

Human health effects of PFAS “The forever chemicals”

[Wendy McLean](#) | Educator

09/02/21



Per- and poly-fluoroalkyl substances, also known as PFAS, are a class of synthetic, fluorinated chemicals resistant to heat, water, and oil ([1]).

These manufactured chemicals have been used for over 70 years in many consumer and industrial products, including stain- and water-resistant coating for clothing, furniture and carpets (Scotchgard and GoreTex) ([2],[3]), non-stick coatings (e.g. Teflon) ([4],[5]), food packaging ([6],[7],[8]), cosmetics and personal care products ([9],[10]), and fire-fighting foams ([11]).

More than 4,700 PFAS chemicals exist, with perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) the most extensively produced and studied ([12]).

The chemical backbone of PFAS is made of carbon-fluorine bonds, which is the strongest known chemical bond. As a result, PFAS are incredibly resistant to environmental degradation, earning them the moniker “forever chemicals” ([13]).

Decades of high-volume production of PFAS, coupled with the environmental persistence of these chemicals, have led to widespread PFAS contamination of soil, water and air, even in remote areas including Antarctica, and bioaccumulation across entire ecological food chains ([13],[14]).

Global biomonitoring studies have detected PFAS in 70-100% of human blood serum, lung, liver, and breast milk samples ([15],[16],[17],[18]). PFAS are universally detected in the serum of pregnant women, neonates, and children worldwide, indicating that exposure is ubiquitous, and these chemicals can cross the placenta and influence infant development ([19],[20],[21]).

PFAS are a significant health concern due to their persistence, bioaccumulation, and potential toxicity. They are increasingly linked to reproductive and developmental toxicity, hepatotoxicity, carcinogenesis, and disruption of immunological, metabolic, and endocrine pathways

([14],[22],[23]). The International Agency for Research on Cancer (IARC) has classified PFOA as a possible carcinogen ([24]).

Even with efforts to reduce or eliminate the production of PFOA, PFOS and similar PFAS in the United States and other industrial countries, large-scale production is still occurring in countries such as China, and human exposure remains high worldwide ([25]).

Furthermore, the pressure to phase out some PFAS has led to a proliferation of unstudied and unregulated novel replacement chemicals (e.g. GenX) which are difficult to detect using standard laboratory methods ([26]). These chemicals may also be more persistent and mobile, less degradable, and equally or more toxic than the older PFAS compounds ([27]).

Human Exposure Pathways

Due to the widespread production and use of PFAS, their improper disposal and their resistance to degradation, humans are exposed to PFAS daily (Table 1; Figure 1). The highest exposures to PFAS are typically through the dietary intake ([28],[29],[30],[31],[32]) and drinking water ([33]). However, the relative contribution of each source category varies significantly according to dietary patterns, drinking water source, demographic group, and population.

Food

Among all foods, fish and shellfish generally have the highest PFAS concentration ([32],[34]), and a positive relationship between serum PFAS levels and fish consumption has been established ([35]).

PFAS have been found in other dietary sources including meat, dairy products, eggs, beverages, and vegetables, bread, and microwave popcorn ([36],[37],[38],[39],[40],[41],[42],[43]).

PFAS can directly migrate from food packaging and non-stick cookware ([44],[45]). The extent of migration of PFAS from food packaging into food depends on the amount, type, and chain length of PFAS used, the type of food (e.g., fat- vs water-based), the contact time, and the temperature ([44],[46],[47]). A 2017 USA study found that 46% of fast-food wrappers contained PFAS, and a weak association between fast food consumption and serum PFAS was detected ([48]).

Water

PFAS are prevalent drinking water contaminants because of their mobility, persistence, and widespread use ([49]). PFAS contamination of drinking water supplies often occurs near landfills, wastewater treatment plants and other sites where PFAS-containing aqueous film-forming foams (AFFFs) are used ([50],[51],[52]). Near contaminated sites, drinking water can account for up to 75% of total PFAS exposure ([30],[53],[54]).

An Australian study found PFOS and PFOA in 49% and 44% of samples collected from drinking water taps. Based on the detected levels, the estimated contribution of drinking water to daily

PFOS and PFOA intakes was 2-3%, with a maximum of 22% and 24%, respectively ([55]).

PFAS are detected in bottled water worldwide ([56]). Sources of PFAS include contamination of water prior to bottling ([57],[58]); the plastic of the bottles ([57]); and potentially ink from labels ([58]).

Exposure to even low levels of PFAS in drinking water can significantly increase levels in the body, with serum PFOA levels in adults found to increase by more than 100 times the drinking water concentration ([22]). Exposure in infants (breast-fed or formula-fed), is even higher than in adults using the same drinking water source due to the greater drinking water intake of infants on a bodyweight basis and the persistence of PFAs in breast milk ([22]).

Consumer products, indoor air, and dust

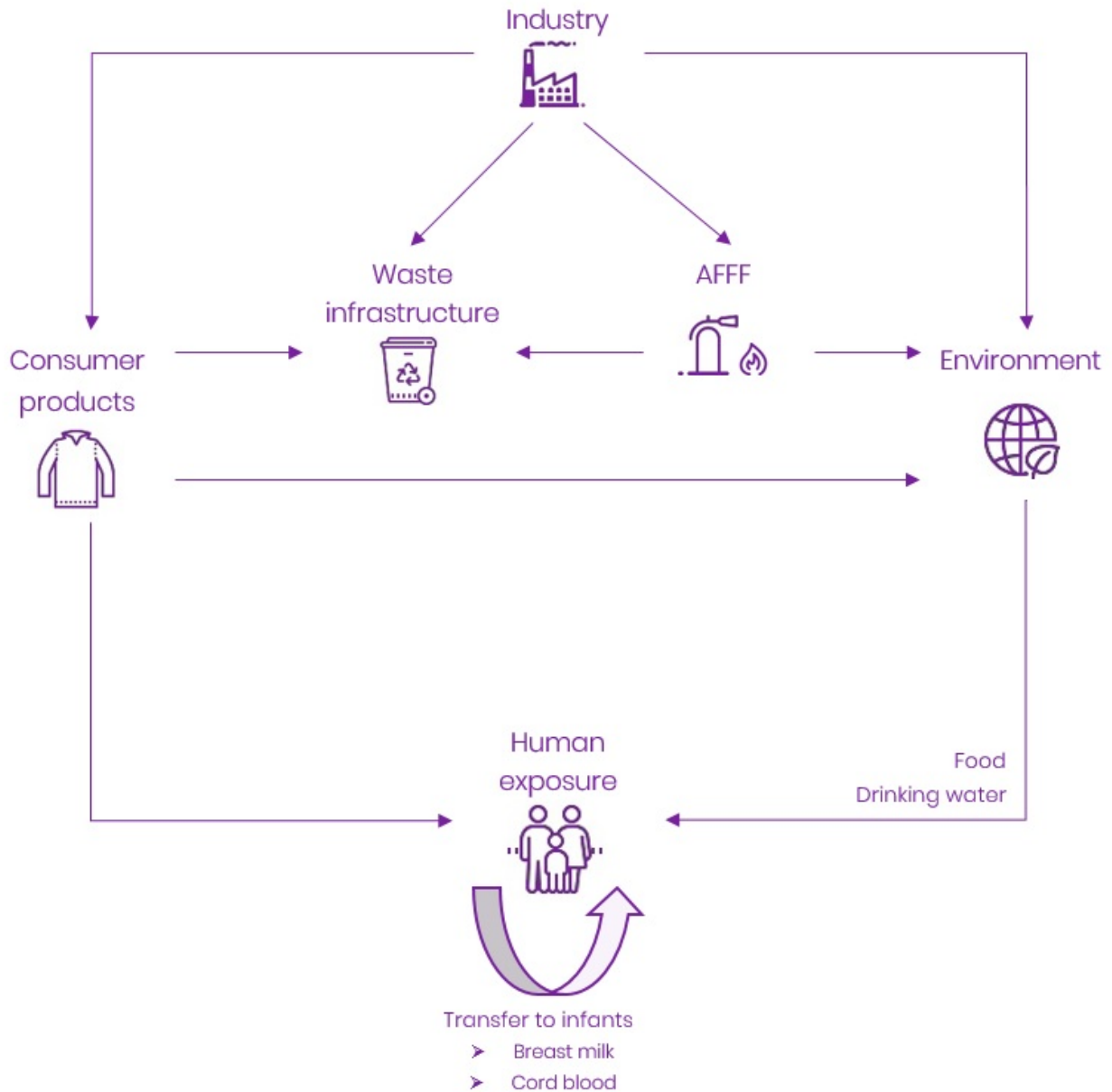
Daily exposure PFAs can occur through consumer products such as clothing and cosmetics, and other items commonly found in the home, office, or car ([59],[60],[61]).

PFAS are volatile compounds that are easily released into indoor environments (via air and dust) from treated furniture and floor coverings, and other household products (e.g. cleaning agents), due to their low water solubility and high vapour pressure ([61],[62],[63]). Studies have found that indoor exposure routes can account for up to 50% of total exposure in some indoor environments ([61]).

Table 1. Sources and pathways of human exposure ([64])

Sources	Pathways		
	Ingestion	Inhalation	Dermal absorption
Dietary sources			
Fish and shellfish	X		
Other foods (e.g. dairy, eggs, meat, vegetables)	X		
Drinking water	X		
Food-packaging materials	X		
Non-stick cookware	X		
Non-dietary sources			
Indoor air		X	
Indoor dust		X	
Soil and sediment			X
Furniture and carpet			X
Cosmetics		X	X
Other consumer products (e.g. outdoor clothing)		X	X
Occupational exposure in workplaces that produce PFAS		X	X

Figure 1. Typical PFAS exposure pathways



Health impacts of PFAS exposure

The long-term adverse effects of PFAS exposure on humans are not yet well understood due to the vast number of compounds and the limited toxicology data. However, a growing body of evidence from epidemiological studies links certain PFAS compounds, particularly PFOS and PFOA, with a variety of adverse health effects. The most consistent findings from human studies are elevated cholesterol levels ([14],[23]) with more limited findings related to developmental and reproductive outcomes, immune, endocrine, and metabolic effects, liver and kidney function, and cancer (Table 2).

The toxic effects of PFAS depend on the chemical composition and chain length of the compound, the magnitude, duration, and route of exposure, and factors associated with exposed individuals including age, sex, health status and genetic susceptibility ([23]).

Exposure to PFAS during pregnancy is of great concern as PFAS can be transferred from maternal blood to cord blood through the placental barrier and have detrimental effects on maternal outcomes and infant development ([65],[66],[67]).

There are currently no known treatments to accelerate the clearance of PFAS from the body ([68]), and minimising exposure is the best way to reduce adverse health risks.

Figure 2. Effects of PFAS on human health ([23]) [CC BY 2.5](#)

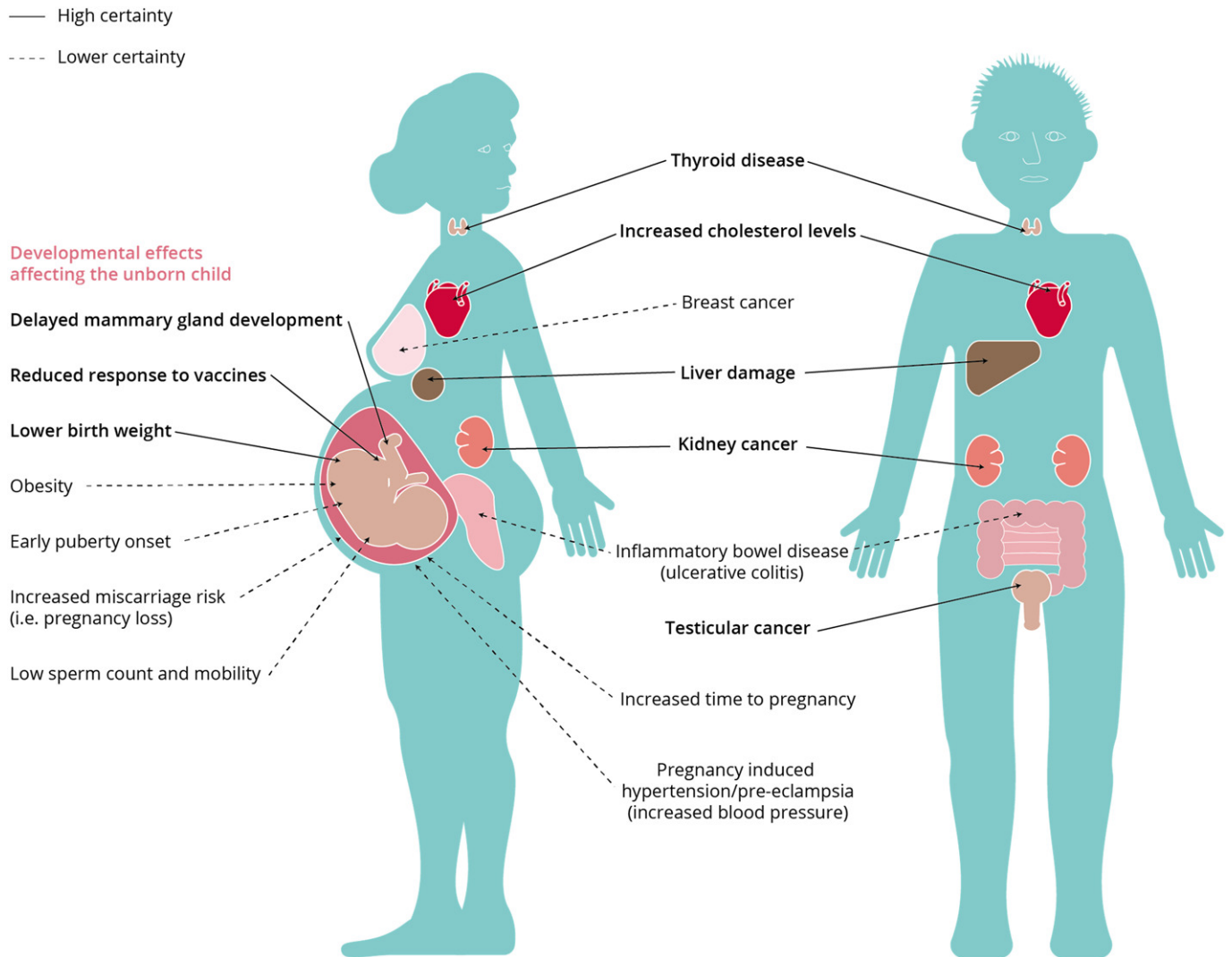


Table 2.

Health impacts from epidemiological studies

Cholesterol

- There is relatively consistent evidence from epidemiological studies of modest positive associations of PFAS exposure with elevated cholesterol and other serum lipid parameters in adults and children, including increased risk of clinically defined high cholesterol ([69],[70],[71],[72],[73],[74]).

- Metabolic effects (insulin dysregulation)**
- Emerging longitudinal and diabetes clinical trial data indicate that PFAS may increase human insulin resistance, associated with dysregulated lipogenesis activity ([71],[75]).
 - Several longitudinal studies of clinically diagnosed diabetes have found an association between PFAS exposure and diabetes ([76]) and changes in glycaemic markers ([77]); however, other studies have found no association ([78],[79]).
- Immunological effects (vaccine response, asthma, and autoimmunity)**
- Several studies demonstrate an association between prenatal exposure to PFAS and reduced vaccine responses, and PFAS exposure and increased childhood infections, suggesting PFAS cause immunosuppression ([80],[81],[82],[83],[84],[85]).
 - PFAS immunotoxicity can also affect vaccine response later in life, as PFOA levels in adults' blood corresponded to reduced immunity from a flu vaccine ([86]).
 - Population studies investigating the possible effects of PFAS on asthma and allergy-related outcomes (hypersensitivity) have produced conflicting results ([84],[85],[88],[89]).
 - Chronic autoimmune outcomes, including thyroid disease and inflammatory bowel disease (ulcerative colitis), have been associated with PFAS exposure ([90]).
- Liver function**
- Several studies demonstrate significant associations of long-chain PFAS (>6 fluorinated carbons) exposure to higher liver enzymes, such as alanine aminotransferase in adults and adolescents ([91],[92],[93],[94],[95],[96],[97],[98]). However, evidence to date is insufficient to link PFAS exposure with liver disease.
- Kidney function (uric acid)**
- Several studies show a link between PFAS and reduced kidney function and increased uric acid levels in the blood ([99],[100],[101],[102],[103]).
 - However, reduced kidney function would cause an increase in both serum uric acid and serum PFAS concentrations ([104]); thus, the association between PFAS and kidney function could be influenced by reverse causation.
 - Several studies demonstrate small associations between thyroid hormones and PFAS; however, the pattern of changes in levels of the different thyroid hormones are not consistent, and the clinical significance is not known ([104]).
- Endocrine function (thyroid disease)**
- Some studies note an association between various PFAS with thyroid hormone levels among susceptible populations such as pregnant women; however, the implications for maternal outcomes and foetal neurodevelopmental are not known ([105],[106],[107]).
 - In environmentally exposed communities and in the general population, the most consistent effect of exposure to PFOA, and to a less extent to PFOS, is the occurrence of hypothyroidism in women ([104],[108]).

Neonatal, infant, and maternal outcomes

- PFAS exposure is associated with an increased risk of pregnancy-induced hypertension/pre-eclampsia and gestational diabetes ([109],[110],[111]).
- Prenatal PFAS exposure is associated with low birth weight ([112],[113],[114],[115]).
- Maternal PFAS exposure may be related to adverse outcomes in offspring including respiratory tract infection ([85]); increased adiposity ([116],[117]), but not insulin resistance ([19],[118],[119]).
- During childhood, higher serum PFAS concentrations are associated with cardiometabolic risk factors, including, increased adiposity, later onset of puberty, dyslipidaemia, and alterations in glucose homeostasis ([75],[120],[121],[122]).
- Several studies suggest an association between higher PFAS concentrations and ADHD ([123],[124],[125],[126]); however, the evidence on the neurodevelopmental effects of PFAS remains unclear ([21]).
- Observational studies have shown that PFAS exposure could delay menarche ([120]), disrupt menstrual cycle regularity ([127]), cause early menopause ([128]) and premature ovarian insufficiency ([129]) and alter the levels of circulating sex steroid hormones ([130]).

Reproductive outcomes

- The most recent evidence suggests PFAS exposure may cause menopause to occur 2 years earlier than natural menopause ([131]).
- Higher serum levels of PFOS and PFOA have been found in women with PCOS compared to females with no PCOS ([132],[133]).
- Epidemiological studies have reported an association between PFAS, and infertility caused by endometriosis ([134],[135]). However, overall results of studies investigating PFAS (PFOS or PFOA) exposure and female fertility are inconsistent. Several studies indicated impaired fecundability in relation to exposure to one or both compounds ([136],[137],[138],[139]), while others did not ([140],[141],[142]).
- Higher exposure to PFAS is associated with lower serum testosterone levels and sperm concentrations ([143],[144],[145],[146],[147]) and deleterious markers of sperm quality ([148],[149]).

Cancer

- The International Agency for Research on Cancer (IARC) has classified PFOA as possibly carcinogenic ([24]) and USA EPA has concluded that both PFOA and PFOS are possibly carcinogenic to humans ([150],[151],[152]).
- Some studies have found increases in prostate, kidney, and testicular cancers in workers exposed to PFAS and people living near a PFOA facility ([153],[154]).

Toxicokinetics of PFAS compounds

The adverse health effects of PFAS are related to the unique toxicokinetic properties of PFAS compounds (Table 3), which allow them to bioaccumulate and persist in the body for many years. These toxicokinetic properties often vary with chain length, branching and chemical composition ([155],[156]). However, due to the vast number of compounds, toxicokinetic data does not exist for most PFAS chemicals ([157]).

The uptake and elimination of PFAS varies depending on several factors including age, race, menstrual status, childbirth, and breast-feeding status ([14]).

Table 3.

Toxicokinetics of PFAS compounds ([64],[155],[156],[157])

- Absorption**
- Via oral, inhalation, and dermal exposure
 - Absorption ranges from >50% to >95%, depending on PFAS compound.
 - Do not accumulate in adipose tissue due to hydrophobic and lipophobic properties.
- Distribution**
- Highest concentrations occur in the liver, kidneys, and blood (bound to albumin and other proteins).
 - Certain PFAS, including PFOA and PFOS, are transferred across the placenta to the foetus, and are found in breast milk.
- Metabolism**
- Not biotransformed or metabolised in the body.
 - Primarily eliminated in the urine, with smaller amounts eliminated in faeces and breast milk.
 - Long elimination half-life for long-chain PFAS (2 – 27 years).
- Excretion**
- Bioaccumulate in the body due to enterohepatic recirculation and renal tubular reabsorption.
 - Menstrual bleeding could be an important elimination pathway in women due to 90-99% of PFAS binding to serum albumin.

Mechanisms of action

The mechanisms of action by which PFAS may cause adverse biological effects are not well understood. However, PFAS are known endocrine disruptors, and many of their effects are believed to occur through modulating nuclear receptors, such as oestrogen receptors and peroxisome proliferator-activated receptors (PPARs) ([158],[159]).

Experimental studies demonstrate that several PFAS can activate various PPARs (PPAR α , PPAR γ , PPAR β/δ) which regulate energy homeostasis, lipid and glucose metabolism, adipocyte differentiation and function, inflammation, and metabolism and function of sex steroids ([160],[161],[162],[163],[164]). Activation by PPAR α activating compounds by PFOA causes liver tumours in animals ([22]).

In addition to PPAR activation, experimental evidence suggests that lipid- and liver enzyme-related metabolic disturbances result from alteration of lipid transport- and metabolism-related genes. Alteration of these genes induce adipogenesis, impair bile acid metabolism/ synthesis, alter fatty acid transport, and cause lipid accumulation in the liver ([165],[166],[167],[168],[169],[170],[171],[172]).

PFAS can impair thyroid hormone signalling, increase metabolic excretion, and inhibit thyroid hormones synthesis ([108]). PFAS can interact with thyroid hormone-binding proteins ([173]) and impair thyroid peroxidase enzyme activity, resulting in decreased production and activation of thyroid hormones ([174]).

Some PFAS may have oestrogenic activity, and mechanisms of action may involve increased oestrogen levels ([22]). Animal studies suggest that PFOA promotes liver tumour development through an oestrogenic mechanism ([175],[176],[177]).

There is insufficient evidence to assess whether PFAS can directly interact with DNA to cause damage; however, PFAS may have indirect mechanisms of action which can induce epigenetic alterations and influence cell proliferation and increase cancer risk ([178]).

Takeaway on PFAS

- PFAS have become a serious global health concern due to their high stability, ubiquitous presence in the environment, bioaccumulation and biomagnification potential, and potential toxicity.
- Early PFAS chemicals are being replaced by newer novel compounds that may be more persistent and mobile, less degradable, and equally or more toxic.
- Ongoing exposure to even relatively low drinking water concentrations of long-chain PFAS substantially increases human body burdens, which remain elevated for many years after exposure ends. Additionally, infants, a sensitive subpopulation, receive much higher exposures than adults from the same drinking water source.
- The health effects of PFAS compounds are not well understood. Due to the large number of PFAS continuously being detected at trace levels in the environment, it is challenging to quantify each compound's exposure rates or effects.
- Early PFAS chemicals, known as PFOS and PFOA, are linked to cancer, high cholesterol, low birth weight, immune suppression, thyroid disease, and other health effects. While these two chemicals are being phased out, they remain ubiquitous in drinking water, soil, food, and air.
- More research is urgently required to understand the mode of action for PFAS toxicity, PFAS toxicokinetics, and adverse health effects that might occur at environmentally relevant exposures, especially at sensitive life stages.
- There has been little scientific research into clinical detoxification of PFAS and minimising ongoing exposure to these compounds is the best approach to improve health outcomes.

Click [here](#) for a Patient Handout guide to avoiding toxic PFAS chemicals.

References

- 1 Macmillan J. Interim Guideline on the Assessment and Management of Perfluoroalkyl and Polyfluoroalkyl Substances (PFAS) Contaminated Sites Guidelines. Perth (AU): Government of Western Australia Department of Environment and Regulation; 2016 Jan. 34 p
- 2 Hill PJ, Taylor M, Goswami P, Blackburn RS. Substitution of PFAS chemistry in outdoor apparel and the impact on repellency performance. *Chemosphere*. 2017 Aug 1;181:500-7.
- 3 Lee JH, Lee CK, Suh CH, Kang HS, Hong CP, Choi SN. Serum concentrations of per- and poly-fluoroalkyl substances and factors associated with exposure in the general adult population in South Korea. *International Journal of Hygiene and Environmental Health*. 2017 Aug 1;220(6):1046-54.
- 4 Bradley EL, Read WA, Castle L. Investigation into the migration potential of coating materials from cookware products. *Food additives and contaminants*. 2007 Mar 1;24(3):326-35.
- 5 Sinclair E, Kim SK, Akinleye HB, Kannan K. Quantitation of gas-phase perfluoroalkyl surfactants and fluorotelomer alcohols released from nonstick cookware and microwave popcorn bags. *Environmental science & technology*. 2007 Feb 15;41(4):1180-5.
- 6 Begley TH, White K, Honigfort P, Twaroski ML, Neches R, Walker RA. Perfluorochemicals: potential sources of and migration from food packaging. *Food additives and contaminants*. 2005 Oct 1;22(10):1023-31.
- 7 Schaidler LA, Balan SA, Blum A, Andrews DQ, Strynar MJ, Dickinson ME, Lunderberg DM, Lang JR, Peaslee GF. Fluorinated compounds in US fast food packaging. *Environmental science & technology letters*. 2017 Mar 14;4(3):105-11.
- 8 Trier X, Granby K, Christensen JH. Polyfluorinated surfactants (PFS) in paper and board coatings for food packaging. *Environmental Science and Pollution Research*. 2011 Aug 1;18(7):1108-20.
- 9 Schultes L, Vestergren R, Volkova K, Westberg E, Jacobson T, Benskin JP. Per- and polyfluoroalkyl substances and fluorine mass balance in cosmetic products from the Swedish market: implications for environmental emissions and human exposure. *Environmental Science: Processes & Impacts*. 2018;20(12):1680-90.
- 10 Boronow KE, Brody JG, Schaidler LA, Peaslee GF, Havas L, Cohn BA. Serum concentrations of PFASs and exposure-related behaviors in African American and non-Hispanic white women. *Journal of exposure science & environmental epidemiology*. 2019 Mar;29(2):206-17.
- 11 Xu Y, Fletcher T, Pineda D, Lindh CH, Nilsson C, Glynn A, Vogts C, Norström K, Lilja K, Jakobsson K, Li Y. Serum half-lives for short- and long-chain perfluoroalkyl acids after ceasing exposure from drinking water contaminated by firefighting foam. *Environmental health perspectives*. 2020 Jul 10;128(7):077004.
- 12 Costello MC, Lee LS. Sources, Fate, and Plant Uptake in Agricultural Systems of Per- and Polyfluoroalkyl Substances. *Current Pollution Reports*. 2020 Dec 15:1-21.
- 13 Sinclair GM, Long SM, Jones OA. What are the effects of PFAS exposure at environmentally relevant concentrations?. *Chemosphere*. 2020 Jun 12:127340.
- 14 Sunderland EM, Hu XC, Dassuncao C, Tokranov AK, Wagner CC, Allen JG. A review of the pathways of human exposure to poly- and perfluoroalkyl substances (PFASs) and present understanding of health effects. *Journal of exposure science & environmental epidemiology*. 2019 Mar;29(2):131-47.

- 15 Maestri L, Negri S, Ferrari M, Ghittori S, Fabris F, Danesino P, Imbriani M. Determination of perfluorooctanoic acid and perfluorooctanesulfonate in human tissues by liquid chromatography/single quadrupole mass spectrometry. *Rapid Communications in Mass Spectrometry: An International Journal Devoted to the Rapid Dissemination of Up-to-the-Minute Research in Mass Spectrometry*. 2006 Sep 30;20(18):2728-34.
- 16 Pérez F, Nadal M, Navarro-Ortega A, Fàbrega F, Domingo JL, Barceló D, Farré M. Accumulation of perfluoroalkyl substances in human tissues. *Environment international*. 2013 Sep 1;59:354-62.
- 17 Poothong S, Thomsen C, Padilla-Sanchez JA, Papadopoulou E, Haug LS. Distribution of novel and well-known poly- and perfluoroalkyl substances (PFASs) in human serum, plasma, and whole blood. *Environmental science & technology*. 2017 Nov 21;51(22):13388-96.
- 18 Völkel W, Genzel-Boroviczény O, Demmelmair H, Gebauer C, Koletzko B, Twardella D, Raab U, Fromme H. Perfluorooctane sulphonate (PFOS) and perfluorooctanoic acid (PFOA) in human breast milk: results of a pilot study. *International Journal of Hygiene and Environmental Health*. 2008 Jul 15;211(3-4):440-6.
- 19 Johnson PI, Sutton P, Atchley DS, Koustas E, Lam J, Sen S, Robinson KA, Axelrad DA, Woodruff TJ. The Navigation Guide—evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. *Environmental health perspectives*. 2014 Oct;122(10):1028-39.
- 20 Shoaff J, Papandonatos GD, Calafat AM, Chen A, Lanphear BP, Ehrlich S, Kelsey KT, Braun JM. Prenatal exposure to perfluoroalkyl substances: infant birth weight and early life growth. *Environmental epidemiology (Philadelphia, Pa.)*. 2018 Jun;2(2).
- 21 Braun JM. Early-life exposure to EDCs: role in childhood obesity and neurodevelopment. *Nature Reviews Endocrinology*. 2017 Mar;13(3):161-73.
- 22 Post GB, Cohn PD, Cooper KR. Perfluorooctanoic acid (PFOA), an emerging drinking water contaminant: a critical review of recent literature. *Environmental research*. 2012 Jul 1;116:93-117.
- 23 Fenton SE, Ducatman A, Boobis A, DeWitt JC, Lau C, Ng C, Smith JS, Roberts SM. Per- and Polyfluoroalkyl Substance Toxicity and Human Health Review: Current State of Knowledge and Strategies for Informing Future Research. *Environmental Toxicology and Chemistry*. 2020 Oct 5;00(00):1-25.
- 24 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Some Chemicals Used as Solvents and in Polymer Manufacture. Lyon (FR): International Agency for Research on Cancer; 2017. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 110.
- 25 Abunada Z, Alazaiza MY, Bashir MJ. An Overview of Per- and Polyfluoroalkyl Substances (PFAS) in the Environment: Source, Fate, Risk and Regulations. *Water*. 2020 Dec;12(12):3590.
- 26 Wang Z, DeWitt JC, Higgins CP, Cousins IT. A Never-Ending Story of Per- and Polyfluoroalkyl Substances (PFASs)? *Environmental Science & Technology* 2017; 51: 2508-2518.
- 27 Li F, Duan J, Tian S, Ji H, Zhu Y, Wei Z, Zhao D. Short-chain per- and polyfluoroalkyl substances in aquatic systems: Occurrence, impacts and treatment. *Chemical Engineering Journal*. 2020 Jan 15;380:122506.

- 28 Tittlemier SA, Pepper K, Seymour C, Moisey J, Bronson R, Cao XL, Dabeka RW. Dietary exposure of Canadians to perfluorinated carboxylates and perfluorooctane sulfonate via consumption of meat, fish, fast foods, and food items prepared in their packaging. *Journal of agricultural and food chemistry*. 2007 Apr 18;55(8):3203-10.
- 29 Trudel D, Horowitz L, Wormuth M, Scheringer M, Cousins IT, Hungerbühler K. Estimating consumer exposure to PFOS and PFOA. *Risk Analysis: An International Journal*. 2008 Apr;28(2):251-69.
- 30 Vestergren R, Cousins IT. Tracking the pathways of human exposure to perfluorocarboxylates. *Environmental science & technology*. 2009 Aug 1;43(15):5565-75.
- 31 Haug LS, Huber S, Becher G, Thomsen C. Characterisation of human exposure pathways to perfluorinated compounds—comparing exposure estimates with biomarkers of exposure. *Environment international*. 2011 May 1;37(4):687-93.
- 32 Domingo JL, Nadal M. Per- and polyfluoroalkyl substances (PFASs) in food and human dietary intake: a review of the recent scientific literature. *Journal of agricultural and food chemistry*. 2017 Jan 25;65(3):533-43.
- 33 Domingo JL, Nadal M. Human exposure to per- and polyfluoroalkyl substances (PFAS) through drinking water: A review of the recent scientific literature. *Environmental research*. 2019 Oct 1;177:108648.
- 34 Jian JM, Guo Y, Zeng L, Liang-Ying L, Lu X, Wang F, Zeng EY. Global distribution of perfluorochemicals (PFCs) in potential human exposure source—a review. *Environment international*. 2017 Nov 1;108:51-62.
- 35 Shi Z, Zhang H, Ding L, Feng Y, Xu M, Dai J. The effect of perfluorododecanonic acid on endocrine status, sex hormones and expression of steroidogenic genes in pubertal female rats. *Reproductive Toxicology*. 2009 Jun 1;27(3-4):352-9.
- 36 Domingo JL, Jogsten IE, Eriksson U, Martorell I, Perelló G, Nadal M, van Bavel B. Human dietary exposure to perfluoroalkyl substances in Catalonia, Spain. Temporal trend. *Food chemistry*. 2012 Dec 1;135(3):1575-82.
- 37 Eriksson U, Kärrman A, Rotander A, Mikkelsen B, Dam M. Perfluoroalkyl substances (PFASs) in food and water from Faroe Islands. *Environmental science and pollution research*. 2013 Nov 1;20(11):7940-8.
- 38 Gebbink WA, Glynn A, Darnerud PO, Berger U. Perfluoroalkyl acids and their precursors in Swedish food: The relative importance of direct and indirect dietary exposure. *Environmental Pollution*. 2015 Mar 1;198:108-15.
- 39 Haug LS, Salihovic S, Jogsten IE, Thomsen C, van Bavel B, Lindström G, Becher G. Levels in food and beverages and daily intake of perfluorinated compounds in Norway. *Chemosphere*. 2010 Aug 1;80(10):1137-43.
- 40 Herzke D, Huber S, Bervoets L, D'Hollander W, Hajslova J, Pulkrabova J, Brambilla G, De Filippis SP, Klenow S, Heinemeyer G, de Voogt P. Perfluorinated alkylated substances in vegetables collected in four European countries; occurrence and human exposure estimations. *Environmental science and pollution research*. 2013 Nov 1;20(11):7930-9.
- 41 Heo JJ, Lee JW, Kim SK, Oh JE. Foodstuff analyses show that seafood and water are major perfluoroalkyl acids (PFAAs) sources to humans in Korea. *Journal of hazardous materials*. 2014 Aug 30;279:402-9.
- 42 Vestergren R, Berger U, Glynn A, Cousins IT. Dietary exposure to perfluoroalkyl acids for the Swedish population in 1999, 2005 and 2010. *Environment international*. 2012 Nov 15;49:120-7.

- 43 Zhang T, Sun HW, Wu Q, Zhang XZ, Yun SH, Kannan K. Perfluorochemicals in meat, eggs and indoor dust in China: assessment of sources and pathways of human exposure to perfluorochemicals. *Environmental science & technology*. 2010 May 1;44(9):3572-9.
- 44 Begley TH, White K, Honigfort P, Twaroski ML, Neches R, Walker RA. Perfluorochemicals: potential sources of and migration from food packaging. *Food additives and contaminants*. 2005 Oct 1;22(10):1023-31.
- 45 Schaidler LA, Balan SA, Blum A, Andrews DQ, Strynar MJ, Dickinson ME, Lunderberg DM, Lang JR, Peaslee GF. Fluorinated compounds in US fast food packaging. *Environmental science & technology letters*. 2017 Mar 14;4(3):105-11.
- 46 Yuan G, Peng H, Huang C, Hu J. Ubiquitous occurrence of fluorotelomer alcohols in eco-friendly paper-made food-contact materials and their implication for human exposure. *Environmental Science & Technology*. 2016 Jan 19;50(2):942-50.
- 47 Begley TH, Hsu W, Noonan G, Diachenko G. Migration of fluorochemical paper additives from food-contact paper into foods and food simulants. *Food additives and contaminants*. 2008 Mar 1;25(3):384-90.
- 48 Susmann HP, Schaidler LA, Rodgers KM, Rudel RA. Dietary Habits Related to Food Packaging and Population Exposure to PFASs. *Environmental health perspectives*. 2019 Oct 9;127(10):107003.
- 49 Cordner A, Vanessa Y, Schaidler LA, Rudel RA, Richter L, Brown P. Guideline levels for PFOA and PFOS in drinking water: the role of scientific uncertainty, risk assessment decisions, and social factors. *Journal of exposure science & environmental epidemiology*. 2019 Mar;29(2):157-71.
- 50 Filipovic M, Woldegiorgis A, Norström K, Bibi M, Lindberg M, Österås AH. Historical usage of aqueous film forming foam: A case study of the widespread distribution of perfluoroalkyl acids from a military airport to groundwater, lakes, soils and fish. *Chemosphere*. 2015 Jun 1;129:39-45.
- 51 Eschauzier C, Raat KJ, Stuyfzand PJ, De Voogt P. Perfluorinated alkylated acids in groundwater and drinking water: identification, origin and mobility. *Science of the total environment*. 2013 Aug 1;458:477-85.
- 52 Szabo D, Coggan TL, Robson TC, Currell M, Clarke BO. Investigating recycled water use as a diffuse source of per-and polyfluoroalkyl substances (PFASs) to groundwater in Melbourne, Australia. *Science of the Total Environment*. 2018 Dec 10;644:1409-17.
- 53 Emmett EA, Shofer FS, Zhang H, Freeman D, Desai C, Shaw LM. Community exposure to perfluorooctanoate: relationships between serum concentrations and exposure sources. *Journal of occupational and environmental medicine/American College of Occupational and Environmental Medicine*. 2006 Aug;48(8):759-70.
- 54 Seals R, Bartell SM, Steenland K. Accumulation and clearance of perfluorooctanoic acid (PFOA) in current and former residents of an exposed community. *Environmental health perspectives*. 2011 Jan;119(1):119-24.
- 55 Thompson J, Eaglesham G, Mueller J. Concentrations of PFOS, PFOA and other perfluorinated alkyl acids in Australian drinking water. *Chemosphere*. 2011 May 1;83(10):1320-5.
- 56 Akhbarizadeh R, Dobaradaran S, Schmidt TC, Nabipour I, Spitz J. Worldwide bottled water occurrence of emerging contaminants: A review of the recent scientific literature. *Journal of Hazardous Materials*. 2020 Jun 15;392:122271.

- 57 Llorca M, Farré M, Picó Y, Müller J, Knepper TP, Barceló D. Analysis of perfluoroalkyl substances in waters from Germany and Spain. *Science of the total environment*. 2012 Aug 1;431:139-50.
- 58 Schwanz TG, Llorca M, Farré M, Barceló D. Perfluoroalkyl substances assessment in drinking waters from Brazil, France and Spain. *Science of the total environment*. 2016 Jan 1;539:143-52.
- 59 Glüge J, Scheringer M, Cousins IT, DeWitt JC, Goldenman G, Herzke D, Lohmann R, Ng CA, Trier X, Wang Z. An overview of the uses of per- and polyfluoroalkyl substances (PFAS). *Environmental Science: Processes & Impacts*. 2020;22(12):2345-73.
- 60 Kotthoff M, Müller J, Jürling H, Schlummer M, Fiedler D. Perfluoroalkyl and polyfluoroalkyl substances in consumer products. *Environmental Science and Pollution Research*. 2015 Oct 1;22(19):14546-59.
- 61 Haug LS, Huber S, Schlabach M, Becher G, Thomsen C. Investigation on per- and polyfluorinated compounds in paired samples of house dust and indoor air from Norwegian homes. *Environmental science & technology*. 2011 Oct 1;45(19):7991-8.
- 62 Langer V, Dreyer A, Ebinghaus R. Polyfluorinated compounds in residential and nonresidential indoor air. *Environmental science & technology*. 2010 Nov 1;44(21):8075-81.
- 63 Yao Y, Zhao Y, Sun H, Chang S, Zhu L, Alder AC, Kannan K. Per- and polyfluoroalkyl substances (PFASs) in indoor air and dust from homes and various microenvironments in China: implications for human exposure. *Environmental science & technology*. 2018 Feb 8;52(5):3156-66.
- 64 Ding N, Harlow SD, Randolph JF, Loch-Caruso R, Park SK. Perfluoroalkyl and polyfluoroalkyl substances (PFAS) and their effects on the ovary. *Human Reproduction Update*. 2020 May 29;26(5):724-52.
- 65 Kashino I, Sasaki S, Okada E, Matsuura H, Goudarzi H, Miyashita C, Okada E, Ito YM, Araki A, Kishi R. Prenatal exposure to 11 perfluoroalkyl substances and fetal growth: A large-scale, prospective birth cohort study. *Environment International*. 2020 Mar 1;136:105355.
- 66 Lee YJ, Kim MK, Bae J, Yang JH. Concentrations of perfluoroalkyl compounds in maternal and umbilical cord sera and birth outcomes in Korea. *Chemosphere*. 2013 Feb 1;90(5):1603-9.
- 67 Pan Y, Zhu Y, Zheng T, Cui Q, Buka SL, Zhang B, Guo Y, Xia W, Yeung LW, Li Y, Zhou A. Novel chlorinated polyfluorinated ether sulfonates and legacy per-/polyfluoroalkyl substances: placental transfer and relationship with serum albumin and glomerular filtration rate. *Environmental science & technology*. 2017 Jan 3;51(1):634-44.
- 68 Genuis SJ, Birkholz D, Ralitsch M, Thibault N. Human detoxification of perfluorinated compounds. *Public health*. 2010 Jul 1;124(7):367-75.
- 69 Dong Z, Wang H, Yu YY, Li YB, Naidu R, Liu Y. Using 2003–2014 US NHANES data to determine the associations between per- and polyfluoroalkyl substances and cholesterol: Trend and implications. *Ecotoxicology and environmental safety*. 2019 May 30;173:461-8.
- 70 Li Y, Barregard L, Xu Y, Scott K, Pineda D, Lindh CH, Jakobsson K, Fletcher T. Associations between perfluoroalkyl substances and serum lipids in a Swedish adult population with contaminated drinking water. *Environmental Health*. 2020 Dec;19(1):1-1.
- 71 Lin PI, Cardenas A, Hauser R, Gold DR, Kleinman KP, Hivert MF, Fleisch AF, Calafat AM, Webster TF, Horton ES, Oken E. Per- and polyfluoroalkyl substances and blood lipid levels in pre-diabetic adults—longitudinal analysis of the diabetes prevention program outcomes study. *Environment international*. 2019 Aug 1;129:343-53.

- 72 Steenland K, Tinker S, Frisbee S, Ducatman A, Vaccarino V. Association of perfluorooctanoic acid and perfluorooctane sulfonate with serum lipids among adults living near a chemical plant. *American journal of epidemiology*. 2009 Nov 15;170(10):1268-78.
- 73 Winquist A, Steenland K. Modeled PFOA exposure and coronary artery disease, hypertension, and high cholesterol in community and worker cohorts. *Environmental health perspectives*. 2014 Dec;122(12):1299-305.
- 74 Zeng XW, Qian Z, Emo B, Vaughn M, Bao J, Qin XD, Zhu Y, Li J, Lee YL, Dong GH. Association of polyfluoroalkyl chemical exposure with serum lipids in children. *Science of the Total Environment*. 2015 Apr 15;512:364-70.
- 75 Alderete TL, Jin R, Walker DI, Valvi D, Chen Z, Jones DP, Peng C, Gilliland FD, Berhane K, Conti DV, Goran MI. Perfluoroalkyl substances, metabolomic profiling, and alterations in glucose homeostasis among overweight and obese Hispanic children: A proof-of-concept analysis. *Environment international*. 2019 May 1;126:445-53.
- 76 Sun Q, Zong G, Valvi D, Nielsen F, Coull B, Grandjean P. Plasma concentrations of perfluoroalkyl substances and risk of type 2 diabetes: a prospective investigation among US women. *Environmental health perspectives*. 2018 Mar 1;126(3):037001.
- 77 Cardenas A, Gold DR, Hauser R, Kleinman KP, Hivert MF, Calafat AM, Ye X, Webster TF, Horton ES, Oken E. Plasma concentrations of per- and polyfluoroalkyl substances at baseline and associations with glycemic indicators and diabetes incidence among high-risk adults in the Diabetes Prevention Program Trial. *Environmental health perspectives*. 2017 Oct 2;125(10):107001.
- 78 Karnes C, Winquist A, Steenland K. Incidence of type II diabetes in a cohort with substantial exposure to perfluorooctanoic acid. *Environmental research*. 2014 Jan 1;128:78-83.
- 79 Donat-Vargas C, Bergdahl IA, Tornevi A, Wennberg M, Sommar J, Kiviranta H, Koponen J, Rolandsson O, Åkesson A. Perfluoroalkyl substances and risk of type II diabetes: A prospective nested case-control study. *Environment international*. 2019 Feb 1;123:390-8.
- 80 Grandjean P, Andersen EW, Budtz-Jørgensen E, Nielsen F, Mølbak K, Weihe P, Heilmann C. Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. *Jama*. 2012 Jan 25;307(4):391-7.
- 81 Grandjean P, Heilmann C, Weihe P, Nielsen F, Mogensen UB, Budtz-Jørgensen E. Serum vaccine antibody concentrations in adolescents exposed to perfluorinated compounds. *Environmental Health Perspectives*. 2017 Jul 26;125(7):077018.
- 82 Granum B, Haug LS, Namork E, Stølevik SB, Thomsen C, Aaberge IS, van Loveren H, Løvik M, Nygaard UC. Pre-natal exposure to perfluoroalkyl substances may be associated with altered vaccine antibody levels and immune-related health outcomes in early childhood. *Journal of immunotoxicology*. 2013 Oct 1;10(4):373-9.
- 83 Goudarzi H, Miyashita C, Okada E, Kashino I, Chen CJ, Ito S, Araki A, Kobayashi S, Matsuura H, Kishi R. Prenatal exposure to perfluoroalkyl acids and prevalence of infectious diseases up to 4 years of age. *Environment international*. 2017 Jul 1;104:132-8.
- 84 Impinen A, Longnecker MP, Nygaard UC, London SJ, Ferguson KK, Haug LS, Granum B. Maternal levels of perfluoroalkyl substances (PFASs) during pregnancy and childhood allergy and asthma related outcomes and infections in the Norwegian mother and child (MoBa) cohort. *Environment international*. 2019 Mar 1;124:462-72.

- 85 Impinen A, Nygaard UC, Carlsen KL, Mowinckel P, Carlsen KH, Haug LS, Granum B. Prenatal exposure to perfluoroalkyl substances (PFASs) associated with respiratory tract infections but not allergy-and asthma-related health outcomes in childhood. *Environmental research*. 2018 Jan 1;160:518-23.
- 86 Looker C, Luster MI, Calafat AM, Johnson VJ, Burleson GR, Burleson FG, Fletcher T. Influenza vaccine response in adults exposed to perfluorooctanoate and perfluorooctanesulfonate. *toxicological sciences*. 2014 Mar 1;138(1):76-88.
- 87 Qin XD, Qian ZM, Dharmage SC, Perret J, Geiger SD, Rigdon SE, Howard S, Zeng XW, Hu LW, Yang BY, Zhou Y. Association of perfluoroalkyl substances exposure with impaired lung function in children. *Environmental research*. 2017 May 1;155:15-21.
- 88 Timmermann CA, Budtz-Jørgensen E, Jensen TK, Osuna CE, Petersen MS, Steuerwald U, Nielsen F, Poulsen LK, Weihe P, Grandjean P. Association between perfluoroalkyl substance exposure and asthma and allergic disease in children as modified by MMR vaccination. *Journal of immunotoxicology*. 2017 Jan 1;14(1):39-49.
- 89 Kvaalem HE, Nygaard UC, Carlsen KL, Carlsen KH, Haug LS, Granum B. Perfluoroalkyl substances, airways infections, allergy and asthma related health outcomes—implications of gender, exposure period and study design. *Environment international*. 2020 Jan 1;134:105259.
- 90 Steenland K, Zhao L, Winquist A, Parks C. Ulcerative colitis and perfluorooctanoic acid (PFOA) in a highly exposed population of community residents and workers in the mid-Ohio valley. *Environmental health perspectives*. 2013 Aug;121(8):900-5.
- 91 Attanasio R. Sex differences in the association between perfluoroalkyl acids and liver function in US adolescents: Analyses of NHANES 2013–2016. *Environmental Pollution*. 2019 Nov 1;254:113061.
- 92 Darrow LA, Groth AC, Winquist A, Shin HM, Bartell SM, Steenland K. Modeled perfluorooctanoic acid (PFOA) exposure and liver function in a mid-Ohio valley community. *Environmental health perspectives*. 2016 Aug;124(8):1227-33.
- 93 Gallo V, Leonardi G, Genser B, Lopez-Espinosa MJ, Frisbee SJ, Karlsson L, Ducatman AM, Fletcher T. Serum perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) concentrations and liver function biomarkers in a population with elevated PFOA exposure. *Environmental health perspectives*. 2012 May;120(5):655-60.
- 94 Gleason JA, Post GB, Fagliano JA. Associations of perfluorinated chemical serum concentrations and biomarkers of liver function and uric acid in the US population (NHANES), 2007–2010. *Environmental research*. 2015 Jan 1;136:8-14.
- 95 Nian M, Li QQ, Bloom M, Qian ZM, Syberg KM, Vaughn MG, Wang SQ, Wei Q, Zeeshan M, Gurram N, Chu C. Liver function biomarkers disorder is associated with exposure to perfluoroalkyl acids in adults: Isomers of C8 Health Project in China. *Environmental research*. 2019 May 1;172:81-8.
- 96 Sakr CJ, Kreckmann KH, Green JW, Gillies PJ, Reynolds JL, Leonard RC. Cross-sectional study of lipids and liver enzymes related to a serum biomarker of exposure (ammonium perfluorooctanoate or APFO) as part of a general health survey in a cohort of occupationally exposed workers. *Journal of occupational and environmental medicine*. 2007 Oct 1;49(10):1086-96.
- 97 Sakr CJ, Leonard RC, Kreckmann KH, Slade MD, Cullen MR. Longitudinal study of serum lipids and liver enzymes in workers with occupational exposure to ammonium perfluorooctanoate. *Journal of occupational and environmental medicine*. 2007 Aug 1;49(8):872-9.

- 98 Yamaguchi M, Arisawa K, Uemura H, Katsuura-Kamano S, Takami H, Sawachika F, Nakamoto M, Juta T, Toda E, Mori K, Hasegawa M. Consumption of seafood, serum liver enzymes, and blood levels of PFOS and PFOA in the Japanese population. *Journal of occupational health*. 2013 May;55(3):184-94.
- 99 Geiger SD, Xiao J, Shankar A. Positive association between perfluoroalkyl chemicals and hyperuricemia in children. *American journal of epidemiology*. 2013 Jun 1;177(11):1255-62.
- 100 Obermayr RP, Temml C, Gutjahr G, Knechtelsdorfer M, Oberbauer R, Klauser-Braun R. Elevated uric acid increases the risk for kidney disease. *Journal of the American Society of Nephrology*. 2008 Dec 1;19(12):2407-13.
- 101 Qin XD, Qian Z, Vaughn MG, Huang J, Ward P, Zeng XW, Zhou Y, Zhu Y, Yuan P, Li M, Bai Z. Positive associations of serum perfluoroalkyl substances with uric acid and hyperuricemia in children from Taiwan. *Environmental pollution*. 2016 May 1;212:519-24.
- 102 Steenland K, Tinker S, Shankar A, Ducatman A. Association of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) with uric acid among adults with elevated community exposure to PFOA. *Environmental health perspectives*. 2010 Feb;118(2):229-33.
- 103 Zeng XW, Lodge CJ, Dharmage SC, Bloom MS, Yu Y, Yang M, Chu C, Li QQ, Hu LW, Liu KK, Yang BY. Isomers of per- and polyfluoroalkyl substances and uric acid in adults: Isomers of C8 Health Project in China. *Environment international*. 2019 Dec 1;133:105160.
- 104 Buckley N, Sim M, Douglas K, Håkansson H. Expert Health Panel for Per- and Poly-Fluoroalkyl Substances (PFAS). Department of Health AG; 2018 March:446p.
- 105 Kato S, Itoh S, Yuasa M, Baba T, Miyashita C, Sasaki S, et al. Association of perfluorinated chemical exposure in utero with maternal and infant thyroid hormone levels in the Sapporo cohort of Hokkaido Study on the Environment and Children's Health. *Environ Health Prev Med*. 2016;21(5):334-44.
- 106 Kim S, Choi K, Ji K, Seo J, Kho Y, Park J, et al. Trans-placental transfer of thirteen perfluorinated compounds and relations with fetal thyroid hormones. *Environ Sci Technol*. 2011;45(17):7465-72.
- 107 Inoue K, Ritz B, Andersen SL, Ramlau-Hansen CH, Høyer BB, Bech BH, Henriksen TB, Bonfeld-Jørgensen EC, Olsen J, Liew Z. Perfluoroalkyl substances and maternal thyroid hormones in early pregnancy; findings in the Danish National Birth Cohort. *Environmental health perspectives*. 2019 Nov 12;127(11):117002.
- 108 Coperchini F, Awwad O, Rotondi M, Santini FE, Imbriani M, Chiovato L. Thyroid disruption by perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA). *Journal of endocrinological investigation*. 2017 Feb 1;40(2):105-21.
- 109 Rylander L, Lindh CH, Hansson SR, Broberg K, Källén K. Per- and Polyfluoroalkyl Substances in Early Pregnancy and Risk for Preeclampsia: A Case-Control Study in Southern Sweden. *Toxics*. 2020 Jun;8(2):43.
- 110 Savitz DA, Stein CR, Bartell SM, Elston B, Gong J, Shin HM, Wellenius GA. Perfluorooctanoic acid exposure and pregnancy outcome in a highly exposed community. *Epidemiology (Cambridge, Mass.)*. 2012 May;23(3):386.
- 111 Stein CR, Savitz DA, Dougan M. Serum levels of perfluorooctanoic acid and perfluorooctane sulfonate and pregnancy outcome. *American journal of epidemiology*. 2009 Oct 1;170(7):837-46.
- 112 Bach CC, Bech BH, Nohr EA, Olsen J, Matthiesen NB, Bossi R, Uldbjerg N, Bonfeld-Jørgensen EC, Henriksen TB. Serum perfluoroalkyl acids and time to pregnancy in nulliparous women. *Environmental research*. 2015 Oct 1;142:535-41.

- 113 Starling AP, Adgate JL, Hamman RF, Kechris K, Calafat AM, Ye X, Dabelea D. Perfluoroalkyl substances during pregnancy and offspring weight and adiposity at birth: examining mediation by maternal fasting glucose in the healthy start study. *Environmental health perspectives*. 2017 Jun 26;125(6):067016.
- 114 Wikström S, Lin PI, Lindh CH, Shu H, Bornehag CG. Maternal serum levels of perfluoroalkyl substances in early pregnancy and offspring birth weight. *Pediatric Research*. 2020;87(6):1093.
- 115 Xiao C, Grandjean P, Valvi D, Nielsen F, Jensen TK, Weihe P, Oulhote Y. Associations of exposure to perfluoroalkyl substances with thyroid hormone concentrations and birth size. *The Journal of Clinical Endocrinology & Metabolism*. 2020 Mar;105(3):735-45.
- 116 Mora AM, Oken E, Rifas-Shiman SL, Webster TF, Gillman MW, Calafat AM, Ye X, Sagiv SK. Prenatal exposure to perfluoroalkyl substances and adiposity in early and mid-childhood. *Environmental health perspectives*. 2017 Mar;125(3):467-73.
- 117 Chen Q, Zhang X, Zhao Y, Lu W, Wu J, Zhao S, Zhang J, Huang L. Prenatal exposure to perfluorobutanesulfonic acid and childhood adiposity: A prospective birth cohort study in Shanghai, China. *Chemosphere*. 2019 Jul 1;226:17-23.
- 118 Fleisch AF, Rifas-Shiman SL, Mora AM, Calafat AM, Ye X, Luttmann-Gibson H, Gillman MW, Oken E, Sagiv SK. Early-life exposure to perfluoroalkyl substances and childhood metabolic function. *Environmental health perspectives*. 2017 Mar;125(3):481-7.
- 119 Gardener H, Sun Q, Grandjean P. PFAS concentration during pregnancy in relation to cardiometabolic health and birth outcomes. *Environmental Research*. 2020 Oct 8;192:110287.
- 120 Lopez-Espinosa MJ, Mondal D, Armstrong BG, Eskenazi B, Fletcher T. Perfluoroalkyl substances, sex hormones, and insulin-like growth factor-1 at 6–9 years of age: a cross-sectional analysis within the C8 Health Project. *Environmental health perspectives*. 2016 Aug;124(8):1269-75.
- 121 Nelson JW, Hatch EE, Webster TF. Exposure to polyfluoroalkyl chemicals and cholesterol, body weight, and insulin resistance in the general US population. *Environmental health perspectives*. 2010 Feb;118(2):197-202.
- 122 Rappazzo KM, Coffman E, Hines EP. Exposure to perfluorinated alkyl substances and health outcomes in children: a systematic review of the epidemiologic literature. *International journal of environmental research and public health*. 2017 Jul;14(7):691.
- 123 Gump BB, Wu Q, Dumas AK, Kannan K. Perfluorochemical (PFC) exposure in children: associations with impaired response inhibition. *Environmental science & technology*. 2011 Oct 1;45(19):8151-9.
- 124 Hoffman K, Webster TF, Weisskopf MG, Weinberg J, Vieira VM. Exposure to polyfluoroalkyl chemicals and attention deficit/hyperactivity disorder in US children 12–15 years of age. *Environmental health perspectives*. 2010 Dec;118(12):1762-7.
- 125 Høyer BB, Ramlau-Hansen CH, Obel C, Pedersen HS, Hernik A, Ogniev V, Jönsson BA, Lindh CH, Rylander L, Rignell-Hydbom A, Bonde JP. Pregnancy serum concentrations of perfluorinated alkyl substances and offspring behaviour and motor development at age 5–9 years—a prospective study. *Environmental Health*. 2015 Dec 1;14(1):2.
- 126 Stein CR, Savitz DA. Serum perfluorinated compound concentration and attention deficit/hyperactivity disorder in children 5–18 years of age. *Environmental health perspectives*. 2011 Oct;119(10):1466-71.

- 127 Zhou W, Zhang L, Tong C, Fang F, Zhao S, Tian Y, Tao Y, Zhang J, Shanghai Birth Cohort Study. Plasma perfluoroalkyl and polyfluoroalkyl substances concentration and menstrual cycle characteristics in preconception women. *Environmental health perspectives*. 2017 Jun 22;125(6):067012.
- 128 Taylor KW, Hoffman K, Thayer KA, Daniels JL. Polyfluoroalkyl chemicals and menopause among women 20–65 years of age (NHANES). *Environmental health perspectives*. 2014 Feb;122(2):145-50.
- 129 Zhang S, Tan R, Pan R, Xiong J, Tian Y, Wu J, Chen L. Association of perfluoroalkyl and polyfluoroalkyl substances with premature ovarian insufficiency in Chinese women. *The Journal of Clinical Endocrinology & Metabolism*. 2018 Jul;103(7):2543-51.
- 130 Barrett ES, Chen C, Thurston SW, Haug LS, Sabaredzovic A, Fjeldheim FN, Frydenberg H, Lipson SF, Ellison PT, Thune I. Perfluoroalkyl substances and ovarian hormone concentrations in naturally cycling women. *Fertility and sterility*. 2015 May 1;103(5):1261-70.
- 131 Ding N, Harlow SD, Randolph JF, Calafat AM, Mukherjee B, Batterman S, Gold EB, Park SK. Associations of Perfluoroalkyl Substances with Incident Natural Menopause: the Study of Women's Health Across the Nation. *The Journal of Clinical Endocrinology & Metabolism*. 2020 Jun 3;105(9):e3169-82.
- 132 Heffernan AL, Cunningham TK, Drage DS, Aylward LL, Thompson K, Vijayasathya S, Mueller JF, Atkin SL, Sathyapalan T. Perfluorinated alkyl acids in the serum and follicular fluid of UK women with and without polycystic ovarian syndrome undergoing fertility treatment and associations with hormonal and metabolic parameters. *International Journal of Hygiene and Environmental Health*. 2018 Aug 1;221(7):1068-75.
- 133 Vagi SJ, Azziz-Baumgartner E, Sjödin A, Calafat AM, Dumesic D, Gonzalez L, Kato K, Silva MJ, Ye X, Azziz R. Exploring the potential association between brominated diphenyl ethers, polychlorinated biphenyls, organochlorine pesticides, perfluorinated compounds, phthalates, and bisphenol a in polycystic ovary syndrome: a case-control study. *BMC endocrine disorders*. 2014 Dec 1;14(1):86.
- 134 Campbell S, Raza M, Pollack AZ. Perfluoroalkyl substances and endometriosis in US women in NHANES 2003–2006. *Reproductive toxicology*. 2016 Oct 1;65:230-5.
- 135 Wang B, Zhang R, Jin F, Lou H, Mao Y, Zhu W, Zhou W, Zhang P, Zhang J. Perfluoroalkyl substances and endometriosis-related infertility in Chinese women. *Environment international*. 2017 May 1;102:207-12.
- 136 Fei C, McLaughlin JK, Lipworth L, Olsen J. Maternal levels of perfluorinated chemicals and subfecundity. *Human reproduction*. 2009 May 1;24(5):1200-5.
- 137 Jørgensen KT, Specht IO, Lenters V, Bach CC, Rylander L, Jönsson BA, Lindh CH, Giwercman A, Heederik D, Toft G, Bonde JP. Perfluoroalkyl substances and time to pregnancy in couples from Greenland, Poland and Ukraine. *Environmental health*. 2014 Dec 1;13(1):116.
- 138 Vélez MP, Arbuckle TE, Fraser WD. Maternal exposure to perfluorinated chemicals and reduced fecundity: the MIREC study. *Hum Reprod*. 2015 Mar;30(3):701-9.
- 139 Whitworth KW, Haug LS, Baird DD, Becher G, Hoppin JA, Skjaerven R, Thomsen C, Eggesbo M, Travlos G, Wilson R, Longnecker MP. Perfluorinated compounds and subfecundity in pregnant women. *Epidemiology (Cambridge, Mass.)*. 2012 Mar;23(2):257.
- 140 Bach CC, Bech BH, Nohr EA, Olsen J, Matthiesen NB, Bossi R, Ulbjerg N, Bonfeld-Jørgensen EC, Henriksen TB. Serum perfluoroalkyl acids and time to pregnancy in nulliparous women. *Environmental research*. 2015 Oct 1;142:535-41.

- 141 Louis GM, Sundaram R, Schisterman EF, Sweeney AM, Lynch CD, Gore-Langton RE, Maisog J, Kim S, Chen Z, Barr DB. Persistent environmental pollutants and couple fecundity: the LIFE study. *Environmental health perspectives*. 2013 Feb;121(2):231-6.
- 142 Vestergaard S, Nielsen F, Andersson AM, Hjöllund NH, Grandjean P, Andersen HR, Jensen TK. Association between perfluorinated compounds and time to pregnancy in a prospective cohort of Danish couples attempting to conceive. *Human reproduction*. 2012 Mar 1;27(3):873-80.
- 143 Joensen UN, Bossi R, Leffers H, Jensen AA, Skakkebaek NE, Jørgensen N. Do perfluoroalkyl compounds impair human semen quality?. *Environmental health perspectives*. 2009 Jun;117(6):923-7.
- 144 Joensen UN, Veyrand B, Antignac JP, Blomberg Jensen M, Petersen JH, Marchand P, Skakkebaek NE, Andersson AM, Le Bizec B, Jørgensen N. PFOS (perfluorooctanesulfonate) in serum is negatively associated with testosterone levels, but not with semen quality, in healthy men. *Human reproduction*. 2013 Mar 1;28(3):599-608.
- 145 Lopez-Espinosa MJ, Mondal D, Armstrong BG, Eskenazi B, Fletcher T. Perfluoroalkyl substances, sex hormones, and insulin-like growth factor-1 at 6–9 years of age: a cross-sectional analysis within the C8 Health Project. *Environmental health perspectives*. 2016 Aug;124(8):1269-75.
- 146 Raymer JH, Michael LC, Studabaker WB, Olsen GW, Sloan CS, Wilcosky T, Walmer DK. Concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) and their associations with human semen quality measurements. *Reproductive toxicology*. 2012 Jul 1;33(4):419-27.
- 147 Zhou Y, Hu LW, Qian ZM, Chang JJ, King C, Paul G, Lin S, Chen PC, Lee YL, Dong GH. Association of perfluoroalkyl substances exposure with reproductive hormone levels in adolescents: By sex status. *Environment international*. 2016 Sep 1;94:189-95.
- 148 Louis GM, Chen Z, Schisterman EF, Kim S, Sweeney AM, Sundaram R, Lynch CD, Gore-Langton RE, Barr DB. Perfluorochemicals and human semen quality: the LIFE study. *Environmental health perspectives*. 2015 Jan;123(1):57-63.
- 149 Pan Y, Cui Q, Wang J, Sheng N, Jing J, Yao B, Dai J. Profiles of Emerging and Legacy Per-/Polyfluoroalkyl Substances in Matched Serum and Semen Samples: New Implications for Human Semen Quality. *Environmental health perspectives*. 2019 Dec 16;127(12):127005.
- 150 Environmental Protection Agency. Drinking Water Health Advisory for Perfluorooctanoic Acid (PFOA). Washington, DC, USA, US Environmental Protection Agency Office of Water (4304T) Health and Ecological Criteria Division; 2016. EPA Document Number: 822-R-16-005.
- 151 Environmental Protection Agency. Drinking Water Health Advisory for Perfluorooctane Sulfonate (PFOS). Washington, DC, USA, US Environmental Protection Agency Office of Water (4304T) Health and Ecological Criteria Division; 2016. EPA Document Number: 822-R-16-004
- 152 Environmental Protection Agency. Human Health Toxicity Values for Hexafluoropropylene Oxide (HFPO) Dimer Acid and Its Ammonium Salt (CASRN 13252-13-6 and CASRN 62037-80-3) Also Known as "GenX Chemicals". Washington, DC, USA, US Environmental Protection Agency Office of Water (4304T) Health and Ecological Criteria Division; 2018. EPA Document Number: EPA Document Number: 823-P-18-001.
- 153 Barry V, Winqvist A, Steenland K. Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. *Environmental health perspectives*. 2013;121(11-12):1313-8.

- 154 Vieira VM, Hoffman K, Shin HM, Weinberg JM, Webster TF, Fletcher T. Perfluorooctanoic acid exposure and cancer outcomes in a contaminated community: a geographic analysis. *Environ Health Perspect.* 2013 Mar;121(3):318-23.
- 155 Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for Perfluoroalkyls. (Draft for Public Comment). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. 2018; 852 p.
- 156 Kemp MJ, Boyd CA. PFAS Toxicology–The Science Behind the Variation in Drinking Water Standards. *Journal of the New England Water Works Association.* 2019 Dec 1;133(4):243-55.
- 157 Genuis SJ, Curtis L, Birkholz D. Gastrointestinal elimination of perfluorinated compounds using cholestyramine and *Chlorella pyrenoidosa*. *International Scholarly Research Notices.* 2013;2013.
- 158 Behr AC, Plinsch C, Braeuning A, Buhrke T. Activation of human nuclear receptors by perfluoroalkylated substances (PFAS). *Toxicology in Vitro.* 2020 Feb 1;62:104700.
- 159 White SS, Fenton SE, Hines EP. Endocrine disrupting properties of perfluorooctanoic acid. *The Journal of steroid biochemistry and molecular biology.* 2011 Oct 1;127(1-2):16-26.
- 160 Huang Q, Chen Q. Mediating roles of PPARs in the effects of environmental chemicals on sex steroids. *Ppar Research.* 2017 Oct;2017.
- 161 Rosen MB, Lee JS, Ren H, Vallanat B, Liu J, Waalkes MP, Abbott BD, Lau C, Corton JC. Toxicogenomic dissection of the perfluorooctanoic acid transcript profile in mouse liver: evidence for the involvement of nuclear receptors PPAR α and CAR. *Toxicological Sciences.* 2008 May 1;103(1):46-56.
- 162 Rosen MB, Das KP, Rooney J, Abbott B, Lau C, Corton JC. PPAR α -independent transcriptional targets of perfluoroalkyl acids revealed by transcript profiling. *Toxicology.* 2017 Jul 15;387:95-107.
- 163 Wolf CJ, Schmid JE, Lau C, Abbott BD. Activation of mouse and human peroxisome proliferator-activated receptor- α (PPAR α) by perfluoroalkyl acids (PFAAs): further investigation of C4–C12 compounds. *Reproductive toxicology.* 2012 Jul 1;33(4):546-51.
- 164 Zhang L, Ren XM, Wan B, Guo LH. Structure-dependent binding and activation of perfluorinated compounds on human peroxisome proliferator-activated receptor γ . *Toxicology and applied pharmacology.* 2014 Sep 15;279(3):275-83.
- 165 Behr AC, Kwiatkowski A, Ståhlman M, Schmidt FF, Luckert C, Braeuning A, Buhrke T. Impairment of bile acid metabolism by perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) in human HepaRG hepatoma cells. *Archives of Toxicology.* 2020 Apr 6:1-4.
- 166 Bijland S, Rensen PC, Pieterman EJ, Maas AC, van der Hoorn JW, van Erk MJ, Havekes LM, Willems van Dijk K, Chang SC, Ehresman DJ, Butenhoff JL. Perfluoroalkyl sulfonates cause alkyl chain length–dependent hepatic steatosis and hypolipidemia mainly by impairing lipoprotein production in APOE* 3–Leiden CETP mice. *Toxicological Sciences.* 2011 Sep 1;123(1):290-303.
- 167 Bjork JA, Butenhoff JL, Wallace KB. Multiplicity of nuclear receptor activation by PFOA and PFOS in primary human and rodent hepatocytes. *Toxicology.* 2011 Oct 9;288(1-3):8-17.
- 168 Das KP, Wood CR, Lin MT, Starkov AA, Lau C, Wallace KB, Corton JC, Abbott BD. Perfluoroalkyl acids-induced liver steatosis: Effects on genes controlling lipid homeostasis. *Toxicology.* 2017 Mar 1;378:37-52.

- 169 Guruge KS, Yeung LW, Yamanaka N, Miyazaki S, Lam PK, Giesy JP, Jones PD, Yamashita N. Gene expression profiles in rat liver treated with perfluorooctanoic acid (PFOA). *Toxicological Sciences*. 2006 Jan 1;89(1):93-107.
- 170 Salihovic S, Fall T, Ganna A, Broeckling CD, Prenni JE, Hyötyläinen T, Kärrman A, Lind PM, Ingelsson E, Lind L. Identification of metabolic profiles associated with human exposure to perfluoroalkyl substances. *Journal of exposure science & environmental epidemiology*. 2019 Mar;29(2):196-205.
- 171 Schlezinger J, Puckett H, Oliver J, Nielsen G, Heiger-Bernays W, Webster T. Perfluorooctanoic acid activates multiple nuclear receptor pathways and skews expression of genes regulating cholesterol homeostasis in liver of humanized PPAR α mice fed an American diet. 2020 Oct 15; 405:115204.
- 172 Zhang H, He J, Li N, Gao N, Du Q, Chen B, Chen F, Shan X, Ding Y, Zhu W, Wu Y. Lipid accumulation responses in the liver of *Rana nigromaculata* induced by perfluorooctanoic acid (PFOA). *Ecotoxicology and environmental safety*. 2019 Jan 15;167:29-35.
- 173 Berg V, Nøst TH, Hansen S, Elverland A, Veyhe AS, Jorde R, Odland JØ, Sandanger TM. Assessing the relationship between perfluoroalkyl substances, thyroid hormones and binding proteins in pregnant women; a longitudinal mixed effects approach. *Environment international*. 2015 Apr 1;77:63-9.
- 174 Song M, Kim YJ, Park YK, Ryu JC. Changes in thyroid peroxidase activity in response to various chemicals. *Journal of environmental monitoring*. 2012;14(8):2121-6.
- 175 Benninghoff AD, Bisson WH, Koch DC, Ehresman DJ, Kolluri SK, Williams DE. Estrogen-like activity of perfluoroalkyl acids in vivo and interaction with human and rainbow trout estrogen receptors in vitro. *Toxicological sciences*. 2011 Mar 1;120(1):42-58.
- 176 Hemmer, M.J., Benninghoff, A.D., Salinas, K.A., Williams, D.E. Proteomic screening of perfluoroalkyl acids for estrogenic activity using mass spectrometry. *Toxicologist*. 2010; 114: 93.
- 177 Tilton SC, Orner GA, Benninghoff AD, Carpenter HM, Hendricks JD, Pereira CB, Williams DE. Genomic profiling reveals an alternate mechanism for hepatic tumor promotion by perfluorooctanoic acid in rainbow trout. *Environmental health perspectives*. 2008 Aug;116(8):1047-55.
- 178 Temkin AM, Hocevar BA, Andrews DQ, Naidenko O V., Kamendulis LM. Application of the key characteristics of carcinogens to per and polyfluoroalkyl substances. *Int J Environ Res Public Health*. 2020;17(5):1.