What Do Human Studies Tell Us About the Toxicity of PFAS?

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Per and poly-fluoroalkyl substances, or PFAS, are a large and diverse class of man-made chemicals used to make products resistant to heat, stains, grease, and water. There are many types of PFAS, and the best-known examples are perfluorooctane sulfonate ("PFOS") and perfluorooctanoic acid ("PFOA").

Research studies have shown that there are potential associations between exposure to specific PFAS and health effects including altered immune system, liver function, and cancer. However, the PFAS science is full of uncertainties and inconsistent interpretations by scientists. This overview will explain the strengths and limitations associated with human studies. It will also provide a summary of the current information related to health effects that may be associated with some individual PFAS where information exists.

Summary

- Despite hundreds of studies that have been published, the science on PFAS human health risk is full of uncertainties and inconsistent interpretations by scientists, even for the most well-studied PFAS - PFOS and PFOA.

- Not all scientists agree on the potential health effects related to PFOS or PFOA in drinking water.

- It is generally agreed that there may be an association between exposure to PFOA and kidney and testicular cancer. PFOS and PFOA may be associated with increased cholesterol levels, decreased vaccine response for some vaccines in children, and kidney disease.

- Additional research may change our understanding of the relationship between PFAS exposure and human health effects.

How is chemical toxicity studied?

When asking whether a chemical is toxic to humans, it is important to understand how the term "toxic" is used by toxicologists. Toxicologists are scientists who study whether chemicals may cause harm to human health. For harm to occur, two things need to happen: exposure must occur through ingestion, inhalation, or skin contact; and the level of exposure must be high enough and long enough to cause an adverse effect. Therefore, a chemical may not present a health risk to humans if the exposure is less than the levels that are sufficient to cause an adverse effect.

Toxicologists rely on a "weight-of-evidence" evaluation from many different studies when evaluating chemical toxicity. This evaluation looks for indications that exposure to a chemical may cause a human health effect based on:

- consistency of results from several studies (including human and laboratory experiments),
- strength of associations, and
- a biological explanation for how the chemical may cause the health effect.

Epidemiology studies evaluate whether the incidence and distribution of diseases in human populations vary in relation to exposures. When epidemiology studies show evidence of an association between an exposure and risk of disease it is important to evaluate whether the association is due to a cause-and-effect relationship or whether some other explanation is more plausible. Chance, bias, and confounding must be excluded as plausible explanations for the association. (Confounding is the presence of some other factor besides the exposure of interest that alters the apparent association between the exposure of interest and risk of disease.) It is important to evaluate the strength of the association, whether the association has been seen consistently in other studies, whether the risk of disease increases with increasing exposure, whether there are exposure levels at which there is no increased risk of disease, whether the timing between exposure and occurrence of disease makes sense, and whether there is a plausible mechanism of disease. This evaluation is critically important because some associations are not due to causal relationships, but occur for other reasons. It is often challenging to identify why there are difference across scientific studies and how these differences affect our interpretation of the evidence. The scientific evidence on the health effects of PFAS requires careful consideration of all these issues.

Why are data on PFAS and human health effects inconclusive?

Although many PFAS have been around for decades, research into the possible human health effects that might occur as a result of exposures to PFAS has mostly been generated within the past 20 years, and primarily on PFOS and PFOA. Figure 1 shows how the number of studies looking at the potential association of PFOS or PFOA and a human disease has dramatically increased since about 2005.

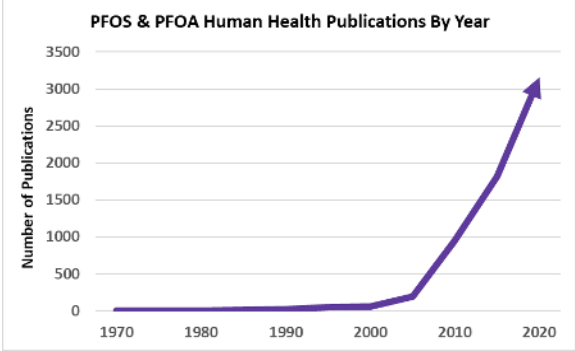


Figure 1. Number of publications of human health studies per year in the National Library of Medicine database (PubMed).

PFAS can be found in the blood of animals and humans worldwide. Although the number of PFAS scientific studies is rapidly increasing, the general public's exposure to PFOS and PFOA has decreased since manufacturing and use of these two chemicals stopped in the United States and Europe. The U.S. Centers for Disease Control and Prevention (CDC) has been sampling and tracking the general population's blood for potential exposure to PFOS and PFOA. Figure 2 shows that the levels of PFOS in the blood of the general population has decreased by 86% since 1999 and the level of PFOA has decreased by 73% since 1999. Importantly, surveys of blood levels of PFAS do not tell us whether there are or are not health effects from these chemicals, nor do they predict whether any potential health effects will occur.

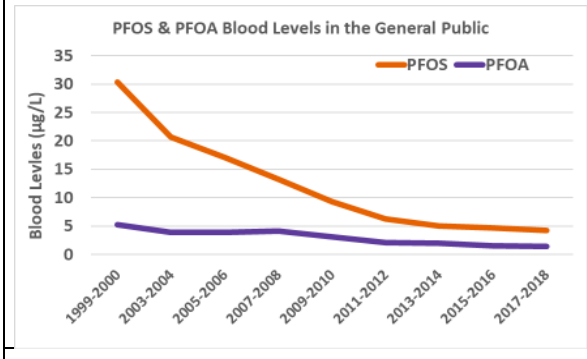


Figure 2. Geometric mean blood levels for the general public from the U.S. CDC National Health and Nutrition Examination

However, these blood levels *can* be helpful for comparing the exposures for different groups of people.

The "C8 Health Project" was one of the first major studies of a community along the Ohio River Valley exposed to PFOA from a manufacturing facility. This study was started as part of a lawsuit settlement agreement, and results were published in a series of papers from 2010 to 2012. The project found "probable links" between PFOA and six different human health effects (kidney and testicular cancer, pregnancy-induced high blood pressure, thyroid disease, high cholesterol, and ulcerative colitis (an autoimmune inflammatory bowel disease). Since then, hundreds of studies have been published that examine the possible relationships between exposure to PFAS and harmful health effects in people. Studies include people who worked in plants manufacturing these chemicals, firefighters, people with contaminated drinking water, and the general community. However, differences in study design and reporting make comparisons of studies difficult.

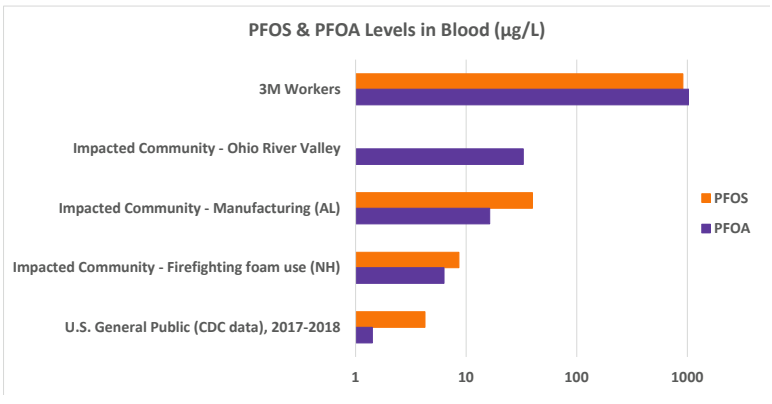


Figure 3. Comparison of exposure to PFOS and PFOA between different groups of people. Data (log scale) adapted from ATSDR (https://www.atsdr.cdc.gov/pfas/health-effects/us-population.html).

For example, PFAS exposure levels and associated blood levels were very different among the groups of people that have been studied. The amount of PFAS found in the blood of the general public are lower, often by orders of magnitude, than PFAS found in the blood of people who worked in the manufacturing plants or for people who lived in areas with drinking water impacted by nearby PFAS manufacturing (see Figure 3).

The differences in study populations, exposure levels, study types, and study quality, all make it difficult to conclude that a potential adverse health effect is associated with PFAS exposure. Additionally, studies may not have included enough people to determine if the occurrence of a disease among an exposed population is greater than the occurrence in the general population. The effect of small sample sizes on the interpretation of an epidemiology study can be important if a disease is relatively rare, such as for certain cancers.

Challenges with evaluating human data on PFAS exposure include:

- associations between exposure and health effects are often weak and inconsistent among studies;
- incidence of actual disease is low and most of the findings in even the highest exposed people generally fall within normal ranges of occurrence for the general population;

- there is not a clear biological mechanism that explains how PFAS may be causing the health effect; and
- for some effects, it is not clear whether the exposure caused the health effect or whether the health effect was preexisting and caused an increase in internal PFAS accumulation (a phenomenon called "reverse causation").

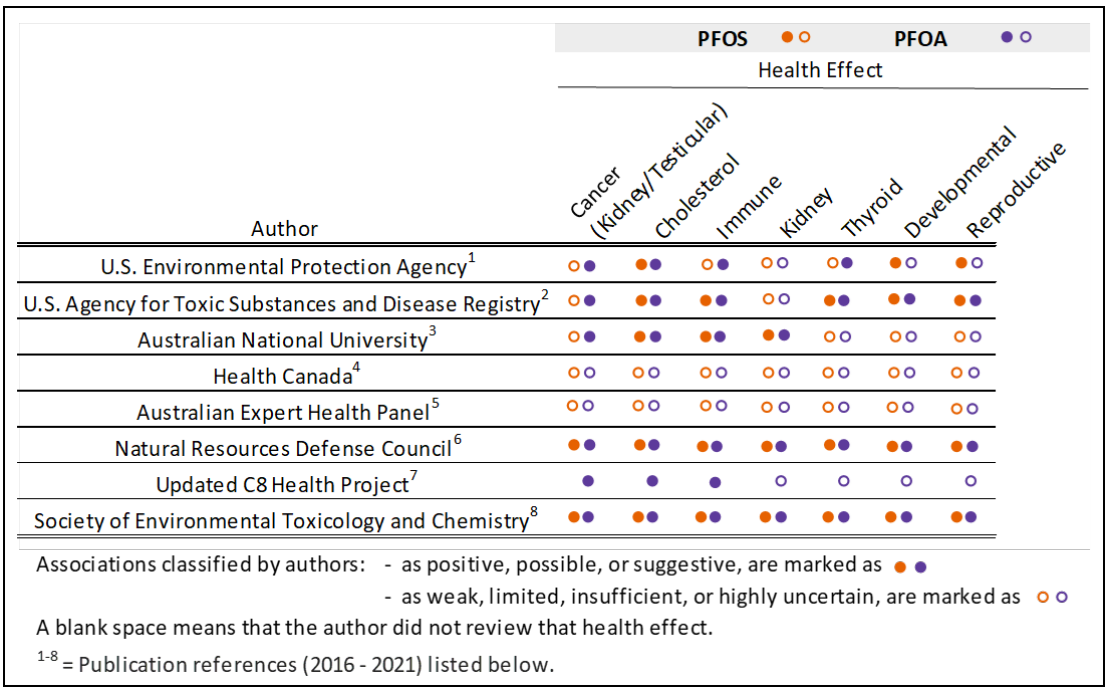
The data on potential health effects associated with PFAS exposure have been reviewed by toxicologists worldwide. The initial "probable link" associations reported in the C8 Health Project for PFOA have not been consistently identified in other epidemiology studies. In general, studies for all PFAS and health effects have been inconsistent and generally weak. Professional judgements must be applied and are often conflicting.

What are the potential health effects associated with exposure to PFOS or PFOA?

The table below shows recent conclusions made by government agencies or groups of toxicologists regarding either PFOS (orange) or PFOA (purple) and associations with various health effects. There are not enough data on most other PFAS to evaluate these health outcomes.

Not all toxicologists agree on all health effects. However, there is generally greater agreement regarding an association between exposure to PFOS and PFOA for the following human health effects:

- Kidney and testicular cancer (PFOA only)
- Increased cholesterol levels
- Decreased vaccine response for some vaccines in children
- Kidney disease or reduced kidney function



Having an "association" between exposure and a health effect means that a relationship between PFAS exposure and the health effect has been observed in a study. However, this does not necessarily mean that the PFAS has caused the effect, or that all levels of exposure to PFAS would result in that health effect, or that exposure to any different specific PFAS or mixture of PFAS would result in that health effect.

Observations regarding major health effects are summarized below.

- ***Kidney and Testicular Cancer:*** Some studies have shown no link between PFAS exposure and cancers. However, other studies have shown a possible link between PFOA exposure and a slightly increased risk of kidney and testicular cancers, but not other cancers. We do not know how PFOA, or other PFAS, could cause cancer in humans. Associations identified in epidemiology studies between exposure to other PFAS, including PFOS, and cancer are weak or have not been studied enough.
- ***Cholesterol:*** Some studies show a possible link between PFOS and PFOA exposure and increased blood cholesterol. The reported increases in blood cholesterol are small and within normal range and they have not been consistently associated with the development of cardiovascular diseases.
- ***Immune system:*** A few studies have suggested a possible link between PFAS exposure and decreased vaccine response for some, but not all vaccines. However, most studies have not found any significant increase in human infections or disease. Toxicologists have different opinions about this health effect. Many consider the overall human evidence for decreased vaccine response weak, while others think it is a possible health effect caused by PFAS exposure.

- ***Kidney function:*** Some studies show a link between PFAS and increased risk of having reduced kidney function. It has not been shown that PFAS exposure damages the kidneys or is linked to kidney disease. PFAS are eliminated from the body by the kidney. People with pre-existing kidney disease might not be able to get rid of PFAS as efficiently as other people and would have higher levels of PFAS in their body because they have kidney disease. This is known as 'reverse causation'. More research is needed to determine if there is a link between PFAS and kidney damage.

Could PFOA or PFOS exposure cause other health effects?

Studies on other health effects, such as liver effects, thyroid effects, high blood pressure or pre-eclampsia in pregnant women, reduced birth weight in infants and reproductive effects have had mixed results. Studies show weak or no associations between exposure and a clear adverse health effect.

There is currently no consistent evidence that exposure to PFOS, PFOA, or other PFAS causes health problems for pregnant women or their babies. Current studies do not support PFAS exposure being a major cause of pregnancy-induced high blood pressure (hypertension and pre-eclampsia) or other pregnancy complications. There are some studies that show an association between slightly lower-than-average birth weight in babies and increasing PFAS levels in maternal or cord blood in mothers. However, the birth weight decreases are small and within the normal range for newborn birth weight. On the other hand, some studies have shown there is no link between lower birth weight and PFAS exposure during pregnancy.

For all the effects discussed above, additional research may change our understanding of the relationship between exposure to PFAS and human health effects. Science is based on evidence: as the evidence grows the scientific conclusions likely will evolve and change.

What are other health concerns related to PFAS exposure in drinking water?

Community members that have been exposed to PFAS through their drinking water have been understandably concerned and upset. The uncertainty of the science regarding potential human health effects adds to their anger and frustration because no clear answers can be given by medical and public health experts. In addition, inconsistent messages can be found in the published science and the media. Recent work has highlighted that the socioeconomic impacts to a community, including the stress and anxiety about their own health and the health of their children and loved ones, should not be dismissed, and needs more attention.

Conclusions

The general public's exposure to PFOS and PFOA has declined significantly over the last two decades. At the same time, research into the potential health effects associated with exposure to PFOA and PFOS has rapidly increased. However, the PFAS science is still full of data gaps, uncertainties, and inconsistent interpretations by scientists. Evidence suggests that there may be an association between exposure to PFOA and kidney and testicular cancer, and that PFOS and PFOA are associated with increased cholesterol levels, decreased vaccine response for some vaccines in children, and kidney disease. However, this does not necessarily mean that exposure to PFOS or PFOA will cause

the effect, or that all levels of exposure to these chemicals would result in that health effect, or that exposure to different PFAS or PFAS mixtures would result in that health effect. Research is ongoing and additional research may change our understanding of the relationship between exposure to PFAS and human health effects.

Where to go for more information:

U.S. EPA https://www.epa.gov/pfas

U.S. ATSDR https://www.atsdr.cdc.gov/pfas/index.html

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