PFAS in Drinking Water 2019

Scientific and Policy Assessment for Addressing Per- and Polyfluoroalkyl Substances (PFAS) in Drinking Water

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April 12, 2019

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EXECUTIVE SUMMARY

Over the past few decades per- and poly-fluoroalkyl substances (PFAS) contamination has grown into a serious global health threat. PFAS are a large class of several thousand chemically-related synthetic chemicals that are widely used for their water- and oil-repellant properties in a variety of industrial processes and consumer goods. A defining feature of PFAS is their carbon-fluorine bonds, which impart high thermal stability and resistance to degradation. PFAS are also highly mobile in the environment and many have been found to bioaccumulate, or build up, in humans and animals. People are concurrently exposed to dozens of PFAS chemicals daily through their drinking water, food, air, indoor dust, carpets, furniture, personal care products, and clothing. As a result, PFAS are now present throughout our environment and in the bodies of virtually all Americans.

PFAS are associated with many serious health effects such as cancer, hormone disruption, liver and kidney damage, developmental and reproductive harm, changes in serum lipid levels, and immune system toxicity - some of which occur at extremely low levels of exposure. Additionally, because PFAS are chemically related, they may have additive or synergistic effects on target biological systems within our bodies.

Despite the known health impacts and known contamination in people's homes and in the environment, no enforceable national drinking water standards have been set. The few, mostly non-enforceable, advisories or guidelines that do exist at the federal and state levels are mainly for perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS). PFOA and PFOS are the most extensively studied PFAS to-date and, as such, their toxicity has been well characterized in humans and animal models. Although the database for other PFAS is not as robust as for PFOA and PFOS, evidence is growing quickly that indicates they collectively pose similar threats to human health and the environment, often at exceedingly low doses. These toxicity data, combined with concerns over their similar environmental mobility and persistence and widespread human and environmental exposure, have led independent scientists and other health professionals from around the globe to express concern about the continued and increasing production and release of PFAS.

The purpose of this report is to provide relevant scientific information which will help states make informed decisions about how to protect its citizens. This report discusses the most critical health effects known to be associated with PFAS, the risk of additive/synergistic effects from concurrent exposure to multiple PFAS, existing or proposed standards and advisories, and detection and treatment technologies available. Special attention has been given to comparing and analyzing existing or proposed standards and advisories, from which our recommendations arise. For this analysis, we focused on PFOA and PFOS, and two additional PFAS, perfluorononanoic acid (PNFA), and perfluorohexane sulfonic acid (PFHxS), because the Agency for Toxic Substances and Disease Registry has generated minimal risk levels for all four. GenX chemicals, used as a replacement for PFOA, were also analyzed in this report, as their toxicity was recently assessed by the US Environmental Protection Agency (EPA).

Our analysis of current literature and standards/advisories for PFOA, PFOS, PFNA, PFHxS, and GenX show that existing standards and advisories are not health protective. For example, Michigan's PFAS Science Advisory Panel concluded that, "*the research supports the potential for health effects resulting from long term exposure to drinking water with concentrations below 70 ppt*" (the EPA's lifetime health advisory for PFOA and PFOS). If toxicity assessments were based on the most sensitive health effect, protective of the most vulnerable population, and fully acknowledged uncertainties in the toxicity assessment process, maximum contaminant level goals (MCLGs)[a], which are to be set at a level fully protective of human health, would range from 0 to 2 ppt for drinking water. As technology for detection and water treatment do not currently allow for the complete removal of PFAS from drinking water, maximum contaminant levels (MCLs)[b] for PFOA, PFOS, PFNA, PFHxS, and GenX should be based on the best detection and treatment technologies available. Our review of detection and treatment capabilities suggests, a combined MCL of 2 ppt is feasible for PFOA, PFOS, PFNA, and PFHxS, with a separate MCL of 5 ppt for GenX.

However, we conclude that setting a MCLG of zero for the class is needed to provide an adequate margin of safety to protect public health from a class of chemicals that is characterized by extreme persistence, high mobility, and is associated with a multitude of different types of toxicity at very low levels of exposure. If only a handful of PFAS are regulated, there will be swift regrettable substitution with other, similarly toxic PFAS - creating an ongoing problem where addressing one chemical at a time incentivizes the use of other toxic chemicals and we fail to establish effective safeguards to limit this growing class of dangerous chemicals.

The problems with PFAS as a class are highlighted by the fact that many complex PFAS have the potential to break down into less complex perfluoroalkyl acids (PFAAs), a subgroup of PFAS that includes PFOA and PFOS, for which there are substantial known health risks. These problems are compounded by the fact that the production of certain PFAS, such as fluoropolymers, requires the use of PFAAs in their manufacture. This use increases total PFAA contamination and exposure through industrial discharge, as was seen with the production of Teflon®, as well as through impurities in PFAS-containing products.

At present, there is no single methodology for isolating, identifying, and quantifying all PFAS compounds in drinking water. We recommend that the state explore an analytical method, such as total oxidizable precursor assay (TOPA)[c], or combination of methods, that can be used as a surrogate for total PFAS. Until a comprehensive analytical method has been approved to

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[a] An MCLG is the maximum level of a contaminant in drinking water at which no known or anticipated adverse effect on the health of persons would occur, allowing an adequate margin of safety. MCLGs are non-enforceable health goals and consider only public health and not the limits of detection and treatment technology effectiveness.
[b] An MCL is the legal threshold of the amount of a chemical that is allowed in public water systems under the Safe Drinking Water Act. An MCL is based on the concentration established by its corresponding MCLG, but may be adjusted up for feasibility reasons, reflecting difficulties in measuring small quantities of a contaminant, or a lack of available, adequate treatment technologies.
[c] TOPA estimates the full array of potential polyfluoroalkyl acid (PFAA) precursors in a sample. TOPA replicates what micro-organisms in the environment would achieve after many years by rapidly converting precursors into PFAAs such as PFOA, using a hydroxyl radical-based chemical oxidation method.

quantify PFAS compounds as a class, we recommend reverse osmosis, or other treatment method at least as effective as reverse osmosis, as a treatment technique – an enforceable treatment procedure to ensure contamination control - for public water supplies. Reverse osmosis is the preferred treatment technology because it has been demonstrated to effectively remove a broad range of PFAS compounds, it is the most robust technology for protecting against unidentified contaminants, and it does not require frequent change out of treatment media or release elevated concentrations of pollutants after media is spent. We recommend the evaluation of the safest disposal method for high-strength waste streams and spent/used membranes, and that disposal require full destruction of PFAS compounds before entering the environment.

In summary, this report finds that the current available scientific evidence supports the need for:

1) comprehensive testing of drinking water;

2) a maximum contaminant level goal of zero for total PFAS;

3) a combined maximum contaminant level of 2 parts per trillion (ppt) for PFOA, PFOS, PFNA, and PFHxS, and a maximum contaminant level of 5 ppt for GenX; and

4) the setting of a Treatment Technique – an enforceable treatment procedure to ensure contamination control – for the PFAS class based on the best available detection and treatment technologies.

INTRODUCTION

Per- and poly-fluoroalkyl substances (PFAS) are synthetic chemicals that are widely used in a variety of industrial processes and consumer goods. The carbon-fluorine bonds in PFAS impart high thermal stability and resistance to degradation. While useful chemicals, PFAS are highly resistant to environmental degradation and persist in the environment. As a result, PFAS are now present throughout our environment and in the bodies of virtually all people.

PFAS have been associated with a wide variety of adverse health effects including cancer, hormone disruption, liver damage, developmental harm, and immune system toxicity - some of which occur at extremely low levels of exposure. PFAS are widely prevalent in drinking water sources across the country. Consequently, there is an urgent need to take action to address this growing health threat. Yet, there are still no enforceable regulations for PFAS in drinking water at the federal level, and very few regulations addressing PFAS in drinking water at the state level.

In response to a national PFAS contamination crisis in drinking water, this report provides a summary of relevant scientific information on PFAS, including information on PFAS exposure, their effects on human health, and how existing or proposed standards and advisories have been developed. Based on this information, we make recommendations on how states can protect the health of their citizens by addressing PFAS contamination in its drinking water.

This report is organized into six parts: Part I is an introduction to the PFAS class of chemicals. Part II provides an overview of the widespread presence of PFAS in drinking water and in people. Part III discusses the health risks associated with PFAS exposure. Part IV compares and analyzes existing health thresholds set or recommended for levels of certain PFAS (PFOA, PFOS, PFNA, PFHxS and GenX chemicals[d]). Part V provides an overview of detection/analytical methods and treatment technologies for PFAS removal from water. Part VI offers conclusions and recommendations on how PFAS contamination in drinking water can be addressed.

PART I: WHAT ARE PFAS

PFAS are a large class of synthetic fluorochemicals that are widely used for their water- and oil-repellant properties. PFAS can be found in consumer products such as non-stick cookware, clothing, leather, upholstery, and carpets; in paints, adhesives, waxes and polishes; in aqueous

[d] As explained by the U.S. Environmental Protection Agency, "GenX is a trade name for a processing aid technology developed by DuPont (now Chemours). In 2008, EPA received new chemical notices under the Toxic Substance Control Act from DuPont (which is now Chemours) for two chemical substances that are part of the GenX process (Hexafluoropropylene oxide (HFPO) dimer acid and the ammonium salt of HFPO dimer acid)." See EPA, GenX Chemicals Studies, available online at https://www.epa.gov/pfas/genx-chemicals-studies, visited December 4, 2018.

fire-fighting foams; and industrially as surfactants, emulsifiers, wetting agents, additives and coatings.[1,2,3]

A defining feature of PFAS are their carbon-fluorine bonds, which impart high thermal stability and resistance to degradation.[4,5] As a result, PFAS are highly resistant to environmental degradation and persist in the environment. They are relatively water-soluble and have been detected in drinking water sources and in finished (treated) drinking water. Due to their water solubility, after exposure by any route, these chemicals are found in human blood serum rather than in body fat where fat-soluble persistent organic pollutants such as PCBs reside. With half-lives of years, PFAS persist in humans and are found in the blood serum of almost all US residents and populations worldwide.[2,6] PFAS are commonly found together in samples from contaminated water[7] and are identified as co-contaminants in blood serum.[6]

The two most well-known PFAS, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), were manufactured between the 1940s and mid-2010 when they were voluntarily phased out from U.S. manufacturing due to health concerns.[8] However, PFOA and PFOS are still manufactured and used internationally and may enter the U.S. through imported goods.[9] There is widespread contamination of PFOA and PFOS in the environment and their toxicity has been well characterized in humans and animal models.[5] PFOA and PFOS are the most extensively studied PFAS to-date, and as such, they are often the only PFAS chemicals with exposure guidelines in drinking water or other environmental media.

However, issues related to the entire PFAS class, which has now grown to an estimated 4,700 chemicals, have been of increasing concern for researchers and health authorities.[10,11,12] Although there is not a robust toxicity database for the suite of PFAS, it is generally recognized that these chemicals are structurally similar, and it is reported that the health risks associated with one PFAS are expected for other PFAS as well.[2,10,13,14] Moreover, as discussed below, many PFAS have the potential to convert into perfluoroalkyl acids (PFAAs), a subgroup of PFAS that includes PFOA and PFOS, for which there are substantial known health risks. Health risks of PFAS include cancer, immune system disfunction, liver damage, hormone disruption, low birth weight and other developmental effects, changes in serum lipid levels, and reproductive harm.[5] While some scientific uncertainties exist, the weight of scientific evidence is substantial: in experimental animals, in exposed residential populations drinking contaminated water, and in occupational studies, PFOA, PFOS, and related PFAS cause adverse health effects, particularly on the young, and increase cancer risks[15] in exposed populations (discussed further in Part III).

PFAS Classification

PFAS can be classified into various subgroups (see Figure 1 below for a simplified classification diagram).[10] The PFAS subgroup with the most toxicological information is perfluoroalkyl acids (PFAAs), which includes PFOA and PFOS.[5] Another PFAS subgroup is PFAA precursors, which consists of PFAS that can be converted into PFAAs.[16,17] PFAA precursors include fluorotelomer-based substances and PASF (perfluoroalkane sulfonyl fluoride)-based substances.

In a recent review of the global distribution of PFAS, authors concluded that PFAA precursors should be given attention in addition to PFOA, PFOS and other PFAAs.[18] For example, one PFAA precursor subgroup, polyfluorinated phosphate esters (PAPs), are not routinely measured or widely investigated, however recent studies show that they are present in house dust, sometimes at extremely high levels that exceed other PFAS subgroups.[19] Additionally, PAPs were found to be incorporated into produce, such as pumpkin, grown on contaminated soils.[20] PFAA precursors can pose health risks associated with their precursor form and when broken down into PFAAs. Germany and Sweden have proposed a restriction under REACH (a 2006 European regulation that addresses the registration and production of chemical substances) to cover six PFAS and any substance that can degrade into one of the six. The Swedish Chemicals Agency estimates that the restriction will cover a group of about 200 PFAS.[21]

Figure 1: Simplified Classification of PFAS Class

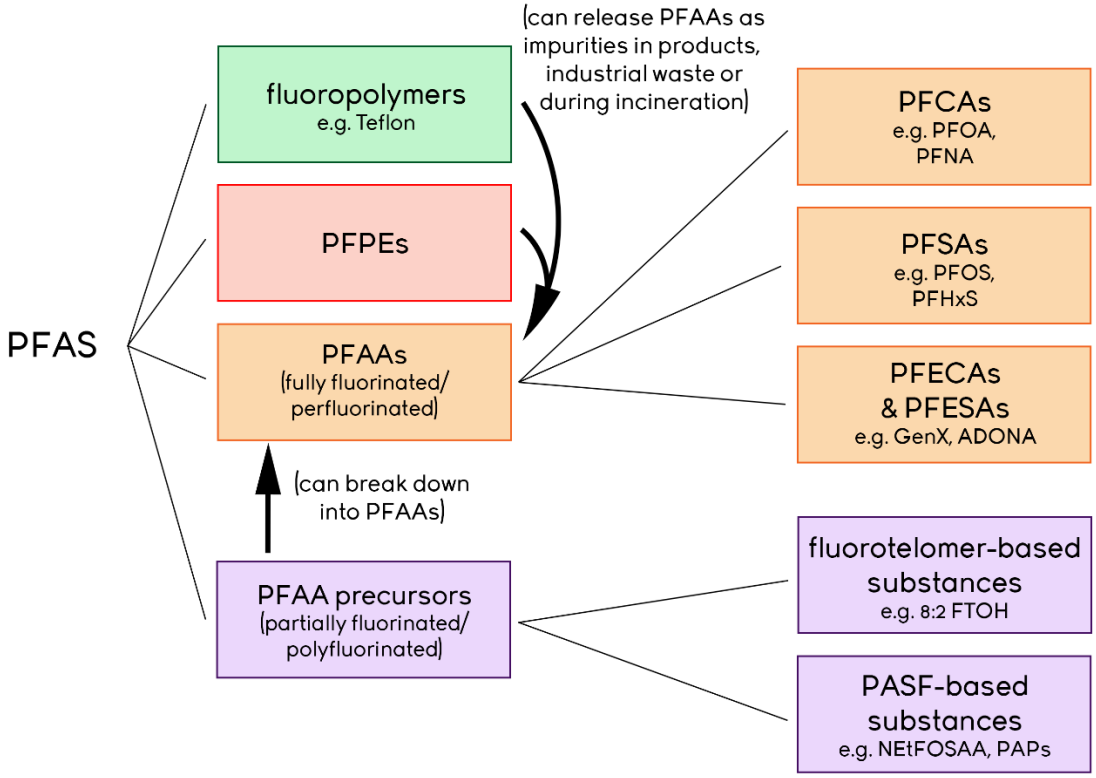

Figure 1 shows the relationship between various subgroups within the PFAS class. This classification scheme is not inclusive of all PFAS subgroups. PFAS (per- and polyfluoroalkyl substances), PFPEs (perfluoropolyethers), PFAAs (perfluoroalkyl acids), PFCAs (perfluoroalkyl carboxylic acids), PFSAs (perfluoroalkyl sulfonic acids), PFECAs (perfluoroether carboxylic acids), PFESAs (perfluoroether sulfonic acids), PASF (perfluoroalkane sulfonyl fluoride).

Perfluoropolyethers (PFPEs) are large molecular sized PFAS with ether linkages and fluoropolymers are composed of multiple repeating units of PFAS.[10,17] While neither are known to actively degrade into PFAAs, they are highly persistent and PFAAs are used in their manufacture, can occur as impurities in the final product, and can be formed when the polymers are heated or incinerated. A well-known fluoropolymer is polytetrafluoroethylene, also known as Teflon. The use of PFAAs such as PFOA and GenX chemicals in the manufacture of perfluoropolyethers and fluoropolymers has resulted in severe environmental contamination around manufacturing and processing plants.[22]

There is concern that simply substituting one PFAS that has been shown to be toxic for another, often less studied PFAS, will result in a regrettable substitution that is not protective of public health. Regrettable substitutions of certain PFAS compounds with others demonstrating similar toxicological characteristics have already occurred. For example, GenX is a replacement technology for PFOA and perfluorobutane sulfonic acid (PFBS) is a replacement for PFOS. The US Environmental Protection Agency (EPA) released draft toxicity assessments in November of 2018 on two GenX chemicals (hexafluoropropylene oxide (HFPO) dimer acid and its ammonium salt) and PFBS confirming that GenX chemicals are associated with liver and pancreatic cancers and adverse effects on the kidneys, blood, liver, immune system, and development.[23] In addition, PFBS is associated with thyroid and kidney effects and reproductive and developmental toxicity.[24]

Table 1: Replacements for PFOA and PFOS are Associated with Similar Health Effects

	Cancer	Immune	Liver or Kidney	Developmental & Reproductive	Endocrine
PFOA	●	●	●	●	●
GenX	●	●	●	●	
PFOS	●	●	●	●	●
PFBS		○	●	●	●

Table 1 compares several health effects associated with exposure to PFOA and its replacement GenX, and PFOS and its replacement PFBS. Based on human and animal evidence (not inclusive of all associated health effects).[e,f,g]

Indeed the EPA, in an evaluation of alternative PFAS to PFOA and PFOS, stated that there is, *"concern that these … substances will persist in the environment, could bioaccumulate, and be toxic ("PBT") to people, wild mammals, and birds."*[25] The Michigan PFAS Science Advisory

[e] ATSDR, 2018. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Perfluoroalkyls. Draft for Public Comment, June 2018.
[f] U.S. Environmental Protection Agency, 2018. Toxicity Assessment: Human Health Toxicity Values for Hexafluoropropylene Oxide (HFPO) Dimer Acid and Its Ammonium Salt (CASRN 13252-13-6 and CASRN 62037-80-3). November 2018. EPA 823-P-18-001.
[g] U.S. Environmental Protection Agency, 2018. Toxicity Assessment: Human Health Toxicity Values for Perfluorobutane Sulfonic Acid (CASRN 375-73-5) and Related Compound Potassium Perfluorobutane Sulfonate (CASRN 29420-49-3). November 2018. EPA 823-R-18-0307.

Panel has recommended that, although there is limited data on PFAS other than PFOA and PFOS, Michigan should "consider setting advisory limits for these additional PFAS in light of their similar chemical structures and toxicity."[26] Vermont is in the process of setting a combined standard for drinking water for 5 PFAS based on their structural and chemical similarity. Furthermore, the 2014 Helsingør[11] and 2015 Madrid Statements,[12] founded on extensive reviews of the scientific literature, provide consensus from more than 200 scientists on the potential for harm associated with the entire class of PFAS.

PART II: HOW ARE PEOPLE EXPOSED TO PFAS

Almost all Americans tested have one or more PFAS in their bodies.[6,27] Widespread use of PFAS has resulted in the ubiquitous presence of these chemicals in the environment including in rivers, soil, air, house dust, food and drinking water from surface water and groundwater sources. We are exposed to PFAS by inhaling house dust contaminated with PFAS due to their use in consumer products, such as treated upholstery and carpet, and from ingesting small amounts in drinking water, food and food packaging.

PFAS in People

Persistent, bioaccumulative chemicals such as those in the PFAS family are characterized by long periods during which the body retains these chemicals after exposure ceases.[3,5,28] PFOA, PFOS, PFNA, PFHxS, and related PFAS are known to bioaccumulate in the bodies of people of all ages, even before birth. Government agencies estimate the human adult half-life (the time it takes to reduce the concentration of a chemical by half) of various PFAS to be on the order of years. Half-life estimates for the PFAS discussed in this report are: 2.3 to 3.8 years for PFOA; 5.4 years for PFOS, 8.5 years for PFHxS, and 2.5 to 4.3 years for PFNA.

The use of PFOA and PFOS in manufacturing has been phased out in the United States, and levels in blood serum have started to decrease as reported in national surveys.[6] However, PFOA and PFOS bioaccumulate and do not degrade in the environment, therefore they will persist in the environment and continue to be a source of exposure for many years in the future.

Blood serum can be used as a long-term measure of exposure for some PFAS and can indicate an increase in risk of disease at the population level. Blood serum concentrations of several PFAS have been evaluated in a large representative sample of the US populations age 12 and older by the National Health and Nutrition Examination Survey (NHANES).[6] The table below (Table 2) summarizes the geometric mean blood serum concentration in ng/L, or parts per trillion (ppt), of different PFAS measured by NHANES since 1999. Note that blood serum concentration is usually expressed in ppb (ug/L or ng/mL) but was converted to ppt in this report to facilitate comparisons to drinking water levels, usually reported in ppt for PFAS.

Table 2: Results of NHANES Biomonitoring Data

Survey Year	PFBS	PFDA	PFDoA	PFHpA	PFHxS	PFNA
1999-2000	NA	*	*	*	2130	551
2003-04	*	*	*	*	1930	966
2005-06	*	355	*	*	1670	1090
2007-08	*	286	*	*	1950	1220
2009-10	*	279	*	*	1660	1260
2011-12	*	199	*	*	1280	881
2013-14	*	185	*	*	1350	675
Survey Year	**PFOA**	**PFOS**	**PFOSA**	**EtFOSAA**	**MeFOSAA**	**PFUA**
1999-2000	5210	30400	355	642	846	*
2003-04	3950	20700	*	*	*	*
2005-06	3920	17100	*	*	410	*
2007-08	4120	13200	*	*	303	*
2009-10	3070	9320	*	*	198	172
2011-12	2080	6310	*	*	*	*
2013-14	1940	4990	NA	NA	*	*

Table 2 shows the geometric mean levels in blood serum in ng/L (ppt) from NHANES biomonitoring data. "" indicates mean was not calculated, proportion of results below limit of detection was too high to provide a valid result. "NA" indicates the PFAS was not measured in that round of NHANES.*

State and regional biomonitoring trends, as well as trends among different age groups and sexes can differ from the national trends represented in NHANES. For example, one study found that children 2 to 5 years old and adults over 60 had a higher blood serum PFOA (median 600 ppb) in the Little Hocking Water Association district compared with residents in all other age groups (median 321 ppb).[29] The authors note that infants and children proportionally drink more water per unit of body weight than adults, and children and the elderly tend to spend more time at home with exclusive use of residential water than other age groups. Additionally, NHANES biomonitoring measures a limited number of PFAS and is likely not reflective of current exposures to PFAS. Alternative methods for detecting PFAS in blood serum are showing an increasing trend of unidentified organofluorine in blood serum samples, which suggest that people are being exposed to new and unidentified PFAS.[30,31]

Fetal and Infant Exposure to PFAS

Fetuses, infants and children are particularly susceptible to the impacts of exposure to toxic chemicals due to their rapidly growing and developing bodies. As such, they are at increased risk of harmful health effects due to PFAS exposure (discussed in further detail in Part II of this

report). Almost all fetuses and infants will have some degree of exposure to PFAS, including fetal exposure during pregnancy through placental transfer.[2,5] For infants, PFAS exposure may be further elevated due to ingestion of contaminated breast milk (a result of the mother's ingestion of contaminated water, and other sources) or infant formula contaminated by PFAS-containing food packaging and/or prepared with contaminated drinking water.[32,33] Fetuses and nursing infants' exposures are influenced by the mother's past exposures or "body burden," as measured by blood serum concentrations.

PFAS have been detected in virtually all umbilical cord blood tested, indicating that PFAS can cross the placental barrier, exposing fetuses *in utero*.[5] Researchers have studied the transfer of PFAS during pregnancy and found a positive correlation between maternal plasma and serum with cord serum levels, concluding that either maternal plasma or serum could be used to estimate fetal exposure to PFAS.[34]

Infant formula can be contaminated with PFAS through the use of PFAS-contaminated water when reconstituting powdered formula. PFAS has also been detected in infant formula itself. For example, one study detected PFAS in all infant milk formulas and baby cereals tested, with the highest levels coming from PFOA, PFOS, PFNA, and PFDA.[33] Contamination of infant formula and cereal could be due to migration from food packaging and/or from containers during production.[35]

ATSDR summarizes reports on breast milk concentrations of PFAS found in the general population.[5] Numerous PFAS, including PFOS, PFOA, PFBS, PFHxS, PFNA, perfluorodecanoic acid (PFDeA), perfluorododecanoic acid (PFDoA), perfluoroundecanoic acid (PFUA), and perfluorooctanesulfonamide (PFOSA), have been detected in breast milk samples in women in China, Korea, Japan, Malaysia, Cambodia, India, Korea, Vietnam, Indonesia, Norway, Philippines, Sweden, and the United States.

PFAS levels in breast milk are higher than what is typically found in drinking water, due to the mothers' past accumulated exposures and transfer to breast milk. For example, in biomonitoring studies average concentrations of PFOA in breast milk range from 2.5%[36] to 9%[37] of the concentration of PFOA in mothers' blood serum. Therefore, breast milk concentrations can be up to an order of magnitude higher than drinking water concentrations because PFOA maternal blood serum levels are approximately 100 times greater than the drinking water she ingested over time.

PFAS in Drinking Water

Drinking water is the dominant source of exposure to PFAS for people living in communities with drinking water highly contaminated with these chemicals, far exceeding exposure from other sources.[38] Even relatively low PFAS concentrations in drinking water can be associated with substantial increases in blood serum levels. For example, since the clearance of PFOA is slow and because it accumulates in blood, after a long period of exposure, a person's blood

serum PFOA level will be about 100 times greater than the PFOA concentration ingested via drinking water.[2]

In 2009, researchers evaluated the contribution of water, diet, air and other sources for various exposure scenarios to PFOA.[38] They found that when drinking water concentrations of PFOA are low, dietary exposure is the dominant source of exposure. However, as drinking water concentrations increase, the ingestion of contaminated water becomes the predominant source of exposure. Drinking water concentrations of 100 ppt and 400 ppt are predicted to contribute 71% and 91%, respectively, of total exposure; and are estimated to increase blood serum levels, on average, by 250% and 1000%, respectively.[2]

Analysis of EPA's Unregulated Contaminant Monitoring Rule (UCMR3) data shows that about 4% of tested public water supplies in the U.S. (about 200 of 5,000 public water supplies studied), serving 16.5 million Americans in 33 states, 3 territories and an American Indian community, have levels of PFAS above the EPA-specified reporting limits[h] for UCMR3.[7] Sixty-six tested public water supplies, serving six million Americans, had at least one sample above EPA's 2016 PFOA and PFOS non-enforceable lifetime health advisory of 70 ppt.[3,28] PFOA was the most frequently detected PFAS in drinking water, followed by PFOS. Exceedances of the EPA's health advisory have been detected in California, New Jersey, North Carolina, Alabama, Florida, Pennsylvania, Ohio, New York, Georgia, Minnesota, Arizona, Massachusetts and Illinois. High levels of PFAS in drinking water were strongly associated with proximity to major PFAS industrial sites, civilian airports, and military fire training areas.

As concerning as the UCMR3 data are, they significantly underestimate how many drinking water sources are contaminated by PFAS. This is in part because the lowest levels of PFAS that are required to be reported to EPA, sometimes referred to as the "Minimum Reporting Levels" or "Method Reporting Levels" under the UCMR3 were very high, meaning that even if PFAS were detected at levels below these cutoffs, they are not required to be reported to EPA. Indeed, these cutoffs are significantly higher than the limit of quantitation reported in most published studies and by a prominent laboratory using the same method, which completed about one-third of the PFAS monitoring under the UCMR3.[39] The UCMR3's overall limitations have been well described:

> *"The [Minimum Reporting Levels] (10−90 ng/L) in the UCMR3 database are up to 2 orders of magnitude higher than the limit of quantitation in most published studies, and more than 10 times higher than the drinking water limit (1 ng/L) suggested by human and animal studies. Because PFASs are detectable in virtually all parts of the environment, we infer that the large fraction of samples below reporting limits is driven in part by high [Minimum Reporting Levels]."* [7]

Moreover, the UCMR3 only required testing for 6 PFAS out of the several thousand PFAS that have been cleared for use in the United States.[40] The UCMR3 data are further limited by the

[h] Reporting limits for UCMR3 were: PFOA - 20 ppt, PFOS - 40 ppt, PFHxS - 30 ppt, PFNA - 20 ppt, perfluorohepatanoic acid (PFHpA) - 10 ppt, and perfluorobutane sulfonic acid (PFBS) - 90 ppt

inclusion of only 0.5 % of the nation's small public water supplies and no testing results for private wells.

PART III: HEALTH RISKS ASSOCIATED WITH EXPOSURE TO PFAS

There is a sufficiently robust body of scientific research to evaluate the adverse health effects of several PFAS, with the most highly studied being PFOA, PFOS, PFNA and PFHxS. Both human studies and animal studies should be used to evaluate adverse effects of chemical exposures (see Box 8 for further discussion). Animal and human studies show similar adverse effects and cancer risks.

Due to the structural similarity and the co-occurrence of PFOA and PFOS in the environment and in people, public health protection and guidance usually address both PFOA and PFOS. In June 2018, minimal risk levels were also generated by the Agency for Toxic Substances and Disease Registry (ATSDR) for PFNA and PFHxS, which are chemically related and often co-occur with PFOA and PFOS.[5] In November of 2018, the EPA released human health toxicity values (reference doses) for PFBS and hexafluoropropylene oxide (HFPO) dimer acid and its ammonium salt, also known as GenX chemicals.[23,24] PFBS is a replacement chemical for PFOS and GenX is a replacement technology for PFOA, and both were found to be associated with a variety of adverse health effects. Considerably less information is available for the larger group of PFAS, however, as stated above, due to the structural similarity of these contaminants, it is expected that many PFAS will have similar health effects. [2,13,14]

Several reviews of the scientific literature on the health effects associated with PFAS exposure have recently been published.[1,2,5,14,15,41,42,43] ATSDR has performed the most recent and comprehensive review. This review is summarized below, as an overview of health effects associated with PFAS exposure. This summary is followed by sections that discuss in further detail cancer risk and two of the most common and sensitive health effects for PFAS, development harm and immunotoxicity. Understanding these health effects is particularly important to determining how to best protect the public from PFAS contamination.

ATSDR Draft Toxicological Profile for Perfluoroalkyls

ATSDR performs risk assessment and evaluation of chemicals as part of the U.S. Centers for Disease Control and Prevention (CDC). ATSDR released a draft Toxicological Profile for Perfluoroalkyls in June 2018.[5] The toxicological profile on perfluoroalkyl compounds included the suite of chemicals in that group that have been measured in the blood serum collected as part of the NHANES 2003-2004 survey, and other monitoring studies. The 14 perfluoroalkyl compounds included in the toxicological profile are:

Perfluorobutyric acid (PFBA, CAS 375-22-4)
Perfluorohexanoic acid (PFHxA, CAS 307-24-4)

Perfluoroheptanoic acid (PFHpA, CAS 375-85-9)
Perfluorooctanoic acid (PFOA, CAS 335-67-1)
Perfluorononanoic acid (PFNA, CAS 375-95-1)
Perfluorodecanoic acid (PFDeA, CAS 335-76-2)
Perfluoroundecanoic acid (PFUA, CAS 2058-94-8)
Perfluorododecanoic acid (PFDoA, CAS 307-55-1)
Perfluorobutane sulfonic acid (PFBS, CAS 375-73-5)
Perfluorohexane sulfonic acid (PFHxS, CAS 355-46-4)
Perfluorooctane sulfonic acid (PFOS, CAS 1763-23-1)
Perfluorooctane sulfonamide (PFOSA, CAS 754-91-6)
2-(N-Methyl-perfluorooctane sulfonamide) acetic acid (Me-PFOSA-AcOH, CAS 2355-31)
2-(N-Ethyl-perfluorooctane sulfonamide) acetic acid (Et-PFOSA-AcOH, CAS 2991-50-6)

ATSDR provided an exhaustive assessment of these 14 PFAS in their Toxicological Profile for Perfluoroalkyls. Their assessment found that there is consistent association between PFAS exposure and several health outcomes. The table (Table 3) below summarizes health effects ATSDR found linked to the 14 PFAS reviewed in the profile.

Table 3: Summary of ATSDR's Findings on Health Effects from PFAS Exposure

	Immune e.g. decreased antibody response, decreased response to vaccines, increased risk of asthma diagnosis	**Developmental & Reproductive** e.g. pregnancy-induced hypertension/pre-eclampsia, decreased fertility, small decreases in birth weight, developmental toxicity	**Lipids** e.g. increases in serum lipids, particularly total cholesterol and low-density lipoprotein	**Liver** e.g. increases in serum enzymes and decreases in serum bilirubin levels	**Endocrine** e.g. increased risk of thyroid disease, endocrine disruption	**Body Weight** e.g. decreased body weight	**Blood** e.g. decreased red blood cell count, decreased hemoglobin and hematocrit levels
PFOA	✖	✖	✖	✖	✖	✖	✖
PFOS	✖	✖	✖	✖	✖	✖	✖
PFHxS	✖			✖			✖
PFNA	✖		✖			✖	
PFDeA	✖	✖	✖	✖	✖	✖	
PFDoA	✖	✖				✖	
PFUA	✖	✖				✖	✖
PFHxA		✖					✖
PFBA		✖		✖	✖		✖
PFBS				✖			✖

Table 3 summarizes ATSDR's findings on the associations between PFAS exposure and health outcomes in human and animal studies (not an exhaustive list of health outcomes).

ATSDR determined that there was sufficient data to support generating minimal risk levels for PFOA, PFOS, PFNA, and PFHxS. Our maximum contaminant level recommendations are, in part, based on these minimal risk levels, which is discussed in Part III of this report.

Cancer Risks from PFOA, PFOS, PFNA, PFHxS, and GenX Exposure

Chemical exposures that contribute to an increase in cancer risk have a significant impact on public health. As the National Cancer Institute states, "*the years of life lost due to premature deaths, the economic burden due to lost productivity and the costs associated with illness and therapy, and the long-term effects of cancer and its treatment on the quality of life of survivors take a toll at a population level*."[44]

Toxicological studies in humans and animals have found associations between increased cancer risk and PFOA and PFOS exposure, and several authoritative bodies have made findings on their carcinogenic potential. PFNA, PFHxS, and GenX are less well studied, however, their chemical similarity to PFOA and PFOS and the data that is available suggests that there is reason to be concerned about increased cancer risk.

PFOA and PFOS

Carcinogens are chemicals that cause cancer. The C8 Science Panel[i] has identified PFOA as a probable carcinogen[15], and the International Agency for Research on Cancer (IARC) has classified PFOA as a possible[45] carcinogen. The EPA Science Advisory Board and the EPA Office of Water have concluded that PFOA and PFOS demonstrate likely[46] or suggestive[3] evidence of carcinogenic potential, respectively.

From 2005-2013 the C8 Science Panel determined blood levels and collected health information from communities in the Mid-Ohio Valley that had been potentially affected by the release of PFOA emitted from a DuPont plant since the 1950s.[15,47,48] They then assessed the links between PFOA exposure and a number of diseases. Based on epidemiologic and other data available to the C8 Science Panel, they concluded that there is a probable link between exposure to PFOA and testicular and kidney cancer (as well as high cholesterol, ulcerative colitis, thyroid disease and pregnancy-induced hypertension). Because these studies relied largely on a survivor cohort, results regarding associations with PFOA may be biased toward the null (i.e. a greater chance of failing to identify an association) for highly aggressive cancers like pancreatic, lung and kidney cancers, which should not be ruled out based on this study.

[i] The C8 Science Panel was established as a result of a class action lawsuit against DuPont and charged with assessing probable links between PFOA (also called C8) exposure and disease in communities near the DuPont Washington Works plant in Parkersburg, West Virginia.

IARC, the specialized cancer agency of the World Health Organization, has classified PFOA as "possibly carcinogenic to humans" (Group 2B) based on limited evidence that PFOA causes testicular and renal cancer, and limited evidence in experimental animals."[45] IARC considers human, animal, and mechanistic data in making its determinations of evidence for cancer risk to humans. The human data considered by IARC in making this determination included increases in cancer among highly exposed members of the C8 Health Project study population[47,48] discussed above, and among workers in the DuPont Washington Work plant in Parkersburg, WV.[49] Researchers studied the mortality of 5,791 workers at the DuPont chemical plant in Parkersburg, West Virginia from 1952-2008. The authors found exposure-response relationships with PFOA for chronic renal disease, both malignant and non-malignant.[49]

The EPA Office of Water concluded that there is suggestive evidence of carcinogenic potential of PFOA in humans.[3] This conclusion was based on Leydig cell testicular tumors in rats, and the reported probable link to testicular and renal tumors among the members of the C8 Health Project. EPA also concluded that there is suggestive evidence of carcinogenic potential of PFOS in humans based on liver and thyroid adenomas observed in a chronic rat bioassay.[28,50]

Cancers other than kidney and testicular cancer have also shown positive associations in studies of occupational exposure, though they have not reached statistical significance. One study reported a non-significant positive association between PFOA and prostate cancer in employees of DuPont in West Virginia.[51] Another study reported modestly elevated risk of prostate and bladder cancer in employees of 3M in Minnesota.[52]

Two small studies of the Inuit population in Greenland found significantly increased risk of breast cancer associated with certain PFAS, including PFOA and PFOS,[53] and a greater elevated odds ratio for breast cancer in women with both high PFAS levels and specific genetic variations that affect levels of hormones such as estrogens.[54] A later, larger study evaluated the association between PFAS serum levels in pregnant Danish women and the risk of premenopausal breast cancer.[55] This study did not find convincing evidence establishing a causal link between PFAS exposures and increased risk of breast cancer 10 to 15 years later. These data suggest the need for further research on this topic, especially considering the effects PFAS exposure can have on mammary gland development (see Box 6).

While there have been some studies that do not support a relationship between PFAS exposure and cancer, those studies have notable limitations. For example, New York State Department of Health (NYSDOH) conducted an evaluation of cancer occurrence in the Hoosick Falls population where residents' blood serum median levels were 23,500 ppt.[56] In that study, no relationship was found between PFOA exposure and testicular, kidney, prostate or bladder cancer. However, studies of community exposures have inherent limitations and are difficult to evaluate in low number populations. As noted by NYSDOH, limitations of this study include small population and incomplete inclusion of the potentially exposed populations.

PFNA, PFHxS, and GenX

PFNA and PFHxS have been studied to a lesser degree than PFOA and PFOS. One study reported a significantly higher risk for prostate cancer among subjects with a hereditary risk and blood serum PFHxS levels above the median, finding a significant odds ratio of 4.4 (1.7-12).[57] An increased, though non-significant, odds ratio of 2.1 (1.2-6.0) was also reported among subjects with a hereditary risk for prostate cancer and blood serum PFNA levels above the median.

Researchers evaluated participants in the C8 Health studies for associations between PFNA and PFHxS and elevated serum levels of prostate-specific antigen, a biomarker that can be used to screen for prostate cancer.[58,59] Their findings were non-significant, however, one limitation with this study is that changes in prostate-specific antigen levels are not exclusively due to cancer but can also be attributed to other factors such as prostate inflammation, urinary retention, local trauma and increase in age.

In EPA's draft toxicity assessment of GenX, the EPA determined that "*there is Suggestive Evidence of Carcinogenic Potential of oral exposure to GenX chemicals in humans, based on the female hepatocellular adenomas and hepatocellular carcinomas and male combined pancreatic acinar adenomas and carcinomas [in rats]*."[23] The EPA also notes that evidence suggest that mice are more sensitive to the effects of GenX than rats, and that a lack of data evaluating cancer in mice is a database deficiency. There are currently no studies evaluating cancer risk from GenX exposure in humans.

Further research is needed to understand the relationship between PFOA and PFOS exposure and various cancers other than kidney and testicular cancer, such as prostate, bladder, ovarian and breast cancer, which have limited, but suggestive evidence for association with PFAS exposure. Additionally, more research is needed to understand the carcinogenic potential of other PFAS, which, due to similar chemical characteristics to PFOA and PFOS, are likely to also increase the risk for certain cancers.

Risks to Fetal Development and the Young

Developing infants and children are particularly susceptible to the impacts of exposure to toxic chemicals. The impacts of PFAS exposure on fetal development and the young have been studied in both humans and animals. These studies find similar and profound adverse health effects.

Since infants and children consume more water per body weight than adults, their exposures may be higher than adults in communities with PFAS in drinking water. In addition, the young may also be more sensitive to the effects of PFAS due to their immature developing immune system, and rapid body growth during development.[1,5,60,61,62] Exposure to PFAS before birth or in early childhood may result in decreased birth weight, decreased immune responses, and hormonal effects later in life.

Recent literature has identified developmental effects of significance from exposure to PFAS. For a review of effects on children from PFAS exposure, sixty-four studies were evaluated for six categories of health outcome: immunity, infection, asthma, cardio-metabolic, neurodevelopmental/attention, thyroid, renal, and puberty onset.[62] The review found evidence of later age at menarche (menstruation), effects on renal function and lipid serum levels, and immunotoxicity (asthma and altered vaccine response).

A particularly significant developmental effect linked to PFAS exposure is alterations to mammary gland development. Prenatal exposure of mice to PFOA results in delays in mammary gland development in offspring of treated females, including reduced ductal elongation and branching, delays in timing and density of terminal end buds (developmental structures important for forming proper mammary gland ductal structure), and decreases in mammary epithelial growth.[63,64,65] These studies found that PFOA-induced effects on mammary tissue occur at extremely low doses - much lower than effects on liver weight. Due to the low-dose sensitivity of mammary glands to PFOA in mice, a no-observable adverse effect level for mammary gland developmental delays could not be determined. In other words, the studies found that all dose levels were associated with effects on mammary gland development. (see Box 6 for a discussion on the biological relevance of altered mammary gland development)

Risk to Immune System Function

Evidence from both animal and human studies suggest that the immune system is also highly sensitive to PFAS exposure. For instance, immunotoxicity is currently the most sensitive health endpoint identified for PFOS exposure and occurs at doses at least an order of magnitude less than other health endpoints. As documented in the ATSDR profile, both animal and epidemiology studies provide strong evidence linking PFAS exposure to immunotoxic effects.[5]

The strongest evidence of the PFAS-associated immunotoxicity in humans comes from epidemiology studies finding associations evaluating the antibody response to vaccines.[5] Associations have been found for PFOA, PFOS, PFHxS, and PFDeA; with limited evidence for PFNA, PFUA, and PFDoA. Increases in asthma diagnosis and effects on autoimmunity, specifically ulcerative colitis, have also been linked to PFAS exposure. Animal studies suggest the immune system is a highly sensitive target of PFAS-induced toxicity; observed effects include impaired responses to T-cell dependent antigens, impaired response to infectious disease, decreases in spleen and thymus weights, and in the number of thymic and splenic lymphocytes.[5,23]

The immunotoxic effects of PFAS could have significant detrimental impacts on public health. For example, PFAS is associated with reduced antibody titer rise in response to vaccines,[5,66] resulting in increased risk of not attaining the antibody level needed to provide long-term protection from serious diseases such as measles, mumps, rubella, tetanus and diphtheria. PFAS can also be transferred to fetuses *in utero*, and to infants via breast milk[67] or PFAS-contaminated infant formula, which presents a particular hazard to the adaptive immune system during this critical window of development. As noted by the Michigan PFAS Science Advisory Panel, "*the developing immune system is especially sensitive to environmental stressors… Disruption of immune development is likely to have broader impacts than the antibody changes that are directly measured in these studies and may have long lasting consequences.*"[26]

Box 1: Immunotoxicity of PFOA, PFOS

In 2016, the National Toxicology Program conducted a systematic review to evaluate immunotoxicity data on PFOA and PFOS. It concluded that both are presumed to constitute immune hazards to humans based on a high level of evidence that they suppress antibody response in animal studies and a moderate level of evidence from studies in humans. They also identified additional evidence linking PFOA exposure to reduced infectious disease resistance, increased hypersensitivity-related outcomes, and increased autoimmune disease incidence (human studies), and PFOS exposure to suppressed disease resistance and lowered immune cell activity (animal studies).[66]

In 2018, the Michigan PFAS Science Advisory Panel recommended adding immunologic effects to ATSDR's list of health conditions of concern, "*particularly those that arise during prenatal exposure and childhood…based on strong toxicologic findings and supporting epidemiologic evidence*."[26]

Short-chain PFAS

Short-chain PFAS (less than six or seven carbons, depending on the PFAS subclass) have been introduced as 'safer' alternatives due to their supposed shorter half-lives in humans, but little research is publicly available on the toxic effects related to exposure, retention, and persistence. The evidence that does exist suggests short-chain PFAS are associated with similar adverse health effects as the long-chain, legacy PFAS that they have replaced.[68,69] Importantly, short-chain PFAS are still highly persistent and are even more mobile in the environment than long-chain PFAS.[70]

Some short-chain PFAS are not detected frequently or detected at low levels in human blood; therefore, some industry groups have claimed that short-chain PFAS are readily eliminated from the body. However, recent research does not support this conclusion. Short-chain PFAS are found to accumulate in

interior organs, some at concentrations that are higher than long-chain PFAS, such as PFOA and PFOS.[77] As Dr. Philippe Grandjean pointed out in his testimony to the Michigan State Legislature, "*Given the inability to assess organ concentrations in clinical studies, our understanding of the health risks associated with the short-chained compounds is extremely limited*." Biomonitoring programs are currently exploring other forms of media, such as urine, as more appropriate measures of short-chain PFAS exposure and retention.

Additionally, developing science on short-chain PFAS metabolism indicates, "*that some fluorinated alternatives have similar or higher toxic potency than their predecessors when correcting for differences in toxicokinetics* [rate a chemical enters the body, is metabolized, and excreted]".[69] The rate a chemical will enter the body and the process of excretion and metabolism in the body may in fact be an inadequate measure of health threats to humans from chemicals with chronic exposure. The widespread use of short-chain PFAS in commerce and their persistence in the environment could lead to chronic exposures in people. Researchers find:

> "*Considering that the exposure to short-chain PFAAs is unlikely to be stopped shortly, there will be increasing continuous and poorly reversible environmental background concentrations of short-chain PFAAs. Consequently, organisms and humans will be permanently exposed to short-chain PFAAs, resulting in continuous and poorly reversible internal concentrations. The poorly reversible internal concentrations in organisms are caused by the persistence of short-chain PFAAs and their continuous presence in the environment. Therefore, the organismal elimination efficiencies are of secondary relevance*."[68]

Finally, it is important to acknowledge that exposure to short-chain and other replacement PFAS, is happening on top of a pre-existing health burden from historically used, long-chain PFAS, as discussed further in the following section.

Box 2: Persistence, Mobility, and Toxicity

The German Environment Agency has shifted the classification of emissions, registered under REACH, to specific intrinsic properties that indicate a hazard to sources of drinking water.[71] These properties include persistence (P) in the environment, mobility (M) in the aquatic environment, and toxicity (T) (PMT). Substances that are considered very persistent in the environment (vP) and very mobile in the aquatic environment (vM), regardless of their toxicity, must also be considered, due to their increased probability of reaching and accumulating in sources of drinking water.[72] Because very short chain PFAS are volatile and can be dispersed far from areas of direct exposure,[73,74] recent efforts have shifted the focus toward mobility as a key chemical parameter of concern, moving from the established criteria persistent (P), bioaccumulative (B), and toxic (T) (PBT) toward PMT.[71,75] This new criteria has prompted the designation of PFAS substances as posing an "equivalent level of concern" under REACH, thereby prompting the need for a new paradigm for chemical assessment and authorization.[76]

Additive and Synergistic Effects of Exposure to Multiple PFAS

Importantly, exposures to PFAS do no occur in isolation. Biomonitoring studies demonstrate that Americans have chronic exposure to multiple PFAS chemicals throughout their lifetimes. CDC's national biomonitoring studies, NHANES, reveal that nearly every American has PFOS, PFOA, PFHxS and PFNA detected in their blood stream, including young children.[6] At least eight other PFAS are detected in blood serum by NHANES studies: MeFOSAA, PFDeA, PFUA, PFHpA, PFBS, FOSA, EtFOSAA, PFDoA, and PFHpA.[6] Most other PFAS chemicals are not routinely included in biomonitoring studies. As mentioned previously, alternative methods in biomonitoring suggest that humans are being exposed to new and unidentified PFAS.[30,31]

Multiple PFAS are found in drinking water, food, dust, personal care products and a variety of different environmental media. In drinking water PFOA, PFOS, PFNA, PFHxS, PFBS, PFHpA (measured in UCMR3), and other PFAS are often found in conjunction.[7] Food contact materials and packaging in the United States has shown detectable levels of PFOA, PFHxS, PFDA, PFHpA, PFDoA, PFHxA, PFBA, PFPeA, PFUA, PFOS and 8:2 FTOH,[78] and likely contain other unknown PFAS. A single consumer product such as carpet, clothing, outdoor gear, or dental floss can contain up to nine different identifiable PFAS compounds[79] along with other undetermined PFAS. Samples of dust collected throughout homes and offices have shown high concentrations of 8:2 FTOH, PFDA, PFHpA, PFNA, 10:2 FTOH, PFDoA and PFTeDA with detection frequencies over 70%.[80]

Figure 2: Possible Sources of PFAS Exposure

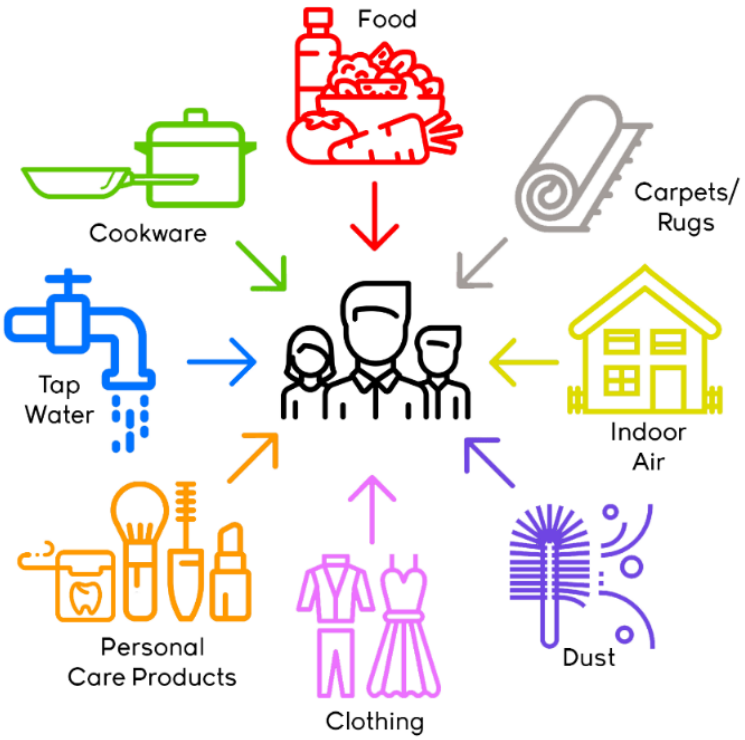

Figure 2 shows the most common pathways of PFAS exposure for humans. PFAS can be found in people's bodies as a result of exposure from multiple environmental sources. [j,k]

Therefore, risk and safety assessments cannot assume that exposures occur in isolation. A person is concurrently exposed to dozens of PFAS chemicals daily, and their exposures extend throughout their lifetimes. Health evaluations should consider the impacts of multiple PFAS chemicals that target the same body systems regardless of detailed knowledge of the underlying mechanism of action. Because PFAS are chemically related, they may have additive or synergistic effects on target systems. An additive effect is when the combined effect of multiple chemicals is the sum of each of the chemicals' effects alone. A synergistic effect is caused when concurrent exposure to multiple chemicals results in effects that are greater than the sum of each of the chemicals' effects alone. For example, many PFAS have been associated with immunological effects. Exposure to a mixture of PFAS could result in adverse effects on the immune system that represents the total dose of all PFAS in the mixture or even greater adverse effects than predicted by summing the dose of all PFAS in the mixture.

PART IV: COMPARISON AND ANALYSIS OF EXISTING HEALTH THRESHOLDS

A number of regulatory and non-regulatory health-based thresholds have been developed for PFAS (mainly PFOA and PFOS) by both federal and state agencies. The data used, and decisions made by these agencies are discussed in this section.

Health advisories issued by the EPA are non-enforceable and non-regulatory. Health advisories provide technical information to state agencies and other public health officials on health effects, analytical methodologies, and treatment technologies associated with drinking water contamination.

Guidance values are state-specific values – used, for example, by the Minnesota Department of Health to evaluate potential human health risks from exposures to chemicals in groundwater – that are non-enforceable goals, benchmarks, or indicators of potential concern. There are three types of guidance values used by Minnesota, health risk limits which are guidance values that have been adopted, and health-based values and risk assessment advice which provide technical guidance but have not yet been formally adopted. In Minnesota, the state develops guidance values by considering health impacts to the most sensitive and most exposed populations across all stages of human development.

Notification levels are state-specific values. California's Division of Drinking Water, for example, has established advisory levels for chemicals in drinking water that lack maximum

[j] ATSDR, 2018. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Perfluoroalkyls. Draft for Public Comment, June 2018.
[k] Guo, Z, et al., 2009. Perfluorocarboxylic acid content in 116 articles of commerce. *Research Triangle Park, NC: US Environmental Protection Agency*

contaminant levels (MCLs, see below). When these chemicals are detected at concentrations greater than their notification levels, state actions include consumer notification and, for larger exceedances, removal of the source water from the drinking water supply.

EPA defines a **Reference dose (RfD)** as "*an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is generally expressed in units of milligrams per kilogram of bodyweight per day (mg/kg/day)*."[81]

A **minimal risk level (MRL)** is an estimate made by ATSDR of the daily human total exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route, including routes other than drinking water exposure, and a specified duration of exposure. MRLs serve as screening tools to help public officials decide where to look more closely and identify contaminants of concern at hazardous waste sites. Like EPA's health advisories, MRLs do not carry regulatory weight by requiring agency-initiated cleanup or setting of action or maximum contaminant levels. MRLs are based on noncancer effects only. These MRLs can be used, similar to reference doses, to generate maximum contaminant level goals for drinking water.

A **maximum contaminant level goal (MCLG)** is the maximum level of a contaminant in drinking water at which no known or anticipated adverse effect on the health of persons would occur, allowing an adequate margin of safety. When determining a MCLG under the federal Safe Drinking Water Act, the EPA considers adverse health risk to sensitive subpopulations, such as infants, children, the elderly, those with compromised immune systems and chronic diseases. MCLGs are non-enforceable health goals and consider only public health and not the limits of detection and treatment technology effectiveness. Therefore, they sometimes are set at levels which water systems cannot meet because of technological limitations.

A **maximum contaminant level (MCL)** is the legal threshold of the amount of a chemical that is allowed in public water systems under the federal Safe Drinking Water Act. A MCL is based on the concentration established by its corresponding MCLG but may be adjusted for feasibility reasons, reflecting difficulties in measuring small quantities of a contaminant, or a lack of available, adequate treatment technologies. The MCL is an enforceable standard and exceedance of the MCL requires water systems to take certain steps, including providing public education, notifying consumers, and adjusting treatment or making structural changes or repairs to come into compliance with the standard for public health protection.

Current or proposed state and federal health thresholds for PFOA and PFOS in drinking water range from 10 ppt to 70 ppt and higher. Although the health thresholds for PFOA and PFOS in drinking water vary, the thresholds cluster at low ppt levels, orders of magnitude lower than thresholds set for many other environmental contaminants. The thresholds are based on adverse health effects, such as developmental effects and cancer risks, and health authorities uniformly acknowledge the serious concerns related to exposure from consuming PFOA and/or PFOS contaminated drinking water. The selection of critical endpoints to use, uncertainty factors to

apply, and estimates of exposure parameters are the major determinants for the variation in the concentrations developed as thresholds. However, none of the federal and state assessments dispute that very serious adverse health effects are associated with exposure to PFOA and PFOS at very low levels of exposure.

The generation of health thresholds by various agencies for PFOA, PFOS, PFNA, PFHxS, and GenX chemicals are **summarized and compared in Tables 4-7** and described in further detail below. Notably, advisories have become more stringent over time as more information becomes available on the exposure to and toxicity of these chemicals.

Table 4: Selected Thresholds for Drinking Water and/or Groundwater- PFOA

Author	Threshold type	Threshold (ppt)	Critical Dose includes UFs (mg/kg/day)	Total UFs	Study Endpoint 2	Drinking water exposure assumptions	Notes
				PFOA			
USEPA	health advisory	70	2×10^{-5}	300	Developmental effects on bone growth and male puberty (Lau, 2006)	0.054 L/kg/day, 90th percentile for lactating women, RSC = 20%	combined with PFOS
Minnesota	guidance value	35	2×10^{-5}	300	Developmental effects on bone growth and male puberty, increased liver weights (Lau, 2006)	modeled for breast- or formula-fed infants, including fetal exposure, RSC = 50%	adopted guidance value - health risk limit - for groundwater
Vermont	health advisory	20	2×10^{-5}	n/a	based on EPA	0.175 L/kg/day for a infants less than 1 year of age, RSC = 20%	combined with PFOS, PFNA, PFHxS, PFHpA (also a ground water enforcement standard); to be adopted as a combined MCL
New Jersey	MCL	14	2×10^{-6}	300	Increased liver weights (Loveless, 2006) + UF for mammary gland effects	0.029 L/kg/day, default adult assumptions, RSC = 20%	proposed; groundwater criteria also proposed at 10 ppt
California	notification level	14	n/a	n/a	Developmental, immunotoxicity, liver toxicity, and cancer	n/a	interim notification levels based on NJ & ATSDR values
ATSDR	environmental media evaluation guide	21	3×10^{-6}	300	Developmental: altered activity, skeletal alterations (Onishchenko, 2011; Koskela, 2016)	0.143 L/kg/day for a infant, RSC = 100%	minimal details provided on calculation of drinking water concentrations from MRL
ATSDR - more protective	estimated MCL	3*	3×10^{-6}	300	Developmental: altered activity, skeletal alterations (Onishchenko, 2011; Koskela, 2016)	**0.175 L/kg/day for a infants less than 1 year of age, RSC = 20%**	*threshold for water based on ATSDR's minimal risk level (for total exposure)
NJ - more protective	estimated MCL	0.1	1×10^{-7}	30	**altered mammary gland development**	**0.175 L/kg/day for a infants less than 1 year of age, RSC = 20%**	using RfD calculated by New Jersey
Protective choices combined	**MCLG (goal)**	0.01	1×10^{-8}	300**	**altered mammary gland development**	**0.175 L/kg/day for a infants less than 1 year of age, RSC = 20%**	****an additional UF of 10, to protect fetuses, infants, children added**

**An additional uncertainty factor of 10 to protect fetuses, infants and children is recommended by the National Academy of Sciences (NAS 1993) for pesticides and as required in the Food Quality Protection Act. 21 U.S.C. §346a(b)(2)(C)(ii)(II).

More protective choices highlighted in bold

Table 5: Selected Thresholds for Drinking Water and/or Groundwater - PFOS

Author	Threshold type	Threshold (ppt)	Critical Dose includes UFs (mg/kg/day)	Total UFs	Study Endpoint 2	Drinking water exposure assumptions	Notes
USEPA	health advisory	70	2×10^{-5}	30	Developmental: decreased pup weight (Leubker, 2005)	0.054 L/kg/day, 90th percentile for lactating women, RSC = 20%	combined with PFOA
Minnesota	guidance value	27	5×10^{-6}	100	Developmental: decreased pup weight (Leubker, 2005)	modeled for breast- or formula-fed infants, including fetal exposure, RSC = 50%	health-based value, provides technical guidance for groundwater
Vermont	health advisory	20	2×10^{-5}	n/a	based on EPA	0.175 L/kg/day for a infants less than 1 year of age, RSC = 20%	combined with PFOS, PFNA, PFHxS, PFHpA (also a ground water enforcement standard); to be adopted as a combined MCL
New Jersey	MCL	13	2×10^{-6}	30	Immunotoxicity: decreased plaque forming response (Dong, 2009)	0.029 L/kg/day, default adult assumptions, RSC = 20%	proposed; groundwater criteria also proposed at 10 ppt
California	notification level	13	n/a	n/a	Developmental, immunotoxicity, liver toxicity, and cancer	n/a	interim notification levels based on NJ & ATSDR values
ATSDR	environmental media evaluation guide	14	2×10^{-6}	300	Developmental: delayed eye opening, decreased pup weight (Leubker, 2005) + UF for immunotoxicity	0.143 L/kg/day for a infant, RSC = 100%	minimal details provided on calculation of drinking water concentrations from MRL
ATSDR - more protective	estimated MCL	2*	2×10^{-6}	30	Developmental: delayed eye opening, decreased pup weight (Leubker, 2005) + UF for immunotoxicity	**0.175 L/kg/day for a infants less than 1 year of age, RSC = 20%**	*threshold for water based on ATSDR's minimal risk level (for total exposure)
NJ - more protective	estimated MCL	2	2×10^{-6}	30	Immunotoxicity (Dong, 2009)	**0.175 L/kg/day for a infants less than 1 year of age, RSC = 20%**	
ATSDR - more protective	estimated MCL	0.02	2×10^{-8}***	30	**Immunotoxicity (Peden-Adams, 2008)**	**0.175 L/kg/day for a infants less than 1 year of age, RSC = 20%**	***critical dose estimated by ATSDR's MRL method
Protective choices combined	**MCLG (goal)**	0.002	2×10^{-9}	300**	**Immunotoxicity**	**0.175 L/kg/day for a infants less than 1 year of age, RSC = 20%**	**an additional UF of 10, to protect fetuses, infants, children added**

**An additional uncertainty factor of 10 to protect fetuses, infants and children is recommended by the National Academy of Sciences (NAS 1993) for pesticides and as required in the Food Quality Protection Act. 21 U.S.C. §346a(b)(2)(C)(ii)(II).

More protective choices highlighted in bold

Table 6: Selected Thresholds for Drinking Water and/or Groundwater - PFNA

Author	Threshold type	Threshold (ppt)	Critical Dose includes UFs (mg/kg/day)	Total UFs	Study Endpoint 2	Drinking water exposure assumptions	Notes
Vermont	health advisory	20	n/a	n/a	based on class similarity to PFOA/PFOS, added to original PFOA/PFOS combined MCL	n/a	combined with PFOS, PFNA, PFHxS, PFHpA (also a ground water enforcement standard); to be adopted as a combined MCL
New Jersey	maximum contaminant level (MCL)	13	5 ng/mL ^	1000	Increased liver weights (Das, 2015)	RSC of 50% for 95th percentile general population	adopted; ^ internal serum level, not external dose
ATSDR	environmental media evaluation guide	21	3×10^{-6}	300	Developmental delays, decreased body weight (Das, 2015)	0.143 L/kg/day for a infant, RSC = 100%	minimal details provided on calculation of drinking water concentrations from MRL
ATSDR - more protective	estimated MCL	3*	3×10^{-6}	300	Developmental delays, decreased body weight (Das, 2015)	**0.175 L/kg/day for a infants less than 1 year of age, RSC = 20%**	*threshold for water based on ATSDR's minimal risk level (for total exposure)
ATSDR - more protective	estimated MCL	2*	2×10^{-6} #	300	Developmental delays, decreased body weight (Das, 2015)	**0.175 L/kg/day for a infants less than 1 year of age, RSC = 20%**	**# Using longer, more representative (men and older women) half-life estimate than ATSDR used (young women)**
Protective choices combined	**MCLG (goal)**	0.2	2×10^{-7}	3000**	Develomental toxicity	**0.175 L/kg/day for a infants less than 1 year of age, RSC = 20%**	****an additional UF of 10, to protect fetuses, infants, children added**
**An additional uncertainty factor of 10 to protect fetuses, infants and children is recommended by the National Academy of Sciences (NAS 1993) for pesticides and as required in the Food Quality Protection Act. 21 U.S.C. §346a(b)(2)(C)(ii)(II).							

More protective choices highlighted in bold

Table 7: Selected Thresholds for Drinking Water and/or Groundwater - PFHxS

Author	Threshold type	Threshold (ppt)	Critical Dose includes UFs (mg/kg/day)	Total UFs	Study Endpoint 2	Drinking water exposure assumptions	Notes
ATSDR	environmental media evaluation guide	140	2×10^{-5}	300	Thyroid follicular cell damage (Butenhoff, 2009; Hoberman & York, 2003)	0.143 L/kg/day for a infant, RSC = 100%	minimal details provided on calculation of drinking water concentrations from MRL
Minnesota	guidance value	27	n/a	n/a	based on class similarity to PFOS	n/a	risk assessment advice - for ground water; use PFOS as surrogate for PFHxS until more data is available
ATSDR - more protective	estimated MCL	23*	2×10^{-5}	300	Thyroid follicular cell damage (Butenhoff, 2009; Hoberman & York, 2003)	**0.175 L/kg/day for a infants less than 1 year of age, RSC = 20%**	*threshold for water based on ATSDR's minimal risk level (for total exposure)
Vermont	health advisory	20	n/a	n/a	based on class similarity to PFOA/PFOS, added to original PFOA/PFOS combined MCL	n/a	combined with PFOS, PFNA, PFHxS, PFHpA (also a ground water enforcement standard); to be adopted as a combined MCL
Protective choices combined	**MCLG (goal)**	2	2×10^{-6}	3000**	developmental and thyroid toxicity	**0.175 L/kg/day for a infants less than 1 year of age, RSC = 20%**	****an additional UF of 10, to protect fetuses, infants, children added**
**An additional uncertainty factor of 10 to protect fetuses, infants and children is recommended by the National Academy of Sciences (NAS 1993) for pesticides and as required in the Food Quality Protection Act. 21 U.S.C. §346a(b)(2)(C)(ii)(II).							

More protective choices highlighted in bold

PFOA

Comparison

In May 2016, the EPA issued a drinking water health advisory for PFOA of 70 ppt.[3] In the case of co-occurrence of PFOA and PFOS, the sum of the concentrations is not to exceed 70 ppt. The EPA applied a combined uncertainty factor of 300 (10 for human variability, 3 for animal to human toxicodynamic differences, 10 for use of a lowest-observed-adverse-effect-level (LOAEL) instead of a no-observed-adverse-effect-level (NOAEL)) on a LOAEL for decreased bone development in the fore and hind limbs, in pup mice (both sexes) and accelerated puberty in male mice[85] to generate a reference dose of 2×10^{-5} mg/kg/day.

The EPA used drinking water intake and body weight parameters for lactating women in the calculation of their lifetime health advisory due to the potential increased susceptibility during this time window. EPA assumed a drinking water ingestion rate of 0.054 L/kg-day, which represents the 90th percentile water ingestion estimate for a lactating woman, based on direct and indirect water intake of community water supply consumers.[86] The EPA also concluded that there are significant sources of PFOA and PFOS exposure other than drinking water ingestion. As information is not available to quantitatively characterize exposure from all of these different sources, the EPA used a default relative source contribution (RSC, discussed in Box 3) of 20% of daily exposure coming from drinking water and 80% from other sources.

Box 3: Uncertainty Factors

The use of uncertainty factors (UFs) has a long history in developing regulatory standards and guidance for chemicals. Uncertainty refers to our inability to know all the adverse effects related to a chemical, often due to incomplete data. When assessing the potential for risks to people, toxicology studies often involve exposing test animals (generally rats and mice) which are used as a surrogate for humans.[82] A thorough review of the development and use of science-based uncertainty factors is provided by the EPA and National Academy of Sciences.[82,83,84]

Risk assessment for public health protection must account not only for what is known about a chemical's adverse effects, but also what is not known about differences between toxic effects in animals compared to humans; children compared to adults; differences in absorption, metabolism and excretion; and other unknown factors. The selection of uncertainty factors is designed to account for the incomplete understanding or availability of studies upon which toxicity is appraised.

The EPA typically uses factors of 1, 3 (an approximation of $\sqrt{10}$), or 10, depending on the level of uncertainty for each factor.

In June 2016, Vermont published a health advisory for combined exposure to PFOA and PFOS not to exceed 20 ppt based on EPA's selected developmental effects.[87] It also applied combined uncertainty factors of 300 using EPA's rationale, however generated a lower health advisory due to selection of drinking water exposure parameters for a breastfeeding or formula-fed infant. Breastfeeding and formula-fed infants is a population that drinks the largest volume per body

weight and is the most vulnerable to the toxic effects of exposure to PFAS. The 95th \percentile Body Weight Adjusted Water Intake Rate for the first year of life based on combined direct and indirect water intake from community water supplies for consumers only is 0.175 L/kg-day.[86,89] Vermont also used a relative source contribution from drinking water of 20%.

In August 2018, Minnesota adopted a guidance value (health risk limit) of 35 ppt for PFOA in groundwater based the same critical health effect as the EPA.[90] Minnesota applied a combined uncertainty factor of 300 including: 10 for human variability, 3 for animal to human toxicodynamic differences, 3 for use of a LOAEL instead of a NOAEL, and 3 for database uncertainty. Like Vermont, Minnesota's more protective guidance values are due to the use of drinking water exposure estimates based on infants, but also the accounting of a pre-existing body burden through placental transfer (Minnesota calculated a placental transfer factor of 87% based on average cord to maternal serum concentration ratios). Minnesota estimated breastmilk concentrations by applying a breast milk transfer factor of 5.2%, which is an estimate of the amount of PFOA that is transferred from a mother's serum to her breastmilk. Minnesota published this transgenerational toxicokinetic model for PFOA in January 2019.[91] As serum levels for PFOA are approximately 100 times the concentration in a person's drinking water, a breast milk transfer factor of 5.2% would result in breast milk concentrations approximately 5 times higher than in the drinking water. However, Minnesota also used a less conservative relative source contribution of 50%, resulting in drinking water values approximately half of EPA's.

In March 2017, New Jersey Drinking Water Quality Institute derived a recommended MCL in water for PFOA of 14 ppt based on increased liver weight in rodent studies.[92] Previously in 2007, New Jersey issued a preliminary drinking water guidance level for PFOA of 40 ppt, which was

Box 4: Relative Source Contribution

One important factor that should be considered when generating a health-protective drinking water limit for a contaminant is the percentage of the total allowable dose (RfD or MRL) that comes from water, versus other exposure routes. The portion of a total daily dose that comes from a specific exposure route (such as drinking water) is represented by a relative source contribution (RSC).

EPA suggest RSC's for drinking water range from 0.2 to 0.8 (20% to 80% coming from drinking water). In the absence of complete data, the EPA's default RSC value is 0.2.

- Studies demonstrate that there are many other sources of PFAS exposure, including food and consumer products, though the relative contribution from each source is still poorly understood.
- For children, researchers estimated exposure to PFOA and PFOS from hand-to-mouth transfer from treated carpets to be 40–60% of the total uptake in infants, toddlers, and children.[88]
- Therefore, the RSC from drinking water for this vulnerable population should not exceed 0.4 (40%). Importantly, as we do not understand all the exposure sources for this population, the default value of 0.2 is the most protective and recommended.

revised in 2016 to a more stringent level of 14 ppt based on chronic exposure from drinking water for cancer and non-cancer

endpoints. Non-cancer endpoints were derived based on increased liver weight with applied uncertainty factors of 300 (10 for human variability, 3 for animal to human toxicodynamic differences, and 10 to protect against more sensitive toxicological effects). The more protective health threshold is mainly due to the use of an additional uncertainty factor of 10 to protect against more sensitive toxicological effects (delayed mammary gland development), which is explained by New Jersey in the following excerpt:

> *"Delayed mammary gland development from perinatal exposure is the most sensitive systemic endpoint for PFOA with data appropriate for dose-response modeling. It is a well-established toxicological effect of PFOA that is considered to be adverse and relevant to humans for the purposes of risk assessment.*
>
> *To the knowledge of the Health Effects Subcommittee, an RfD for delayed mammary gland development has not previously been used as the primary basis for health-based drinking water concentrations or other human health criteria for environmental contaminants. Because the use of this endpoint as the basis for human health criteria is a currently developing topic, the Health Effects Subcommittee decided not to recommend a Health-based MCL with the RfD for delayed mammary gland development as its primary basis. However, the occurrence of this and other effects at doses far below those that cause increased relative liver weight (the endpoint used as the primary basis for the recommended Health-based MCL) clearly requires application of an uncertainty factor to protect for these more sensitive effects."*[92]

The recommended MCL based on cancer endpoints was derived from testicular tumor data from chronic dietary exposure in rats and also resulted in a MCL of 14 ppt. New Jersey used values for adult drinking water exposure (0.029 L/kg-day) and a relative source contribution of 20%. In January 2019, New Jersey announced a proposed specific ground water quality criteria based on the same reasoning for its proposed MCL, however, since interim ground water criteria are rounded to one significant figure in New Jersey, the proposed criteria for PFOA is 10 ppt (0.01 µg/L).[93] In April 2019, New Jersey announced a rule proposal to adopt the New Jersey Drinking Water Quality Institute's recommended MCL of 14 ppt.[94]

In June 2018, ATSDR generated a MRL for PFOA.[5] A MRL exposure scenario of 3×10^{-6} mg/kg/day was based on a LOAEL of 0.000821 mg/kg/day for neurodevelopmental and skeletal effects in mice[95,96] with an uncertainty factor of 300 (10 for use of a LOAEL instead of a NOAEL, 3 for extrapolation from animals to humans with dosimetry adjustments, and 10 for human variability). A MCLG based on ATSDR's MRL for PFOA would be 11 ppt, using the same assumptions and parameters the EPA used for calculating their health advisory (based on lactating mothers), or 3 ppt, using drinking water exposure assumptions based on breastfeeding and formula-fed infants (see Appendix C for MCLG calculations).

Box 5: ATSDR's Environmental Media Evaluation Guides

In November 2018 ATSDR posted on its website a webpage entitled "ATSDR's Minimal Risk Levels (MRLs) and Environmental Media Evaluation Guides (EMEGs) for PFAS."[97] ATSDR provides the body weights and drinking water intake rates it would use for an average adult or child (under one year) and lists what the corresponding drinking water concentrations would be if converted from ATSDR's proposed MRLs: for an adult 78 ppt for PFOA, 52 ppt for PFOS, 517 ppt for PFHxS, and 78 ppt for PFNA; and for a child, 21 ppt for PFOA, 14 ppt for PFOS, 140 ppt for PFHxS, and 21 ppt for PFNA. ATSDR does not provide any details as to how it derived the values presented on the webpage. However, based on the information ATSDR did provide, drinking water values, body weight and intake rates, we were able to calculate the relative source contribution used by ATSDR. According to our calculations, ATSDR used a relative source contribution of 1, which assumes that 100% of a person's exposure comes from drinking water, not 20% or 50%, as all other agencies have adopted (see Appendix E for calculations).

Studies demonstrate that there are many other sources of PFAS exposure, including food and consumer products. For example, NHANES demonstrates that greater than 95 percent of Americans have detectable PFAS in their bodies, however many of these Americans do not have detectable PFAS in their drinking water. Therefore, the assumption that a person would be only exposed to PFAS from drinking water is not supported by the scientific literature.

In June 2018, at the request of the California State Water Resources Control Board, the California Office of Environmental Health Hazard Assessment (OEHHA) recommended an interim notification level of 14 ppt for PFOA in drinking water.[98] The notification level is based on developmental toxicity, immunotoxicity, liver toxicity, and cancer. OEHHA reviewed currently available health-based advisory levels and standards, including the documents and process used by New Jersey to derive its water advisory levels. OEHHA found New Jersey's process to be both rigorous and sufficient for establishing an interim notification level for PFOA. They note that this level is similar to that derived by ATSDR, whose minimal risk level equates to a drinking water advisory level of 13 ppt for PFOA, as calculated by OEHHA. OEHHA is currently completing its own derivation of a recommended drinking water notification level for PFOA.

In December 2018, the New York Drinking Water Quality Council recommended that the New York Department of Health adopt MCLs of 10 ppt each for PFOA and PFOS.[99] Although no supporting documentation is currently available in relation to this recommendation, the council notes that these levels "take into consideration the national adult population's "body burden," or the fact that all adults already have some level of exposure to these and other related chemicals."

Analysis

Although altered mammary gland development is the most sensitive endpoint for PFOA exposure,[63,64,65] both the EPA and ATSDR did not consider altered mammary gland development as the critical effect in their toxicity assessment of PFOA.

The EPA excluded the results of the mammary gland findings based on the agency's view that the effects were of "unknown biological significance," concern for variability in the sensitivity for these effects amongst mice strains,[65] the fact that the mode of action for these effects are unknown, and that mammary gland effects had not been previously used for risk assessment.[3] Similarly, ATSDR classified altered mammary gland development as not adverse due to uncertainty around the effect's biological significance.

However, experts in the field have concluded that changes in mammary gland growth and differentiation, including changes in developmental timing, are a health concern.[100] Studies have shown a relationship between altered breast development, lactational deficits and breast cancer (discussed further in Box 6). Therefore, unless it can be shown that this relationship does not exist for PFOA, altered mammary gland growth and differentiation should be considered an adverse health effect of PFOA exposure and the critical endpoint for PFOA.

Box 6: "Is altered mammary development an adverse effect?"

Both the EPA and ATSDR did not consider altered mammary gland development as the critical effect in their toxicity assessment of PFOA. However, in a 2009 a workshop of experts in mammary gland biology and risk assessment came to the consensus that changes in mammary gland growth and differentiation, including changes in developmental timing, are a health concern.[100] Altered mammary gland development may lead to difficulty in breastfeeding and/or an increase in susceptibility to breast cancer later in life.[101]

Only one animal study has assessed the effects of PFOA exposure on mammary gland growth and differentiation for multiple generations.[64] The authors saw striking morphological abnormalities in the lactating glands of dams (mothers) chronically exposed to environmentally relevant levels of PFOA; however, no effects on body weight of their pups were seen. It is possible that compensatory behavior, such as increased number of nursing events per day or longer nursing duration per event masked a decreased potential in milk production by the dams, however the authors did not evaluate these endpoints in the study. It is also possible that PFOA exposure could increase time to peak milk output through the reduction in number and density of alveoli available to produce milk.

For human mothers, low-level functional effects on lactation that cause even a short delay in substantial milk output might result in cessation in breastfeeding before the recommended time-frame. This is supported by a cohort study that found an inverse correlation between levels of maternal serum PFOA and duration of breastfeeding.[102]

Early life exposures to factors that disrupt development may influence susceptibility to carcinogens later in life. For example, hormone disruption is an important determinant of breast cancer susceptibility in humans and rodents.[103] Proliferating and undifferentiated

structures, such as terminal end buds, display elevated DNA synthesis compared to other mammary gland structures; which is why terminal end buds are considered the most vulnerable mammary gland target structure of carcinogen exposure.[104] Delays in mammary gland development would result in a prolonged window of increased vulnerability to carcinogens. In humans, perturbations to the timing of menarche is linked to breast cancer.[105] This further raises the concern that changes in patterns of breast development in U.S. girls could be contributing to an increased risk of breast cancer or other adult diseases later in life.[106] However, an increase in susceptibility to breast cancer later in life was not explored in the multigeneration mammary gland development study.[64]

In general, "*developmental delay can reflect an overall detrimental effect of chemical exposure that lead to growth and developmental deficit in the offspring*."[26]

New Jersey did classify delayed mammary gland development as adverse, though, it stopped short of using it to generate their MCL for PFOA. However, New Jersey did calculate a reference dose, 1.1×10^{-7} mg/kg/day, based on delayed mammary gland development. If this more protective reference dose were used, the MCLG for PFOA would be less than 1 ppt, regardless of which population the drinking water parameters are based on (see Appendix D for calculation). The MCLG would be lowered even further below 1 ppt if an additional uncertainty factor of 10 was applied to ensure adequate protection of fetuses, infants and children, as recommended by the National Academy of Sciences and as required in the Food Quality Protection Act (see Box 7).

PFOS

Comparison

In May 2016, the EPA issued a drinking water health advisory for PFOS of 70 ppt,[28] with the sum of PFOA and PFOS concentrations not to exceed 70 ppt. The EPA applied combined uncertainty factors of 30 (10 for human variability, 3 for animal to human toxicodynamic differences) on a NOAEL of decreased pup weight in a two-generation rat study.[107] As with PFOA, the EPA used drinking water intake and body weight parameters for lactating women and a relative source contribution of 20%.

As mentioned above, in June 2016 Vermont published a health advisory for total concentrations of PFOA and PFOS in drinking water at 20 ppt based on EPA's selected developmental effects and drinking water exposure parameters for breastfeeding or formula-fed infants.[87]

In May 2017, Minnesota proposed a groundwater guidance value (health-based value) of 27 ppt for PFOS based the same critical endpoints as the EPA.[108] However, Minnesota applied a larger combined uncertainty factor than the EPA. Minnesota applied a total uncertainty factor of 100

including: 3 for animal to human toxicodynamic differences, 10 for human variability and an additional 3 for database uncertainty (based on the need for additional immunotoxicity data). Minnesota accounted for a pre-existing body burden through a placental transfer factor of 46%, used drinking water exposure estimates based on infants with an estimated breast milk transfer factor of 1.3%, and used a relative source contribution of 50%.

In June 2018, New Jersey derived a recommended MCL in water for PFOS of 13 ppt for chronic exposure from drinking water based on immune suppression in mice,[110] an endpoint that is significantly more sensitive than the endpoint used by EPA.[111] New Jersey applied a combined uncertainty factor of 30 (10 for human variability and 3 for animal to human toxicodynamic differences) to an internal NOAEL of 674 ng/ml of PFOS in animal serum to generate an human serum target level. This target level was then multiplied by a clearance factor to arrive at a reference dose of 1.8×10^{-6} mg/kg/day. New Jersey used values for adult drinking water exposure and a relative source contribution of 20%. Like for PFOA, in January 2019, New Jersey announced a proposed specific ground water quality criteria based on the same reasoning for its proposed MCL, however, since interim ground water criteria are rounded to one significant figure in New Jersey, the proposed criteria for PFOS is 10 ppt (0.01 µg/L).[112] In April 2019, New Jersey announced a rule proposal to adopt the New Jersey Drinking Water Quality Institute's recommended MCL of 13 ppt.[94]

Box 7: Additional Protection for Fetuses, Infants, and Children

The National Academy of Sciences has recommended the use of an additional uncertainty factor of 10 to ensure protection of fetuses, infants and children who often are not sufficiently protected from toxic chemicals such as pesticides by the traditional intraspecies (human variability) uncertainty factor.[109] Congress adopted this requirement in the Food Quality Protection Act for pesticides in foods. 21 U.S.C. 346a(b)(2)(C)(ii)(II)

Considering the many health effects linked to PFAS that affect this vulnerable population and the substantial data gaps on exposure and toxicity of these compounds in complex mixtures, we recommend the use of this uncertainty factor when deriving health-protective thresholds for PFAS.

In June 2018, ATSDR generated a MRL for PFOS based on delayed eye opening and decreased pup weight[107] in rats.[5] A MRL exposure scenario of 2×10^{-6} mg/kg/day was based on a NOAEL of 0.000515 mg/kg/day using an uncertainty factor of 300 (10 for concern that immunotoxicity may be a more sensitive endpoint than developmental toxicity, 3 for extrapolation from animals to humans with dosimetry adjustments, and 10 for human variability). A MCLG based on ATSDR's MRL for PFOS would be 7 ppt, using EPA's drinking water exposure assumptions, or 2 ppt, using drinking water exposure assumptions based on breastfeeding and formula-fed infants (see Appendix C for MCLG calculations).

In June 2018, at the request of the California State Water Resources Control Board, OEHHA recommended an interim notification level of 13 ppt for PFOS in drinking water.[98] The notification level is based on the same analysis performed for PFOA, described above. OEHHA

notes that this level is similar to that derived by ATSDR, whose minimal risk level equates to a drinking water advisory level of 9 ppt for PFOS, as calculated by OEHHA. OEHHA is currently completing its own derivation of recommended drinking water notification levels for PFOS.

As noted above, a MCL of 10 ppt each for PFOA and PFOS were recommended by the New York Drinking Water Quality Council.[99]

Analysis

Immunotoxicity is currently the most sensitive health endpoint known for PFOS exposure. As documented in the ATSDR's profile, both animal and epidemiology studies provide strong evidence linking PFOS exposure to immunotoxic effects (decreased antibody response to vaccines in humans, decreased host resistance to viruses, and suppressed immune response to antigens in animals). The National Toxicology Program also reviewed the immunotoxicity data on PFOA and PFOS in 2016 and concluded that both are presumed to constitute immune hazards to humans[66] (discussed further in Box 1).

Again, although immunotoxicity is the most sensitive endpoint for PFOS exposure, the EPA excluded immune system effects based on uncertainties related to mode of action, variation in dose effects between studies, differences in sensitivity between males and females, and lack of a *"demonstrated clinically recognizable increased risk of infectious diseases as a consequence of a diminished vaccine response."*[28]

ATSDR states concern that immunotoxicity is a more sensitive endpoint than developmental toxicity; however, it stops short of deriving a MRL from this endpoint. Instead, ATSDR posits that an additional modifying, or uncertainty factor of 10 is sufficient to address the doses where immunotoxic effects have been observed. However, this value is only consistent with the immunotoxicity study with the highest LOAEL.[113] The other immunotoxicity studies all result in MRLs approximately 2.5-100 times lower than those currently calculated (see Appendix A for MRL derivations). If a MCLG were generated from the most sensitive health endpoint (immunotoxicity) and from the study with the lowest LOAEL, as is normally done by ATSDR, it would be less than 1 ppt (see Appendix C for MCLG calculations). The MCLG would be lowered even further below 1 ppt if an additional uncertainty factor of 10 was applied to ensure adequate protection of fetuses, infants and children, as recommended by the National Academy of Sciences and as required in the Food Quality Protection Act. Additionally, a MCLG based on benchmark dose calculations for immunotoxicity in children would also be approximately 1 ppt.[114]

New Jersey did select immunotoxicity as its critical health effect, resulting in the lowest generated reference dose for PFOS. However, the use of adult drinking water assumptions results

in a higher proposed MCL than what we have calculated using estimated MRLs based on immunotoxicity (see Appendix A and C).[l]

PFNA

Comparison

In July 2015, New Jersey proposed a MCL for PFNA of 13 ppt for chronic exposure from drinking water based on increased liver weight in rodents[115] with a total uncertainty factor of 1000 (10 for human variability and 3 for animal to human toxicodynamic differences, 10 for less than chronic exposure duration, and 3 for database uncertainty).[116] Extrapolation from animal to human dose levels were made on the basis of internal serum levels rather than administered dose and were based on an estimated 200:1 ratio between PFNA serum levels and drinking water concentration in humans. A chemical-specific relative source contribution of 50% was developed using the "subtraction" approach. A subtraction approach is used when other sources of exposure (air, food, consumer product, etc.) can be considered background, and can thus be subtracted from the total dose to arrive at the allowable limit or dose from drinking water.[117] New Jersey based their calculations on the 2011-12 NHANES biomonitoring data for the 95th percentile PFNA serum level in the U.S. general population. This MCL was adopted into law in September 2018.[118] As of January 2019, this is the only finalized, enforceable drinking water limit for a PFAS chemical. New Jersey also has a specific ground water quality criteria for PFNA set at 13 ppt, based on its MCL for PFNA.

In July 2018, Vermont updated its drinking water health advisory level to include (based on class similarity) PFOA, PFOS, PFHxS, PFHpA, and PFNA for a combined total not to exceed 20 ppt.[119] Based on its health advisory, Vermont updated its enforceable groundwater standard to include all 5 PFAS at a combined 20 ppt.[120] In January 2019, Vermont announced it will initiate the process of adopting its health advisory for these five PFAS as an enforceable MCL.[121]

For PFNA, ATSDR based its assessment on decreased body weight and developmental delays in mice pups.[5,115] A MRL exposure scenario of 3×10^{-6} mg/kg/day was based on a NOAEL of 0.001 mg/kg/day using an uncertainty factor of 300 (10 for database limitations, 3 for extrapolation from animals to humans with dosimetry adjustments, and 10 for human variability).[5] A MCLG based on ATSDR's MRL for PFNA would be 11 ppt, using EPA's drinking water exposure assumptions for PFOA and PFOS, or 3 ppt, using drinking water exposure assumptions based on breastfeeding and formula-fed infants (see Appendix C for MCLG calculations).

Analysis

[l] Additionally, there are a couple of differences between New Jersey's and ATSDR's approach to generating a RfD/MRL, including the use of slightly different clearance factors and ATSDR's use of the trapezoid rule to estimate a time weighted average serum concentration for the animal point of departure.

Importantly, ATSDR underestimated the half-life of PFNA in humans. In the paper used to estimate the half-life of PFNA,[122] two different half-life values were derived: one of 900 days for young women and one of 1,570 days for everyone else. Younger women of childbearing age have additional excretion pathways for PFAS than other populations, including through breastmilk and menstruation. ATSDR provided no rationale for why the shorter half-life was selected. The longer half-life represents a larger population with minimal excretion pathways for PFNA and would result in a more protective MRL value. Importantly, New Jersey's 200:1 estimated ratio between PFNA serum levels and drinking water concentration in humans is based on the longer, more representative half-life of 1,570 days.[116] When the longer half-life is used, the resulting MRL is 2×10^{-6} mg/kg/day (see Appendix B for MRL calculations). A MCLG based on this more protective MRL for PFNA would be 7 ppt, using EPA's drinking water exposure assumptions for PFOA and PFOS, or 2 ppt, using drinking water exposure assumptions based on breastfeeding and formula-fed infants (see Appendix C for MCLG calculations). The MCLG would be below 1 ppt if an additional uncertainty factor of 10 was applied to ensure adequate protection of fetuses, infants and children, as recommended by the National Academy of Sciences and as required in the Food Quality Protection Act.

PFHxS

Comparison

As mentioned above, Vermont's drinking water health advisory and its groundwater standard now includes PFOA, PFOS, PFHxS, PFHpA, and PFNA for a combined total not to exceed 20 ppt and Vermont is now in the process of adopting the advisory as a MCL. [119,121]

Minnesota recently recommended using PFOS as surrogate for PFHxS until more data is available, setting a guidance value (risk assessment advice) of 27 ppt for PFHxS.[123]

For PFHxS, ATSDR based its assessment on thyroid follicular cell damage in rats.[124,125] A MRL exposure scenario of 2×10^{-5} mg/kg/day was based on a NOAEL of 0.0047 mg/kg/day using an uncertainty factor of 300 (10 for database limitations, 3 for extrapolation from animals to humans with dosimetry adjustments, and 10 for human variability).[5] A MCLG based on ATSDR's MRL for PFHxS would be 74 ppt, using EPA's drinking water exposure assumptions for PFOA and PFOS, or 23 ppt, using drinking water exposure assumptions based on breastfeeding and formula-fed infants (see Appendix C for MCLG calculations). The MCLG would be lowered to 2 ppt if an additional uncertainty factor of 10 was applied to ensure adequate protection of fetuses, infants and children, as recommended by the National Academy of Sciences and as required in the Food Quality Protection Act.

GenX

Comparison

In 2017, North Carolina set a non-enforceable health goal for the GenX chemical, HFPO dimer acid, to 140 ppt in drinking water.[126] The health goal was based on a reference dose of 1×10^{-4} mg/kg/day, generated from a NOAEL for liver toxicity in mice (single-cell necrosis in hepatocytes and correlative increases in liver enzymes) with combined uncertainty factor of 1000 (10 for human variability, 10 for animal to human toxicodynamic differences, 10 for extrapolating from subchronic to chronic exposure duration). According to North Carolina Department of Human Health Services, their health goal for GenX is for "the most vulnerable population – i.e. bottle-fed infants, the population that drinks the largest volume of water per body weight."[126] The state used drinking water exposure assumptions based on bottle-fed infants (0.141 L/kg/day) and a relative source contribution of 20%.

In November 2018, the EPA proposed a chronic reference dose of 8×10^{-5} mg/kg/day for two GenX chemicals, HFPO dimer acid and its ammonium salt.[23] The EPA applied a combined uncertainty factor of 300 (10 for human variability, 3 for animal to human toxicodynamic differences, 3 for database limitations, and 3 for extrapolation from subchronic to chronic exposure duration) on a NOAEL for single-cell necrosis in livers of male mice from a DuPont study.[127] The EPA did not provide drinking water values in their toxicity assessment of GenX chemicals, however, using EPA's drinking water exposure assumptions for PFOA and PFOS, a MCLG would be 296 ppt, or 91 ppt using drinking water exposure assumptions based on breastfeeding and formula-fed infants (see Appendix F for calculations).

Analysis

The EPA notes that there are the following database deficiencies for GenX chemicals: no human data from epidemiological studies, limited testing for developmental toxicity and immunological responses, lack of a full two-generational reproductive toxicity study, and lack of a chronic study in mice (which appear to be more sensitive to GenX than rats). Additionally, of the studies considered for the development of the reference dose, only two were published in a peer-reviewed journal. These are significant limitations in the toxicity data available for GenX, and as such, an uncertainty factor of 3 is unlikely to be sufficient. Importantly, North Carolina does not apply an uncertainty factor for database limitations at all. In comparison, ATSDR used an uncertainty factor of 10 for database limitations for PFNA and PFHxS due to a lack of or limited testing of developmental and immunological effects, which ATSDR states are two of the most sensitive PFAS endpoints.[5]

To extrapolate from animal to human dose, the EPA used the Body Weight$^{3/4}$ allometric scaling approach, which is based on body surface area and basal metabolic rate in adults. This approach does not account for differences in toxicokinetics between animals and humans, which for PFAS are often vastly different. The Netherland's National Institute for Public Health and the Environment (RIVM) determined that although the elimination rates for GenX are faster than PFOA in animal models, without data in humans, it is not possible to make assumptions on the toxicokinetics of GenX chemicals in humans.[128] Due to the uncertainty from lack of human toxicokinetic data on GenX chemicals, RIVM calculated and applied an additional uncertainty factor to account for the potential kinetic difference between animals and humans.

This additional toxicokinetic factor used by RIVM is based on the difference in half-lives between cynomolgus monkeys and humans for PFOA. A half-life ratio was calculated using a half-life of 1378 days in humans[129] and of 20.9 days in male cynomolgus monkeys[130] resulting in an additional toxicokinetic factor of 66 (1378 / 20.9). This additional uncertainty factor to account for the potential kinetic difference between animals and humans is an example of an alternative approach to extrapolating animal doses to human doses for PFAS like GenX that do not yet have human toxicokinetic data. Considering the limitations of EPA's scaling approach, an uncertainty factor of 3 to account for interspecies toxicokinetic differences is likely to be insufficient.

Finally, North Carolina used an uncertainty factor of 10 to extrapolate from subchronic to chronic exposure duration, compared to the EPA's use of an uncertainty factor of 3. The EPA states that effects for the subchronic study it selected (performed in mice) are consistent with effects seen for the single chronic study available. However, the chronic study is in rats, a species that the EPA acknowledges is much less sensitive to the effects of GenX than mice. Therefore, this logic is not supported by the EPA's own findings.

If uncertainty factors that properly reflected the deficiencies in toxicity data (database, sub-chronic to chronic, children's vulnerability, human variability, animal to human differences) were used, the combined uncertainty factor could be as high as 100,000, which would result in a MCLG of less than 1 ppt for GenX chemicals (see Appendix F for calculations). This highlights the current considerable level of uncertainty in determining a safe level of exposure for GenX chemicals.

Box 8: Epidemiological Data in Risk Assessment

To generate accurate and relevant health thresholds, all toxicological information available should be evaluated. Epidemiological studies provide direct information on effects of chemical exposures in people. However, epidemiological data from human health studies are not always utilized. Human studies should be used in conjunction with animal studies to best inform risk assessment.

Use of epidemiology data in risk assessment is not a new approach, for example, epidemiological data was used quantitatively in an EPA evaluation of risk for methylmercury, as recommended by the National Academy of Sciences.[131] The EPA based the oral reference dose on lasting neurological effects in children exposed during early life.[132] In 2018, the European Food Safety Authority (EFSA) derived health-based guidance values for PFOA and PFOS based on epidemiological studies.[133] EFSA used benchmark modelling of serum levels to generate daily tolerable intakes (similar to a reference dose, a daily or weekly tolerable intake is an estimate of the amount of a substance in food or drinking water which can be consumed over a lifetime without presenting an appreciable risk to health) of 0.8 ng/kg/bw for PFOA based on increased serum cholesterol in adults and 1.8 ng/kg/bw for PFOS based on increased serum cholesterol in adults and decrease in antibody response at vaccination in

children. These values are approximately 10-20 times stricter than the reference dose generated by the EPA, 20 ng/kg/bw.

Another powerful way of using epidemiological data is demonstrated by the Michigan PFAS Science Advisory Panel's use of epidemiology data to evaluate the EPA's health advisory level of 70 ppt for PFOA and PFOS.[26] The Panel estimated that drinking water with 70 ppt of PFOA over several years would result in serum concentrations around 10,000 ppt in adults and 16,500 ppt among those with higher consumption (such as nursing mother and infants). For adults, the Panel used a model[134] to estimate that 8,000 ppt would result from drinking water that contained 70 ppt PFOA, which is in addition to 2,000 ppt from background exposures (as estimated from NHANES national biomonitoring data).

A PFOA serum concentration of 10,000 ppt would represent the first quartile in the C8 study (contaminated community) and the top bracket in epidemiology studies of the general population. Many health effects have been seen in epidemiology studies at these blood serum concentrations. The Panel concludes, ***"…this evaluation places those with chronic exposure to 70 ppt or higher levels of PFOA in their drinking water well within the range at which credible associations with health effects were found by the C8 Science Panel studies."***[26] In other words, human data shows that the EPA's health advisory for PFOA and PFOS is not health protective.

Conclusions

Differences in the selection of critical endpoints and the application of uncertainty factors have led to the generation of different health thresholds for PFOA, PFOS, PFNA, PFHxS and GenX chemicals. Another source of variation in health thresholds comes from differences in exposure assumptions, such as drinking water intake rate, body weight and relative source contribution from drinking water. For example, the exposure levels of an average male adult versus a lactating mother versus a breastfeeding or formula-fed infant vary greatly. For an in-depth discussion of the main sources of variation in current health thresholds for PFOA and PFOS, including "*managing scientific uncertainty, technical decisions and capacity, and social, political, and economic influences from involved stakeholders*," see recently published article by researchers from Whitman College, Silent Spring Institute, and Northeastern University.[135]

Evidence shows that PFAS exposure poses a high risk to fetuses, infants, children and pregnant women. There is particular risk for sensitive members of the population from chemicals of such persistence and clear adverse effects at very low levels of exposure. Decisions made when developing a health threshold, such as evaluation of data gaps, the selection of uncertainty factors, and the choice of exposure parameters to use, should be made to be protective of the most vulnerable populations, particularly developing fetuses, infants, and children.[136]

Taking into consideration the above information, for risk assessment we recommend: 1) the use of the most sensitive health endpoint, regardless of whether the endpoint has been used in a risk assessment previously; 2) the use of drinking water exposure parameters that protect vulnerable populations, particularly breastfeeding or formula-fed infants; 3) the use of an additional uncertainty factor of 10 to protect fetuses, infants and children as recommended by the National Academy of Sciences[109] and as required in the Food Quality Protection Act (see Box 7); 4) the use of both human and animal data when assessing the toxicity of a chemical, or group of chemicals (see Box 8); and 5) the examination of possible additive or synergistic effects from exposure to mixtures of similar chemicals that target the same biological systems (see Box 9).

Box 9: Real-World Exposures

Fundamentally, exposures to PFAS occur as mixtures. With individual PFAS targeting many of the same biological systems, concurrent exposures to multiple PFAS likely have additive or synergistic effects. Therefore, traditional toxicity assessments that assume exposures to a chemical occur in isolation could be significantly underestimating the real-world effects of PFAS.

PART V: DETECTION/ANALYTICAL METHODS AND TREATMENT TECHNOLOGIES

As discussed in this section, PFOA, PFOS, PFNA, PFHxS, and GenX chemicals can be reliably quantified and treated to low levels, therefore, it is feasible for the state to establish strict MCLs for such PFAS. At present, there is no single methodology for isolating, identifying, and quantifying all PFAS in drinking water. Until total PFAS can be reliably quantified, the state should establish a treatment technique for the class of PFAS chemicals.

Analytical Methods for Detecting and Measuring Concentrations of PFAS

When a laboratory measures an chemical, the laboratory often reports the method detection limit (MDL) and the method reporting limit (also sometimes called the minimum reporting limit or limit of quantification).[137] The MDL is the minimum concentration of a substance that can be measured and reported with 99% confidence that the chemical is present in a concentration greater than zero; any concentration measured below the minimum detection limit is considered non-detect. The method reporting limit is the lowest chemical concentration that meets data quality objectives that are developed based on the intended use of this method; concentrations

above this limit are considered quantified with statistical rigor. A laboratory may also report the single laboratory lowest concentration minimum reporting limit (LCMRL), a value between the method detection and reporting limits, which is the "lowest true concentration for which the future recovery is predicted to fall, with high confidence (99%), between 50 and 150% recovery."[137] Action levels, such as a MCL, should be set at or above the method reporting limit.

Figure 3: Detection, Quantification and Reporting Limits

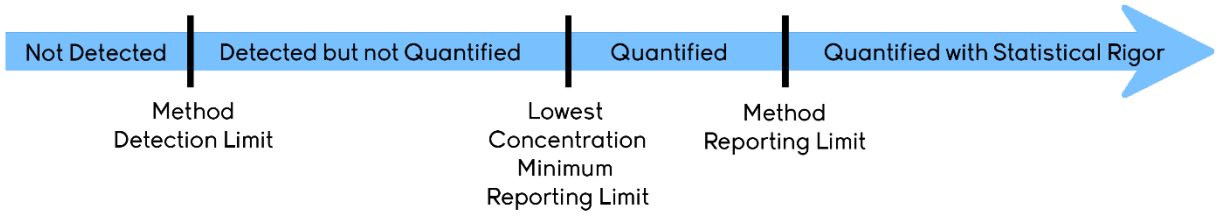

Figure 3 shows the relationship between the types of detection and quantification limits for laboratory testing. The method detection limit (MDL) is the lowest concentration that can be detected. The lowest concentration minimum reporting limit (LCMRL) is the lowest concentration that can be quantified and the method reporting limit, also known as the limit of quantification (LOQ), is the lowest concentration that can be reliably quantified and meets data quality objectives.[m]

The detection sensitivity of PFAS varies depending on the method of analysis used to quantify the results and the laboratory conducting the analysis. Historically, laboratories have used a liquid chromatography-tandem mass spectrometry method such as EPA Method 537, or a modified version,[138] with quantified reporting limits in the low single-digit ppt range. EPA Method 537, updated in November 2018 and referred to as Method 537.1, now includes detection limits ranging from 0.53 to 2.8 ppt for the 18 PFAS compounds included in the updated testing method.[139] In studies where an alternative method is used, researchers were able to achieve reporting limits below 1 ppt for PFOS, PFNA, and PFHxS. In Europe and Australia, reporting limits of less than 1 ppt for PFOA have been achieved.[140] Prominent laboratories that provide analytical detection services for PFAS have already established reporting limits of 2 ppt for at least 17 PFAS compounds including PFOA, PFOS, PFNA, and PFHxS, and a reporting limit of 5 ppt for GenX, using EPA Method 537 or Method 537.1; and one company confirms a 2 ppt reporting limit for the additional PFAS compounds in the updated EPA Method 537.1 will be achievable, except for GenX, which would typically be reported at 5 ppt, but can be lowered to a 2 ppt with an alternative analytical method.[141]

EPA Method 537.1

EPA Method 537.1 is a solid phase extraction (SPE) liquid chromatography/tandem mass spectrometry (LC/MS/MS) method for the determination of selected PFAS in drinking water.[139] This method can be used to quantify 18 PFAS compounds including PFOA, PFOS, PFNA,

[m] Adapted from https://acwi.gov/monitoring/webinars/mpsl_qa_services_intro_rls_012517.pdf

PFHxS, and a GenX chemical, HFPO dimer acid. The EPA states that detection limits range from 0.53 to 1.9 ppt and single laboratory LCMRLs range from 0.53 – 2.7 ppt for PFOA, PFOS, PFNA, PFHxS, and HFPO-DA. We recommend that, at minimum, the state require the use EPA Method 537.1 with method reporting limits of 2 ppt, 5 ppt for GenX, when testing for PFAS in drinking water.

Table 8: Method Reporting Limits from three sources that use EPA Method 537 and/or 537.1

Contaminant	CAS Registry Number	Method Reporting Limits (ppt)			
		EPA 537.1[n]	UCMR3[o]	Eaton Analytics[p]	Vista Analytical[q]
PFOS	1763-23-1	2.7	40	2	2
PFOA	335-67-1	0.82	20	2	2
PFNA	375-95-1	0.83	20	2	2
PFHxS	355-46-4	2.4	30	2	2
HFPO-DA	13252-13-6	4.3	Not available	5	Not available

Table 8 shows the method reporting limits documented for the new EPA Method 537.1, the method reporting limits under the unregulated contaminant monitoring rule 3 (UCMR3) for EPA Method 537, and the method reporting limits reported by two laboratories that conduct testing of PFAS compounds, Eaton Analytical and Vista Analytical.

Alternative Analytical Methods

A Water Research Foundation report published in 2016[142] evaluated the ability of a wide spectrum of full-scale water treatment techniques to remove PFASs from contaminated raw water or potable reuse sources. One of the studies in the report was conducted at Southern Nevada Water Authority's Research and Development laboratory where researchers used a methodology that was able to achieve reporting limits below 1 ppt for several PFAS compounds, including PFOS, PFNA and PFHxS. The method used by researchers in this study is described as "*an analysis…via liquid-chromatography tandem mass-spectrometry (LC-MS/MS) using a previously reported method,[143] adapted and expanded to include all analytes of interest"*. This method achieved minimum reporting limits below 1 ppt for PFOS, PFNA, and PFHxS.

[n] LCMR from https://cfpub.epa.gov/si/si_public_file_download.cfm?p_download_id=537290&Lab=NERL

[o] https://www.epa.gov/dwucmr/third-unregulated-contaminant-monitoring-rule

[p] http://greensciencepolicy.org/wp-content/uploads/2017/12/Andy_Eaton_UCMR3_PFAS_data.pdf

[q] http://www.vista-analytical.com/documents/Vista-PFAS-rev3.pdf

Table 9: Minimum Reporting Levels Using Southern Nevada Water Authority Method

Contaminant	CAS Registry Number	Minimum Reporting Level (ppt)
PFOS	1763-23-1	0.25
PFOA	335-67-1	5
PFNA	375-95-1	0.5
PFHxS	355-46-4	0.25

Table 9 shows the minimum reporting levels achieved by the Southern Nevada Water Authority's analytical method for detecting selected PFAS.[r]

International Analytical Methods

A study conducted in Catalonia, Spain analyzed the concentrations of 13 perfluorinated compounds (PFBS, PFHxS, PFOS, THPFOS, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUA, PFDoA, PFTeA, and PFOSA) in municipal drinking water samples collected at 40 different locations.[140] Detection limits ranged between 0.02 ppt (PFHxS) and 0.85 ppt (PFOA). Analysis was performed "*using an Acquity UPLC coupled to a Quattro Premier XE tandem mass spectrometer (Waters Corporation, Milford, CT, USA) with an atmospheric electrospray interface operating in the negative ion mode (ES-MS/MS)*". Reporting limits or limits of quantification were not reported for this study.

Another study, conducted in Germany, was aimed at determining concentrations of PFAS in various sources of water intended for human consumption.[144] The study analyzed up to 19 PFAS compounds, including PFOS, PFOA, PFNA, and PFHxS, and the limits of quantification, or reporting limits, for all 19 compounds were 1 ppt. The researchers note that the water samples were measured *"using UPLC-MS/MS (Aquity with a TQ-detector, both from Waters, Eschborn, Germany) on a Kinetex column (2.6 µm, C18, 100A, 100 × 2.1 mm; Phenomenex, Aschaffenburg, Germany).*"

A third study conducted in Australia evaluated the fate of perfluorinated sulfonates (PFSAs) and carboxylic acids (PFCAs) in two water reclamation plants.[145] For this study, instrumental detection limits ranged from 0.2–0.7 ppt and reporting limits were set at double this, ranging from 0.4–1.5 ppt. Authors describe the analysis as "*using a QTRAP 4000 MS/MS (AB/Sciex, Concord, Ontario, Canada) coupled with a Shimadzu prominence HPLC system (Shimadzu, Kyoto Japan) using a gradient flow of mobile phase of methanol/water with 5 mM ammonium acetate. A Gemini C18 column (50 mm _ 2 mm i.d. 3 lm 110 Å) (Phenomenex, Torrance, CA) was used for separation, and an additional column (Altima, C18, 150 mm _ 2 mm i.d. 5 lm, 100 Å)(Grace Davison, Deerfield, IL) was installed between the solvent reservoirs and sample injector to separate peaks consistently present in the system from those in the samples (e.g. small*

[r] Dickenson ERV and Higgins C, 2016. Treatment Mitigation Strategies for Poly- and Perfluoroalkyl Substances. Water Research Foundation, Web Report #4322 http://www.waterrf.org/PublicReportLibrary/4322.pdf

peaks for PFDoDA (C12 PFCA), and for PFOA present in the mobile phase, and/or from fluoropolymer components in the LC system)."

Table 10: Detection and Reporting Limits for PFOA, PFOS, PFNA, PFHxS Internationally

Contaminant	Detection Limit (ppt)[s]	Reporting Limit (ppt)[t]
PFOS	0.12	1
PFOA	0.85	1
PFNA	0.15	1
PFHxS	0.02	1

Table 10 provides examples of detection and reporting limits achieved by two different international studies for PFOA, PFOS, PFNA, and PFHxS.

Comprehensive PFAS Assessment Techniques

At present, there is no single methodology for isolating, identifying, and quantifying all PFAS in drinking water. Current commercial laboratory methodologies are typically able to quantify between 14 and 31 PFAS compounds and only a very small number of PFAA precursors can be quantitatively analyzed by commercial laboratories.[146] For instance, N-ethyl perfluorooctanesulfonamidoacetic acid and N-methyl perfluorooctanesulfonamidoacetic acid are the only two precursors included in EPA Method 537.1. For classes other than PFCAs between 4-14 carbons long and PFSAs that are 4, 6, or 8 carbons long, methodologies are generally not available outside academic settings.[26] The Michigan PFAS Science Advisory Panel summarizes the advantages and disadvantages of some available analytical methodologies to quantify PFAS as a class. These are included in Table 11 below (with additional information as cited).[26]

We recommend states determine an analytical method, or combination of methods, that can be used as a surrogate for total PFAS. In particular, we recommend the evaluation of alternative detection methodologies, particularly TOPA, to measure the concentration of non-discrete and difficult to measure PFAS compounds that are not determined by conventional analytical methods.

[s] Ericson I, et al., 2009. Levels of Perfluorinated Chemicals in Municipal Drinking Water from Catalonia, Spain: Public Health Implications. *Arch Environ Contam Toxicol* 57:631–638

[t] Gellrich V, et al., 2013. Perfluoroalkyl and polyfluoroalkyl substances (PFASs) in mineral water and tap water. *J Environ Sci Health* 48:129–135

Table 11: Comparison of Various Analytical Approaches to Quantifying PFAS

Method	Advantages	Limitations
Method 537 V 1.1 Liquid Chromatography-Tandem Mass Spectrometry LC- MS/MS	• commercially available • QA/QC extensive • UCMR3/Method 537/SW-846 8327&8328/ASTM based on instrument • Differentiates branched/linear • Suited for analysis of ionic compounds[u]	• expensive • approved for a limited number of PFAS (18 in drinking water)[v] • value for forensics depends on number of PFAS evaluated
Total Oxidizable Precursor (TOP) assay	• commercially available • QA/QC improving • some chain length & branched and linear isomer information • reveals presence of significant precursors in AFFF-contaminated water, sediment, soil, and wastewater • data sets obtained by this methodology are comparable between sites and across states	• twice as expensive • no information on individual PFAS • conservative (lower estimate) • limited comparative data at this time • results treated with caution, especially for health and ecological risk assessments[w] • limited value for forensics
Suspect screening (LC-HRMS)	• unlimited number of PFAS • stored data can be searched in future • value as a forensics tool • a reference standard is not needed, the exact mass and isotopic pattern calculated from the molecular formula is used to screen for substances[x]	• instruments available but PFAS analysis by LC-HRMS not commercially available in US (research tool) • expensive • no standards for the other PFAS • data are 'screening' level or semi-quantitative • limited comparable data - data obtained on different instruments, ratioing to various internal standards may not be comparable between sites and across states (generates lab- specific data until standardized)
Particle Induced Gamma Ray Emission (PIGE)	• quantifies fluorine • currently captures anionic PFAS, currently being adapted for cationic/zwitterionic PFAS • less expensive • availability through academic institutions	• only quantifies total fluorine (the atom) • no information on individual PFAS • small database (few comparative data) • cannot analyze different isotopes[y] • limited value for forensics • detection limits are in the µg/L range, regulatory standards are now increasingly at ng/L levels[z]

[u] https://pfas-1.itrcweb.org/wp-content/uploads/2018/03/pfas_fact_sheet_site_characterization_3_15_18.pdf
[v] https://www.epa.gov/water-research/epa-drinking-water-research-methods
[w] https://www.alsglobal.com/-/media/als/resources/services-and-products/environmental/data-sheets-canada/pfas-by-top-assay.pdf
[x] https://link.springer.com/article/10.1007/s00216-018-1028-4
[y] https://www.sciencedirect.com/science/article/pii/0168583X86903812
[z] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5895726/

Total adsorbable organic fluorine (AOF)	• quantifies total fluorine • captures broad spectrum of PFAS • can be compared to individual PFAS analysis to determine presence of other PFAS (e.g., precursors)	• measures total fluorine (the atom) • no information on individual PFAS • not commercially available in US (or elsewhere) • must convert total fluorine in units of molar F to equivalents, assuming a specific PFAS to compare measurements • few comparable data • detection limits are in the µg/L range, regulatory standards are now increasingly at ng/L levels[aa]

Table 11 summarizes advantages and limitations of various analytical approaches to quantifying PFAS.[bb]

Treatment

There are a number of treatment options available to public water systems to address PFAS contamination.

On August 23, 2018, EPA published the results of its efforts to study a variety of technologies used to remove PFAS from drinking water.[147] The EPA's treatability analysis for PFAS compounds demonstrates that current treatment technologies can reduce concentrations of PFOA, PFOS, PFNA, and PFHxS to concentrations below 2 ppt. Full-scale treatment facilities in the U.S., Europe, and Australia have demonstrated effective removal of PFAS compounds through a variety of treatment technologies, most successfully with activated carbon or membrane filtration. The EPA's treatability analysis did not include data on the treatment of GenX, but pilot studies conducted in North Carolina have demonstrated reductions of GenX to below 2 ppt. [148]

Under federal law, standards for synthetic organic contaminants such as PFAS must be "feasible," and that term is defined to be a level that is at least as stringent as the level that can be achieved by Granular Activated Carbon (GAC). Specifically, the Safe Drinking Water Act provides, *"granular activated carbon is feasible for the control of synthetic organic chemicals, and any technology, treatment technique, or other means found to be the best available for the control of synthetic organic chemicals must be at least as effective in controlling synthetic organic chemicals as granular activated carbon."* Safe Drinking Water Act §1412(b)(4)(D). Therefore, states should establish MCLs for PFAS at levels at least as stringent as can be achieved by GAC.

In this report, we recommend MCLs for PFOS, PFOA, PFNA, PFHxS, and GenX that have been demonstrated to be achievable with GAC. However, for total PFAS, greater protections can be

[aa] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5895726/

[bb] Michigan PFAS Science Advisory Panel, 2018. Scientific Evidence and Recommendations for Managing PFAS Contamination in Michigan. December 7, 2018.

achieved with reverse osmosis than GAC (discusses below), therefore we recommend a treatment technique of reverse osmosis, or other treatment method that has been demonstrated to be at least as effective as reverse osmosis for removing all identified PFAS chemicals.

Granular Activated Carbon (GAC) Treatment

According to the EPA, "*Activated carbon treatment is the most studied treatment for PFAS removal. Activated carbon is commonly used to adsorb natural organic compounds, taste and odor compounds, and synthetic organic chemicals in drinking water treatment systems. Adsorption is both the physical and chemical process of accumulating a substance, such as PFAS, at the interface between liquid and solids phases. Activated carbon is an effective adsorbent because it is a highly porous material and provides a large surface area to which contaminants may adsorb*."[147] Activated carbon is made from organic materials with high carbon contents and is often used in granular form called granular activated carbon but can also be used in a powdered form called powdered activated carbon.

Granulated active carbon has been used for more than 15 years to remove PFOA and PFOS from water. The most common carbonaceous materials include raw coal, coconut, and wood. According to the Rapid Scale Small Column Testing Summary Report by Calgon Carbon, *"bench scale studies have shown that reagglomerated bituminous coal-based GAC significantly out performs other GAC materials including direct activated coconut GAC.*"[149]

While the EPA notes that, "*GAC has been shown to effectively remove PFAS from drinking water when it is used in a flow through filter mode after particulates have already been removed*,"[147] it should be noted that GAC has only been demonstrated to be effective for a certain PFAS chemicals. Factors impacting the effectiveness of GAC treatment include:

- the type of carbon used,
- the depth of the bed of carbon,
- flow rate of the water,
- the specific PFAS to be removed,
- temperature, and
- the degree and type of organic matter as well as other contaminants, or constituents, in the water.

A report reviewing the effectiveness of emerging technologies for treatment of PFAS chemicals noted that "*GAC is a widely used water treatment technology for the removal of PFOS and PFOA, and, to a lesser extent, other PFAAs from water…It is an established technology that can be deployed at scales between municipal water treatment and domestic point of entry systems, either as a standalone technology or part of a treatment train*."[150] And while GAC can consistently remove PFOS at parts per billion concentrations with an efficiency of more than 90 percent, it can be inefficient at removing PFOA[151] and becomes progressively less effective for

removing shorter chain PFCAs such as PFHxA, PFPeA, PFBS, and PFBA as the chain length diminishes.[152,153]

There are several examples of full-scale treatment systems using GAC to remove PFAS from drinking water sources. A report prepared for the New Jersey Department of Environmental Protection[154] included several case studies, two of which are included below.

Amsterdam, Netherlands - A study of the removal of a number of PFAS from several steps in the treatment process from raw water to finished water found that longer chain PFAA were readily removed by the GAC treatment step.[155] In this study, a final GAC adsorber was able to reduce both PFOS and PFNA measured in the raw samples at values of 6.7 to 10 ppt and 0.5 to 0.8 ppt, respectively to levels measured below the limits of quantitation (0.23 ppt and 0.24 ppt, respectively). PFOA concentrations in the influent ranged between 3.8 to 5.1 ppt and in the final GAC adsorber ranged between 3.6 to 6.7 ppt. GAC adsorption for this study was done in two stages with adsorbers operated in series, each with a 20-minute empty bed contact time. The GAC in the lag adsorber is placed in the lead position after 15 months of operation and replaced with fresh GAC. The GAC used in this study was Norit ROW 0.8S.

New Jersey American Water, Logan System Birch Creek - Water samples from the Logan System Birch Creek had detectable levels of PFNA (18 – 72 ppt) and of PFOA (33 – 60 ppt), in addition to three other PFAS.[154] GAC treatment removed all detectable PFAS below the reporting level of 5 ppt. GAC adsorbers were operated with an empty-bed contact time of approximately 15 minutes. The GAC used in this study was Calgon F-400.

Additionally, on-going pilot studies being conducted by engineering firm CDM demonstrates effective GAC treatment for GenX and other PFAS with reductions below detection limits of 2 ppt.[148] According to an April 2018 report by CDM for Brunswick County Public Utilities, long-term effective treatment with GAC requires media changeout to avoid breakthrough of compounds and the study indicates approximately 8,000 bed volumes (approximately 4 months at 20-minute contact time) is the appropriate frequency of media changeout for GenX and most PFAS.

GAC treatment can produce contaminated spent carbon or, if regenerated, contaminated air emissions, which require safe disposal. The Michigan PFAS Science Advisory Panel notes that, "*When regenerating PFAS-loaded activated carbon, the off-gases should be treated by high temperature incineration to capture and destroy any PFAS in the stack gases and to prevent the release of PFAS and/or partially oxidized byproducts to the atmosphere."*[26] For example, for complete destruction of PFOS, researchers recommend that incineration be performed at temperatures over 1,000ºC.[156] If an incinerator operates at temperatures below 1,000ºC, it will likely result in incomplete destruction and the formation of byproducts, and therefore require stack treatment to prevent PFAS release.

In sum, use of GAC by multiple water utilities at scale have achieved reductions of greater than 90 percent to below detection limits for certain PFAS chemicals, including PFOS, PFOA, PFNA,

PFHxS, and GenX. GAC has not been demonstrated to be effective for removing other PFAS chemicals, particularly short-chain PFAS.

Ion Exchange (IX) Treatment

Ion exchange resins essentially act as "magnets," attracting the contaminated materials as it passes through the water system.[147] Ion exchange resins can be cationic or anionic; positively charged anion exchange resins (AER) are effective for removing negatively charged contaminants, like PFAS. Ion exchange resins are made up of highly porous, polymeric hydrocarbon materials that are acid, base, and water insoluble.

As summarized by the EPA,

> *"AER has shown to have a high capacity for many PFAS; however, it is typically more expensive than GAC. Of the different types of AER resins, perhaps the most promising is an AER in a single use mode followed by incineration of the resin. One benefit of this treatment technology is that there is no need for resin regeneration so there is no contaminant waste stream to handle, treat, or dispose. Like GAC, AER removes 100 percent of the PFAS for a time that is dictated by the choice of resin, bed depth, flow rate, which PFAS need to be removed, and the degree and type of background organic matter and other contaminants of constituents*."[147]

Reverse Osmosis Treatment

According to the EPA, high-pressure membranes, such as nanofiltration or reverse osmosis (RO), have been effective at removing a broad array of PFAS compounds.[147] High-pressure membranes can be more than 90 percent effective at removing a wide range of PFAS, including shorter chain PFAS.

In a 2011 paper, researchers examined the fate of PFAS in two water reclamation plants in Australia.[145] The authors found that:

> "*Both facilities take treated water directly from wastewater treatment plants (WWTPs) and treat it further to produce high quality recycled water. The first plant utilizes adsorption and filtration methods alongside ozonation, whilst the second uses membrane processes and advanced oxidation to produce purified recycled water. At both facilities perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS), perfluorohexanoic acid (PFHxA) and perfluorooctanoic acid (PFOA) were the most frequently detected PFCs [perfluorinated compounds]. At the second plant, influent concentrations of PFOS and PFOA ranged up to 39 and 29 ppt. All PFCs present were removed from the finished water by reverse osmosis (RO) to concentrations below detection and reporting limits (0.4–1.5 ppt).*"[145]

Preliminary results of an on-going pilot study at Northwest Water Treatment Plant in North Carolina indicate that RO is expected to provide high level of removal (90 percent or greater) for the PFAS compounds, including GenX.[148] The RO membranes being proposed for this project and being tested in the pilot study are standard commercially available brackish water RO membranes rated for 99.3 percent rejection of a standard 2000 mg/L sodium chloride salt solution; this is considered a high rejection, broad spectrum RO membrane. The study also evaluated GAC, IX, and advanced treatment trains and concluded that low-pressure reverse osmosis was the preferred alternative for both removal efficiency and cost-effectiveness. The CDM report states:

> "*RO is recommended over the other options for the following reasons:*
>
> - *RO is the Best Technology for Removal of PFAS. Some PFAS, such as GenX, PFMOAA and PFO2HxA would require very frequent change-out of GAC and IX for removal.*
> - *GAC and IX would likely result in higher finished water concentrations of GenX, PFMOAA, and PFO2HxA than RO (technologies are not equal).*
> - *RO has the lowest net present worth costs for removing 90% or more of the Target Contaminants.*
> - *RO is the most robust technology for protecting against unidentified contaminants.*
> - *RO treated water concentrations will not vary as much with influent concentrations as with GAC and IX. RO treated water quality does not rely on frequent media change-out to protect from the spills and contaminants in the Cape Fear River.*
> - *RO does not release elevated concentrations after bed life is spent as can happen with GAC and IX if feed concentration drops."*[148]

Like GAC, RO treatment technology generates contaminated waste material including liquid concentrate and spent/used membranes. We recommend states evaluate the safest disposal method for contaminated waste, and that disposal require full destruction of PFAS compounds before entering the environment.

Furthermore, the EPA also suggests,

> "*Because reverse osmosis removes contaminants so effectively, it can significantly lower the alkalinity of the product water. This can cause decreased pH and increased corrosivity of the product water. The product water may need to have corrosion inhibitors added or to have the pH and alkalinity adjusted upwards by the addition of alkalinity. These actions may avoid simultaneous compliance issues in the distribution system such as elevated levels of lead and copper*."[157]

<u>Treatment Trains</u>

A treatment train is a sequence of multiple treatment techniques designed to meet specific water quality parameters. According to the Water Research Foundation, when evaluating treatment trains,

> *"Quiñones and Snyder (2009) saw the best removal of PFOA, PFOS, PFNA, and PFHxS using an integrated membrane treatment consisting of microfiltration (MF) and RO and ultraviolet (UV) (medium pressure) followed by SAT [soil aquifer treatment]. This treatment train caused concentrations to drop from the low ng/L [ppt] range to below detection levels. Their success in removing these substances was most likely due to the use of RO. Takagi (2008) looked at the effectiveness of rapid sand filtration followed by GAC and then chlorination on PFOA and PFOS and measured a drop from 92 ng/L to 4.1 ng/L and 4.5 ng/L to <0.1 ng/L, respectively. GAC was most likely responsible for the majority of the removal. Snyder et al. (2014) detected >90% removal of PFOA and >95% removal of PFOS using a treatment train (70 MGD) consisting of MF/RO/UV-advanced oxidation process (AOP)/direct injection (DI). Again, their success was likely due to the RO membrane step using Hydranautics EPSA2 RO dismembranes."*[142]

Although there is still additional research that can be done, removal rates of greater than 90 percent and effluent concentrations of less than 2 ppt for PFOA, PFOS, PFNA, PFHxS, and GenX can be achieved currently with a combination of treatment technologies, along with careful monitoring.

Innovative Technologies

This section describes promising innovative technologies that are designed to treat and/or destroy PFAS chemicals.

- Diamond Technology – According to researchers at Michigan State University-Fraunhofer USA, Inc. Center for Coatings and Diamond Technologies (MSU-Fraunhofer), "*the MSU-Fraunhofer team has a viable solution to treat PFAS-contaminated wastewater that's ready for a pilot-scale investigation. The electrochemical oxidation system uses boron-doped diamond electrodes. The process breaks down the contaminants' formidable molecular bonds, cleaning the water while systematically destroying the hazardous compounds*."[158] While this treatment technology has been developed to treat wastewater, further research may demonstrate effectiveness for removing PFAS from drinking water or waste streams produced by membrane filtration as well.

- AECOM DE-FLUORO Technology – This technology was designed to destroy PFAS compounds concentrated on spent media after treatment.[159] According to AECOM's informational sheet:

> "*Mass transfer technologies (e.g., granular activated carbon, ion exchange resin, reverse osmosis) do not destroy PFAS but concentrate PFAS on the spent media. The spent media may require off-site incineration or regeneration for filtration media reuse that will produce regenerant wastes requiring further management and treatment ... As of today, electrochemical oxidation is one of the most documented PFAS destruction technologies. AECOM has successfully used a proprietary electrode to complete mineralization of C4 ~C8 perfluoroalkyl acids (PFAAs) with evidence of complete defluorination and desulfurization. PFAS are destructed via direct electron transfer on "nonactive" anodes under room temperature and atmospheric pressure with relatively low energy consumption. AECOM has also successfully used this proprietary electrode to treat PFAS in ion-exchange regenerant waste and other PFAS-impacted wastewater*."[159]
>
> In the information sheet, AECOM notes that this technology may also be effective for treating drinking water.

The available research demonstrates that both GAC and IX can be effective treatment techniques for certain PFAS compounds that have been studied, including PFOA, PFOS, PFNA, PFHxS, and GenX, when there is appropriate design, operation, and maintenance. RO has been demonstrated to be an effective treatment technology for removing all PFAS that have been studied and is the most effective treatment technique for effectively removing unknown contaminants. Due to the nature of GAC and IX treatment, water suppliers run the risk of releasing PFAS compounds back into the finished water after GAC bed life is spent or if IX feed concentration drops. Additionally, frequent changeout of GAC or IX to maintain removal efficiency can make the lifecycle costs more expensive than alternatives, such as RO. While GAC, IX, or RO can be effective at removing certain PFAS, RO is advantageous for treating total PFAS because it is the most robust technology for protecting against unidentified contaminants and provides greater protection from future unidentified PFAS. Potential considerations for RO are that it often has a higher capital cost, it can require a 10 to 20 percent higher treatment capacity because it produces a reject stream, and it requires safe disposal of the reject water which will have higher concentrations of contaminants than the source water.

PART VI: CONCLUSIONS AND RECOMMENDATIONS

Taking into consideration the information provided in this report, the following actions are recommended to address PFAS contamination in drinking water:

1. Comprehensive Monitoring of Drinking Water

Understanding the extent of PFAS contamination in drinking water is an important step in protecting people from exposure to these toxic chemicals. Based on national monitoring 4 years ago, there are approximately 16 million people drinking PFAS contaminated water. However, due to limitations in the national survey, including high reporting limits, a focus on large public

water systems, and a limited number of PFAS chemicals tested, the actual numbers are likely much larger, suggesting that there could be significantly more people drinking PFAS contaminated water.

For reference, when expanded testing was carried out by Michigan, the estimates of affected population went from less than 200,000 people to approximately 1.5 million people. The national survey resulted in 3 detections in Michigan. However, once Michigan became aware that they had a PFAS contamination problem, they performed their own site investigations for sites deemed at risk and tested all of their public water systems serving over 25 people. Furthermore, Michigan tested for between 14-24 PFAS at lower health-relevant reporting limits (2 ppt). With this improved testing, they found over 40 contamination sites and over 100 of their public water systems were contaminated with PFAS. Importantly, there are sites of contamination that are not reflected in their public water system survey, and vice versa, public water system contamination not fully predicted through site investigation. The comparison of these two surveys highlights how important comprehensive testing is for understanding the extent of PFAS contamination of drinking water.

Therefore, states should perform both site investigations for at risk sites and a comprehensive statewide survey of public water systems. States should also offer testing of private water systems and private wells serving residences that are near known or suspected PFAS contamination sites, or as requested by a private well user. Priority for testing and monitoring should be sites near former PFAS manufacturing or processing facilities; near fire-fighting stations where PFAS was or continues to be used for training; near military bases and airports which may still use PFAS; and near landfills.

Periodic rounds of PFAS testing should be performed to account for testing variability, to ensure no additional discharges of PFAS are occurring, and to evaluate treatment effectiveness. The analyses should be conducted using the most sensitive detection methods for a comprehensive assessment, which at minimum should now include the expanded EPA 537.1 list at reporting limits of 2 ppt for all PFAS covered by the method, except for GenX, whose reporting limit should be no greater than 5 ppt. We also recommend that states evaluate newer methodologies, particularly the total oxidizable precursor assay, as an analytical technique to help measure the concentration of non-discrete and difficult to measure PFAS compounds that are not determinable by conventional analytical methods.

Data on PFAS in drinking water supplies should be provided to residents served by the tested water supplies, researchers, and the public. Where both biomonitoring data and water testing data are available, that information should be provided to individuals participating in the biomonitoring program so that participants are informed of their own body burden and drinking water exposures. Biomonitoring data and water testing data should also be provided to researchers (in matched pairs, if possible, and with identifying information removed to protect the confidentiality of participants) so that the contribution of PFAS-contaminated drinking water to total PFAS exposure can be studied further. Additionally, unique values for all detected levels of individual PFAS compounds should be publicly reported. All data should be provided in a timely manner and in a common format on a publicly-available database.

2. Set a MCLG of Zero for Total PFAS.

PFAS share similar structure and properties, including extreme persistence and high mobility in the environment. Many PFAS are also associated with similar health endpoints, some at extremely low levels of exposure. There is additionally potential for additive or synergistic toxicity among PFAS. Given the similarity among chemicals of the PFAS class and the known risk of the well-studied PFAS, there is reason to believe that other members of the PFAS class pose similar risk. Therefore, health-protective standards for PFAS should be based on the known adverse effects of the well-studied members of the PFAS class.

First, there is sufficient evidence to classify PFOA as a known or probable carcinogen. Therefore, a MCLG of zero should be promulgated for PFOA, consistent with EPA's approach to regulating known or probable carcinogens (see Box 10). Both IARC's and EPA's findings on PFOA's carcinogenic potential are based heavily on the C8 study, whose Science Panel determined that PFOA is a probable carcinogen. There is also significant additional animal and human evidence for an association between PFOA exposure and cancer, particularly kidney and testicular cancer.

Box 10: Maximum Contaminant Level Goals for Carcinogens

The EPA derives a MCLG under the Federal Safe Drinking Water Act by first considering the carcinogenic potential of the contaminant, or suite of contaminants. For known or probable carcinogens, EPA sets a MCLG of zero for the contaminant, or for the contaminant class, under the federal framework. This is because EPA assumes that, in the absence of other data, there is no known threshold at which no adverse health effects would occur. For chemicals suspected as carcinogens, the agency considers the weight of evidence, including animal bioassays and epidemiological studies. Information that provides indirect evidence, such as mutagenicity and other short-term test results, is also considered by the agency. Known human carcinogens, under EPA's classification scheme, are chemicals for which there exists sufficient evidence of carcinogenicity from epidemiological studies. Probable human carcinogens demonstrate either limited evidence of carcinogenicity in humans or sufficient evidence in animals without corresponding human data, under this classification scheme. See *56 Fed. Reg. 20, 3532* (Jan. 30, 1991).

In addition to being a carcinogen, PFOA causes adverse non-cancer health effects at exceedingly low doses. A MCLG based on altered mammary gland development would be well below 1 ppt for PFOA, further supporting our recommendation of zero for a MCLG (see Table 12 below).

Although the evidence of carcinogenic potential for PFOS is not as well established as PFOA, given the similarities in structure and toxicity of PFOS to PFOA, we recommend a MCLG of zero for PFOS as well. The weight of evidence indicates that PFOS also causes adverse non-cancer health effects at exceedingly low doses. A MCLG based on immunotoxicity would be

well below 1 ppt for PFOS, further supporting our recommendation of zero for a MCLG (see Table 12 below).

There is less information on the carcinogenic potential of PFNA, PFHxS, and GenX, however, given the similarities in structure and toxicity of these PFAS to PFOA and PFOS, their potential for the carcinogenicity cannot be ruled out. Other shared health effects that occur at extremely low levels, such as immunotoxicity, developmental harm, and liver damage, along with their co-occurrence in our environment, must also be considered in setting a health protective MCLG for PFNA, PFHxS, and GenX.

A MCLG for PFNA based on developmental toxicity is below 1 ppt, approximately 2 ppt for PFHxS based on thyroid toxicity, and below 1 ppt for GenX based on liver toxicity (see Table 12 below).

Please see Appendices A, B, C, D and F for more detailed calculations.

Table 12: NRDC Recommended MCLGs for PFOA, PFOS, PFNA, PFHxS, and GenX

Threshold (ppt)	Threshold type	Study Endpoint	Total UFs	Critical Dose includes UFs (mg/kg/day)	Drinking water exposure assumptions	Notes
PFOA						
0	proposed MCLG (goal)	cancer and altered mammary gland development				
0.01		altered mammary gland development	300**	1×10^{-8}	0.175 L/kg/day for a infants, RSC = 20%	**additional UF of 10, to protect fetuses, infants, children
PFOS						
0	proposed MCLG (goal)	class similarity to PFOA (supported by immunotoxicity)				
0.002		Immunotoxicity	300**	2×10^{-9}	0.175 L/kg/day for a infants, RSC = 20%	**additional UF of 10, to protect fetuses, infants, children
PFNA						
0	proposed MCLG (goal)	class similarity to PFOA (supported by develomental toxicity)				
0.3		Develomental toxicity	3000**	3×10^{-7}	0.175 L/kg/day for a infants, RSC = 20%	**additional UF of 10, to protect fetuses, infants, children
PFHxS						
0	proposed MCLG (goal)	class similarity to PFOA (supported by developmental and thyroid toxicity)				
2		developmental and thyroid toxicity	3000**	2×10^{-6}	0.175 L/kg/day for a infants, RSC = 20%	**additional UF of 10, to protect fetuses, infants, children
GenX						
0	proposed MCLG (goal)	class similarity to PFOA (supported by liver toxicity)				
0.2		liver toxicity	100000#	2×10^{-6}	0.175 L/kg/day for a infants, RSC = 20%	# due to data limitations, uncertainty could be up to 100,000
**An additional uncertainty factor of 10 to protect fetuses, infants and children is recommended by the National Academy of Sciences (NAS 1993) for pesticides and as required in the Food Quality Protection Act. 21 U.S.C. §346a(b)(2)(C)(ii)(II).						

PFOA, PFOS, PFNA, PFHxS, and GenX share similar structure and properties and are associated with similar health endpoints, many at extremely low levels of exposure, across animal and epidemiological studies. Thus, because they often co-occur in our environment, there is potential for additive toxicity among these PFAS. New Jersey noted that the modes of action and health effects are generally similar for PFAS and acknowledged the possibility that the effects may be additive.[92] Given the above information we recommend a combined MCLG of zero for PFOA, PFOS, PFNA, PFHxS, and GenX.

However, this reasoning should be applied to the PFAS class as a well. Information on and lessons learned from these more extensively studied PFAS need to be used to guide regulations and ensure actions taken are adequately protective of human health in the long term. While there is limited toxicity data on many of the newer short-chain or other alternative PFAS replacing long-chain PFAS in various applications, evidence suggests that they collectively pose similar threats to human health and the environment. The rise in use of alternative PFAS and concerns with the environmental fate and persistence of these alternative PFAS have led to a call from independent scientists from around the globe to address PFAS as a class both in terms of their impacts and in limiting their uses.[12]

The structure of the fluorine-carbon bond and the impacts documented on the studied PFAS already available support concern over the health impacts of the entire class. This is supported by the constant exposure to short-chain chemicals, even if they have a relatively short presence in the body, as well as the fact that in many cases the use of these chemicals may be much higher than their long-chain cousins. Furthermore, many PFAS can convert into PFAAs (a PFAS subgroup, which includes PFOA and PFOS, that is linked to many adverse health effects) or PFAAs are used in their manufacture and can be contaminants in their final product.

Box 11: Regulating Classes in Tap Water - The PCB Precedent

There is precedent for regulating a group of chemicals as a class. For example, polychlorinated biphenyls (PCBs) are a class hundreds of man-made chlorinated hydrocarbons that are persistent in the environment, can bioaccumulate, and have a range of toxicity, including cancer and disruption of the immune, reproductive, endocrine, and nervous systems.[160] Drinking water standards and regulations regarding their clean up, disposal and storage apply to the class and are not set separately for each PCB in use.

In promulgating drinking water regulations for the large class of PCBs, EPA found that although statistically significant evidence of carcinogenicity had been demonstrated only in PCBs that were 60 percent chlorinated, the evidence justified regulation of the whole class of PCB compounds, given the structural complexity of the compounds, and the incomplete data regarding toxicity of the isomers in PCB compounds. EPA, 56 Fed. Reg. 3526, at 3546 (January 30, 1991)[161]

Setting a MCLG of zero for the class is needed to provide an adequate margin of safety to protect public health from a class of chemicals that is characterized by extreme persistence, high mobility, and is associated with a multitude of different types of toxicity at very low levels of exposure. If we regulate only a handful of PFAS, there will be swift regrettable substitution with other, similarly toxic PFAS - creating an ongoing problem where addressing one chemical at a time incentivizes the use of other toxic chemicals and we fail to ever establish effective safeguards to limit this growing class of dangerous chemicals.

3. Immediately Set a Combined MCL of 2 ppt for PFOA, PFOS, PFNA, and PFHxS, and a MCL of 5 ppt for GenX

As discussed in our second recommendation, NRDC's review of the toxicity studies for five PFAS compounds finds evidence that they are linked to cancer and other serious adverse health effects. Following conventional risk assessment protocols, we determine that the goal for PFOA, PFOS, PFNA, PFHxS and GenX should be zero exposure to these chemicals in drinking water.

As technologies for detection and water treatment do not currently allow for the complete removal of PFAS from drinking water, a MCL for PFOA, PFOS, PFNA, PFHxS, and GenX should be based on the best detection and treatment technologies available. Our review suggests a combined MCL of 2 ppt is feasible for PFOA, PFOS, PFNA, and PFHxS, with a separate MCL of 5 ppt for GenX.

Laboratory methods support a reporting limit of 2 ppt with EPA Method 537.1 (5 ppt for GenX), and therefore all water testing should be required to achieve this limit for the PFAS chemicals detectable with this method. Further, the removal of PFOA, PFOS, PFNA, PFHxS, and GenX has been demonstrated to be effective with technologies such as GAC and RO to below detection levels, supporting our determination that the MCL meets technological feasibility.

Residents who rely on private wells for drinking water depend on the safety of their state's groundwater, therefore a groundwater cleanup standard should also be set to 2 ppt for PFOA, PFOS, PFNA and PFHxS and to 5 ppt for GenX, consistent with the recommended MCL for public water systems.

4. Develop a Treatment Technique Requirement for the PFAS Class Within Two Years

As discussed in our second recommendation, setting a MCLG of zero for the class is needed to protect public health and the environment from all types of PFAS that share common negative qualities including extreme persistence, high mobility, and the association with a multitude of different types of toxicity at very low levels of exposure. The replacement of PFOA with GenX is a perfect example of regrettable substitution where a well-studied, toxic PFAS was replaced by a poorly-studied but structurally similar PFAS.

Technology for detection and treatment cannot achieve a MCLG of zero for total PFAS. In the absence of a reliable method that is economically and technically feasible to measure a contaminant at concentrations to indicate there is not a public health concern, the state should establish a treatment technique. A treatment technique is a minimum treatment requirement or a necessary methodology or technology that a public water supply must follow to ensure control of a contaminant.

At present, there is no single methodology for isolating, identifying, and quantifying all PFAS in drinking water. We recommend that states explore an analytical method, or combination of methods, that can be used as a surrogate for total PFAS. In particular, we recommend that states evaluate alternative detection methodologies, such as the total oxidizable precursor assay, to measure the concentration of non-discrete and difficult to measure PFAS compounds that are not determined by conventional analytical methods.

Furthermore, we recommend reverse osmosis, or other treatment method that has been demonstrated to be at least as effective as reverse osmosis for removing all identified PFAS chemicals, as the treatment technique for public water supplies. Reverse osmosis is currently the preferred treatment technology for the following reasons:

- Reverse osmosis has been demonstrated to effectively remove a broad range of PFAS compounds.[148]
- Reverse osmosis is the most robust technology for protecting against unidentified contaminants.[148]
- Reverse osmosis would likely result in lower finished water concentrations of GenX and other PFAS compounds such as PFMOAA and PFO2HxA.[148]
- Reverse osmosis does not require frequent change out of treatment media and does not release elevated concentrations after granular activated carbon bed life is spent or ion exchange feed concentration drops.[148]

Reverse osmosis requires considerations for the safe disposal of high-strength waste streams and spent/used membranes. We recommend states evaluate the safest disposal method for contaminated waste, and that disposal require full destruction of PFAS compounds before entering the environment.

UNITS AND DEFINITIONS

AER - anion exchange resins

ATSDR – Agency for Toxic Substances and Disease Registry

C8 - PFOA

CDC - Centers for Disease Control and Prevention

EPA – U.S. Environmental Protection Agency

EtFOSAA - 2-N-Ethyl-perfluorooctane sulfonamide

FOSE – perfluorooctane sulfonamide ethanol

FTOH - fluorotelomer alcohol

GAC – granular activated carbon

GenX – HFPO dimer acid and its ammonium salt

HFPO - hexafluoropropylene oxide

IARC – International Agency for Research on Cancer

IX - strong base anion exchange resin

LCMRL - lowest concentration minimum reporting limit

LC/MS/MS - liquid chromatography/tandem mass spectrometry

LOAEL – lowest-observable-adverse-effect-level

LOQ – limit of quantitation

MCL - maximum contaminant level

MCLG – maximum contaminant level goal

MDL – minimum detection level

MeFOSAA - 2-N-Methyl-perfluorooctane sulfonamide

MRL - minimal risk level

NAS – National Academy of Sciences

NHANES – National Health and Nutrition Examination Survey

NOAEL – no-observable-adverse-effect-level

OEHHA – California Office of Environmental Health Hazard Assessment

PBT – persistent bioaccumulative toxic

PFAA – perfluoroalkyl acid

PFAS – per- and polyfluoroalkyl substances

PFBS - perfluorobutane sulfonic acid, also known as PFBuS

PFCA – perfluorocarboxylic acid

PFDeA - perfluorodecanoic acid, also known as PFDeDA

PFDoA - perfluorododecanoic acid, also known as PFDoDA

PFHpA - perfluoroheptanoic acid

PFHxS - perfluorohexane sulfonic acid

PFNA - perfluorononanoic acid

PFOA - perfluorooctanoic acid

PFOS - perfluorooctane sulfonic acid

PFOSA - perfluorooctane sulfonamide

PFSA – perfluorosulfonic acid

PFTeA – perfluorotetradecanoic acid, also known as PFTDA

PFUA - perfluoroundecanoic acid, also known as PFUnDA or PFUnA

PMT – persistent mobile toxic

ppt - parts per trillion = nanograms per liter (ng/L) (usually used to express water concentration)

ppb - parts per billion = micrograms per liter (ug/L) (usually used to express blood serum concentration)

PWS – public water system

RfD - reference dose

RO – reverse osmosis

RSC – relative source contribution

THPFOS - 1H,1H,2H,2H-perfluorooctanesulfonic acid

TOP or TOPA – total oxidizable precursor assay

UCMR3 – EPA’s Unregulated Contaminant Monitoring Rule 3

UF - uncertainty factor

APPENDIX A - MRL CALCULATIONS FOR PFOS USING IMMUNOTOXICITY ENDPOINT

Based on information from: https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf

Immunotoxicity is currently the most sensitive health endpoint for PFOS exposure. Although ATSDR states concern that immunotoxicity is a more sensitive endpoint than developmental toxicity, it stops short of deriving a MRL from this endpoint. Instead, ATSDR claims that a modifying factor of 10 is sufficient to address the doses where immunotoxic effects have been observed. This statement is based on ATSDR calculating a candidate MRL for one of the four immunotoxicity studies in rodents identified by ATSDR, Dong et al., 2011, but not the other studies (ATSDR, 2018, see page A-43 of Appendix A).

However, Dong et al. 2011 is the immunotoxicity study with the highest LOAEL, which is not consistent with ATSDR's practice of choosing the study with the lowest LOAEL when selecting the principle study for MRL derivation. The other immunotoxicity studies all result in MRLs approximately 2.5-100 times lower than the MRL proposed by ATSDR (Table 1, calculations to follow, performed as described in ATSDR, 2018, Appendix A).

Table 13: Comparison of candidate MRLs for PFOS

Source	Year	Critical Endpoint	Minimal Risk Level (mg/kg/day)
ASTDR	2018	Developmental toxicity (delayed eye opening, decreased pup weight) + Modifying Factor	2 x 10-6 MRL
Dong et al.	2011	Immunotoxicity (impaired response to sRBC)	2.7 x 10-6 Estimated MRL[a]
Dong et al.	2009	Immunotoxicity (impaired response to sRBC)	7.8 x 10-7 Estimated MRL[a]
Guruge et al.	2009	Immunotoxicity (decreased resistance to influenza virus)	2.2 x 10-7 Estimated MRL[a]
Peden-Adams et al.	2008	Immunotoxicity (impaired response to sRBC)	2.1 x 10-8 Estimated MRL[a]

a – Calculated using the derivation method described on pg. A43 of the ATSDR profile

In equation A-6 from Appendix A, ATDSR defines an expression relating the external steady-state dosage and steady-state serum concentration:

$$D_{SS} = (C_{SS} \times k_e \times V_d) / AF$$

Where:

D_{SS} = steady-state absorbed dosage (mg/kg/day)

C_{SS} = steady-state serum concentration in humans (mg/L)

k_e = elimination rate constant (day-1)

V_d = assumed apparent volume of distribution (L/kg)

AF = gastrointestinal absorption fraction

ATSDR provided the following First Order One-Compartment Model Parameters for PFOS in Table A-4:

$K_e = 3.47 \times 10^{-4}$

$V_d = 0.2$

AF=1

ATSDR made the assumption that "humans would have similar effects as the laboratory animal at a given serum concentration." Therefore, the time weighted average serum levels from animal studies (C_{TWA}) are used to back-calculate D_{SS} by imputing C_{TWA} as C_{SS} in equation A-6.

The immunotoxicity studies, are the most sensitive endpoints, having NOAELs 6-625 times lower than the NOAEL for the developmental endpoint chosen for deriving the MRL. Though they did report serum levels, the immunotoxicity studies were performed in different strains/species of animals than those used for the pharmacokinetic modeling completed by Wambaugh et al. As such, they were not chosen for calculation of an MRL, though the ATSDR used other methods to calculate TWA concentrations for PFHxS and PFNA (the trapezoid rule) which were also lacking pharmacokinetic modeling.

From ATSDR (Appendix A, pg. A-43):

"A candidate MRL was calculated using the NOAEL of 0.0167 mg/kg/day identified in the Dong et al. (2011)...A TWA concentration was estimated using a similar approach described for

PFHxS and PFNA in the MRL approach section. The estimated TWA concentration was 1.2 µg/mL for the 0.0167 mg/kg/day; this estimated TWA concentration was used to calculate a human equivalent dose (HED) of 0.000083 mg/kg/day. A candidate MRL of 3x10-6 was calculated using an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustments and 10 for human variability)."

Following this logic:

The time weighted average (TWA) serum levels for the other immunotoxicity studies can be predicted by using the trapezoid rule, as was done for PFNA, PFHxS, and the candidate PFOS MRL based on Dong et al., 2011.

Dong et al. 2009:

Measured serum level at NOAEL dose of 0.0083 mg/kg/day: 0.674 ug/mL

Estimated TWA = (0.674 ug/mL - 0 ug/mL) / 2 = 0.337 ug/mL = 0.337 mg/L

Guruge et al. 2009:

Measured serum level at NOAEL dose of 0.005 mg/kg/day: 0.189 ug/mL

Estimated TWA = (0.189 ug/mL - 0 ug/mL) / 2 = 0.0945 ug/mL = 0.0945 mg/L

Peden-Adams et al. 2008:

Measured serum level at NOAEL dose of 0.00016 mg/kg/day: 0.0178 ug/mL

Estimated TWA = (0.0178 ug/mL - 0 ug/mL) / 2 = 0.0089 ug/mL = 0.0089 mg/L

These estimated TWA serum levels can then be inputted into equation A6 as the steady state serum concentration, C_{SS}, using the same values used by ATSDR for the other parameters to generate candidate MRLs for these immunotoxicity studies.

$$D_{SS} = (C_{SS} \times 0.000347\ day^{-1} \times 0.2\ L/kg) / 1$$

Dong et al. 2009:

D_{SS} = (0.337 mg/L x 0.000347 day-1 x 0.2 L/kg) / 1 = 2.34 x 10^{-5} mg/kg/day

Then, divide by UF of 30

MRL = 7.8 x 10^{-7} mg/kg/day

Guruge et al. 2009:

D_{SS} = (0.0945 mg/L x 0.000347 day-1 x 0.2 L/kg) / 1 = 6.56 x 10^{-6} mg/kg/day

Then, divide by UF of 30

MRL = 2.2 x 10^{-7} mg/kg/day

Peden-Adams et al. 2008:

D_{SS} = (0.0089 ug/mL x 0.000347 day-1 x 0.2 L/kg) / 1 = 6.2 x 10^{-7} mg/kg/day

Then, divide by UF of 30

MRL = 2.1 x 10^{-8} mg/kg/day

APPENDIX B - MRL CALCULATIONS FOR PFNA USING LONGER HALF-LIFE

Based on information from: https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf

In equation A-6 from Appendix A, ATDSR defines an expression relating the external steady-state dosage and steady-state serum concentration:

$$D_{SS} = (C_{SS} \times k_e \times V_d) / AF$$

Where:

D_{SS} = steady-state absorbed dosage (mg/kg/day)

C_{SS} = steady-state serum concentration in humans (mg/L)

k_e = elimination rate constant (day-1)

V_d = assumed apparent volume of distribution (L/kg)

AF = gastrointestinal absorption fraction

ATSDR provided the following First Order One-Compartment Model Parameters for PFNA in Table A-4:

$k_e = 7.59 \times 10^{-4}$

$V_d = 0.2$

AF=1

The $k_e = 7.59 \times 10^{-4}$ is based on a half-life estimate of 900 days for young women. Based on Eq. A-5, a half-life of 1570 days for all other adults would result in a k_e of 4.4×10^{-4} (k_e = ln(2) / half-life).

Thus, if the k_e representing the longer, more representative half-life for PFNA was used, along with ATSDR's estimated C_{SS} of 6.8 mg/L:

$D_{SS} = (6.8 \text{ mg/L} \times 0.000441 \text{ day-1} \times 0.2 \text{ L/kg}) / 1 = 6 \times 10^{-4}$ mg/kg/day

Then, divide by UF of 300

MRL = 2×10^{-6} mg/kg/day

APPENDIX C - MCLG CALCULATIONS

From EPA's Drinking Water Health Advisory for PFOA and PFOS (EPA, 2016 a and b)

The EPA used drinking water intake and body weight parameters for lactating women in the calculation of a lifetime health advisory for PFOA and PFOS. EPA used the rate of 54 mL/kg-day representing the consumers only estimate of combined direct and indirect community water ingestion at the 90th percentile for lactating women (see Table 3-81 in EPA 2011).

First, a Drinking Water Equivalent Level (DWEL) is derived from the reference dose (RfD) and assumes that 100% of the exposure comes from drinking water. The RfD is multiplied by body weight and divided by daily water consumption to provide a DWEL.

$$DWEL = (RfD \times bw) / DWI = RfD / (DWI/bw)$$

Where:

RfD = critical dose (mg/kg/day)

bw = body weight (kg)

DWI = drinking water intake (L/day)

DWI/bw = 0.054 L/kg-day

Then, the DWEL is multiplied by the relative source contribution (RSC). The RSC is the percentage of total drinking water exposure, after considering other exposure routes (for example, food, inhalation). Following EPA's Exposure Decision Tree in its 2000 methodology (EPA, 2000), significant potential sources other than drinking water ingestion exist; however, information is not available to quantitatively characterize exposure from all of these different sources (Box 8B in the Decision Tree). Therefore, EPA recommends a RSC of 20% (0.20) for PFOA and PFOS.

Thus, the lifetime health advisory (HA) is calculated after application of a 20% RSC as follows:

$$HA = DWEL \times RSC$$

The two above equations can be combined to generate:

HA = (RfD / (DWI/bw)) x RSC

For these purposes, we can assume that ATSDR's MRL is equivalent to a RfD, and an HA equivalent to a MCLG.

MCLG = (MRL / (DWI/bw)) x RSC

The EPA used estimated drinking water parameters for lactating mothers, making the equation:

MCLG = (MRL / 0.054 L/kg-day) x 0.2

*NOTE:

DWI/bw for average adult = 0.029 L/kg-day, used by New Jersey;

DWI/bw for lactating mother = 0.054 L/kg-day, used by EPA; and

DWI/bw for breastfeeding or formula-fed infant = 0.175 L/kg-day, used by Vermont

This equation can be applied to proposed and candidate MRLs from ATSDR (final values are rounded):

Using ATSDR's proposed MRLs and drinking water assumptions for lactating women:

PFOA

MCLG = (3×10^{-6} mg/kg/day / 0.054 L/kg-day) x 0.2 = 1.11×10^{-5} mg/L = 11 ng/L or ppt

PFOS

MCLG = (2×10^{-6} mg/kg/day / 0.054 L/kg-day) x 0.2 = 7.41×10^{-6} mg/L = 7 ng/L or ppt

PFNA

MCLG = (3×10^{-6} mg/kg/day / 0.054 L/kg-day) x 0.2 = 1.11×10^{-5} mg/L = 11 ng/L or ppt

PFHxS

MCLG = (2 x 10^{-5} mg/kg/day / 0.054 L/kg-day) x 0.2 = 7.41 x 10^{-5} mg/L = 74 ng/L or ppt

Using NRDC's estimated MRLs for immunotoxicity studies and drinking water assumptions for lactating women:

In Appendix A we noted that ATSDR did not choose to use the most sensitive endpoint for PFOS. Here we show the MCLGs that would result if the studies with most sensitive endpoints were to be chosen for calculation of MRL as in Appendix A and translated to MCLGs using the drinking water assumptions for lactating women.

Dong et al. 2011

MCLG = (3 x 10^{-6} mg/kg/day / 0.054 L/kg-day) x 0.2 = 1.11 x 10^{-5} mg/L = 11 ng/L or ppt

Dong et al. 2009

MCLG = (8 x 10^{-7} mg/kg/day / 0.054 L/kg-day) x 0.2 = 2.96 x 10^{-6} mg/L = 3 ng/L or ppt

Guruge et al. 2009

MCLG = (2 x 10^{-7} mg/kg/day / 0.054 L/kg-day) x 0.2 = 7.41 x 10^{-7} mg/L, **0.7 ng/L (< 1 ppt)**

Peden-Adams et al. 2008

MCLG = (2 x 10^{-8} mg/kg/day / 0.054 L/kg-day) x 0.2 = 7.41 x 10^{-8} mg/L, **0.07 ng/L (< 1 ppt)**

In Appendix B we noted that ATSDR did not use the half-life for PFNA that was the most representative. Here we show the MCLG that would result if the longer, more representative half-life were to be chosen for calculation of the MRL as in Appendix B and translated to a MCLG using drinking water assumptions for lactating women.

MCLG = (2 x 10^{-6} mg/kg/day / 0.054 L/kg-day) x 0.2 = 7.41 x 10^{-6} mg/L = 7 ng/L or ppt

Using ATSDR's proposed MRLs and drinking water assumptions for infants:

Vermont used the drinking water assumptions for breastfeeding or formula-fed infants of 0.175 L/kg-day. If this value is used, the equation becomes:

MCLG = (MRL / 0.175 L/kg-day) x 0.2

This equation can be applied to proposed and candidate MRLs from ATSDR (final values are rounded):

PFOA

MCLG = (3×10^{-6} mg/kg/day / 0.175 L/kg-day) x 0.2 = 3.43×10^{-6} mg/L = 3 ng/L or ppt

PFOS

MCLG = (2×10^{-6} mg/kg/day / 0.175 L/kg-day) x 0.2 = 2.29×10^{-6} mg/L = 2 ng/L or ppt

PFNA

MCLG = (3×10^{-6} mg/kg/day / 0.175 L/kg-day) x 0.2 = 3.43×10^{-6} mg/L = 3 ng/L or ppt

PFHxS

MCLG = (2×10^{-5} mg/kg/day / 0.175 L/kg-day) x 0.2 = 2.29×10^{-5} mg/L = 23 ng/L or ppt

Using NRDC's estimated MRLs for immunotoxicity studies and drinking water assumptions for infants:

Candidate MRL's (rounded) for immunotoxicity studies identified by ATSDR, calculated in Appendix B:

Dong et al. 2011

MCLG = (3×10^{-6} mg/kg/day / 0.175 L/kg-day) x 0.2 = 3.43×10^{-6} mg/L = 3 ng/L or ppt

Dong et al. 2009

MCLG = (8×10^{-7} mg/kg/day / 0.175 L/kg-day) x 0.2 = 9.14×10^{-7} mg/L, **0.9 ng/L (< 1 ppt)**

Guruge et al. 2009

MCLG = (2×10^{-7} mg/kg/day / 0.175 L/kg-day) x 0.2 = 2.28×10^{-7} mg/L, **0.2 ng/L (< 1 ppt)**

Peden-Adams et al. 2008

MCLG = (2×10^{-8} mg/kg/day / 0.175 L/kg-day) x 0.2 = 2.28×10^{-8} mg/L, **0.02 ng/L (< 1 ppt)**

Candidate MRL's (rounded) for PFNA using longer half-life estimate, calculated in Appendix C:

MCLG = (2 x 10^{-6} mg/kg/day / 0.175 L/kg-day) x 0.2 = 2.28 x 10^{-6} mg/L = **2 ng/L or ppt**

****ALSO NOTE:** All estimated MCLGs presented here would be an order of magnitude lower/stricter if an additional UF of 10 was applied to the RfD or MRL to protect fetuses, infants and children as recommended by the National Academy of Sciences (NAS, 1993) for pesticides and as required in the Food Quality Protection Act. 21 U.S.C. §346a(b)(2)(C)(ii)(II).

APPENDIX D - MCLG CALCULATIONS FOR PFOA BASED ON REFERENCE DOSE CALCULATED BY NEW JERSEY FOR ALTERED MAMMARY GLAND DEVELOPMENT

Based on information from Gleason et al., 2017, found at:
https://www.nj.gov/dep/watersupply/pdf/pfoa-appendixa.pdf

Selected Study

The New Jersey Drinking Water Quality Institute selected the late gestational exposure study conducted by Macon et al. 2011[63] because it was the only developmental exposure study of mammary gland development that provides serum PFOA data from the end of the dosing period (PND 1) that can be used for dose-response modeling.

Determination of Point of Departure (POD)

EPA Benchmark Dose Modeling Software 2.1.2 was used to perform Benchmark Dose (BMD) modeling of the data for two endpoints, mammary gland developmental score and number of terminal endbuds, at PND 21 from Macon et al. 2011[63], using serum PFOA data from PND 1 as the dose. Continuous response models were used to obtain the BMD and the Benchmark Dose Lower (BMDL) for a 10% change from the mean for the two endpoints. The lowest significant BMDL, for decreased number of terminal endbuds, of 22.9 ng/ml in serum was used as the POD for reference dose (RfD) development.

Target Human Serum Level

Uncertainty factors (UFs) were applied to the POD to obtain the Target Human Serum Level. The Target Human Serum Level (ng/ml in serum) is analogous to a RfD but is expressed in terms of internal dose rather than administered dose. The total of the uncertainty factors (UFs) applied to the POD serum level was 30 (10 for human variation and 3 for animal-to-human extrapolation).

The target human serum level is: (22.9 ng/ml) / 30 = 0.8 ng/ml (800 ng/L).

Reference Dose (RfD)

EPA used a pharmacokinetic modeling approach to develop a species-independent clearance factor, 1.4×10^{-4} L/kg/day that relates serum PFOA level (μg/L) to human PFOA dose (μg/kg/day). The clearance factor can be used to calculate the RfD, as follows:

RfD = Target Human Serum Level x Clearance factor

RfD = 800 ng/L x 1.4 x 10^{-4} L/kg/day = 0.11 ng/kg/day

Where:

Target Human Serum Level = 800 ng/L

Clearance factor = 1.4 x 10-4 L/kg/day

RfD = Reference Dose = 0.11 ng/kg/day

Maximum Contaminant Level Goal (MCLG) for Drinking Water

Default relative source contribution (RSC) of 20% is used to develop the Health-based MCLG.

To calculate a Health-based MCLG based on mammary gland effects instead of hepatic effects:

MCLG = (RfD x bw x RSC) / DWI

MCLG = (0.11 ng/kg/day x 70 kg x 0.2) / (2 L/day) = **0.77 ng/L (< 1 ppt)**

Where:

RfD = Reference Dose for altered mammary gland development = 0.11 ng/kg/day

bw = assumed adult body weight = 70 kg

RSC = Relative Source Contribution from drinking water = 0.2

DWI = assumed adult daily drinking water intake = 2 L/day

***NOTE:** A MCLG based on mammary gland effects using EPA's drinking water exposure assumptions (for a lactating mother) or Vermont's drinking water exposure assumptions (breastfeeding infant) would result in an even lower MCLG than calculated above. (See Appendix C)

For example, if the drinking water exposure parameters for lactating mothers (EPA) is used:

MCLG = (0.11 ng/kg/day / 0.054 L/kg-day) x 0.2 = **0.41 ng/L (<1 ppt)**

If drinking water exposure parameters for infants under 1 year of age is used (as was done in Vermont):

MCLG = (0.11 ng/kg/day / 0.175 L/kg-day) x 0.2 = **0.13 ng/L (<1 ppt)**

APPENDIX E – APPROXIMATION OF RSC USED BY ATSDR FOR DRINKING WATER ENVIRONMENTAL MEDIA EVALUATION GUIDES

In November 2018 ATSDR published the webpage https://www.atsdr.cdc.gov/pfas/mrl_pfas.html, which stated:

"When ATSDR uses an average adult's or child's weight and water intake to convert these MRLs into drinking water concentrations, the individual PFOA, PFOS, PFHxS, and PFNA concentrations are

- PFOA: 78 ppt (adult) and 21 ppt (child)
- PFOS: 52 ppt (adult) and 14 ppt (child)
- PFHxS: 517 ppt (adult) and 140 ppt (child)
- PFNA: 78 ppt (adult) and 21 ppt (child)"

In posting this webpage, ATSDR provided minimal information as to how the proposed drinking water values were calculated and what assumptions were made and used in their derivation. According to ATSDR, their calculations were based on,

"…the guidelines published in the Public Health Assessment Guidance Manual, and the EPA 2011 Exposure Factors Handbook External. For example, for an estimate of a child's drinking water exposure, ATSDR bases this calculation on an infant (age birth to one year old) weighing 7.8 kg and an intake rate of 1.113 liters per day. For an adult's drinking water exposure, ATSDR bases this calculation on a body weight of 80 kg and an intake rate of 3.092 liters per day. Scientists may use different assumptions when calculating concentrations from dosages."

In this Appendix we back calculate to derive the missing information, namely the relative source contribution (RSC).

From Appendix C:

$$MCLG = (MRL / (DWI/bw)) \times RSC$$

Where (values provided by ATSDR on website):

DWI for adults = 3.092 L/day

and

bw for adults = 80 kg

thus,

DWI/bw for adults = 0.0387 L/kg/day

DWI for children = 1.113 L/day

and

bw for children = 7.8 kg

thus,

DWI/bw for children = 0.142 L/kg/day

So, for adults:

MCLG = (MRL / (0.039 L/kg/day)) x RSC*

And for children:

MCLG = (MRL / (0.142 L/kg/day)) x RSC*

*RSC not provided by ATSDR, however, drinking water values provided by ATSDR can be used with these equations to solve for the RSC used by ATSDR. For example, for PFOA:

Adults:

RSC = (MCLG x DWI/bw) / MRL

RSC = (78 ng/L x 0.0387 L/kg/day) / 3 ng/kg/day

RSC = 1

Children:

RSC = (MCLG x DWI/bw) / MRL

RSC = (21 ng/L x 0.142 L/kg/day) / 3 ng/kg/day

RSC = 1

APPENDIX F – RFD AND MCLG CALCULATIONS FOR GENX

From EPA's Draft Toxicity Assessment of GenX chemicals:

https://www.epa.gov/sites/production/files/2018-11/documents/genx_public_comment_draft_toxicity_assessment_nov2018-508.pdf

"…POD human equivalent dose is 0.023 mg/kg/day. UF applied include a 10 for intraspecies variability, 3 for interspecies differences, and 3 for database deficiencies, including immune effects and additional developmental studies, to yield a subchronic RfD of 0.0002 mg/kg/day. In addition to those above, a UF of 3 was also applied for extrapolation from a subchronic to a chronic duration in the derivation of the chronic RfD of 0.00008 mg/kg/day."

If uncertainty factors that properly reflected the deficiencies in toxicity data (database, sub-chronic/chronic, children's vulnerability, inter/intra species) were used, the combined uncertainty factor could be as high as 100,000 (see Part IV, section GenX).

From pg. 58 of EPA's Draft Toxicity Assessment of GenX chemicals:

RfD = POD/total UF

With NRDC recommended UFs:

RfD = (0.023 mg/kg/day)/100,000 = 2.3×10^{-7} mg/kd/day

Where:

POD = Point of departure human equivalent dose

Total UF = 10 for intraspecies variability, 10 for interspecies differences, 10 for database limitations, 10 for extrapolation from subchronic to chronic duration, and 10 to protect fetuses, infants and children.

From Appendix C:

MCLG = (RfD / (DWI/bw)) x RSC

Using drinking water exposure parameters for lactating mothers, DWI/bw = 0.054 L/kg-day, the MCLG based on liver toxicity would be (rounded):

MCLG = (2 x 10^{-7} mg/kd/day / 0.054 L/kg-day) x (0.2 RSC) = 7.41 x 10^{-7} mg/L = **0.7 ppt**

Using drinking water exposure parameters for an infant under 1 year, DWI/bw = 0.175 L/kg-day, the MCLG based on liver toxicity would be (rounded):

MCLG = (2 x 10^{-7} mg/kd/day / 0.175 L/kg-day) x (0.2 RSC) = 2.29 x 10^{-7} mg/L = **0.2 ppt**

*NOTE: A MCLG based on EPA's proposed RfD for GenX based on liver toxicity would be (rounded):

Using drinking water exposure parameters for lactating mothers

MCLG = (8 x 10^{-5} mg/kd/day / 0.054 L/kg-day) x (0.2 RSC) = 2.96 x 10^{-4} mg/L = 296 ppt

Using drinking water exposure parameters for an infant under 1 year

MCLG = (8 x 10^{-5} mg/kd/day / 0.175 L/kg-day) x (0.2 RSC) = 9.14 x 10^{-5} mg/L = 91 ppt

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ACKNOWLEDGEMENTS

The authors are enormously grateful to Dr. Katie Pelch, Senior Scientist at The Endocrine Disruption Exchange, Dr. Sonya Lunder, Senior Toxics Advisor for the Gender, Equity & Environment Program at Sierra Club, and Dr. Christina Swanson, Director of the Science Center at NRDC, for their careful review and thoughtful comments on this report. The authors also acknowledge the invaluable contributions of: Erik Olson, Mae Wu, Mekela Panditharatne, Cyndi Roper, Joan Leary Matthews, Kim Ong, Miriam Rotkin-Ellman, and Alex Franco.

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