

Perfluorooctane sulfonic acid (PFOS) | 2019

Substance Overview

Perfluorooctane sulfonate (PFOS) is a chemical in a group of contaminants called per- and polyfluoroalkyl substances (PFAS). Because of its chemical properties, PFOS has been used as stain repellants in commercial products like carpet and fabric, as a coating for packaging, and in some fire-fighting foams.¹ PFOS can persist in the environment and in the body for long periods of time.¹

Recommendations

Wisconsin does not currently have a NR140 Groundwater Quality Public Health Enforcement Standard for PFOS.

DHS recommends an enforcement standard of 20 nanograms per liter (ng/L) for PFOS. This standard is based on the Agency for Toxic Substances and Disease Registry's (ATSDR's) intermediate oral minimum risk level for PFOS.

This standard applies to the sum of PFOS and PFOA concentrations in groundwater.

DHS recommends that the NR140 Groundwater Quality Public Health Preventive Action Limit for PFOS be set at 10% of the enforcement standard because PFOS have been shown to have carcinogenic, teratogenic, and interactive effects.

Health Effects

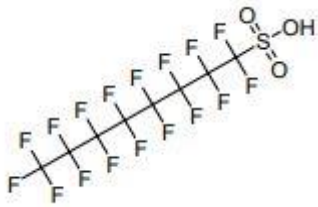
Studies in workers and people living in areas with high levels of PFOS in drinking water show that PFOS may increase cholesterol, damage the liver, cause pregnancy-induced hypertension, increase the risk for thyroid disease, decrease antibody response to vaccines, decrease fertility, and cause small decreases in birth weight.¹⁻³ Studies in research animals have found that PFOS can cause damage to the liver and the immune system. PFOS has also been shown to cause birth defects, delayed development, and newborn deaths in animals, indicating that PFOS can cause teratogenic effects.

The EPA has classified PFOS as having suggestive evidence of carcinogenic potential.^{2,3} PFOS has not been shown to have mutagenic effects.¹⁻³ Both PFOA and PFOS have been shown to cause the same or similar effects on the immune system, development, and reproduction in people and research animals indicating that PFOS can cause interactive effects.¹⁻³

Current Standards	
Enforcement Standard:	N/A
Preventive Action Limit:	N/A
Year:	N/A

Recommended Standards	
Enforcement Standard:	20 ng/L
Preventive Action Limit:	2 ng/L (sum of PFOS and PFOA)

Chemical Profile

PFOS	
Structure:	
CAS Number:	1763-23-1
Formula:	C ₈ H _F ₁₇ O ₃ S
Molar Mass:	500.03 g/mol
Synonyms:	perfluorooctane sulfonate 1-perfluorooctanesulfonic acid heptadecafluoro-1-octanesulfonic acid heptadecafluorooctan-1-sulphonic acid perfluorooctylsulfonic acid 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8- heptadecafluoro 1-octanesulfonic acid

Exposure Routes

People can be exposed to PFOS by drinking contaminated water, eating fish caught from contaminated waterbodies, swallowing contaminated soil or dust, eating food that was packaged in material that contains PFOS, and using consumer products such as non-stick cookware, stain resistant carpeting, and water-repellant clothing.¹

Research indicates that the majority of exposure to PFOS comes from food. Drinking water can be a major source of PFOS if levels are high.¹ Babies born to mothers exposed to PFOS can be exposed during pregnancy and during breastfeeding.¹

Current Standard

There are no current groundwater standards for PFOS in Wisconsin.⁴

Standard Development

Federal Numbers

Maximum Contaminant Level:	N/A	
Lifetime Health Advisory Level:	70 ng/L	(2016)
Drinking Water Concentration (Cancer Risk):	N/A	

State Drinking Water Standard

NR809 Maximum Contaminant Level:	N/A
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Acceptable Daily Intake

EPA Oral Reference Dose:	0.00002 mg/kg-d	(2016)
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Oncogenic Potential

EPA Cancer Slope Factor:	N/A
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Guidance Values

ATSDR Minimum Risk Level:	0.0000027 mg/kg-d	(2018)
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Literature Search

Search Dates:	2016 – 2019
Total studies evaluated:	Approximately 300
Key studies found:	Yes

Federal Numbers

Chapter 160, Wis. Stats., requires that DHS use the most recent federal number as the recommended enforcement standard unless one does not exist or there is significant technical information that was not considered when the federal number was established and that indicates a different number should be used.

Maximum Contaminant Level

The EPA does not have a maximum contaminant level for PFOS.⁵

Health Advisory

In 2016, the EPA Office of Water established a Lifetime Health Advisory of 70 ng/L for PFOS.^{2,3} The EPA evaluated several studies including those that observed effects on development, reproduction, and liver and kidney toxicity. They selected a 2005 study by Luebker et al. that observed reduced body weight in offspring after maternal exposure during pregnancy as the critical study.⁶ In this study, pregnant rats were exposed to PFOS for two generations. PFOS caused delayed eye opening and reduced weight in offspring.⁶ The EPA identified a No Observable Adverse Effect Level (NOAEL) of 0.1 milligrams PFOS per kilogram body weight per day (mg/kg-d) from this study.

Summary of EPA's Health Advisory for PFOS	
NOAEL:	0.1 mg/kg-d (100,000 ng/kg-d)
Half-life used:	5.4 years
Human equivalent dose:	0.00051 mg/kg-d (510 ng/kg-d)
Total uncertainty factor:	30
Oral reference dose:	0.00002 mg/kg-d (20 ng/kg-d)
Water concentration:	70 ng/L

The EPA used pharmacokinetic modeling to estimate a human equivalent dose, which is the amount that a person would have to ingest every day to cause this effect. The model used by EPA converted the level of PFOS in animal serum at which adverse effects were observed to a corresponding human serum level. The human equivalent dose was then estimated by taking into consideration the amount of time that PFOS stays in the body (half-life) and how much blood is in the human body.

The EPA estimated a human equivalent dose of 510 nanograms PFOS per kilogram body weight per day (ng/kg-d) for PFOS by using the NOAEL and a half-life of 5.4 years from a 2010 study by Olsen et al. that estimated the half-life in occupationally-exposed workers.⁷ The EPA applied a total uncertainty factor of 30 to account for differences between people and research animals (10) and differences among people (3). This resulted in an oral reference dose of 20 ng/kg-d.

To set the advisory, the EPA used a water consumption rate for pregnant women (0.054 L/kg-d) because the effect occurred in offspring after maternal exposure to PFOS during pregnancy. The EPA applied the default relative source contribution of 20% to account for exposure from other sources (such as food and air).

The EPA recommended that the lifetime health advisory of 70 ng/L applies to the sum of PFOA and PFOS. They recommended this combined approach because the adverse effects observed in humans and animals are the same or similar for the two substances and the critical effect used to set the oral reference doses for both PFOA and PFOS are developmental endpoints.

Drinking Water Concentration as Specified Risk Levels

The EPA has not established drinking water concentrations at specified cancer risk levels for PFOS.²

State Drinking Water Standard

Chapter 160, Wis. Stats., requires that DHS use a state drinking water standard as the recommended enforcement standard if there are no federal numbers and a state drinking water standard is available.

NR 809 Maximum Contaminant Level

Wisconsin does not have a drinking water standard for PFOS.⁵

Acceptable Daily Intake

If a federal number and a state drinking water standard are not available, ch. 160, Wis. Stats., requires that DHS use an acceptable daily intake (ADI) from the EPA to develop the recommendation. Statute allows DHS to recommend a different value if an ADI from the EPA does not exist or if there is significant technical information that is scientifically valid, was not considered when the federal ADI was set, and indicates a different number should be used. The EPA provides ADIs, termed oral reference doses, as part of a health advisory, human health risk assessment for pesticides, or for use by the Integrated Risk Assessment System (IRIS) program.

EPA Oral Reference Dose

In setting the lifetime health advisory for PFOS, the EPA Office of Water established an oral reference dose of 20 ng/kg-d (see the *Health Advisory* section above for details).^{2,3}

Oncogenic Potential

Chapter 160, Wis. Stats., requires that DHS evaluate the oncogenic (cancer-causing; carcinogenic) potential of a substance when establishing the groundwater standard. If we determine that something is carcinogenic and there is no federal number or ADI from the EPA, DHS must set the standard at a level that would result in a cancer risk equivalent to 1 case of cancer in 1,000,000 people. DHS must also set the standard at this level if the EPA has an ADI but using it to set the groundwater standard would result in a cancer risk that is greater than 1 in 1,000,000.

To evaluate the oncogenic potential of PFOS, we looked to see if the EPA, the International Agency for Research on Cancer (IARC), or another agency has classified the cancer potential of PFOS. If so, we look to see if EPA or another agency has established a cancer slope factor.

Cancer Classification

In 2016, the EPA also evaluated the cancer potential of PFOS when developing their health advisory and determined that there is suggestive evidence that PFOS has carcinogenic potential in humans.^{2,3}

The International Agency for Research on Cancer (IARC) has not evaluated the cancer potential of PFOS.⁸

EPA Cancer Slope Factor

The EPA has not established a cancer slope factor for PFOS.^{2,3} In setting the health advisory, they determined that the weight of evidence for relevance to humans was too limited to support a quantitative assessment and that modeling of the liver and thyroid adenomas observed in rats was not possible because a dose-response relationship was not observed.

Additional Technical Information

Chapter 160, Wis. Stats., allows DHS to recommend a value other than a federal number or ADI from the EPA if there is significant technical information that was not considered when the value was established and indicates a different value is more appropriate.

To ensure the recommended groundwater standards are based on the most appropriate scientific information, we search for relevant health-based guidance values from national and international agencies and for relevant data from the scientific literature.

Guidance Values

For PFOS, we searched for values that have been published since 2016 when the EPA published their health advisory level. We found a relevant guidance value from the Agency for Toxic Substances and Disease Registry (ATSDR).

ATSDR Intermediate Oral Minimum Risk Level (draft)

In 2018, the Agency for Toxic Substances and Disease Registry (ATSDR) released a draft Toxicological Profile for Perfluoroalkyls.¹ In this Profile, they recommended an intermediate oral minimum risk level of 0.000002 mg/kg-d for PFOS.^a

The ATSDR evaluated several studies including those that observed effects on immune response, development, and liver toxicity. The ATSDR also selected the 2005 Luebker et al. study as their critical study and identified a NOAEL of 0.1 mg/kg-d.

The ATSDR also used pharmacokinetic modeling to estimate a human equivalent dose by converting the level of PFOS in animal serum at which adverse effects were observed to a corresponding human serum level. They estimated a human equivalent dose of 0.000515 mg/kg-d for PFOS by using the NOAEL of 0.1 mg/kg-d and a half-life of 5.4 years. The ATSDR, like EPA, selected a half-life of 5.4 years from a 2007 study by Olsen et al.⁷

To obtain the intermediate oral minimum risk level, they applied a total uncertainty factor of 30 to account for differences between people and research animals (3) and differences among people (10). The ATSDR also applied a modifying factor of 10 due to concern that immunotoxicity effects may be a more sensitive endpoint than developmental toxicity.^b In their review, ATSDR compared measured serum levels of PFOS from studies evaluating immune responses with those evaluating developmental toxicity. They found that the measured serum PFOS levels associated with altered immune responses were approximately 10–100% of that predicted to occur at the NOAEL dose.

Summary of ATSDR's Minimum Risk Level for PFOS	
NOAEL:	0.1 mg/kg-d (100,000 ng/kg-d)
Half-life used:	5.4 years
Human equivalent dose:	0.00051 mg/kg-d (510 ng/kg-d)
Total uncertainty factor:	30
Modifying factor:	10
Minimum risk level:	0.000002 mg/kg-d (2 ng/kg-d)

Literature Search

The ATSDR's draft Toxicological Profile on PFAS was published in June 2018. The last literature search conducted by the ATSDR was done in May 2016. To identify recent publications, we conducted a search on the National Institutes of Health's PubMed resource for relevant articles published from January 2016 to April 2019. We searched for studies related to PFOS toxicity or PFOS effects on a disease state in which information on exposure or dose was included as part of the study or studies related to modeling PFOS exposure or dose using pharmacokinetics in animals or humans.^c Previous research has shown that

a The ATSDR's intermediate minimum risk levels are protective of exposures between 15 and 364 days. The ATSDR did not recommend a chronic oral reference dose for PFOS because they felt that the available data for chronic exposure (more than 1 year) are limited and were uncertain whether the most sensitive endpoint for chronic exposure has been identified in the current research.

b Modifying factors are used in a similar manner as uncertainty factors. Modifying factors are typically used on a case-by-case basis and help address additional uncertainty in the available data. For more information on modifying factors, see Ritter et al, 2007.⁶

c The following search terms were used in the literature review:

effects on the immune system, development, and reproduction are the most sensitive, so we searched for new toxicity studies in these areas.^{1,10} Ideally, relevant studies used *in vivo* (whole animal) models and provided data for multiple doses over an appropriate exposure duration.

Approximately 300 studies were returned by the search engine. We excluded studies on non-mammalian or cell systems, non-oral exposure routes, those that did not evaluate health risks, and those only examining a single point of exposure from further review. After applying these exclusion criteria, we located six key toxicity studies and no key pharmacokinetic studies on PFOS (Table A-1 contains a summary of these studies).

To be considered a critical toxicity study, the study must be of an appropriate duration (at least 60 days or exposure during gestation), have identified effects that are consistent with other studies and relevant for humans, have evaluated more than one dose, and have an identifiable toxicity value.^d One of the key studies met the criteria to be considered a critical toxicity study (see Tables A-1 and A-2 for more details).

Critical Toxicity Studies

Lai et al., 2017

Lai et al. exposed pregnant mice to different concentrations of PFOS (0, 0.3, and 3 mg/kg-d) through gavage during pregnancy. They found that both doses caused changes to the lipid mediators in testes and high dose reduced serum testosterone and epididymis sperm count in male offspring at postnatal day (PND) 63.

From this study, we identified a LOAEL of 0.3 mg/kg-d based on changes to the lipid mediators in testes. We estimated an ADI of 0.003 mg/kg-d based on the LOAEL and a total uncertainty factor of 1000 to account for differences between people and research animals (10), differences among people (10), and using a LOAEL instead of a NOAEL.^e

Summary

Title/abstract: PFOS or "Perfluorooctane sulfonate"

Keywords: Development OR immune OR reproduction OR pharmacokinetics OR modeling

Subject area: toxicology OR cancer

Language: English

^d Appropriate toxicity values include the no observable adverse effect level (NOAEL), lowest observable adverse effect level (LOAEL), and benchmark dose (BMD). The NOAEL is the highest dose tested that did not cause an adverse effect, the LOAEL is the lowest dose tested that caused an adverse effect, and the BMD is an estimation of the dose that would cause a specific level of response (typically 5 or 10%).⁸

^e The ADI is the estimated amount of PFOS that a person can be exposed to every day and not experience health impacts. The ADI equals the toxicity value divided by the total uncertainty factor. Uncertainty factors were included as appropriate to account for differences between humans and research animals, differences in sensitivity to health effects within human populations, using data from short term experiments to protect against effects from long-term exposure, and using data where a health effect was observed to estimate the level that does not cause an effect.

A large number of epidemiology studies on the effects of PFOS have been published since 2016 (see Appendix B for a summary of these studies). However, using epidemiology studies for establishing a health-based value is challenging because exposed people are generally exposed to more than one PFAS compounds, and the various PFAS compounds likely have similar health effects.¹¹⁻¹⁰⁷ As such, animal studies where subjects are exposed to a single compound in a controlled environment provide the most useful data for risk assessment. Animal studies published since 2016 confirm that development is a significant endpoint for PFOS.^{108,109}

Standard Selection

DHS recommends a combined enforcement standard of 20 ng/L for PFOS and PFOA.

There is a federal number for PFOS – EPA’s lifetime health advisory level.^{2,3} However, recent studies in people and animals indicate that this level may not be adequately protective.

In establishing their health advisory level, the EPA reviewed a number of studies that evaluated the effect of PFOS on the immune system, but did not quantitatively assess immunotoxicity because of uncertainties related to the mode of action, level, duration, and timing of exposure.^{2,3} Since EPA established their advisory, a number of epidemiological studies have been published evaluating the potential immune effects of PFOS (see Table B-2 for more details on these studies).^{110-113, 47,114, 115-118} While the long half-life of PFOS in people, multiple potential exposure sources, and the ability for other PFAS compounds to cause similar health effects prohibit using these data to establish a health-based value for PFOS, these studies indicate the need to account for this effect. For this reason, the ATSDR included a modifying factor to account for the potential for immunotoxicity effects to be a more sensitive endpoint than developmental toxicity when establishing their minimum risk level for PFOS.¹

Additionally, recent modeling studies with PFOA have indicated that modeling approach taken by EPA may not be adequate to protect infants from exposure during pregnancy and while breastfeeding.^{38,119} PFOS (like PFOA) can cross the placenta during pregnancy and pass through breastmilk. To set their lifetime health advisory level, the EPA estimated how much PFOS a woman has to be exposed to orally during pregnancy for her serum levels to be equivalent to the level where health effects were seen in mice pups (babies).^{10,120} The modeling studies with PFOA modeling of maternal exposure levels may not be adequate to protect infants from exposure during pregnancy and while breastfeeding. These studies suggest that modeling of infant exposure may be a more appropriate approach to protect this sensitive population.

Basis for Recommended Standard

- Federal Number
- Cancer Potential
- EPA Acceptable Daily Intake

Significant technical information

From this information, DHS concludes that there is significant technical information that was not considered when EPA set the lifetime health advisory for PFOS. Therefore, we recommend setting the enforcement standard for PFOS using procedures in s. 160.13(2). DHS selected ATSDR’s intermediate oral minimum risk level of 20 ng/kg-d as the ADI for PFOS. While the ATSDR used the same human

equivalent dose and total uncertainty factor as EPA, the ATSDR also applied a modifying factor of 10 when setting their minimum risk level. The ATSDR applied this factor due to concern that immunotoxicity may be a more sensitive endpoint than developmental toxicity. DHS maintains that the addition of the modifying factor provides protection from potential immune effects and helps address concerns about infant exposures to PFOS during pregnancy and breastfeeding. DHS maintains that using ATSDR's intermediate minimum risk level is appropriate for use in setting the public health enforcement standard, as the critical effect for PFOS is developmental effects with exposure happening during pregnancy (an exposure period of about 9 months). To determine the recommended enforcement standard (ES), DHS used the ADI, and, as required by Ch. 160, Wis. Stats., a body weight of 10 kg, a water consumption rate of 1 L/d, and a relative source contribution of 100%.

DHS recommends a combined enforcement standard of 20 ng/L for PFOS and PFOA. Studies have shown that PFOS and PFOA can cause similar effects in humans and in animals. The critical studies used by DHS to establish the ADI for PFOS and PFOA are developmental studies and recent studies have shown that PFOS and PFOA may cause toxicity through similar mechanisms of action. This approach is consistent with that taken by the EPA in their LHA level.^{10,120} They recommended that the advisory apply to the sum of PFOA and PFOS because the adverse effects in humans and animals are same or similar and the critical effect used to set the oral reference dose for both PFOS and PFOA are developmental endpoints.

DHS recommends a combined preventive action level of 2 ng/L for PFOS and PFOA.

DHS recommends that the preventive action level be set at 10% of the enforcement standard because PFOS and PFOA have both been shown to have carcinogenic and teratogenic effects.¹⁻³ Both PFOA and PFOS have been shown to cause the same or similar effects on the immune system, development, and reproduction in people and research animals indicating that PFOS can cause interactive effects.¹⁻³

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Appendix A: Key Toxicity Studies for PFOS

Table A-I. Toxicity Studies Published since ATSDR's Toxicological Profile

Study Type	Species	Exposure Duration	Doses (mg/kg-d)	Route	Endpoints	Toxicity Value (mg/kg-d)	Reference
Development	Mouse	Gestation	0.3, 3	Gavage	Perturbations of lipid mediators in testes. Reduced serum testosterone and epididymis sperm count at PND63.	LOAEL: 0.3	Lai et al, 2017 ⁽¹⁰⁸⁾
Longer-term	Mouse	49 d	0.3, 3	Diet	Disturbances in lipid and glucose metabolism. Modulated the abundance of metabolism-associated bacteria, but did not affect diversity of gut bacterial species.	LOAEL: 0.3	Lai et al, 2018 ⁽¹⁰⁹⁾
Development	Rat	21 d	5, 10	Gavage	Lowered sperm testosterone levels without altering luteinizing hormone and follicle-stimulating hormone levels on PND 56. Downregulated mRNA and protein levels of Leydig cells.	LOAEL: 5	Li et al, 2018 ⁽¹²¹⁾
Development	Rat	28 d	1, 3, 6	Gavage	Alterations to hormones involved in the hypothalamic-pituitary-testis axis	LOAEL: 1	Lopez-Doval et al, 2016 ⁽¹²²⁾
Immune	Mouse	25 d	2	Gavage	Caused failure to clear <i>Citrobacter rodentium</i> infection	LOAEL: 2	Suo, 2017 ⁽¹²³⁾
Development	Rat	Gestation – Adulthood	0.023, 0.67, 2.0 (1.7, 5, 15 mg/L)	Water	Alterations in biomarkers of cognitive function	LOAEL: 0.023	Zhang, 2019 ⁽¹²⁴⁾

Table A-2. Critical Study Selection

Reference	Appropriate duration?	Effects consistent with other studies?	Effects relevant to humans?	Number of doses	Toxicity value identifiable?	Critical study?
Lai et al., 2017	✓	✓	✓	2	✓	Yes
Lai et al., 2018	⊗	✓	✓	2	✓	No
Li et al., 2018	⊗	✓	✓	2	✓	No
Lopez-Doval et al., 2106	⊗	✓	✓	3	✓	No
Suo et al., 2017	⊗	✓	✓	1	✓	No
Zhang et al., 2019	✓	✓	✓	3	See note	No

To be considered a critical study, the study must be of an appropriate duration (at least 60 days or exposure during gestation), have identified effects that are consistent with other studies and relevant for humans, have evaluated more than one dose, and have an identifiable toxicity value.

Note: While a LOAEL can be identified from this study, expressing this dose in mg/kg-d is challenging given that the authors reported exposure as mg/L, animals were exposed over a lifetime, and water consumption rates were not reported.

Appendix B: Epidemiology Studies of PFOS Published since ATSDR's Toxicological Profile

Table B-I. Summary of Recent Epidemiology Studies of PFAS^f

Category	Examples	Number of Studies
Metabolic	Diabetes (type 1, 2, and gestational), glucose tolerance, insulin resistance, BMI, obesity/overweight, adiposity, cholesterol, triglycerides	41
Birth outcomes	Birth size (weight, length, etc), gestation age, small for gestational age, fetal growth, anogenital distance at birth	25
Neurological	Attention, impulse control, visual and spatial ability, cognitive development, executive function, autism spectrum disorder, intellectual disability	18
Reproductive	Endometriosis, preeclampsia, reproductive hormones, time to pregnancy, fertility, semen characteristics, pregnancy loss, menopause, puberty onset	13
Immune	Asthma, vaccine antibodies, allergic conditions, infectious disease incidence, atopic dermatitis	12
Thyroid	Thyroid hormones, thyroid function	10
Cardiovascular	heart attack, stroke, heart failure, arterial wall stiffness, coronary heart disease, blood pressure, hypertension	7
kidney	Chronic kidney disease, kidney function, glomerular filtration	7
Other	Vitamin D, bone density, lung function, dental carries, gut bacteria and metabolites, mortality,	6
DNA	Telomere length, DNA methylation	5
Liver	ALT (alanine aminotransferase), other liver function biomarkers	4
Cancer	Breast cancer	2

^f The following search terms were used in the literature review:

Subject: "(PFOS OR PFOA OR PFAS OR PFC) AND epidemiology

Language: English

We excluded studies that did not evaluate health effects from our analysis.

Table B-2. Recent Epidemiology Studies evaluating the effects of PFOS on the immune system

Study Type	Population	Time period	Data Source	Outcomes	Results	Reference
Case Control	Adolescents with and without asthma (Taiwan)	2009-2010	The Genetic and Biomarkers study for Childhood Asthma	Interaction between PFAS and reproductive hormones on asthma	After controlling for hormone levels, associations between PFAS exposure and asthma were consistently stronger among children with higher than lower estradiol (For PFOS, OR for asthma was 1.25 among boys (95% CI: 0.90, 1.72) and 1.25 (95% CI: 0.84, 1.86) among girls.	Zhou et al. 2017 ⁽¹¹²⁾
Cross Sectional	Adolescents (USA)	1999 – 2000 2003 – 2004 2005 -2006	NHANES	Association between PFAS serum concentrations and measles, mumps, and rubella antibody concentrations and to allergic conditions Association between PFAS serum concentrations and allergic sensitization	Doubling of perfluorooctane sulfonate (PFOS) concentration among seropositive children was associated with a 13.3% (95% CI: -19.9, -6.2) decrease in rubella antibody concentration and a 5.9% decrease in mumps antibody concentration (95% CI: -9.9, -1.6). No adverse association between exposure and current allergic conditions, including asthma. Children with higher PFOS concentration were less likely to be sensitized to any allergen (OR: 0.74; 95% CI: 0.58, 0.95).	Stein et al. 2016 ⁽¹¹⁰⁾
Case Control	Adolescents with and without asthma (Taiwan)	2009 – 2010	The Genetic and Biomarkers study for Childhood Asthma	Association between PFAS serum concentrations and the level of 16-kDa club cell secretory protein (CC16) ¹	After adjusting for confounding factors, urinary CC16 was significantly, negatively associated with PFASs. In males, For PFOS ($\beta = -0.003$, 95% CI: -0.004, -0.002),	Zhou et al. 2017 ⁽¹¹³⁾
Cross Sectional	Adolescents (USA)	2005 -2006 2007 – 2010	NHANES	Association between PFAS serum concentrations and food sensitization and food allergies	Serum PFOS was statistically significantly associated with higher odds to have self-reported food allergies in NHANES 2007-2010.	Buser et al. 2016 ⁽¹¹⁴⁾

Birth Cohort	Infants (Norway)		The Environment and Childhood Asthma (ECA) prospective birth cohort study	Association between prenatal exposure to PFAS and asthma or other allergic diseases or respiratory tract infections in childhood	The number of reported airways infections were significantly associated with cord blood concentrations of PFAS. For PFOS, lower respiratory tract infections ($\beta = 0.50$ (0.42-0.57)) from 0 to 10 years of age with PFOS	Impinen et al. 2018 ⁽⁴⁷⁾
Birth Cohort	Mother-infant pairs (Japan)		Hokkaido Study on Environment and Children's Health	Association between prenatal exposure to PFAS and prevalence of infectious diseases in children up to 4 years of age	PFOS levels in the highest quartile were associated with increased ORs of total infectious diseases (Q4 vs. Q1 OR: 1.61; 95% CI: 1.18, 2.21; p for trend=0.008) in all children.	Goudarzi et al. 2017 ⁽¹¹⁵⁾
Cross sectional	Adults and Children (USA)	1999-2000 2003-2004	NHANES	Association between serum PFAS concentrations and rubella immunization	There was no significant effect of PFASs on rubella immunity in youths but a significant effect of PFOS in adults, as well as a borderline significant interaction of PFOS x sex.	Pilkerton et al. 2018 ⁽¹¹⁶⁾
Cross sectional	Healthy Adults (USA)	2010-2011	Adults vaccinated during the 2010-2011 influenza season	Association between PFAS serum concentrations and immune response to vaccination with FluMist ²	No readily discernible or consistent pattern between PFAS concentration and baseline cytokine, chemokine, or mucosal IgA concentration, or between PFAS concentration and change in these immune markers between baseline and FluMist-response states was seen.	Stein et al. 2016 ⁽¹¹¹⁾
Birth cohort	Mother-infant pairs (China)	July – October 2013	Guangzhou Birth Cohort Study	Association between prenatal exposure to PFAS and Hand, Foot and Mouth Disease virus antibodies	Cord blood PFAS exposure is associated with lower Hand, Foot and Mouth Disease antibody in infancy. For total PFOS: cord blood OR: 1.66 (1.12, 2.45). Three-month infant: OR: 2.25 (1.44, 3.51).	Zeng et al. 2019 ⁽¹¹⁷⁾
Case Control	Adolescents with and without asthma (Taiwan)	2009-2010	The Genetic and Biomarkers study for Childhood	Association between serum PFAS concentrations and T-lymphocyte-related immunological markers of asthma in children	Asthmatics had significantly higher serum PFAAs concentrations compared with the healthy controls. When stratified by gender, a greater number of significant associations between PFAAs and asthma	Zhu et al. 2016 ⁽¹¹⁸⁾

Asthma

outcomes were found in males than in females (OR for PFOS in males: 4.38 (95% CI: 2.02, 9.50)).

NHANES stands for the National Health and Nutrition Examination Survey; OR = odds ratio; CI = confidence interval

1. CC16 is a prominent biomarker of asthma, among adolescents.
2. FluMist is an intranasal live attenuated influenza vaccine