I get sick?

There is no broad-based, proven link between PFOS/PFOA and illness in humans. Health effects, if any, would depend on many factors including how much one is exposed, the length of the exposure, the route of exposure, age, gender, diet, family traits, lifestyle, and state of health. No definitive causal relationships between PFAS and the health effects has been shown, but research is continuing as the studies conducted thus far have provided contradicting information. Additionally, while blood serum PFC concentrations can tell you how much of certain PFAS are in your body at the time of the test, the results cannot predict health effects which may occur or have occurred.

4.15 Are my vegetables safe to eat if I watered with contaminated water?

Although PFAS can be absorbed into plants via contaminated soils, the actually quantity of PFAS in the edible portion of the plants are not likely to present a significant risk. Risk can be even further reduced by washing produce in clean water after harvesting and peeling root vegetables and washing before consumption. Contamination of future harvests can also be reduced by using clean water to hydrate plants. [5]

4.16 If contamination is persistent, do I need to remove all soil and replant my garden?

Although PFAS do persist in soils, complete removal of the contaminated soils is likely not necessary to reduce uptake of PFAS into fruits and vegetables. Studies have shown that PFC uptake into plants is significantly reduced after cessation of PFC input into the soil. [5]

4.17 Is lawn safe for kids because I watered with contaminated water?

Yes – exposure to PFAS by contact with a lawn watered with contaminated groundwater is very unlikely to be significant. Studies investigating exposure to PFAS have consistently concluded that ingestion of contaminated water is a much more significant source of exposures than those associated with lawns such as ingestion or inhalation of contaminated soil and dermal absorption.

4.18 Is "vaping" with contaminated water safe?

Exposure to PFAS via contaminated e-liquid is possible. Although most PFAS are non-volatile, the nebulizing action of electronic cigarettes can effectively deliver non-volatile compounds to the user via the vapor it generates. However, whether inhaled PFAS can be effectively absorbed via the lungs has yet to be quantified. If the manufacturer of the e-liquid used water with PFC contamination above the HAL, it would be best for sensitive populations such as pregnant or breastfeeding women to avoid using those particular products.

4.19 Is it safe to use "swamp coolers" filled with contaminated water?

Yes, these systems are not expected to present a potential route of exposure to PFAS. Evaporative cooling systems, or "swamp coolers," work by moving hot and dry air through a moist material. Evaporation of water from the material cools the inbound air which is then pumped throughout the building. Since evaporation of water is the main mechanism by which these coolers operate, essentially non-volatile substances such as PFAS are unlikely to be introduced in the indoor air of a home or building by these machines. Therefore, any risks associated with using PFC contaminated water in evaporative coolers are minimal.

5.0 Pregnancy and Children

5.1 If I am pregnant, is it safe to drink tap water?

The EPA has identified pregnant and lactating women as a population sensitive to PFAS in drinking water. As such, if the EPA's Long Term Health Advisory Levels are exceeded, pregnant women should stop drinking tap water and seek an alternative drinking water source until levels of PFOA and PFOS in the drinking water are reduced. You can reduce exposure by using an alternative water source for drinking, food preparation, cooking, brushing teeth, and any activity that might result in ingestion of water. [3]

5.2 Is it safe to breastfeed?

PFAS can be passed from mother to child through breastmilk, but the well-established benefits of breastfeeding such as immunological advantages, lower obesity rates, and greater cognitive development for the infant are expected to far outweigh any possible health effects from PFAS in breastmilk. Concerns about PFAS exposure and breastfeeding should be discussed with a child's pediatrician or other healthcare provider. [3]

5.3 I am using powdered formula to feed my baby, is it safe to use tap water to mix the formula or should I use bottled water?

If the EPA's Long Term Health Advisory Levels are exceeded, bottled water should be used to prepare infant formula. Alternatively, caregivers could use formula that does not require adding water until levels of PFOA and PFOS in the drinking water are reduced. [3]

5.4 What are the potential health effects of PFAS exposure in children?

Over the past few years, researchers have begun to examine the possible effects of PFAS exposures in children. Studies have shown that newborns can be exposed to PFAS through breast milk. Young children may be exposed to PFAS through food and water, similarly to adults. In addition, young children have a higher risk of exposure to PFAS through carpet cleaners and similar products, due to time spent laying and crawling on floors in their early years. As a result, most children in industrialized nations have at least some level of PFAS in their blood.

A variety of health effects in children have been studied in relation to PFC exposure in children; these effects include an increase in serum total cholesterol, serum LDL, and serum triglycerides; decreased vaccine effectiveness; delays in puberty; and some adverse behavioral outcomes. However, as with studies in adults, the evidence linking PFAS to health effects in children is inconclusive, with many studies showing positive associations and many studies showing no associations. Researchers acknowledge that the findings of many of the studies linking PFAS and health effects in children are limited and that more studies are needed. As a result, it is too soon to state whether or not there are special concerns for children. [4]

6.0 Additional Information for Medical Providers Regarding Health Effects Observed in Humans and Laboratory Animals Exposed to PFAS

6.1 Summary of Research Studies

Epidemiological studies in humans have suggested several significant associations between PFC exposures and adverse health effects. According to the ATSDR, the most consistent findings are associations between PFOS and PFOA serum concentrations and increases in serum lipid concentrations, decreases in birth weight, increased risk of thyroid disease, increased risk of high blood pressure or pre-eclampsia in pregnant women, and decreased immune response to vaccines [3] [6]. Several studies have also examined incidences of cancer associated with exposure to PFOS and PFOA. Occupational exposures have been associated with kidney and prostate cancer, and highly exposed non-occupational populations have shown increased rates of kidney and testicular cancer [4]. However, these results should be assessed cautiously because in some studies, control for potential confounding variables was not considered, the number of cancer cases was low, and causal relationships were not established.

Effects in laboratory animals are mostly seen after oral dosing. Some of the effects observed in rats include increases in liver weight, hepatocellular hypertrophy, and decreases in serum cholesterol and triglyceride levels [4]. Developmental effects have also been noted in rodents and include prenatal loss, reduced neonate weight and viability, neurodevelopment toxicity, and delays in mammary gland differentiation, eye opening, vaginal opening, and first estrus . PFOA delayed mammary gland differentiation in mice dosed during gestation. PFOA induced hepatocellular adenomas, Leydig cell adenomas, and pancreatic acinar cell adenomas in rats, and PFOS increased the incidence of hepatocellular adenomas (2 year exposure) and thyroid adenomas (1 year exposure, 1 year recovery). It is important to note that the peroxisome proliferator-activated receptor, PPARα, plays an important role in PFOS and PFOA-induced toxicities in animals, and there are considerable uncertainties associated with the relevancy of this pathway in humans. However, PPARα-independent pathways have also been hypothesized which require further evaluation and study to understand. [4]

6.2 Human Studies

There are numerous epidemiological studies which investigate associations between PFC exposures and health effects, but many of these studies are inconclusive or contradictory. [7] The most commonly noted effects associated with PFC exposures are increases in total serum cholesterol, including high-density lipoproteins (HDLs; 'good cholesterol') and low-density lipoproteins (LDLs). Reproductive and developmental effects have also been associated with exposure to PFAS. These effects include decreases in birth rate and female fertility associated with PFOS exposure and decreased birth weight associated with both PFOS and PFOA exposure. Additionally, pregnancy-induced hypertension and an associated increase in serum protein level known as pre-eclampsia are associated with PFOA exposure. Other associations include a positive association with diagnosed thyroid disease, increased risk of ulcerative colitis, slight effects on the liver, and an association with decreased vaccine responses in highly exposed adults and low exposure children. However, in regards to the latter effect, no association was found between PFC exposure and risk of infectious disease in children.

Epidemiological evidence of cancer associated with PFC exposure is also limited and inconclusive. An occupational cohort exposed to PFOS showed an increased risk of bladder cancer, but this study is likely heavily confounded by the effects of smoking. No other cancers were associated with PFOS exposure to a statistically significant extent. High general population exposures to PFOA have been associated with kidney, prostate, testicular cancers, but a more recent investigation in occupationally-exposed workers found no association between PFOA exposure and risk of dying from any cancer type. According to the EPA, both PFOS and PFOA exhibit suggestive evidence of carcinogenic potential. [7]

It is important to note that, while epidemiological studies can provide evidence of PFC-related health effects in humans, many studies do not report exposure data such as doses and duration. Thus it becomes impossible to determine at what serum concentrations the effects first manifested. Additionally, the number of cancer cases in most studies was low, and a causal relationship between perfluoroalkyls and cancer cannot be established from these studies. However, human epidemiological studies are still adequate to use for qualitative PFC hazard identification according to the EPA. [4]

6.3 Animal Studies

Numerous animal studies have investigated the effects of PFAS on a variety of endpoints. Exposure of laboratory animals to PFOS have routinely shown effects on the liver such as an increase in relative liver weight, hepatic steatosis, and damage to liver tissues. Commonly co-occurring with these effects are decreased total cholesterol and lowered body weight. Effects on development are also noted in laboratory animals exposed to PFOS *in utero* and lactationally. One and two generation studies in rats have demonstrated decreased pup survival and body weights. In addition, developmental neurotoxicity studies have shown increased motor activity, decreased habitation, and increased water maze escape latency (which indicates possible deficits in spatial learning and memory). Similarly exposed rats and mice exhibited an increase in serum glucose concentrations as a result of increased insulin resistance.

For PFOA, chronic and short-term subchronic oral studies in multiple species report developmental effects, immune effects, liver and kidney toxicity, and cancers of the liver, testes, and pancreas. Increased liver weight is the most commonly observed effect of PFOA exposure in animals, but this effect alone is not considered to be adverse in the absence of other conditions such as necrosis, inflammation, steatosis of the liver, or fibrosis. Interpretation of this effect is complicated because increased liver weight and hypertrophy are also associated with PPARα activation, a mechanism largely irrelevant to humans. [8] PFOA is known to activate PPARα, but based on PFOA-induced transcriptional activation of many other genes in PPARα-null mice, other receptors such as the constitutive androstane receptor (CAR), farnesoid receptor (FXR) and pregnane X receptor (PXR) could be involved in PFOA-induced toxicity.

Developmental effects observed in animals include decreased survival, delayed eye opening, reduced ossification, skeletal defects, altered puberty, and altered mammary gland development. A two-generation study reported that male rats had increased liver and kidney weights as well as a decreased body weight at a dosage of 1 mg/kg/day. The same dosage showed developmental toxicity and increased spleen weights in mice. Slightly higher dosages resulted in decreased immunoglobulin levels, as seen in human epidemiological studies.

Evaluation of the carcinogenic potential of PFOS and PFOA is complicated. PFOS carcinogenicity has only been studied in animals once. The one study, performed on rats, found live adenomas and thyroid adenomas, but these incidences lacked a clear dose-response relationship. For PFOA, two animal studies indicate that chronic exposure can lead to liver adenomas, Leydig cell adenomas, and pancreatic acinar cell tumors. Interpretation of these results is complicated by the fact that one or more of these carcinogenic results could be initiated via PPARα activation, a pathway which is essentially irrelevant to humans. There is enough evidence to suggest that PFOA-induced liver adenomas are likely caused by PPARα activation, but more information is needed to confirm whether the Leydig cell or pancreatic acinar cell tumors possess the same mode of action.

It is also very important to note that animal studies of PFAS are conducted at dosages which result in serum concentrations that are many times higher than what is typically found in both the worker and general human populations. There are also very significant differences in the way these chemicals act once absorbed into humans and animals; PFOS and PFOA take nearly 4 years for their concentrations to be reduced by half in human serum compared with merely days to hours in rodents.

Combined with species-specific modes of action like the PPARα receptor activation pathway, these factors make it quite difficult to determine just how relevant the effects seen in rodents are to humans. [4]

7.0 References

[1] U.S. Environmental Protection Agency Office of Water, "Drinking Water Health Advisory for Perfluorooctane Sulfonate (PFOS)," Washington, D.C., 2016.

[2] U.S. Environmental Protection Agency Office of Water, "Drinking Water Health Advisory for Perfluorooctanoic Acid (PFOA)," Washington, D.C., 2016.

[3] ATSDR, "Perfluoroalkyls - ToxFAQs," 2012.

[4] ATSDR, "Toxicology Profile for Perfluoroalkyls (Draft for Public Comment)," U.S. Department of Health and Human Services, Public Health Service, Atlanta, 2018.

[5] Vermont Agency of Agriculture, Food, & Markets, "Frequently Asked Questions About Gardening, Commercial Produce and PFOA," 2016.

[6] P. Grandjean, C. Heilmann, P. Weihe, F. Nielsen, U. B. Mogensen and E. Budtz-Jorgensen, "Serum Vaccine Antibody Concentrations in Adolescents Exposed to Perfluorinated Compounds," *Environmental Health Perspectives,* vol. 125, no. 7, 2016.

[7] C. Lau, K. Anitole, C. Hodes, D. Lai, A. Pfahles-Hutchens and J. Seed, "Perfluoroalkyl Acids: A Review of Monitoring and," *Toxicological Sciences,* vol. 99, no. 2, pp. 366-394, 2007.

[8] T. Ikeda, K. Aiba, K. Fukuda and M. Tanaka, "The Induction of Peroxisome Proliferation in Rat Liver by Perfluorinated Fatty Acids, Metabolically Inert Derivatives of Fatty Acids," *J. Biochem.,* vol. 98, pp. 475-482, 1985.