SCIENTIFIC EVIDENCE AND RECOMMENDATIONS FOR MANAGING PFAS CONTAMINATION IN MICHIGAN


Michigan PFAS Science Advisory Panel

Dr. Scott Bartell
Dr. Jennifer Field
Dr. Dan Jones
Dr. Christopher Lau
Dr. Susan Masten
Dr. David Savitz (Chair)

December 7, 2018

GOVERNOR'S FOREWORD

As governor of the State of Michigan, I have committed to a proactive approach to identifying and defining the extent of per and poly-fluoroalkyl substances (PFAS) contamination in our state. When that contamination has been discovered, the state and local partners act immediately to protect public health.

Significant partnerships have been formed with federal agencies, academia, and stakeholders to help Michigan address the nationally emerging PFAS threat. As part of this initiative, I directed the formation of a PFAS Science Advisory Panel to provide guidance to the state from some of the top minds addressing this issue nationally. As we moved forward, we quickly found that Michigan is leading the nation in many ways and should be used as a model for other states as they begin to address this national problem.

I appreciate the time and generosity of the outstanding scientists who developed this report. I know their work will serve to inform the people of Michigan and others across the nation as the United States comes to grip with a growing contaminant for which the science continues to emerge.

Rick Snyder,
Governor

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Report developed for the Michigan PFAS Action Response Team (MPART), Lansing, MI
December 7, 2018

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THE MICHIGAN PFAS SCIENCE ADVISORY PANEL

Dr. Scott M. Bartell - Dr. Bartell is an Associate Professor in Public Health, Statistics, and Epidemiology at the University of California, Irvine. His research interest is environmental health methodology, with an emphasis on environmental epidemiology, exposure science, and risk assessment. For the C8 Health Project/C8 Science Panel Studies, Dr. Bartell has worked on linking fate and transport models and a pharmacokinetic model for perfluorooctanoic acid (PFOA, or "C8") with individual-level residential histories and health outcomes. He has also developed formal statistical methods for biomarker-based exposure estimation and for estimating the biological half-life from observational data in the presence of ongoing exposures. He has served on scientific advisory committees for the National Research Council, the U.S. Environmental Protection Agency, the Centers for Disease Control and Prevention, the National Institute of Environmental Health Sciences, the U.S. Department of Energy, and the International Agency for Research on Cancer.

Dr. Jennifer Field – Jennifer Field is a Professor in the Department of Environmental and Molecular Toxicology, College of Agriculture Studies at Oregon State University. Dr. Field's current research focuses on the development and application of quantitative analytical methods for organic micropollutants and their transformation products in natural and engineered systems. Early in her career, she focused on field-based research to investigate the fate and transport of surfactants in groundwater and wastewater treatment systems. She participated in interdisciplinary research with hydrologists and engineers in order to develop 'push-pull' tracer test methods for determining *in-situ* rates of reductive dechlorination and anaerobic biodegradation of aromatic hydrocarbons. She was a pioneer in the area of fluorochemical occurrence and behavior, with a focus on groundwater contaminated by fire-fighting foams, municipal wastewater treatment systems, and in municipal landfill leachates. Her current research in the area of environmental analytical chemistry concentrates on the use of large-volume injections with liquid chromatography/mass spectrometry as a quantitative yet cost and time-saving approach for the analysis of aqueous environmental samples. Applications of the large-volume injection technique include measurements of illicit drugs in municipal wastewater as an alternative indicator of community drug use; components of the Corexit oil dispersant in seawater, and newly-identified fluorochemicals in groundwater and landfill leachate. She serves as an Associate Editor for *Environmental Science and Technology* and was an editor for *Water Research* from 2004-2008.

Dr. A. Daniel (Dan) Jones is a Professor in the Department of Biochemistry and Molecular Biology and the Department of Chemistry at Michigan State University, where he also has served as Director of the MSU Mass Spectrometry and Metabolomics Core since 2005. For the past 34 years, his research has focused on development and application of mass spectrometry and chromatographic separations for global metabolite analysis, analysis of protein modification by reactive metabolites of drugs, toxins, and endogenous xenobiotic compounds, and analytical chemistry in clinical, environmental, agricultural, and bioenergy applications. His current research centers on development and application of rapid, sensitive, and information-rich mass spectrometry techniques for large-scale profiling and localization of metabolites (metabolomics), elucidating metabolite structures, and measuring exposures to xenobiotic substances. He currently serves as Secretary and Member of the Board of Directors of the Metabolomics Association of North America.
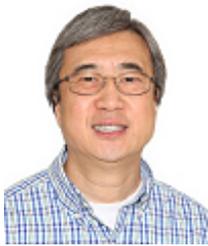
Dr. Christopher Lau – Christopher Lau is Chief of Developmental Toxicology Branch in Toxicity Assessment Division, National Health and Environmental Effects Research Laboratory in the Office of Research and Development at U.S. Environmental Protection Agency. He also holds appointments of Adjunct Assistant Professor at Duke University in the Department of Pharmacology and Cancer Biology, and Adjunct Professor at North Carolina State University the Department of Molecular Biomedical Sciences, College of Veterinary Medicine. He also serves as Associate Editor for *Toxicology, Reproductive Toxicology,* and *PPAR Research*. His research focuses on characterizing the chemically induced developmental toxicity during embryonic and perinatal life stages, understanding their modes of action, and applying such information to human health risk assessment. He has led a team of investigators on PFAS toxicological research for over a decade and published extensively on this topic.

Dr. Susan Masten – Susan Masten is a Professor in the College of Engineering at Michigan State University. Dr. Masten's research involves the use of chemical oxidants for the remediation of soils, water, and leachates contaminated with hazardous organic chemicals. She has conducted research on the *in-situ* use of gaseous ozone to oxidize residual contaminants in saturated soils using ozone sparging and in unsaturated soils using soil venting. Dr. Masten has evaluated the toxicity of the by-products of chemical oxidation processes as measured by gap junction intercellular communication. Her work focused on the ozonation and chlorination of several pesticides, including atrazine, alachlor, and lindane and on the PAHs, especially pyrene. Dr. Masten has also conducted research on the use of ozone-ceramic membrane filtration for the treatment of drinking waters containing organic matter and emerging contaminants. Her current work is focused on the development of treatment technologies to mitigate lead and arsenic in drinking water.

Dr. David Savitz – David Savitz is a Professor of Epidemiology in School of Public Health, at Brown University, he also servs as Associate Dean for Research, and he holds joint appointments in Obstetrics and Gynecology and Pediatrics in the Alpert Medical School. His epidemiological research has addressed a wide range of many important public health issues including environmental hazards in the workplace and community, reproductive health outcomes, and environmental influences on cancer. He has done extensive work on health effects of nonionizing radiation, pesticides, drinking water treatment by-products, and perfluorinated compounds. He is the author of nearly 350 papers in professional journals and editor or author of three books. He was President of the Society for Epidemiologic Research and the Society for Pediatric and Perinatal Epidemiologic Research and North American Regional Councilor for the International Epidemiological Association. Dr. Savitz is a member of the National Academy of Sciences Institute of Medicine. From 2013-2017 he served as Vice President for Research at Brown University.

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Executive Summary

In November 2017, after finding per- and polyfluoroalkyl substances (PFAS) in several locations in Michigan, Governor Rick Snyder issued an Executive Directive that established the Michigan PFAS Action Response Team (MPART). The purpose of MPART is to ensure a comprehensive, cohesive and timely response to the continued mitigation of PFAS across Michigan. Since its inception, MPART has worked to address 34 sites of PFAS groundwater and surface water contamination across the state of Michigan.

The U.S. Environmental Protection Agency (USEPA) classifies PFAS as an emerging contaminant on the national level. Used for more than 50 years, PFAS are a suite of chemicals used in thousands of applications throughout manufacturing, food, and textile industries. Many PFAS are stable chemicals, and thus break down very slowly in the environment, further they are highly soluble and thus easily move from soil into groundwater or surface water. PFAS have been used in many Class B firefighting foams, food packaging, Teflon pans and cleaning products. They have also been used by industries such as electroplating, tanneries, furniture and clothing manufacturing where waterproofing or protective films are required.

Need for Science Advisory Panel

To protect public health and the environment for the people of Michigan, MPART and the Legislature have asked for guidance, based on the most contemporary science available, to address aspects of PFAS, specifically perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) Health Advisory Levels, Adverse Health Outcomes, Remediation and Mitigation, and Environmental Exposure Pathways. Additionally, MPART and the Legislature also requested information on other potentially harmful PFAS other than PFOS and PFOA. This report, produced by a Science Advisory Panel (Panel) of experts from throughout the United States, provides a general understanding of human health risks associated with PFAS in the environment and evidence-based recommendations to Michigan. The state may choose to use this information, in addition to other regulatory and regional considerations and with any federal guidance, to chart a pathway forward, to protect the health and well-being of the citizens of Michigan. While this document discusses environmental pathways for PFAS contamination, its scope is directed towards human health as a first priority.

The Panel met in East Lansing, Michigan in June 2018 to obtain information from State of Michigan agency staff regarding the status of Michigan PFAS issues and the ongoing state efforts to understand the scope of PFAS as a threat to public health. The Panel worked together through email and conference calls for 6 months to the completion of its work. **This report represents the independent work and expert professional judgement from the Panel authors and does not reflect the opinions of their respective employers or the State of Michigan.**

PFAS Types and Environmental Exposure Pathways for Human Risk
Although the range of PFAS in current or recent commercial use is extensive, the most monitored and studied PFAS are small synthetic molecules known for their oil- and water-repellent properties and remarkable chemical stability, even at high temperatures. Their resistance to chemical breakdown comes largely from the strong bond between carbon and fluorine atoms. While some PFAS are large polymer molecules, these are not measured, nor have they been well-studied in terms of environmental fate and transport or toxicity. In addition, new information about environmental contamination by polyfluorinated replacements (such as GenX, ADONA and F-53B) and production byproducts has recently emerged and very little is known about their potential human and ecological health impacts. **As a result, the discussion in this report focuses more on smaller non-polymeric PFAS, as more information is available about their transport and health effects.**

A preponderance of evidence shows that PFAS are transported through water, soil, and the atmosphere and can be found in drinking water, foods, consumer products, and indoor dust. Prior studies suggest that when PFAS levels in drinking water are high, consumption of drinking water is the major route of human PFAS uptake, whereas foods are the dominant source when levels in drinking water are lower. Food contamination may arise from routes including consumption of seafood (primarily fish) and food that has been in contact with PFAS-treated packaging materials and uptake from contaminated waters and biosolids into food products.

The relative contributions of each route of transport remain largely unknown. The impact of the application of contaminated biosolids (sewage sludge) to farm fields and subsequent PFAS transport into foods also has large knowledge gaps. Given the global sources of foods consumed in Michigan and the persistence of perfluorinated chemicals in the environment, management of human exposures to PFAS in foods requires more knowledge about food contamination and biomonitoring (measuring the amount of PFAS in people) to assess exposures. **Despite specific findings of high PFAS levels in some foods such as fish from contaminated waters, surveys have yet to establish strong correlations between food consumption and PFAS levels in blood to suggest that consumption of specific kinds of foods should be generally avoided. Monitoring of PFAS levels in specific foods can guide health advisories.**

Other pathways such as inhalation and dermal exposure have also been noted. Inhalation of house dust represents an additional path of exposure, but there are uncertainties about its contribution to human exposure. Risks associated with dermal exposures, either through direct contact with PFAS-containing materials such as carpets, or bathing/swimming in waters contaminated with PFAS at typical levels, remain largely unknown although the information available suggests that environmental conditions for dermal exposure may not make this a major contributor to overall exposure.

Health Effects, Toxicology and Epidemiology
The health effects of PFAS have been addressed in several assessments, starting with the C8 Science Panel study (c8sciencepanel.org) and continuing with the Agency for Toxic Substances and Disease Registry's (ATSDR) draft Toxicologic Profile report in 2018. Based on those reports, ATSDR has indicated in its *Overview of Perfluoroalkyl and Polyfluoroalkyl Substances and Interim Guidance for Clinicians Responding to Patient Exposure Concerns revised in May 2018* (ATSDR Guide for Clinicians) that there is an array of health outcomes most likely to be associated with elevated exposures to PFAS, based mostly on studies

of PFOA and PFOS, which the Panel has evaluated in relation to the scientific evidence. However, causality between a PFAS chemical and a specific health outcome in humans has not been established in the current scientific literature.

There is extensive toxicologic literature that addresses specific chemicals and associated health outcomes which allows for some broader conclusions. In animal studies, the toxic effects of PFAS can vary widely based on their perfluoroalkyl chain lengths and functional groups, as well as the species and sex differences of the animal models. The hepatotoxic and metabolic effects, immunotoxicity and developmental toxicity of PFAS are supported by the strongest weight of evidence, but their effects are subtle at low doses that are most relevant to environmental exposure. Carcinogenic effects of PFAS and their relevance to human health risks are less certain. Studies of cancer are limited, but the C8 Health Project evidence supported an association of PFAS environmental exposure with kidney and testicular cancer outcomes. PFAS are not known to be genotoxic or mutagenic, but both PFOA and PFOS have been shown to induce tumors in rodents and fish. The International Agency for Research on Cancer recently reviewed the scientific literature on PFOA and cancer and concluded that PFOA is "possibly carcinogenic to humans" based on "limited evidence" in humans, "limited evidence" in experimental animals, and "moderate evidence" for mechanisms of carcinogenicity that are relevant to humans. Combining the evidence from toxicology and epidemiology, the evidence supports the carcinogenicity of PFAS, but cancer may not be the most sensitive health outcome to guide regulation for the protection of public health.

As noted by the National Institutes of Health, immunologic effects of PFAS are supported by epidemiologic studies indicating suppression of children's immunologic reactions to vaccines at low exposure levels and supported by toxicologic evidence of adverse effects on the immune system in laboratory animals. While adverse reproductive and developmental effects are clear from toxicology studies, the human epidemiologic studies suggest a reduction in birth weight.

Toxicologic evidence indicates adverse liver and kidney effects in laboratory animals, with limited human epidemiologic support, and there is mixed evidence regarding endocrine effects (particularly thyroid), neurodevelopment, and obesogenicity (obesity). Future epidemiologic studies that address clinical health outcomes (not just subclinical biomarkers) and toxicologic studies that provide guidance on the full array of PFAS, are most likely to directly impact environmental regulation.

The Panel agrees with the assessment reflected in the ATSDR Guide for Clinicians with regard to associations of PFAS exposure to alterations of thyroid function, high cholesterol, ulcerative colitis, testicular cancer, kidney cancer, pregnancy-induced hypertension, and elevated liver enzymes but have some differing views on specific areas of concern. For example, because elevated serum uric acid could well be a correlate rather than consequence of elevated blood levels of PFAS, the Panel might eliminate that from the list of potential health outcomes due to PFAS. The Panel would add immunologic effects to the list of health condition of concern, particularly those that arise during prenatal exposure and childhood, and reduced birthweight should also be added, based on strong toxicologic findings and supporting epidemiologic evidence.

PFAS health impacts are based on a person's total exposure to PFAS from many sources. However, based on current knowledge, drinking water is the predominant source of exposure for many people consuming

contaminated water, so it remains the focus for health-based regulation, despite potential contributions from consumer products, crops, and other pathways. The USEPA, ATSDR, and a variety of states have determined advisory levels ranging from around 13 to 70 ppt (parts per trillion) for PFOA, PFOS, or the sum of PFOA and PFOS in drinking water, based on immunological, developmental, and other toxicity studies in laboratory animals. The differences in these recommended limits reflect selection of different health outcome, or different assumptions regarding water consumption rates or lactational (breast milk) transfer in toxicologic models that can estimate human risk. The pharmacokinetic models used to link serum concentrations in these animal studies to human doses can also be used to determine the serum concentration expected to result in humans. For example, consumption of 70 ppt PFOA in drinking water over a period of several years is expected to result in an average serum PFOA concentration of about 10 ng/ml in adults, and about 16.5 ng/ml among those with higher rates of water consumption. These serum concentrations fall above the average range of PFOA values reported for a representative sample of the US population in serial National Health and Nutrition Examination studies (NHANES), and within the second or third quartile of exposure categories in several published epidemiological studies in highly exposed populations such as the C8 Science Panel Studies. Increases in ulcerative colitis, some cancers, and other health effects have been reported for these exposure categories. Therefore, **if one accepts the probable links between PFOA exposure and adverse health effects detected in the epidemiological literature as critical effects for health risk assessment, then 70 ppt in drinking water might not be sufficiently protective for PFOA, and possibly by extrapolation to PFOS.**

Based on the available evidence for PFOA, in particular, the combined evidence from toxicology and epidemiology the Panel concludes that the research supports the potential for health effects resulting from long-term exposure to drinking water with concentrations below 70 ppt. The epidemiologic evidence that supports health effects from the serum levels produced by long-term exposure to 70 ppt pertains to developmental immunologic outcomes as well as adult diseases evaluated by the C8 Science Panel and are further supported by the toxicologic studies reviewed as noted in this report.

At present there are no Federal drinking water standards for PFOA, PFOS, perfluorononanoic acid (PFNA) or any of this class of compounds. However, the USEPA has established a health advisory of 70 ppt for lifetime exposure, a Lifetime Health Advisory (LHA) for the sum of PFOS and PFOA. While there is some empirical qualitative evidence supporting an approach that adds together specific forms of PFAS to set health-based limits, there is not yet a firm, quantitative basis for combining them because information is lacking about health effects of exposures to other PFAS compounds, either individually or in mixtures.

Mitigation, Remediation, and Other PFAS
There are no known natural environmental processes in water and soil that can completely destroy perfluorinated chemicals, though aerobic processes often convert polyfluorinated chemicals to other shorter perfluorinated substances that persist and may migrate between environmental media such as soil and water. Complete destruction of PFAS to compounds that are not PFAS requires high-energy remediation processes such as high-temperature incineration.

Regarding mitigation and treatment, anion exchange and granular activated carbon show promise for the removal of PFAS from drinking water supplies. Reverse osmosis also has significant potential however, as with anion exchange and granular activated carbon, the efficacy of removal of short-chain PFAS chemicals

is less than that obtained for the longer-chain compounds. Laboratory-scale and pilot-scale studies are recommended before the implementation of any treatment process since the efficacy of removal varies significantly with the type of PFAS and the pH, temperature, organic matter content, and other properties of the water. Anion exchange, granular activated carbon, and reverse osmosis treatments will result in the production of waste streams that contain PFAS that would need to be further treated before release. For private drinking water supplies, certified point-of-use filters are commercially available for the removal of PFOA and PFOS.

Anion exchange, granular activated carbon, and reverse osmosis can also be used to remove PFAS from wastewater effluent and landfill leachate. However, the presence of organic matter, inorganic chemicals, and particulates will reduce removal efficacy of PFAS as compared to what is typically achievable in drinking waters. High temperature incineration is one of few treatment options that can break down PFAS released from solid material, including granular activated carbon filters, and convert the contaminants to chemicals no longer considered to be PFAS. Although research on new technologies for PFAS destruction in underway, all remediation technologies should be evaluated at laboratory bench and pilot scales to determine the efficiency of destruction and to close the mass balance of organic fluorine from the original waste stream.

Many stakeholders, including those in Michigan, recognize that PFAS contamination is comprised of more than just the two most well-known PFAS, PFOS and PFOA. Analytical methods are being developed to capture perfluorocarboxylic acids (PFCAs), perfluorosulfonic acids (PFSAs), and sulfonamido acetic acids using USEPA Method 537 but soon will also include newer PFAS (e.g., GenX) as high-quality analytical standards become available. Using analytical methods that offer data for a wide range of individual PFAS and the Total Oxidizable Precursor (TOP) assay are likely to aid in characterizing and differentiating sources and for evaluating treatment technologies. At present, USEPA methods do not capture gas-phase PFAS that are known to occur in municipal wastewater and landfill leachates. Additional methods including Particle-induced Gamma Ray Emission (PIGE), total absorbable organic fluorine, and high mass accuracy mass spectrometry offer advantages and limitations but are not yet available in commercial testing laboratories. Forensic approaches for PFAS are under development but it will likely be years before the techniques are fully validated. As fingerprinting capabilities become available, indicator PFAS are likely to be identified and pushed into analytical methods in the commercial market.

The proprietary nature of the PFAS composition of products and goods in the marketplace is problematic for states like Michigan as it impedes the ability to monitor and plan mitigation of human exposure where needed. While concealing the identity of PFAS and other components in products may be important to protect intellectual property and patents, it is problematic when chemicals like PFAS end up in the environment, impacting soil, water, food quality, and ultimately the ecosystem and human health. In order to understand the composition of products (e.g., aqueous film-forming foam) released into the environment and their potential human and ecotoxicological effects, extensive effort is required to identify the different chemicals, although chemical manufacturers and product producers already know the chemical composition of their products. Many PFAS were discovered serendipitously and, recently, some were discovered through a concerted, multi-year, team-based 'reverse engineering' efforts. Such 'reverse engineering', using modern 'non-target' mass spectrometric approaches, incurs a significant financial burden to support the human expertise and instrumentation needed to put together pieces of a complex puzzle. The result is an incomplete patchwork of understanding of the type, number, and

potential effects of PFAS now circulating in the marketplace, the environment, and in humans. States such as California and Washington have restricted the use of various chemical classes; Michigan could consider adopting policies put in place by other states but should consider monitoring for such chemicals independent of the restrictions.

Recommendations for Michigan

The Panel makes the following recommendations specifically for consideration by the State of Michigan:

1. Identification of drinking water supplies with high PFAS levels, and the implementation of PFAS removal treatment from highly-contaminated supplies should be a top priority to minimize risks to human health.

2. When high levels of PFAS contamination are detected at sources of drinking water, a biomonitoring case study should be conducted with volunteer residents to determine if their body burdens exceed those reported by the national survey (NHANES).

3. The Panel recommends that Michigan gather information to understand the extent of PFAS contamination in biosolids and encourage research to assess the fate and transport of PFAS from contaminated biosolids into crop plants and groundwater. Such information will provide guidance regarding when biosolids should not be applied in agriculture (or determine appropriate times between application and planting times) and consider site restrictions, crop harvesting restrictions, monitoring, record-keeping, and reporting requirements where PFAS contamination is a concern.

4. The Panel recommends that the State of Michigan consider both animal and human data for quantification of risk for PFOA and PFOS. Newer advisory levels have been proposed for additional PFAS, for which there are fewer epidemiological studies but sufficient toxicological evidence indicating some common modes of action.

5. For PFAS other than PFOA and PFOS, since there is limited epidemiological evidence and a less firm scientific basis for defining a specific level of drinking water as acceptable or unacceptable, inferences from toxicologic studies with appropriate margins of safety may provide the only basis for making judgments. Nonetheless, the Panel also recommends that the State of Michigan consider setting advisory limits for these additional PFAS in light of their similar chemical structures and toxicity.

6. The options for drinking water standards that we recommend the State of Michigan consider are: (a) adopting one of the advisory values developed by various agencies that are based on toxicological outcome exclusively; (b) adopting a more novel approach and developing an advisory value solely based on epidemiological findings (such as one described in this report) and one used by European Food Safety Authority (EFSA draft document to be released by the end of 2018); or, preferably, (c) developing a new set of values based on weight of evidence and convergence of toxicological and epidemiological data.

7. Given our incomplete understanding but quickly evolving scientific literature on the health effects of specific forms of PFAS, the Panel recommends that all judgments regarding acceptable levels in drinking water should be subject to periodic re-evaluation, with the potential for adopting more or less stringent criteria based on new insights.

8. Water systems facing PFAS contamination should be required to evaluate all possible remedial approaches, including the use of alternative non-contaminated sources. Once several options are chosen, then these choices will need to be tested at the bench and pilot scale using the contaminated water. Numerous factors, including initial concentrations of PFAS, specific PFAS present, background organic and inorganic concentrations, and pH will need to be considered in the design. In addition, operation and maintenance costs, ease of operation, ability to treat multiple compounds, and disposal options need to be considered. Based on these tests, full-scale options can be implemented on a case-by-case basis.

9. 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.

10. The use of NSF International certified filters is recommended where well water is contaminated with PFOA and PFOS and an alternative water source is unavailable.

11. Laboratory-scale and pilot-scale studies are recommended before implementation of treatment technologies to remediate landfill leachate and wastewater effluent contaminated with PFAS. The efficacy of treatment technologies should be evaluated based on the efficiency of destruction and completeness of converting PFAS chemicals to nonhazardous substances.

12. As anion exchange, granular activated carbon, and reverse osmosis result in the production of waste streams that contain PFAS, it is recommended that these streams be treated prior to discharge.

13. Detection of PFAS should move beyond the legacy chemicals of PFOS and PFOA, to include a suite of other PFSAs and PFCAs (Table 1), as well as replacement chemicals (such as GenX) and constituents of aqueous film forming foam (AFFF) that are being identified, when sensitive analytical methods are feasible.

14. For initial waste or site characterization, the Panel recommends use of analytical methods that measure the greatest number of PFAS as well as quantify the branched and linear PFSAs and PFCAs.

15. In cases where water is being treated for use as a drinking water source, the Panel recommends use of analytical methods that quantify short-chain PFAS because they are more difficult to remove under traditional methodologies.

16. The Total Oxidizable Precursor (TOP) assay is commercially available methodology and should be used by analytical laboratories to characterize environmental media including groundwater, wastewater, sediment, soils, and biosolids. This assay signals the presence of precursors, which is useful information when designing and evaluating remedial systems.

17. Agency staff in Michigan should keep abreast of progress in the area of PFAS forensics as techniques undergo validation for stakeholder use.

Recommendations for Research or Monitoring to Address Information Gaps

The Panel recommends the following action as a matter of research and information needed that could be pursued by Michigan or in concert with other state and federal agencies:

1. Biomonitoring of blood PFAS levels in human populations should be conducted in conjunction with measurements of contaminant levels in drinking water to assess the importance of drinking water exposure in relation to potential food, inhalation, or dermal exposures.

2. Research is needed to provide greater understanding of the potential health effects of a broader array of PFAS, not just the legacy compounds. This might include toxicology research to help in developing indices of toxicity or at least inform decisions about which specific forms of PFAS should be combined for regulatory decisions.

3. Toxicologic studies on modes of action are needed to help guide the development of indices of toxicity that would apply across a range of PFAS.

4. Epidemiologic studies of clinical outcomes are needed to build on the extensive body of research addressing biomarkers of health. While the latter can be suggested of likely health effects, direct documentation of clinical disease in relation to quantified PFAS levels is needed.

5. Health outcomes of continued interest that warrant further study include consequences of endocrine disruption, including developmental outcomes and thyroid disorders, consequences of immunologic effects, including autoimmune diseases and infectious diseases, consequences of metabolic effects, and cancer.

6. Research on the development of techniques to effectively remediate water, landfill leachate, wastewater, and biosolids should be conducted.

7. Michigan staff should collaborate with risk assessors from other health and regulatory agencies to develop models and strategies to provide an overall health risk assessment of PFAS *mixtures* that are detected at specific contaminated locales as well as in drinking water.

The Panel recognizes the importance and complexity of the issues facing Michigan and has strived to provide a clear description of the available evidence. **Michigan leadership should be commended for their efforts to address environmental and health concerns with PFAS conscientiously by developing policies that do justice to the current state of knowledge. The questions posed to the Panel are the appropriate for drawing out the information needed to make sound, evidence-based policy decisions. However, by asking these pointed, critical questions, they have also obligated us to reveal how far short the scientific evidence is in providing clear answers to many of them.** The Panel believes that it is beneficial to make use of the evidence that is available, even when it is incomplete, tentative, and subject to change as more research is done on PFAS. It is also important for the many stakeholders concerned with these issues to appreciate that even after assembling and providing a full description of current knowledge, which we have strived to do, the gaps in that knowledge require informed judgment regarding regulation and mitigation. The research does not provide direct indications of the "right" choices but with continuing progress, the uncertainties will be reduced enabling more informed decisions in the future. Although the evidence is still evolving and weak in some important areas, there is sufficient evidence from the toxicologic and epidemiologic findings to justify regulatory efforts to manage exposure for protecting human health. As scientists, the Panel welcomes the opportunity to share our understanding and insights in the service of guiding these critical policy decisions facing the State of Michigan.

SECTION 1 Introduction

In November 2017, after finding per- and polyfluoroalkyl substances (PFAS) in several locations in Michigan, Governor Rick Snyder issued an Executive Directive that established the Michigan PFAS Action Response Team (MPART). The purpose of MPART is to ensure a comprehensive, cohesive and timely response to the continued mitigation of PFAS across Michigan. Through the Executive Directive, MPART is tasked with enhancing cooperation and coordination among local, state and federal agencies charged with identifying, communicating and addressing the potential effects of PFAS in Michigan and protecting public health. The team is chaired by former Michigan Chief Deputy Attorney General Carol Isaacs, who has been authorized by the Governor to coordinate action taken on environmental, public health and public information fronts. Agencies on the team include representatives from the Michigan Departments of Environmental Quality (MDEQ), Health and Human Services (MDHHS), Military and Veterans Affairs (DMVA), Agriculture and Rural Development (MDARD), Natural Resources (MDNR), Licensing and Regulatory Affairs (LARA), and Transportation (MDOT). The team receives additional support from Michigan Departments of State Police (MSP), Technology, Management and Budget (DTMB), Treasury, and Education. MPART also coordinates with the National Guard Bureau, United States Environmental Protection Agency (USEPA), Agency for Toxic Substance and Disease Registry (ATSDR), local health departments, and municipal leaders on PFAS contaminant issues.

Since its inception, MPART has worked to address 34 sites of PFAS groundwater and surface water contamination across the state of Michigan (Figure 1). The identified PFAS sources include current and former Department of Defense sites, chrome electroplating operations, landfills, a shoe manufacturer, a former paper mill, and others. Importantly, MPART's initial response to each site has been to ensure that public health and well-being is protected. Interim response activities have included coordinating the distribution of bottled water to affected residents, installation of water filters, establishing new municipal water supplies, conducting groundwater investigations, and working with responsible parties to clean up these sites of environmental contamination.

The State of Michigan seeks to understand the best mechanisms to protect the public by locating significant PFAS contamination sites and through prevention or mitigation of people's exposure to elevated levels of PFAS. This methodological approach to investigating and defining exposure has resulted in Michigan proactively:

1. Sampling all public water systems, including any system serving more than 25 people. This is the most extensive survey of drinking water ever done within the nation and will cover 75% of the residents in Michigan, with the remaining 25% using private wells;

2. Sampling private wells when there is reason to believe the surrounding ground water may be contaminated with elevated levels of PFAS;

3. Testing waste water treatment plant effluent to determine levels of PFAS discharging into rivers or surface waters and the corresponding need for action;

4. Testing industrial effluent, landfill leachate, and military base water runoff to ensure they are not discharging elevated levels of PFAS into rivers or other surface waters;

5. Testing fish and deer to determine consumption guidance related to PFAS content; and

6. Testing biosolids (treated sewage sludge that is a beneficial resource, containing essential plant nutrients and organic matter as a fertilizer and soil amendment) which may be land applied for PFAS content.
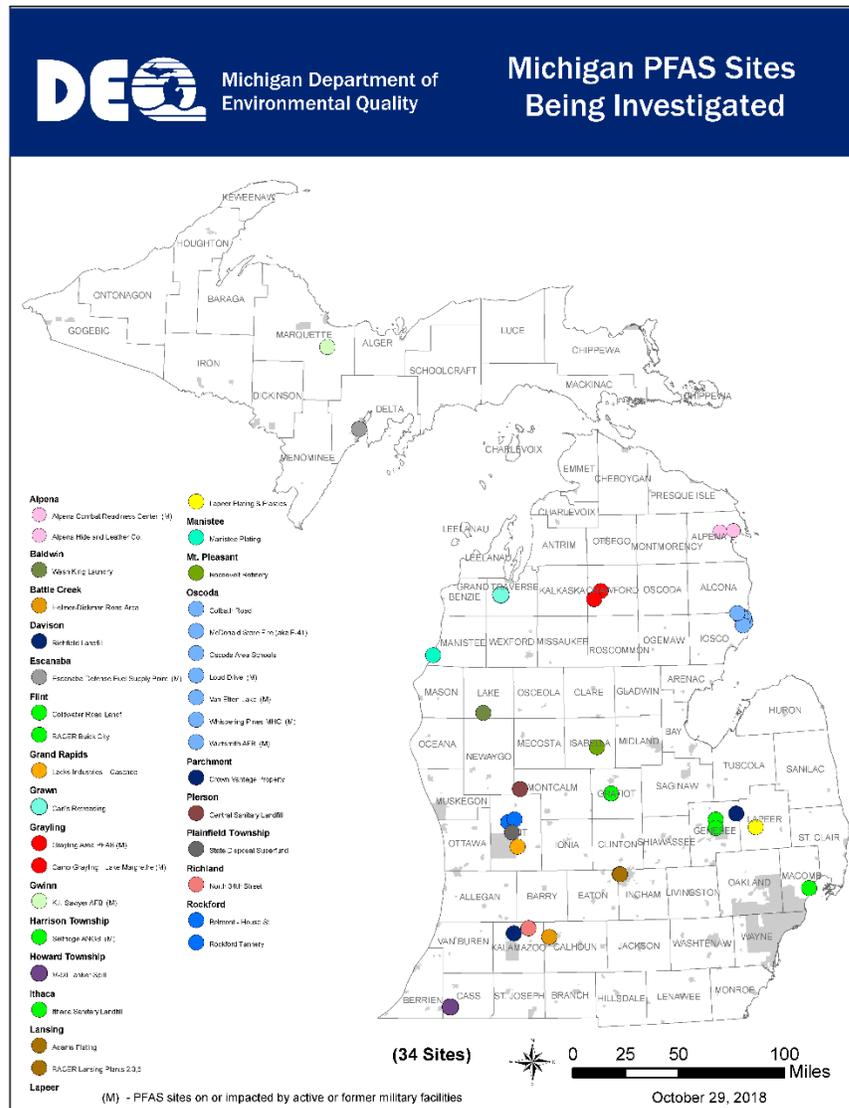

Figure 1. PFAS groundwater and surface water sites under investigation in Michigan, October 29, 2018.

Brief Background on PFAS

The USEPA classifies PFAS as an emerging contaminant on the national level.   Used for more than 50 years, PFAS are a suite of chemicals that were used in thousands of applications throughout the industrial, food, and textile industries. They are stable, breaking down very slowly in the environment, and they are highly soluble, easily transferring from the soil to groundwater or surface water. PFAS have been used in many Class B firefighting foams, food packaging, and cleaning products and also used by industries such as plating, tanneries, furniture or clothing manufacturing where waterproofing or protective films are required.

Thousands of chemicals are in the PFAS family including perfluorooctanoic acid (PFOA), perfluoroctane sulfonate (PFOS), and GenX. Most information known about toxicity and environmental pathways is for PFOS and PFOA which have eight carbons (C8) and are also known as long chain PFAS. The USEPA created a Lifetime Health Advisory for PFOS and PFOA, combined, of 70 parts-per-trillion (ppt). In addition to PFOS and PFOA, perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA) along with a few other PFAS were reviewed in the *ATSDR Toxicological Profile for Perfluoroalkyls, Draft for Public Comment*, released June 20, 2018 (ATSDR 2018).

PFAS that are or could be transformed or broken down to PFOA and/or PFOS should no longer be manufactured in the U.S. under a voluntary agreement by industry with the EPA (https://www.gpo.gov/fdsys/pkg/FR-2007-10-09/pdf/E7-19828.pdf; https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-management-and-polyfluoroalkyl-substances-pfass).
However, these chemicals continue to be a threat to public health because they break down slowly, are persistent in the environment, and they may build up in fish, wildlife, and humans with continued exposure (a.k.a. bioaccumulate).

The Center for Disease Control and Prevention (CDC) has tested U.S. residents' blood for a select number of PFAS. CDC's National Health and Nutrition Examination Surveys has quantified four PFAS (PFOS, PFOA, PFHxS, PFNA) in almost every person's blood sample (CDC 2017). This is likely because of the long half-life within the human body for PFAS, averaging from 2.3 to 12 years based on the type of PFAS (ATSDR 2018), and the historical proliferation and distribution of the PFAS chemicals. The CDC has further demonstrated that PFOS levels declined markedly from 2000 to 2014 in the U.S. population, which coincides with declining PFOS use in the U.S. (Figure 2).

ATSDR, is assisting local, territorial, tribal, state, and federal partners in addressing the public health concern due to human PFAS exposure. While the science surrounding potential human health effects from PFAS contamination is still evolving, available information has increased rapidly over the last decade. Thus, the State of Michigan has asked for advice and counsel from national leading PFAS scientists, in the form of a Scientific Advisory Panel (Panel) related to public health and exposures to PFAS.
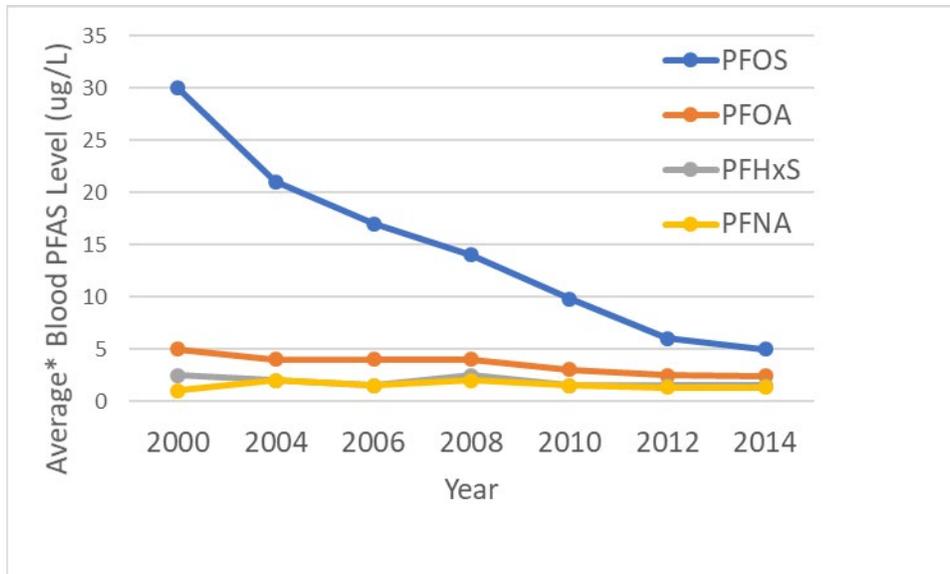
Figure 2. Average (*geometric mean) of blood levels of four PFAS detected in most people in the United States 2000-2014 (CDC 2017).

Charge to the Science Advisory Panel

To protect public health and the environment for the people of Michigan, MPART and the Legislature have asked for guidance, based on the most contemporary science available, to address aspects of PFAS, specifically PFOS and PFOA Health Advisory Levels, Adverse Health Outcomes, Remediation and Mitigation, Environmental Pathways, and PFAS other than PFOS and PFOA. This report, produced by a Science Advisory Panel (Panel) of experts from throughout the United States, will provide recommendations for an evidence-based approach towards the regulation of PFAS and a general understanding of risk to human health associated with PFAS in the environment and the resulting regulation of PFAS. The state may choose to use this information, in addition to other regulatory and regional considerations and with any federal guidance, to chart a pathway forward, to protect the health and well-being of the citizens of Michigan. While this document discusses pathways in the environment for PFAS contamination, its scope was directed towards human health as a first priority.

To help frame the work of the Panel, MPART developed a list of questions, categorized by larger theme areas. The role of the Panel was to provide information and recommendations for each of these questions and provide information regarding key risks and uncertainties associated with the information used to develop the recommendations. Other questions or revisions of these questions and areas could be addressed by the Panel as they determined appropriate. The questions were organized by topic areas and included:

1. **Health Advisory Recommendations**
   - After a review of the basis for the recommendation and all relevant evidence, does the 70 parts per trillion USEPA Lifetime Health Advisory for PFOS and PFOA, individually or in combination, represent a level below which the risk of harm is likely to be minimal?

- After review of the applicable current PFAS research is there a substantial scientific basis to suggest that the standard for Michigan's groundwater should be more restrictive than the current 70 ppt combined for PFOS and PFOA?

2. **Health Outcomes Knowledge and Guidance**
   - Other than the health outcomes listed on the ATSDR interim guidance for clinicians responding to patient exposure concerns (https://www.atsdr.cdc.gov/pfas/docs/pfas_clinician_fact_sheet_508.pdf), are there additional health outcomes more recently identified or associated with PFAS other than PFOS and PFOA that have a similar weight of evidence as those included on the list?
   - Given the chemical-physical, toxicity, and dermal absorption information on PFAS are there any levels in water or soil that would create dermal contact concerns?
   - Has the USEPA determined whether PFAS is a carcinogen?
   - What types of epidemiologic studies of PFAS exposure and health outcomes would have a meaningful impact on the recommended standard for drinking water limits?

3. **Remediation and Mitigation**
   - What are the best degradation techniques to destroy fluorochemicals in the environment? How does this strategy relate to point of service filters and whole house filters to mitigate exposure?

4. **Environmental Pathways for Contamination**
   - Please advise on the application of biosolids that contain PFAS when those biosolids are used on farm fields.
   - Are there food products that should be avoided if grown in PFAS- contaminated water or ground?

5. **PFAS Chemicals other than PFOS and PFOA**
   - Is there sufficient information on other PFAS to guide whether or not they should be included with PFOA and PFOS in the 70 ppt standard to be health protective?
   - Does sufficient research exist to allow the State of Michigan to consider regulation of other PFAS?
   - Are new generation PFAS likely to be less toxic than original longer chain chemicals?

The Panel met in East Lansing, Michigan in June 2018 to obtain information from State of Michigan agency staff regarding the status of PFAS in Michigan and the work that Michigan was conducting to understand the scope of PFAS as a threat to public health. The Panel worked together through email and conference calls over the next five months to complete the report. **This report represents the independent work and expert professional judgement from the Science Advisory Panel authors and does not reflect the opinions of their respective employers or those of the State of Michigan.**

SECTION 2 Types or Classes of PFAS

Though the range of PFAS in current or recent commercial use is extensive, the most monitored and studied PFAS are small synthetic molecules renowned for their oil- and water-repellent properties and remarkable chemical stability, particularly at high temperatures. Their resistance to chemical breakdown comes largely from the strong bond between carbon and fluorine atoms. Though some PFAS are large polymer molecules, these are not routinely measured, nor have they been well-studied in terms of environmental fate and transport or toxicity. As a result, the discussion in this report focuses more on smaller non-polymer PFAS, as more information is available about their transport and health effects.

Most information about PFAS contamination pertains to substances consisting of a chain of carbon atoms, with most attached only to fluorine atoms, other carbon atoms, or a polar group that has attraction to water. These PFAS can be first distinguished by whether they are completely per-fluorinated, meaning that no carbon atoms are attached to hydrogen atoms. The primary classes of perfluorinated chemicals include perfluoroalkylsulfonates (PFSA, of which the 8-carbon compound PFOS is an example) and perfluorocarboxylates (PFCA, e.g. 8-carbon analog PFOA) that include substances varying in carbon chain length. PFSA and PFCA are resistant to oxidative breakdown (or environmental degradation) because they lack carbon-hydrogen bonds. Other PFAS contain carbon atoms (often two carbons, each with two attached hydrogen atoms), with attachments to various polar groups. Since these are still extensively, but not completely fluorinated compounds, they are termed poly-fluorinated chemicals. More recent processes for production of PFAS use a process known as telomerization that involves building of the carbon chain, often two carbon atoms at a time. The two-carbon building blocks may be completely fluorinated or may have hydrogen atoms in place of fluorines. As a result, many are termed fluorotelomer derivatives, annotated by the lengths of the perfluorinated and hydrogen-containing chains (e.g. 6:2 FtS has six perfluorinated carbon atoms and two carbon atoms that bear only hydrogen atoms; Table 1). The distinction between completely (perfluorinated) and partially fluorinated (polyfluorinated) PFAS chemicals is relevant later in the report, in that most perfluorinated chemicals are very resistant to degradation, whereas polyfluorinated chemicals can be aerobically broken down to PFCA.

Table 1. Categories and examples of common PFAS.

Compound class	Features of chemical structure	Classification	Examples
Perfluoroalkylsulfonates (PFSA)	$F_3C{-}[CF_2]_n{-}SO_2{-}O^-$	Perfluorinated	PFOS ($n = 7$) PFHxS ($n = 5$) PFBS ($n = 3$)
Perfluoroalkylcarboxylates (PFCA)	$F_3C{-}[CF_2]_n{-}CO{-}O^-$	Perfluorinated	PFNA ($n = 7$) PFOA ($n = 6$) PFHpA ($n = 5$) PFHxA ($n = 4$) PFBA ($n = 2$)
Fluorotelomer sulfonates (FTSA)	$F_3C{-}[CF_2]_n{-}CH_2{-}CH_2{-}SO_2{-}O^-$	Polyfluorinated	6:2 FtS ($n = 5$) 8:2 FtS ($n = 7$)

SECTION 3 Pathways of Human Exposure to PFAS

PFAS are found in all indoor and outdoor environments across the globe (Blum et al. 2015). The range of PFAS exhibit properties that allow some to migrate through groundwater and surface water (rivers, streams, and lakes), be released into the atmosphere and returned in precipitation, and adsorbed by soil. Some PFAS are taken up and may bioaccumulate into food crops, livestock, wildlife, and the tissues and bodily fluids of humans through consumption of contaminated foods, drinking water, and direct contact with various consumer products (Figure 3). Each transport process has potential for differential fractionation of individual PFAS, including bioaccumulation which enhances levels relative to the surrounding environment.

PFAS vary in how they partition between water and particles, with shorter chain compounds mainly distributed in water and longer chain compounds primarily associated with particles (Ahrens and Bundschuh 2014). The lower solubility of longer chain PFAS in water drives their partitioning into particles and biomass to a greater extent than shorter-chain substances. This variation influences how individual PFAS chemicals are transported through the environment and taken up by living organisms including humans. The implication is that dominant routes of human exposure are not uniform for all types of PFAS.

Large amounts of point-source PFAS releases have occurred at industrial, military, and firefighting operations, and in lesser quantities at individual (non-point) sites when they migrate from consumer products into the environment and/or from deposition from the atmosphere. Their remarkable resistance to natural degradation processes that break down many other pollutants enables their transport across the globe and contributes to multiple pathways of exposure to PFAS in all human populations.

One particularly relevant report, published in 2012 by the Minnesota Pollution Control Agency (MPCA), followed PFAS contamination in the vicinity of the 3M Company's PFAS manufacturing site (Oliaei et al. 2013). Discharges from this facility led to widespread contamination of surface and groundwater including drinking wells, with the more mobile perfluorobutanoic acid (PFBA) reaching levels of 1,170,000 ppt (1.17 mg/L) in downgradient groundwater. Contaminated water was addressed through installation of water treatment systems, connection to alternative water supplies, and excavation and removal of contaminated soils.

The key take-away point from these investigations is that most environmental and treatment process do not completely destroy (or mineralize) PFAS, and at best, convert one PFAS form to another. Such is the case with the polyfluorinated compounds which are often converted to perfluorocarboxylates (PFCAs) that are resistant to further oxidative degradation.
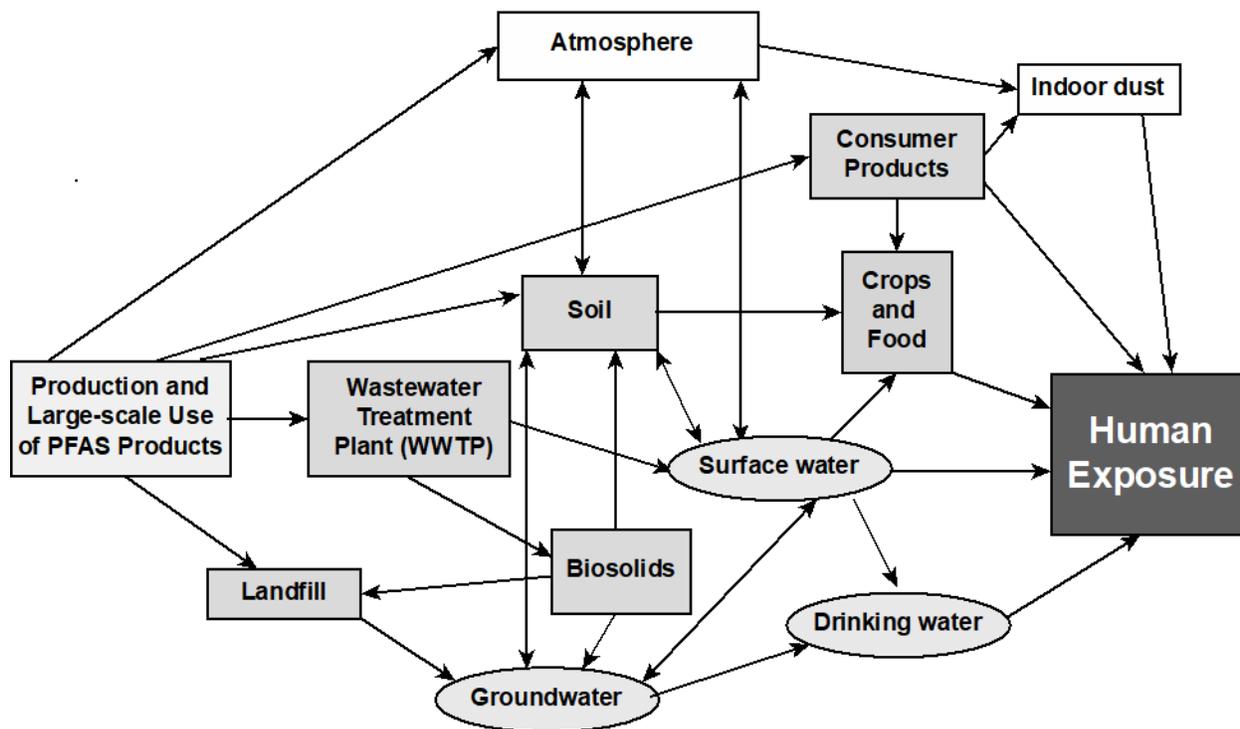
Figure 3. Environmental transport of PFAS in the context of pathways to human exposure. Figure adapted from (Ahrens and Bundschuh 2014).

PFAS contaminants in landfill and wastewater leachates and in wastewater treatment

When PFAS-containing products reach the end of their usefulness, the remainder commonly ends up in landfills, where constituents may leach from the landfill. The leachate from such point sources may be treated on-site or at a wastewater treatment plant, but the effectiveness of these processes in reducing PFAS levels or sequestering them remains in doubt (Benskin et al. 2012).

Removal and destruction of hazardous substances are principal functions of water treatment processes. Detection and remediation of hazardous substances in water are inextricably linked (Shannon et al. 2008), and numerous PFAS are present in both influent and effluent streams of wastewater treatment plants (Field and Seow 2017). Monitoring of levels of a wide range of PFAS substances at ppt (nanograms per liter = parts per trillion or ppt) levels can be costly but it is essential for assessing the fate of PFAS following treatment. Wastewater treatment plants have been recognized as a significant point of release of PFAS into natural waters and for PFAS accumulation into biosolids, particularly when industrial water releases are processed. In addition to removing nutrients and pathogens, many wastewater treatment plant processes often result in destruction of hazardous substances. However, perfluorinated compounds are

notoriously recalcitrant to biodegradation, leaving their separation from water by adsorption or accumulation into biosolids as a central goal. Preferential accumulation of longer chain PFAS into biosolids has been reported (Sinclair and Kannan 2006), but PFAS are often released in wastewater treatment plant discharges. Levels of one PFAS compound (PFOA) discharged into effluent waters by six wastewater treatment plants in New York were on the order of 100 ppt, comparable to the 70 ppt EPA advisory level (Sinclair and Kannan 2006).

Although perfluorinated compounds are extremely resistant to biodegradation, some polyfluorinated compounds, most notably fluorotelomer alcohols, may undergo aerobic degradation during wastewater treatment. However, these substances are primarily converted to polyfluoroalkyl carboxylates (PFCAs) which are resistant to further degradation (Butt 2014, Chen 2017). The chemical identities of many PFAS have yet to be defined.

Direct exposures to PFAS through drinking water, foods, and consumer products

Although human exposures to PFAS occur worldwide, the contributions of specific pathways of exposure may vary across the range of PFAS, and also differ across human populations due to a person's specific use and consumption of contaminated foods and/or water, as well as their exposure to household dust, other consumer products, and in occupational settings.

PFAS occurrence in foods has been attributed to two primary sources: their bioaccumulation in aquatic and terrestrial food chains and the leaching of PFAS from food packaging materials (Schaider et al. 2017; Vestergren and Cousins 2013). Several investigations have assessed PFAS levels in foods, including a 2007 study that measured PFAS in food composite samples from the Canadian Total Diet Study. The authors estimated that mean dietary intake of Canadians for total PFCAs varied with age and gender and fell into the range of 100-480 ng PFCAs per person per day (Tittlemier et al. 2007). The report concluded that foods accounted for 61% of human PFAS exposures among these Canadian participants. Similar estimates of dietary intakes have been reported for other countries including the United States (Schecter et al. 2010), Sweden (Gebbink et al. 2015), the United Kingdom (Clarke et al. 2010), Korea (Heo et al. 2014), Denmark (Danish Ministry of the Environment 2015) and China (Zhang et al. 2011). A 2017 review of worldwide PFAS intake levels commented that regional differences may be associated with varied consumption of fish and other seafood, in which PFAS have been detected at higher levels (Domingo and Nadal 2017). A Danish report that studied only PFOA (Danish Ministry of the Environment 2015) reported a median human intake of PFOA of 2.9 ng/kg body weight/day, with fruits and fruit products being the most important contributors to PFOA exposure, followed by fish and other seafood. As stated above, they conclude that variation is substantial due to differences in diets.

Understanding of the extent of uptake of PFAS into the food chain is more limited, but several publications have explored PFAS content in foods. Vestergren and Cousins (2009) proposed scenarios for PFAS intake by humans that illustrate vast differences in contributions of various pathways of exposure. In situations characterized by background (1.3 ppt) or elevated (40 ppt) levels of PFAS in drinking water, PFAS from the diet, and not drinking water, dominated human intake. For a third scenario representing high (519 ppt) levels of PFAS in drinking water that was contaminated from a polluted point source, drinking water provided more than 75% of the estimated PFAS intake. In the C8 Science Panel Studies, PFOA in drinking

water dominated total estimated human intake for water systems with PFOA concentrations above 100 ppt (Shin et al., 2011a, 2011b). For legacy PFAS with declining human serum concentrations, such as PFOA and PFOS, the relative contribution of contaminated drinking water to the total intake of those PFAS is likely higher now than it was in that past. For example, the pharmacokinetic model for PFOA described later in this report indicates that at a water concentration of 19 ppt or higher, drinking water would provide more than 50% of the estimated PFOA intake. Ghisi et al. (2018) reported low accumulations of PFOA and PFOS in peeled potatoes and cereal seeds, while short-chain compounds were found to accumulate at high levels in leafy vegetables and fruits. Contaminated drinking water also presents an indirect route of exposure through uptake of contaminants into home-grown produce (Scher et al. 2018), particularly for short-chain PFAS.

Biosolids (sewage sludge) are a product of the wastewater treatment process. Approximately 50% of biosolids produced through this process are recycled by applying them to fields, and thus they present another means of PFAS transport into foods and drinking water (USEPA 2018)   Arvaniti & Stasinakis (2015) reviewed the literature on PFAS concentrations in sewage sludge (biosolids) and reported PFOA concentrations that ranged from ~0.7 to 241 ng/g dry weight in the United States. The PFOS concentrations ranged up to 110 ng/g dry weight. Additional data for biosolids levels in Europe and Asia demonstrates the ubiquitous nature of PFAS, with biosolids containing a wide range of PFAS from PFBA at the lower molecular range to N-ethyl-perfluorooctanesulfonamide (N-EtFOSA) at the higher range.   A municipal wastewater treatment plant in Decatur, Alabama processed effluent from industrial PFAS manufacturers, and the resulting biosolids were applied to agricultural fields as soil amendments over a period of 12 years. The findings demonstrated that application of PFAS-contaminated biosolids led to the contamination of ground and surface waters, particularly by the more mobile short chain PFAS (e.g. PFBA at greater than 1000 ppt), whereas the longer chain compounds remained in soil (Lindstrom et al. 2011). A complementary study reported that amended soils with biosolids derived from paper fiber processing and wastewater treatment and showed uptake of polyfluorinated phosphate esters (PAPs) and PFCAs, which are products of PAP biotransformation, into the legume *Medicago truncatula* (a clover like plant that is a model for alfalfa) in greenhouse experiments and pumpkins in field experiments (Lee et al. 2014). PAPs are not routinely measured in most circumstances, and their uptake into pumpkin fruit (to 8 ng/g) has implications for human exposure through foods grown on contaminated soils.

PFAS transport to drinking water is of particular concern when high levels of PFAS from industrial and military sites leach into groundwater or surface water. Both groundwater and surface water are used for drinking water supplies throughout Michigan. Background levels in surface waters in remote areas and groundwater levels in contaminated areas provide a range for context and understanding the levels that are found through Michigan. PFOA and PFOS levels in surface waters collected from 79 fresh water sites across Japan ranging from about 0.1 ppt in remote areas to greater than 400 ppt in a site near Osaka (Saito et al. 2004). The highest levels were observed in water near an industrial wastewater disposal site (67,000 ppt PFOA), which discharges water into a river that is the source of drinking water for Osaka city. Levels of PFOA in Osaka drinking water were significantly higher (40 ppt) than in other regions of Japan. Rayne and Forest (2009) summarized results from dozens of studies reporting the presence of PFAS chemicals in lakes, rivers, and groundwaters. The levels were highly variable, from non-detect to 2,210,000 ppt in the Etobicoke River (Ontario, Canada). The PFCA and perfluoroalkyl sulfonates (PFSA) compounds found most often were the C7 PFCAs and C8 PFSA. The highest groundwater levels reported were near military bases (e.g., Naval Air Station, Fallon, NV: 6,570,000 ppt (6.5 mg/L) C7 PFCA, 380,000 ppt C8 PFSA).

Exposure through the skin, or dermal exposure, is also a pathway for consideration. Substantial levels of PFAS in house dust and soils present the potential for exposure through dermal contact, although the uptake of PFAS through the skin has only been explored for a limited range of compounds. A meta-analysis of exposure to consumer product chemicals in indoor dust relied on the assumption that PFAS intake was largely through ingestion (Mitro et al. 2016.) *In vitro* experiments reported by DuPont have suggested that under certain experimental conditions PFOA can permeate through the skin (Fasano et al. 2005; Franko et al. 2012), and a single *in vivo* study at NIOSH documented dose-dependent uptake of dermally applied PFOA, under experimental and not environmental conditions, into serum of mice (Franko et al. 2012). The PAPs, which are fluorotelomer-based chemicals, have also not been as widely investigated, but their levels in house dust samples from numerous countries were described by Eriksson and Karrman (2015). PAP levels in house dust reached as high as 692 ng/g and exceeded levels of other PFAS classes. PAPs may undergo biodegradation to form PFCAs and reactive electrophiles with potential toxicity (Rand and Mabury 2017), and as such may present a route of indirect exposure to PFCAs through ingestion.

Dermal uptake of PFOS and PFOA from water is expected to be minimal under environmental conditions where both substances exist in negatively-charged ionic forms. The laboratory conditions for the dust exposure work (Fasano et al. 2005 and Frako et al. 2012) were very different than those found in the environment and thus the results may not be directly translatable for conclusions about swimming or bathing. Information about dermal uptake of PFOA and PFOS is quite limited and understanding of uptake of shorter chain PFAS substances remains even more scarce.

The phenomenon of "foam" developing in surface waters contaminated by PFAS has been observed in Michigan and is distinguished from other naturally generated foams by its physical characteristics and brilliant whiteness in appearance. Generally, the composition and concentrations in the foam vary by the groundwater contamination source at each location, but the concentration of PFAS in the foam is markedly high (Michael Jury, MDEQ personal communication). Little to no information exists for understanding the conditions of when the foam forms as foam events are inconsistent on the surface waters where they appear. Appropriate health advisories against contact or ingestion of the foam are advised due to the significance of the PFAS levels in the foam while actual risk is determined through further investigations.

Biomonitoring of PFAS levels in human populations

Biomonitoring (the measurement of the body's concentration of a toxic chemical) of PFAS levels in blood provides important information about human exposures and the source materials to which human populations are exposed. Longitudinal surveys of populations provide evidence when exposures change. The 2003-2004 National Health and Nutrition Examination Survey (NHANES) measured target PFSA and PFCA substances of chain lengths from C6-C12, detecting PFOS, PFOA, PFHxS, and PFNA in 98% of 2094 blood samples from across the U.S., with geometric mean levels in the low µg/L (or parts-per-billion (ppb)) range(Calafat, Wong et al. 2007). More recent measurements showed a gradual decrease relative to the 1999-2000 survey, consistent with the end of electrochemical PFAS production in 2002. Concentrations of PFOA in human serum samples collected from around the world have been interpreted to suggest that background exposures explain serum levels in the 1-10 µg/L range, with higher levels in individuals with

higher occupational or point-source exposures (Vestergren and Cousins 2009). Such background levels of PFOA in blood have been attributed to foods as the likely route of exposure, but the relative contributions of food packaging materials versus bioaccumulation in fruits, fish, plant crops, and meats arising from environmental transport have not been firmly established. Residents near point-sources of contamination often exhibit substantially higher serum levels, and contrasts between serum background and hot-spot levels have been reviewed (IARC, 2017) The C8 Health Project (Frisbee et al., 2009) measured elevated serum PFOA levels (geometric mean of 33 µg/L) in the Ohio River valley region, near a large Teflon production facility and landfill used to dispose of PFAS chemicals, with serum PFOA reaching age- and sex-adjusted mean of 228 µg/L in one water district.

PFAS levels in human milk complement measurements of blood levels and aid interpretation of biomonitoring data for assessment of a child's exposures from breastfeeding. A 2010 report found PFAS in human milk, finding PFOA levels in human milk consistent with biomonitoring data in adult blood, ranging from > 900 ppt to undetected and PFOS ranging from 865 ppt to undetected. Similar levels of PFOA and PFOS were found in powdered infant formula reconstituted in purified water (Llorca et al. 2010), with profiles suggesting contamination from packaging and/or production processes.

Current knowledge gaps and areas for future development

The pathways and processes that lead to human exposures to PFAS are numerous and complex. All human populations have measurable levels of PFAS in their blood, demonstrating that everyone has experienced exposure to PFAS, but the contributions of different pathways of exposure often remain unclear and deserve more investigation. In some cases, particularly for polyfluorinated chemicals, there is limited information about the relative importance of different routes of human exposures, *in vivo* half-lives (Field and Seow 2017), and the importance of *in vivo* biotransformations which have been suggested in the context of "indirect exposures" to PFCA which form by metabolic transformation of other precursors (D'Eon and Mabury 2011). Very little information exists in the literature regarding the importance of dermal absorption of the range of PFAS present in the context of indoor or environmental exposures.

Conclusions and Recommendations

Conclusions
While PFAS are used directly in some consumer products, the preponderance of literature evidence suggests that these PFAS chemicals are transported through water, soil, and the atmosphere and end up in drinking water, foods, consumer products, and indoor dust to which people are exposed. No environmental processes are known to completely destroy perfluorinated chemicals, though aerobic processes often convert polyfluorinated chemicals to shorter perfluorinated substances that persist and may migrate between environmental media. Prior studies suggest that when PFAS levels in drinking water are high consumption of drinking water is the major route of human PFAS uptake, whereas foods are the dominant source when levels in drinking water are lower. Food contamination may arise from other routes including contact with packaging materials and bioaccumulation from contaminated waters and biosolids into food products, but the contributions of each route remain largely unknown. The role of contaminated biosolid land applications to PFAS transport into foods also has large knowledge gaps. Given

the global sources of foods consumed in Michigan and the persistence of perfluorinated chemicals in the environment, management of human exposures to PFAS in foods requires more knowledge about food contamination and biomonitoring to assess exposures. Despite specific findings of high PFAS levels in some foods including fish from contaminated waters, surveys have yet to establish strong correlations between food consumption and PFOA or PFOS levels in blood and thus cannot provide guidance on specific kinds of foods that should be generally avoided. Hoever, monitoring of levels in specific foods could provide the information needed to guide health advisories. Inhalation of house dust represents an additional path of exposure, but there are uncertainties about its contribution to human exposure because many abundant PFAS chemicals in house dust are not routinely measured. Risks associated with dermal exposures, either through direct contact with PFAS-containing materials such as carpets, or bathing/swimming in waters contaminated with PFAS at typical levels, remain largely unknown.

Recommendations
1. Identification of drinking water supplies with high PFAS levels, and the implementation of PFAS removal treatment from highly-contaminated supplies should be a top priority to minimize risks to human health.

2. When high levels of PFAS contamination are detected at sources of drinking water, a biomonitoring study, or Exposure Assessment, should be conducted with volunteered residents to determine if their body burdens exceed those reported by the national survey (NHANES).

3. The Panel recommends that Michigan gather information to understand the extent of PFAS contamination in biosolids and encourage research to assess the fate and transport of PFAS from contaminated biosolids into crop plants and groundwater. Such information will provide guidance regarding when biosolids should not be applied in agriculture (or determine appropriate times between application and planting times) and consider site restrictions, crop harvesting restrictions, monitoring, record-keeping, and reporting requirements where PFAS contamination is a concern.

4. Biomonitoring of blood PFAS levels in human populations should be conducted in conjunction with measurements of contaminant levels in drinking water to assess the importance of drinking water exposure in relation to potential food, inhalation, or dermal exposures.

SECTION 4 Potential Toxicity and Health Effects

This chapter begins with an overview of the epidemiologic and toxicologic evidence regarding potential health effects of PFAS. This is followed by a discussion of specific health outcomes of greatest interest, first presenting the epidemiologic evidence then the toxicologic studies, with particular attention to immunologic effects, reproductive/developmental effects, carcinogenicity, liver disease, and thyroid disorders. These outcomes are emphasized for specific reasons: immunologic effects and reproductive/developmental effects because these are the health outcomes for which there is the most convergence of the toxicology and epidemiology, and cancer, because of the high level of public concern and since it is frequently (but not always) the most sensitive outcomes for long-term exposure. There is also substantial evidence pertaining to liver disease and thyroid disease from toxicology and limited epidemiologic research. Next, there is a brief section on the interpretation of subclinical outcomes which are common in human studies of PFAS. Finally, we consider what types of toxicologic and epidemiologic research could have the greatest impact in guiding regulation of PFAS in drinking water, both toxicology and epidemiology studies.

Multiple assessments have been made of health outcomes potentially associated with exposure to PFAS, largely based on PFOA and PFOS with some literature on PFHxS and PFNA as well (Hekster et al. 2003, Rapazzo et al. 2017, ATSDR 2018). Perhaps the first was the report of the C8 Science Panel charged with evaluating the evidence of a "probable link" between PFOA exposure and health outcomes in the Mid-Ohio Valley. Their review and evaluation identified six health conditions thought to be linked to PFOA with the criterion being "more probable than not": kidney cancer, testicular cancer, ulcerative colitis, thyroid disease, elevated cholesterol, and pregnancy-induced hypertension (http://www.c8sciencepanel.org/). The most comprehensive and recent review is the one developed as a draft Toxicological Profile by the Agency for Toxic Substances and Disease Registries (ATSDR 2018) which methodically tabulates all relevant epidemiology and toxicology studies. Other committees and researchers have evaluated the evidence pertaining to such outcomes as developmental disorders (most notably fetal growth and preterm birth), obesity, immune response, liver and kidney disease, cancer (Benbrahim-Taliaa et al. 2014), and a range of other health conditions.

The Panel is not attempting to conduct a review of the many reviews let alone the hundreds of original papers on which they were based but focus instead on a summary of the recommended guidelines from ATSDR for informing clinicians as a distillation of the evidence that is intended for practical application (ATSDR 2018). In that report, designed to help clinicians respond to inquiries, they indicate a set of diseases for which they believe there is sufficient evidence of a potential effect of PFAS to be suitable for consideration and discussion: thyroid function, high cholesterol, ulcerative colitis, testicular cancer, kidney cancer, pregnancy-induced hypertension, elevated liver enzymes, and high uric acid. This list overlaps with the assessment of the C8 Science Panel and adds two markers of disease risk, elevated liver enzymes and high uric acid. We will consider the evidence that bears on these recommendations. As noted by ATSDR in their guidance document and an important point to emphasize, the research is at a very early stage and quite incomplete in terms of PFAS that have been studied and the volume of informative, high quality epidemiologic studies.

In addition to the list generated by ATSDR, the Panel believes that there is sufficient evidence to consider potential immunologic effects and a range of developmental conditions related to prenatal exposure including reduced fetal growth, preterm birth, obesogenicity (obesity), and neurodevelopmental disorders, as well as developmental immunologic effects. The Panel also notes some of the concerns that may call into question whether the assessment of PFAS being causally related to certain diseases in humans is accurate given the potential for reverse causality. Because PFAS exposure is often measured as a biomarker in blood, and the health condition may also be based on a blood biomarker (e.g., serum uric acid, liver enzymes), in some cases, there is the potential for the biomarker of PFAS to be influenced by the underlying health problem rather than the PFAS causing the health problem, i.e., the health condition affecting the measured serum PFAS levels.

Toxicologic Evidence Indicative of Specific Diseases of Concern

The toxicological effects of PFAS in laboratory animals have been described by several comprehensive reviews (Lau et al. 2007, Lau 2012, DeWitt 2015, Lilienthal et al. 2017, Li et al. 2017) and summarized in great details in recent risk assessment documents (USEPA, 2016(a), (b), NJ DWQI 2015, 2017, 2018, ATSDR 2018, EFSA 2018). Most of the research focuses on PFOA and PFOS, although a few reports on other perfluorocarboxylates (PFCA, such as PFNA, PFHxA and PFBA) and perfluoroalkyl sulfonates (PFSA, such as PFHxS and PFBS) are also available. In general, the PFCA and PFSA examined are well absorbed after oral ingestion, are not metabolized, and are excreted primarily in urine and to a lesser extent in feces. These chemicals have a high affinity for protein binding (e.g. serum albumin, fatty acid binding proteins). In animal studies and a couple of human surveys, PFAS are found to be distributed broadly among tissues, but with the exception of the short chain chemicals (such as C4), they are taken up and stored preferentially in the liver. In fact, liver, kidney and blood compartments can account for greater than half of the body burden of PFAS. During pregnancy, these chemicals can cross the placental barrier readily in both laboratory animals and humans, although the maternal levels of PFAS tend to be higher than those in the fetus. After birth, lactational transfer of PFAS to the offspring has been well documented.

In animal studies, the toxic effects of PFAS can vary widely based on their perfluoroalkyl chain lengths and functional groups, as well as species and sex differences of the animal models (Lau et al. 2007, Lau 2012, 2015). Two prominent issues must be considered to account for this variability: differential pharmacokinetic disposition and varying potency among the homologues of these chemicals. The serum elimination half-lives of PFAS can vary greatly, from hours to years (Table 2). Typically, chemicals with long perfluoroalkyl chain lengths (greater than C4 for PFSAs and greater than C6 for PFCAs) are much more persistent in the body; half-lives tend to increase from rodents (hours-days) to monkeys (days-months) and to humans (months-years),

Table 2. Serum half-life estimates of some perfluoroalkyl substances (adapted from Lau 2015).

		Rat	Mouse	Monkey	Humans
PFBS (C4)	Female	4.0 hours	2.1 hours	3.5 days	28 days
	Male	4.5 hours	3.3 hours	4.0 days	
PFHxS (C6)	Female	1.8 days	25 -27 days	87 days	5.3 - 8.5 years
	Male	6.8 days	28 - 30 days	141 days	
PFOS (C8)	Female	62 - 71 days	31 - 38 days	110 days	3.4 - 5.0 years
	Male	38 - 41 days	36 - 43 days	132 days	
PFBA (C4)	Female	1.0 - 1.8 hours	3 hours	1.7 days	3 days
	Male	6 - 9 hours	12 hours		
PFHxA (C6)	Female	0.4 - 0.6 hours	~1.2 hours	2.4 hours	32 days
	Male	1.0 - 1.6 hours	~1.6 hours	5.3 hours	
PFHpA (C7)	Female	2.4 hours			1.2 - 1.5 years
	Male	1.2 hours			
PFOA (C8)	Female	2 - 4 hours	16 days	30 days	2.1 - 3.8 years
	Male	4 - 6 days	22 days	21days	
PFNA (C9)	Female	1.4 days	26 – 28 days		
	Male	30.6 days	34 – 69 days		
PFDA (C10)	Female	58.6 days			
	Male	39.9 days			
F-53B	Female				15.3 years
	Male				
GenX	Female	2.8 days	1.0 day	3.3 days	
	Male	3.0 days	1.5 days	2.7 days	

and are slightly longer in males than in females (with the exceptions of PFOA, PFNA and PFHxS in rats where tremendous differences in half-life between males and females were seen). Differential renal reabsorption involving organic anion transporters likely contributes to these varying pharmacokinetic profiles of PFAS. The response potency of individual PFAS can also vary significantly among chain lengths, between functional groups and target species (Wolf et al. 2012). For instance, based on peroxisome proliferator-activated receptor-alpha (PPARα) activation in cultured transfected COS-1 cells (where the pharmacokinetic issue of PFAS can be bypassed), it was noted that (a) PFAS of increasing chain lengths produced increasing activity of the mouse and human PPARα, (b) PFCA were stronger activators than PFSA, and (c) the mouse PPARα appeared to be more sensitive to PFAS than the human PPARα. Hence, only nominal adverse effects were seen with PFBA in rodents, in part because of the faster clearance rate of this homologue (hours vs. days) and the weaker potency in its effects. However, possible variations in potency ranking for other responses remains to be elucidated. Thus, extrapolation of PFAS data from animal studies to human health risk assessment must take into consideration the species differences resulting vastly disparate rate of elimination (reflecting biological persistence) and variable potencies relating to chemical structure.

Because multiple PFAS (potentially up to ~5,000 variants) are found in the environment, humans and wildlife, their cumulative risks and potential interactions must be considered. Several *in vitro* studies have addressed the "mixture" effects of selected PFAS. In general, binary combinations of PFCA and PFSA behave additively at low and moderate concentrations. Further investigation with a diverse set of PFAS (different chain lengths and functional groups, as well as the novel polyfluorinated substances) and confirmation of the *in vitro* findings with *in vivo* studies are needed to clarify this key issue. This additivity assumption may afford modeling of a total PFAS effect with attendant "toxic equivalent" approaches (based on persistence and potency) for environmental risk assessment, but the basis for doing so across the full range of compounds has not yet been established.

To date, activation of PPARα (a type of metabolic sensor) is the only established mechanism of action for PFAS. Other putative mechanisms for PFAS include gap junctional inhibition to disrupt cell-cell communication, mitochondrial dysfunction, interference of protein binding, partitioning into lipid bilayers, oxidative stress, altered calcium homeostasis, and inappropriate activation of molecular signals that control cell functions. However, these alternative candidates lack robust evidence to support a pathophysiological role in the multi-faceted effects of PFAS. A better characterization of the modes of action for PFAS toxicities remains an important area of future investigation, and a necessity to improve our understanding of the impacts of these pollutants on human health.

Integrating Evidence from Epidemiology and Toxicology

Seven types of toxicological effects associated with PFOA and PFOS exposure (as well as other related PFAS, but to a lesser extent) have been identified using laboratory animal models: hepatic and metabolic toxicity, developmental toxicity, immunotoxicity, tumor induction, endocrine disruption, neurotoxicity, and obesogenicity. While these outcomes overlap considerably with the epidemiologic evidence, the evidence from toxicology does not provide a definitive connection between the adverse health effects found in animal studies and specific diseases in humans. This is due both to relative scarcity of studies overall but also an inherent limitation in the ability to connect small studies of animals with high levels of

controlled exposure to large studies of human populations with very low levels of uncontrolled exposure. Some of the toxicological effects appear to be of human relevance in regard to some pathways, for example PFOA and PFOS have been shown to reduce serum cholesterol and triglycerides in rodents, whereas in humans PFOA is associated with higher, not lower, levels of cholesterol in most studies (Convertino 2018). Immunosuppressive effects have been reported in both in rodent and epidemiological studies. Adverse effects on growth and development seen in rodent studies are consistent with observations of reduced birth weight and delayed onset of puberty found in some epidemiological studies. Finally, increases in Leydig cell tumor incidence observed in PFOA-treated rodent are in line with a positive association between increases of testicular tumor incidence and elevated PFOA exposure in the C8 Study.

Weighing and combining toxicity evidence from human studies, animal studies, and mechanistic studies is always difficult. Ideally, these studies would use similar biologically effective doses and directly comparable health outcome, with clear supporting information regarding the mode of action for toxicity in each species. In practice, animal studies typically use higher doses than those experienced by humans, identical outcome are often unavailable or impractical to measure in both humans and animals, and it is difficult to ascertain whether a suspected or identified mode of action such as PPARα signaling is the only relevant mechanism for a particular health outcome, or whether other mechanisms may contribute (ATSDR 2018). Rather than expecting concordance of specific study outcomes across animals and humans, risk assessors typically group related outcomes by organ or system, and then compare evidence streams to determine whether similar organs are affected. For example, liver toxicity is a hallmark of PFAS exposure in multiple species (ATSDR 2018), increasing confidence that the liver enzyme changes observed in human studies may have been caused by PFAS exposures.

Immunologic Effects

The developing immune system is especially sensitive to environmental stressors (DeWitt and Keil 2017). Several human studies of immune function in children (up to age 19) have reported associations between PFOA or PFOS serum concentrations and decreased antibody production after vaccination for rubella, diphtheria, mumps, measles, and/or tetanus (Grandjean et al. 2012, Granum et al. 2013, Mogensen et al. 2015, Stein et al. 2016). In two of these studies PFOA and PFOS measurements were obtained from mothers at or near the time of birth, serving as a measure of prenatal exposure (Grandjean et al. 2012, Granum et al. 2013). 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 (DeWitt and Keil 2017) though few studies have addressed clinical health outcomes that might result from changes in immune function. In two studies where mothers were contacted periodically to ask about their children's recent illnesses, the investigators reported associations between PFOA or PFOS and increased frequency of fever, common colds, and gastroenteritis (Granum et al. 2013, Dalsager et al. 2016).

At least two studies have investigated PFOA and PFOS exposure and antibody response in adults after vaccination for influenza, diphtheria, and/or tetanus (Looker et al. 2014, Kielsen 2016). Although some decreases in antibody production were reported for higher levels of PFOA or PFOS exposure, effect sizes were small, and some antibodies were increased rather than decreased, suggesting that effects in children may be stronger or more readily measured. Ulcerative colitis is an immune disorder that has been associated with PFOA exposure in humans (Steenland et al. 2013, Steenland et al. 2018).

In animal studies, a number of long-chain PFAS (PFOS, PFOA, PFNA and PFDA) have been shown to suppress adaptive (acquired) immunity in rodents and non-human primates by reducing thymus and spleen weights, as well as their immune cell populations (Corsini et al. 2014). Immunologic responses by activation of T cell (natural killer cell activity) and B cell (production of antigen-specific immunoglobulins) functions were attenuated. Subchronic exposure to PFOA and PFOS in mice also led to suppression of innate immunity by lowering the number of circulating white blood cells, involving lymphopenia, and reduction of macrophages in bone marrow.

Combining the toxicology and epidemiology research, there is substantial evidence that exposure to PFOA or PFOS may have adverse effects on the immune system. The National Toxicology Program recently conducted a systematic review of 153 published animal, human, and mechanistic studies for PFOA and PFOS, concluding that both chemicals are "presumed to be an immune hazard to humans" due to evidence of suppressed antibody response, with a "high level of evidence" in animals and a "moderate level of evidence" in humans (NTP 2016). The National Toxicology Program report also noted some evidence of increased autoimmune disease and hypersensitivity with PFOA exposure, suppressed natural killer cell activity with PFOS exposure, and reduced infectious disease resistance for both chemicals. Nonetheless, we note that some reviewers conclude the available evidence is insufficient to reach a conclusion regarding a causal effect of PFOA or PFOS on immunological outcomes (Chang et al. 2016).

Reproductive and Developmental Health Outcomes

The body of research addressing fetal exposure and subsequent health outcomes has expanded markedly through studies of maternal levels of PFAS and infant and child health. These include studies of immunologic response in the child (described in the above section) as well as studies of birth weight, preterm birth, obesogenicity, and neurodevelopmental outcomes. Perhaps the most consistency has been found for elevated PFAS being associated with a small decrement in birth weight, though the causal significance of the findings in humans is subject to some uncertainty (Negri et al. 2017 and Steenland et al. 2018). The array of findings on infant development have been quite mixed regarding effects on the rate of growth, obesogenicity, and neurodevelopment with varying associations across timing of PFAS measurement (prenatally or postnatally) and whether there are sex-specific effects. Given the inherent vulnerability of the fetus to environmental insults and epidemiologic evidence that generally supports an association between PFOA and reduced birthweight, there is evidence supporting the potential for adverse effects of PFAS on fetal growth, particularly when combined with the toxicology.

In laboratory studies, profound developmental toxicity has been described with gestational and lactational exposure to PFOS, PFOA and PFNA in mice. Neonatal morbidity and mortality were seen with exposure to high doses of these chemicals, while growth deficits and developmental delays were noted

in offspring exposed to lower doses. Deficits of mammary gland development were also observed in mouse offspring exposed to PFOA during gestation, which persisted into adulthood, although these histological abnormalities did not appear to impede milk production function and neonatal growth of offspring (F1 mice). Systematic reviews of available data also support a relationship between *in utero* exposure to PFOA and PFOS and fetal growth in animals and humans (Koustas et al. 2014 and Bach et al. 2015).

Cancer

The volume of research directly addressing cancer in human populations in relation to PFAS exposure is quite limited, largely because of the low incidence of these diseases (rates are typically expressed "per 100,000") and the resulting requirement of very large studies to produce meaningful results. Among the types of cancer studied, the strongest support for an association with PFAS is for kidney and testicular cancer based largely on the work of the C8 Science Panel. Even without replication in other populations, the evidence linking PFOA with these diseases was clear and consistent and deemed sufficient to warrant the probable link findings. Other cancers with some suggestive evidence include prostate cancer based on early occupational studies and two general population studies (Eriksen et al. 2009 and Hardell et al. 2014) and ovarian cancer based on a registry-based case control study (Vieira et al. 2013). Overall, there is limited research on cancer in relation to PFOA and PFOS, with far less evidence for other PFAS.

PFAS are not known to be genotoxic or mutagenic, but both PFOA and PFOS have been shown to induce tumors in rodents and fish. Indeed, liver adenomas, pancreatic acinar cell tumors and testicular Leydig cell adenomas have been detected in rats treated with PFOA chronically. This "tumor triad" profile is typically associated with the PPARα-mediated molecular signaling pathway. Interestingly, liver tumors involving this mode of action have been considered not to be relevant to humans (Corton et al. 2018), although the human relevance for the PPARα-induced pancreatic and testicular tumors remains to be determined. Induction of liver tumors mediated by estrogen receptor activation has also been reported in fish.

The International Agency for Research on Cancer (IARC 2017) recently reviewed the scientific literature on PFOA and cancer concluded that PFOA is "possibly carcinogenic to humans" based on "limited evidence" in humans, "limited evidence" in experimental animals, and "moderate evidence" for mechanisms of carcinogenicity that are relevant to humans. According to USEPA's *Guidelines for Carcinogen Risk Assessment* (USEPA 2015), coupled with findings for Leydig cell testicular tumors in rats and a probable link to testicular and renal tumors in the C8 Health Project, the Agency concluded that there is "Suggestive Evidence" of Carcinogenic Potential of PFOA in humans. Similarly, USEPA also considered that there is "Suggestive Evidence" of Carcinogenic Potential of PFOS in humans based on the liver and thyroid adenomas observed in the chronic rat bioassays. The human studies included studies of exposed workers, studies of communities exposed to contaminated drinking water (the C8 Health Project/C8 Science Panel study population), and studies of the general population. Some of these studies found higher rates of prostate, kidney, testicular, or thyroid cancer among people with more PFOA exposure. Little additional evidence has been produced since then to clarify the potential carcinogenicity of PFOA exposure in humans, other than registry-based ecological studies of exposed communities (e.g. health department reports in New Hampshire and Minnesota). It should also be noted that some

reviewers interpret the existing evidence differently, finding that the "epidemiologic evidence does not support the hypothesis of a causal association between PFOA or PFOS exposure and cancer in humans" (Chang et al. 2014), whereas we share the perspective offered by the detailed review by IARC of PFOA being "possibly carcinogenic to humans."

Although cancer often receives more attention than other potential adverse health effects that may result from a toxicant exposure, based in part on the presumption that it is the most sensitive outcome, this is not always the case. Indeed, for PFOA and PFOS, developmental and immune effects seem to be among the most sensitive in both animal and human studies and may be more important for setting advisory and regulatory limits on exposure. Developmental, immune, and liver effects were often drivers for determining the recent advisory levels of PFOA and PFOS from EPA, ATSDR, and state agencies.

Liver Disease

Epidemiologic evidence regarding liver disease in relation to PFAS exposure is quite limited and largely unsupportive of an association, though there are a number of studies suggesting reasonably consistent effects on liver enzymes (C8 Science Panel, ATSDR 2018). In contrast, there is extensive toxicologic evidence that hepatic effects are sensitive to both legacy and novel PFAS. Based on their structural resemblance to fatty acids (in fact, PFAS were called perfluorinated fatty acids), a wealth of literature dating back to 1980s has described induction of liver enzymes by PFAS (particularly PFCA) through activation of PPARα. In rodent studies, dose-dependent increases in liver weight, hepatic hypertrophy associated with vacuole formation, and increases in peroxisome proliferation have typically been observed when a significant body burden of these chemicals is reached, especially for the more persistent and potent long-chain homologues. An increase in hepatocyte proliferation and necrosis were also noted at high doses. Correspondingly, transcriptional activation of mouse and human PPARα-related genes in the liver is routinely detected; while activation of other nuclear receptors such as PPARγ, constitutive androstane receptor (CAR) and pregnane X-receptor (PXR) has also been reported. These nuclear receptors are metabolic sensors that regulate lipid and glucose metabolism and transport, as well as inflammation. Indeed, these proteins have been targeted for therapeutic intervention against various metabolic diseases (such as obesity and diabetes), although potency of the pharmaceuticals are typically much higher than those noted for PFAS. Hepatosteatosis (fatty liver) is also a common feature of chronic exposure to PFAS in rodents. Most of these findings are confirmed in a transgenic mouse model where PPARα is "knocked-out". Many of these effects are reversible upon cessation of PFAS treatment, and this observation has been interpreted by some as "adaptive" responses to the exposure. However, this reversibility is not particularly relevant to environmental PFAS exposure from drinking water, because exposure persists until such chemical contamination is remediated.

Thyroid Disease

The C8 Science Panel concluded that there was a probable link between PFOA and thyroid disease despite some anomalous findings that differed between males and females. Despite a much more extensive body of research over the past decade, with a number of suggestive associations, there is not a clear, consistent pattern of specific effects on thyroid hormone levels in human populations (Ballesteros et al. 2016). Nonetheless, endocrine disruption is of some interest as toxicologic evidence that PFAS as induces

hypothyroxinemia and reduction of serum testosterone in rats. It should be noted that the PFAS effects on thyroid hormone economy detected in animal studies are different from the classical hypothyroidism in that reduction of circulating thyroxine (T4) is not accompanied by a compensatory increase thyroid-stimulating hormone (TSH). A possible mechanism of this effect may be related to the propensity of protein binding of PFAS, which displaces T4 binding to its carrier proteins (transthyretin and thyroxine-binding globulin).

Neurotoxicity

Epidemiologic evidence for an adverse effect of PFAS on neurological outcomes is not generally supportive of an association with clinical outcomes such as Attention Deficit Hyperactivity Disorder (Liew et al. 2015) or autism (Lyall et al. 2018). While there are reports of isolated findings of influences on subtle measures of neurobehavioral function (Vuong et al. 2018a, 2018b, Harris et al. 2018), other studies provide evidence against an effect on similar outcomes or possibly a beneficial effect (Stein et al. 2013, 2014). None of the specific associations have been replicated, there is inconsistency regarding which specific PFAS manifests associations, and thus they do not collectively provide substantial support for any influence of environmental levels of PFAS on neurobehavioral outcomes (Braun 2017, Liew et al. 2018). The potential adverse effects of PFAS on the nervous system and functions have not been widely investigated. A few studies have reported neurotoxicity of PFOS, PFHxS and PFOA in cell culture systems, as well as altered behavioral responses and deficits in learning and memory ability in rodents (Slotkin et al. 2008, Johansson et al. 2008, Sato et al. 2009, Mariussen 2012, Wang et al. 2015). In contrast, no significant developmental neurotoxic effects were seen from prenatal exposure to PFOS or PFHxA in USEPA guideline-based studies with rats (Butenhoff et al. 2009).

Interpretation of Subclinical Changes in Biomarkers

The literature on PFAS and human health includes many studies of biomarkers of health relevance, including cholesterol levels, thyroid hormones, liver enzymes, measures of kidney function, immunologic markers, and others. While none of these are diseases per se, they are considered diseases when a threshold is exceeded and are predictive of other more severe health outcomes. These studies are much more extensive than those of clinical health outcomes such as heart disease, cancer, or infection in part because these studies are much easier to conduct. In the biomarker studies, the PFAS levels and the biomarker of health are generally obtained from the same blood sample, with an opportunity to assess a panel of biomarkers in a cost-effective manner to generate an array of findings. The use of biomarkers as continuous measures of health outcome, e.g., liver enzyme levels, allows for smaller studies with statistically precise results in contrast to studies of the actual clinical disease of concern, e.g., chronic liver disease. Both studies have value, but some general points are worth noting about the studies based solely on biomarkers since they are dominant.

First, the simultaneous measurement of PFAS levels and health biomarkers allows for the possibility of reverse causality, in which the health problem alters the measured serum levels through changes in uptake or excretion of PFAS. Presuming that it is chronic exposure that may contribute to the risk of disease, studies that can examine the temporal pattern of exposure and health longitudinally are more informative than cross-sectional studies. Second, the relationship between health-related biomarkers

and actual disease is often modest in magnitude and so the connection of PFAS to clinical health problems may remain unresolved even with high quality studies of biomarkers. For example, even though PFAS exposure elevates cholesterol levels, there is no direct evidence that PFAS increases the incidence of heart disease despite the well-recognized relationship between elevated cholesterol and heart disease. Third, the vast majority of studies relating biomarkers of PFAS exposure to biomarkers of effect were conducted in settings in which the levels of PFAS were in the background range, e.g., from the National Health and Nutrition Examination Surveys, not from populations with notably elevated exposures. In these circumstances, variation in measured PFAS levels may reflect in part physiologic differences and thus not reflect a causal effect of PFAS exposure on health indicators. Many of the epidemiology studies conducted by the C8 Science Panel relied on modelled, rather than measured, serum PFAS concentrations; studies using modelled serum PFAS concentrations are influenced by the accuracy of the exposure model but are not as susceptible to misinterpretation by reverse causation or physiological confounding (Watkins et al. 2013).

For example, key measures of kidney function including serum uric acid and estimated glomerular filtration rate (eGFR) have been associated with measured serum PFOA and PFOS concentrations in cross-sectional studies (Steenland et al. 2010, Shankar et al. 2011, Watkins et al. 2013, and Kataria et al. 2015). However, because PFAS are excreted primarily through the kidneys, impaired kidney function is expected to result in decreased excretion and higher serum PFAS concentrations—inducing an association due to reverse causation. Indeed, studies of eGFR using modelled serum PFAS concentrations have not found any associations, suggesting that the associations of measured serum PFAS with kidney function in cross-sectional studies might be due solely to reverse causation (Watkins et al. 2013 and Dhingra et al. 2017).

That being said, associations of PFAS with biomarkers or other subclinical outcomes in carefully designed epidemiological studies can be informative, especially when similar biomarkers are associated with PFAS exposure in controlled experiments using laboratory animals or *in vitro* systems. Observation of effects on the same biological systems across species in multiple studies provides stronger support for causal interpretation of those effects, which may be important as early indicators of disease development even if they are not overt diseases.

Research that Would Change the Recommended Standard for PFAS in Drinking Water

Toxicologic Studies

Seven types of toxicological effects associated with PFOA and PFOS (as well as other related PFAS, but to a less extent) exposure have been described with laboratory animal models: hepatic and metabolic toxicity, developmental toxicity, immunotoxicity, tumor induction, endocrine disruption, neurotoxicity, and obesogenicity. The weight of evidence is in descending order (i.e., liver effects are most robust, and obesogencity is most equivocal). These findings are based on well-controlled laboratory experiments, with wide dose ranges (but typically in orders of magnitude higher than human exposure) and sometimes multiple species. Some of the phenotypic findings are supported by in vitro mechanistic evaluations and/or molecular queries. Our understanding of the toxicologic properties of PFAS other than PFOA and PFOS is notably less advanced and in the case of some variants, completely unexplored.

The typical risk assessment practice is to select one most sensitive outcome from a dose-response study, based on the lowest benchmark dose (BMD), no or lowest observable level (LOAL/NOAEL), in conjunction with expert opinions on the biological plausibility or relevance of that particular outcome. The decision is seldom made based on the preponderance of evidence (drawn from multiple concurring studies) or convergence of findings from animal studies and epidemiological examinations. In fact, epidemiological findings alone have seldom been used as critical effects for regulatory decision and rulemaking, though some have argued for doing so for PFAS (Grandjean and Clapp 2015, Budtz-Jorgensen and Grandjean 2018).

Epidemiologic Studies

Epidemiologic research that would be capable of justifying a change in recommended drinking water standards would have to provide substantial improvements on the current literature. Much of the ongoing research addresses background levels of PFAS rather than populations that include more highly elevated exposures. Longitudinal studies of clinical outcomes in more highly exposed populations would allow for more definitive health assessments by increasing the statistical power of the studies and reducing concerns with the possibility of physiological confounding or reverse causality. Triangulation using both prospective exposure biomarkers and careful external dosimetry would further strengthen these study findings. Such studies of large, highly exposed populations could corroborate or challenge the findings of the C8 Science Panel and other epidemiological research which forms the basis for current thinking with regard to clinical disease.

Many of the studies of PFAS and health are addressing subclinical indicators of health concern (e.g., liver enzymes, immunologic markers) and few are addressing clinically significant disease (e.g., chronic liver disease, infection). Many published studies are cross-sectional with biomarkers of PFAS and indicators of health measured at the same point in time rather than longitudinally, a less informative approach than relating exposure at one time to disease at a later time. One or more of these fundamental features would need to be addressed to have a significant impact on the overall body of evidence from epidemiologic studies.

Using these improved methods, there would also be a need for identifying health effects with a quantitative measure of exposure levels and some form of a dose-response gradient. The identification of blood levels associated with elevated disease risk would allow for the calculation of steady-state drinking water levels of concern based on assumptions about consumption of water and pharmacokinetics of PFAS. It is likely that building this sort of evidence to markedly strengthen the case for a causal impact of quantified levels of PFAS on clinically significant health outcomes would require not one but rather a series of studies with convergent evidence.

Another important way in which epidemiologic research might be sufficiently informative to change drinking water standards would be to address PFAS in some collective manner to provide some guidance on how to address the mixture of chemicals. If research could begin to determine empirically how these mixtures of compounds act independently or together to affect health it would change the views of what to regulate, i.e., what specific chemicals need to be added together to provide an accurate assessment of the health risks, and whether they should be weighted according to some measure of relative potency such as that recently proposed by Gomis et al. (2018). Research on potential additivity or synergy of PFAS chemical mixtures would be of direct relevance for assessing health risks from PFAS in the environment.

Conclusions and Recommendations

The health effects of PFAS have been addressed in a number of assessments, starting with the C8 Science Panel and continuing with the ATSDR comprehensive draft report in 2018. Based on those reports, ATSDR has indicated in its *Guide for Clinicians* an array of health outcomes most likely to be related to elevated exposure to PFAS, based mostly on studies of PFOA and PFOS, which we have evaluated in relation to the scientific evidence.

There is an extensive amount of toxicology literature that addresses specific chemicals and outcomes and allows for some broader conclusions. In animal studies, the toxic effects of PFAS can vary widely based on their perfluoroalkyl chain lengths and functional groups, as well as species and sex differences of the animal models. The hepatotoxic and metabolic effects, immunotoxicity and developmental toxicity of PFAS are supported by the strongest weight of evidence, but their effects are subtle at low doses that are most relevant to environmental exposure. Carcinogenic effects of PFAS and their relevance to human health risks are less certain. To date, activation of PPARα is the only established mechanism of action for PFAS. Studies of cancer are limited, but the C8 Health Project evidence supported an association with kidney and testicular cancer. PFAS are not known to be genotoxic or mutagenic, but both PFOA and PFOS have been shown to induce tumors in rodents and fish. The International Agency for Research on Cancer (IARC 2017) recently reviewed the scientific literature on PFOA and cancer and concluded that PFOA is "possibly carcinogenic to humans" based "limited evidence" in humans, "limited evidence" in experimental animals, and "moderate evidence" for mechanisms of carcinogenicity that are relevant to humans. As noted by the National Institutes of Health, immunologic effects of PFAS are supported by epidemiologic studies indicating suppression of children's immunologic reactions to vaccines at low exposure levels and supported by toxicologic evidence of adverse effects on the immune system. While adverse reproductive effects are clear from toxicology studies, the epidemiologic studies suggest a reduction in birth weight. Toxicologic evidence indicates adverse hepatic and renal effects, with limited epidemiologic support, and there is mixed evidence regarding endocrine effects (particularly thyroid), neurodevelopment, and obesogenicity. Future epidemiologic studies that address clinical health outcomes, not just subclinical biomarkers, and toxicologic and epidemiologic studies that provide guidance on the full array of PFAS, are most likely to directly impact environmental regulation.

Conclusions

The Panel agrees with the assessment reflected in the ATSDR guidance document about associations of PFAS exposure to health outcomes such as thyroid function, high cholesterol, ulcerative colitis, testicular cancer, kidney cancer, pregnancy-induced hypertension, and elevated liver enzymes but have some differing views on specific areas of concern. Because elevated serum uric acid could well be a correlate rather than consequence of elevated blood levels of PFAS, the Panel recommends eliminating this from the list. The Panel recommends adding immunologic effects to the list of health condition of concern, particularly those that arise during prenatal exposure and childhood, and reduced birthweight, based on strong toxicology findings and supporting epidemiologic evidence.

Health concerns are based on the total exposure to PFAS across many sources, but because drinking water is the predominant source of exposure for many people consuming contaminated water, it remains the focus for health-based regulation based on current knowledge, despite potential contributions from consumer products, crops, and other pathways.

Combining the evidence from toxicology and epidemiology, the evidence supports the carcinogenicity of PFAS, but cancer may not be the most sensitive health outcome to guide regulation.

While there is some empirical evidence supporting an approach that assesses the combined effects of exposure to multiple PFAS to set health-based limits, there is not yet a firm, quantitative basis for doing so.

Recommendations

1. Research is needed to provide greater understanding of the potential health effects of a broader array of PFAS, not just the legacy compounds. This might include toxicology research to help in developing indices of toxicity or at least inform decisions about which specific forms of PFAS should be combined for regulatory decisions.

2. Toxicologic studies on modes of action are needed to help guide the development of indices of toxicity that would apply across a range of PFAS.

3. Epidemiologic studies of clinical outcomes are needed to build on the extensive body of research addressing biomarkers of health. While the latter can be suggested of likely health effects, direct documentation of clinical disease in relation to quantified PFAS levels is needed.

4. Health outcomes of continued interest that warrant further study include consequences of endocrine disruption, including developmental outcomes and thyroid disorders, consequences of immunologic effects, including autoimmune diseases and infectious diseases, consequences of metabolic effects, and cancer.

SECTION 5 Quantification of Risk from Drinking PFAS in Water

In the past decade, health-based advisories on PFOS and PFOA for drinking water and daily food intake have been issued by various agencies worldwide (Table 3), several of which have recently updated these values. The levels vary widely between chemicals, and among the entities that issued them. For instance, there has been up to a 10-fold difference between advisory levels for PFOS and PFOA, and as much as a 150-fold difference among countries, more if the proposed new European Food Safety Authority values presently being considered are enacted. This variation may in part be related to advancing knowledge about the adverse health effects of PFAS over time (based both in laboratory studies and epidemiological studies), but largely reflect discordant risk assessment principles and practices among regulatory groups. Calls for global collaboration to harmonize the risk assessment and regulatory actions on this class of chemicals has emerged (Ritscher et al. 2018) and if successfully pursued, would ultimately reduce the confusion surrounding this issue resulting from differing recommendations. Nonetheless, such agreement is not imminent.

Within the U.S., similar risk assessment activities on PFAS are being conducted by the federal government and various state health organizations. In particular, USEPA, ATSDR, the New Jersey Department of Environmental Protection (NJDEP) and the Minnesota Department of Health (MDH) have recently issued health advisories on a number of individual and combined PFAS for drinking water (most notably PFOS and PFOA, but some also include PFBS, PFBA, PFHxS, and PFNA) (Table 3). Risk assessment for PFBS, PFBA, PFHxS, PFNA and GenX being conducted by the USEPA Office of Water is expected to be available by end of 2018 (and drafts were released for public comment for PFBS and GenX as this report was finalized). Several states have either adopted the USEPA recommendations (such as NH, ME, VT, IA and CO), or are in the process of developing their own guidelines (e.g., CA, PA). The drinking water values for PFOS and PFOA by USEPA (70 ppt for both chemicals), New Jersey (13 ppt and 14 ppt, respectively) and Minnesota (27 ppt and 35 ppt, respectively) are within reasonable agreement given the different assumptions and different approaches. These differences reflect the specific toxicological outcomes identified as critical driver for derivation of the Reference Dose (RfD) and estimates of daily water intake. The basis for point-of-departure (POD), either LOAEL, NOAEL or $BMDL_{10}$, uncertainty factors (UF) of 300 for PFOA and 30 for PFOS, and relative source contribution (RSC) ranging from 20-50% are fairly consistent among these risk assessments, which are all based on studies in laboratory animals. While differences of this magnitude may have profound implications for identifying water sources that require remediation, it must be recognized that there may be only limited scientific justification for claiming one or the other is "better." While each is based on well-defined methods and principles, approaches differ across agencies and lead to different recommendations.

Table 3. Examples of world-wide health-based advisories for PFOS and PFOA.

Locales/Sources	Year	Types	PFOS	PFOA
USEPA	2016	Drinking water	70 ppt*	70 ppt*
ATSDR	2018	Drinking water	52 ppt (adult) 14 ppt (child)	78 ppt (adult) 21 ppt (child)
Alaska, Hawaii, Idaho, Indiana, Louisiana, Maine, Nevada, New Mexico, Oregon, Rhode Island, Virginia, West Virginia	2016	Drinking water	70 ppt^	70 ppt^
California	2018	Drinking water	13 ppt¥	14 ppt¥
Colorado	2018	Drinking water	70 ppt@	70 ppt@
Massachusetts	2018	Drinking water	70 ppt#	70 ppt#
Michigan	2015	Surface water	11 ppt	420 ppt
	2018	Drinking water	70 ppt ^	70 ppt ^
Minnesota	2017	Drinking water	27 ppt	35 ppt
New Jersey	2017	Drinking water	13 ppt	14 ppt
Vermont	2016	Drinking water	20 ppt *	20 ppt *
Australia	2017	Drinking water	70 ppt	560 ppt
	2016	Total daily food intake	150 ng/kg/day	1,500 ng/kg/day
Denmark	2015	Drinking water	100 ppt	100 ppt
	2015	Total daily food intake	30 ng/kg/day	100 ng/kg/day
European Union	2005	Total daily food intake	150 ng/kg/day	1,500 ng/kg/day
	2018	Total daily food intake	1.86 ng/kg/day‡	0.86 ng/kg/day‡
Germany	2006	Drinking water	300 ppt	300 ppt
	2006	Total daily food intake	100 ng/kg/day	100 ng/kg/day
Italy	2017	Drinking water	--	500 ppt
Netherlands	2011	Drinking water	530 ppt	--
	2011	Total daily food intake	150 ng/kg/day	--
Sweden	2014	Drinking water	90 ppt	--
	2011	Total daily food intake	150 ng/kg/day	300 ng/kg/day
United Kingdom	2009	Drinking water	300 ppt	1,000 ppt
	2006	Total daily food intake	300 ng/kg/day	3,000 ng/kg/day

*Value represents individual or combined PFOS and PFOA levels; ^value adopted from US EPA determination; @value reflects sum of PFOS, PFOA and PFHpA levels; ¥value adopted from New Jersey determination; #value reflects combined PFOS, PFOA, PFHxS, PFNA and PFHpA levels; ‡value derived from European Food Safety Authority draft document.

A major challenge in setting standards for human exposure to PFAS arises in extrapolating the exposure doses from laboratory animals to humans due to the profound differences in the rate of elimination of these chemicals between species. There are about 40- to 150-fold differences in serum half-life estimates between rodents and humans for some of the PFAS (Table 2). The exceedingly persistent nature of these chemicals in humans must be taken into consideration for health risk assessment. However, for chronic or subchronic exposure of PFAS, one can assume that both rodents and humans have reached steady state levels. For rodent studies with oral administration of PFOS or PFOA, steady state levels in serum have been observed after 2-3 weeks of daily treatment, depending on administered doses (C. Lau, *personal communication*]. Using slightly different modeling paradigms, USEPA, New Jersey and Minnesota derived a human equivalent dose (HED) from the serum concentrations of PFOS or PFOA in animal studies that corresponded to the critical toxicological effect. Thus, the use of internal dosimetry at steady state (rather than administered doses) allows the risk assessors to bypass the species-specific toxicokinetic issue related to PFAS. The salient features that distinguish among the three risk assessments of PFOS and PFOA will be described.

For PFOS, the USEPA chose reduced rat pup weight after gestational and lactational exposure as an outcome to derive a RfD of 20 ng/kg/day. The choice of this developmental toxicity outcome is reasonable, as a systematic review of a similar chemical (PFOA) supported growth retardation as a consistent adverse effect. A total Uncertainty Factor (UF) of 30 was assigned. To provide additional protection for breastfeeding infants, the risk assessors assumed a more conservative water intake estimate of 0.054 L/kg/day for the lactating mothers, and a RSC of 20%. A Lifetime Health Advisory of 70 ppt was estimated for PFOS. For PFOA, the USEPA selected reduced ossification of fetal mouse phalanges and accelerated onset of puberty in male offspring after gestational and lactational exposure as one of their drivers for RfD derivation. This choice was challenged because reduced bone ossification reflects a developmental delay, rather than an induction of anatomical defect; however, developmental delay can reflect an overall detrimental effect of chemical exposure that lead to growth and developmental deficit in the offspring. The reduced ossification of phalanges in the PFOA-exposed fetuses was accompanied by deficits of postnatal weight gains, delay in eye-opening (another developmental landmark) (Lau et al., 2006; Wolf et al., 2007) and mammary gland development (White et al., 2007) in mice. On the other hand, advanced pubertal maturation was only seen in males and was somewhat inconsistent with a general pattern of developmental delays. However, two other toxicity outcomes evaluated (reduced immunological function in mice, and reduction of body, liver and kidney weights in a 2-generation reproductive toxicity study with rats) yielded an identical RfD (20 ng/kg/day). Although results from the reproductive/developmental toxicity study with rats were confounded by the short half-life of PFOA in female rats (a known gender difference unique to this species), the fact that all three outcomes from different studies produced the same RfD lent confidence to its derivation. A total UF of 300 and a RSC of 20% were assigned. To provide additional protection for breastfeeding infants, the risk assessors assumed a more conservative water intake estimate of 0.054 L/kg/day for lactating mothers. Accordingly, a Lifetime Health Advisory of 70 ppt was estimated for PFOA. Because the similarities of the chemical structure, physicochemical properties and developmental adverse outcomes, the risk assessors considered possible additivity of PFOS and PFOA exposure. Therefore, the sum of PFOS and PFOA concentrations in drinking water is advised by U.S. EPA to not exceed 70 ppt for either long-term consumption or, during pregnancy, short-term consumption ("weeks to months").

For Minnesota, the driver for RfD derivation for PFOS is identical to that employed by USEPA, but these risk assessors assigned a total UF of 100 (3 times higher than that of USEPA) producing a RfD of 5.1 ng/kg/day (about one-fourth of USEPA value). However, they also assumed both prenatal and postnatal exposure using an additional milk transfer factor and a less conservative RSC of 50%, yielding a health-based value of 27 ppt for PFOS, about 2.5 times lower than that estimated by the USEPA. For PFOA, the driver for RfD derivation, and total UF are identical to those used by USEPA, but because of the additional milk transfer factor and less conservative RSC, a health risk limit of 35 ppt was estimated, lower by half of that issued by USEPA.

New Jersey chose a different toxicological outcome of decreased plaque-forming cell response (an assessment of immune function) in male mice after subchronic (60 days) exposure and a total UF of 30 to derive a RfD of 1.8 ng/kg/day for PFOS (about 10 times lower than that by USEPA). The choice of immunotoxicity is supported by a previously described National Toxicology Program systematic review of PFOA and PFOS, which indicated consistent findings in laboratory animals, as well as several epidemiological studies that reported associations between compromised immune responses with PFAS exposure in humans. The New Jersey risk assessors assumed a water consumption of 0.029 L/kg/day by an average adult (lower than the value used by USEPA), and a RSC of 20% (same as USEPA) to produce a MCL of 13 ppt for PFOS (about 5 times lower than that by USEPA). For PFOA, the New Jersey risk assessors selected yet a different toxicological outcome of increased relative liver weight in male mice after subchronic (2 weeks) exposure, and a total UF of 300 to derive a RfD of 2 ng/kg/day (again 10 times lower than that by USEPA) and a MCL of 14 ppt (about 5 times lower than that by USEPA). Liver hypertrophy is a hallmark response of PFAS (particularly the perfluorocarboxylates such as PFOA) in rodent models; compounded with elevated incidence of fatty liver and necrosis noted at high doses of exposure, hepatotoxic effects of PFOA are reasonably supported. The difference between New Jersey values and the USEPA values is primarily driven by different toxicological outcomes chosen to derive the RfD (the 10-fold difference in RfDs is attenuated by a 2-fold difference in drinking water intake rates, in the opposite direction).

In June 2018, the ATSDR released a draft of "Toxicological Profile for Perfluoroalkyls" for public comments (an update from the 2015 draft) (ATSDR 2018). It provides provisional minimal risk levels (MRLs) for oral exposure to PFOS, PFOA, PFHxS and PFNA. These evaluations employed the same human equivalent dose (HED) assumption (using the USEPA algorithms), NOAEL/LOAEL/BMDL, and UF paradigms as USEPA, New Jersey and Minnesota to derive the MRLs. Minimal risk levels are analogous to reference doses and follow similar derivation procedures. The ATSDR document does not provide any direct guidance on the limits of daily drinking water intake of these chemicals that are comparable to the health-based values issued by the USEPA, New Jersey and Minnesota. Although estimates are available at: https://www.atsdr.cdc.gov/pfas/mrl_pfas.html.

For PFOS, the ATSDR risk assessors chose a developmental outcome in rat for POD derivation that is identical to the one selected by the USEPA. The ATSDR MRL estimate, 0.0017 µg/kg/d is 10 times lower than the USEPA RfD value simply because of the 10-fold higher UF that includes a modifying factor of 10 due to concern that immunotoxicity (an outcome not selected by ATSDR, but by New Jersey) may be a more sensitive outcome than developmental toxicity. For PFOA, ATSDR derived their MRL value based on a neurobehavioral and a bone morphological outcome in mice after gestational exposure for POD

derivation. These critical effects were drawn from the same study. It is noteworthy that these "drivers" (statistically significant findings) were selected among many other potentially analogous outcomes evaluated by the authors that were negative. In addition, only a single dose of PFOA was given to pregnant mice (no dose-response evaluation) and adult offspring were evaluated for motor function at 5-8 weeks of age, and bone morphology at 13 or 17 months (i.e. latent effects of PFOA exposure), and only males (but not females) were affected in the behavioral test [only females were evaluated in the bone morphology study]. The UF assumed by ATSDR is the same as USEPA, Minnesota and New Jersey. With a different critical effect chosen for POD derivation, the MRL estimated for PFOA by ATSDR is similar to the RfD determined by New Jersey, but about 10-fold lower than that provided by USEPA and Minnesota.

Health-based advisories of several PFAS other than PFOS and PFOA, which include PFNA, PFBA, PFHxS and PFBS are also available from different sources. New Jersey chose increased maternal liver weight of mouse dams at term after exposure to PFNA from Gestational day 1-17 as an endpoint, and a total UF of 1000 to derive a target serum level, which is used in place of an RfD, of 4.9 ng/ml. The risk assessors assumed a RSC of 50% (assuming that PFNA from contaminated drinking water is the major source of exposure) and a serum to water ratio of 200:1 to produce a MCL of 13 ppt for PFNA, which closely resembles those for PFOS and PFOA. ATSDR also evaluated the health risk of PFNA based on the same animal study used by New Jersey, but these risk assessors focused on a different endpoint of decreased body weight and developmental delays of the offspring after gestational and lactational exposure. They chose the NOAEL as point of departure and a total UF of 300 to derive a MRL of 3 ng/kg/day. Thus, despite a difference of opinion in endpoint and UF selections, the MRL derived by ATSDR is in fact quite comparable to the RfD calculated by New Jersey.

Health-based values for PFBA and PFBS are only available from Minnesota. The driver for health risk evaluation of PFBA is obtained from a 28-day exposure study using rats, where reductions of serum cholesterol and thyroid hormones were observed, and a total UF of 100 is assigned. A RfD of 3800 ng/kg/day is derived, a water consumption of 0.285 L/kg/day for short-term intake is assumed, and a RSC of 50% is estimated to produce a MCL of 7,000 ppt. By comparison, the outcomes chosen by these risk assessors for PFBS are obtained from a rat study where kidney epithelial and tubular/ductal hyperplasia were noted in a 2-generation reproduction study. A similar UF of 100 is assigned to derive a RfD of 1600ng/kg/day. Adopting identical assumptions of water intake rate and RSC as PFBA, a chronic health-based value of 2,000 ppt is proposed for PFBS. It should be noted that the drinking water value estimates for these short-chain PFAS (C4) are about two orders of magnitude higher than those of their long-chain counterparts (C8 and C9), likely reflecting their shorter half-lives (less persistent biologically) and lower potency (less active) (see Toxicological Study section).

To date, only ATSDR has issued a health-based value for PFHxS. The critical effect of increased incidences of thyroid cell hypertrophy, hyperplasia and damage observed in male rat offspring after gestational and lactational exposure to PFHxS was selected as the driver for risk assessment. NOAEL and a total UF of 300 were used to derive a MRL of 20 ng/kg/day for this C6 chemical, which is about 10-fold lower than those estimated for PFOS, PFOA and PFNA, but also 10-fold higher than those for the C4 (PFBA and PFBS) compounds.

In summary, risk assessment of potential environmental contaminants is an art of practice more than an exact science, largely dependent on expert opinions in the selection of critical effects and uncertainty factors to derive a reference dose, as well as methodological principles regarding assumption of exposure (e.g., food consumption and water intake) and relative source of contribution. As shown above, even based on an identical critical effect that drives the risk evaluation, a different set of drinking water values can be derived from various assessors. Hence, interpretation of a specific numerical drinking water values from various health advisories can be subject for debate, until an enforceable limit is available after formal regulatory determinations by the federal or state government. In that regard, guidance to safeguard public health from PFOS and PFOA contamination in drinking water currently relies on a range of values with a lower bound of 13-14 ppt individually or 27 ppt combined (from New Jersey assuming simple additivity) to an upper bound of 70 ppt (individually or combined, from USEPA). The MRLs derived by ATSDR approximate the RfDs estimated by New Jersey, while the Minnesota drinking water values lie between the New Jersey and USEPA values. Thus, the difference between lower and upper bound estimates for PFOS and PFOA combined amounts to a factor of only 2.5, not a great disparity in the realm of risk assessment practice.

As a completely independent approach to deriving or assessing drinking water values, epidemiological evidence (as opposed to toxicological) evidence may be used for PFOA and PFOS, without a need to extrapolate across modes of administration or species (as opposed to relying solely on toxicological), as described in the next sections. Consideration of the epidemiological findings suggests that human health effects may occur at exposures within this range of drinking water values as discussed later in this report.

Table 4. Summary of federal and state PFAS drinking water determinations.

Source	Chemical	Drinking water values and parameters used for development	Reference Dose (RfD) or Minimal Risk Level (MRL)	RfD or MRL Basis	Total Uncertainty Factor (UF)	Uncertainty Factor Basis	Human Equivalent Dose
EPA, 2016	PFOA and PFOS individually or in combination	70 ppt (PFOA individually or in combination with PFOS) Drinking water ingestion for lactating woman: 0.054 L/kg-d, RSC=20%	PFOA: 20 ng/kg/day PFOS 20 ng/kg/day	PFOA: LOAEL; Mice: reduced limb ossification, accelerated male puberty; Mice: reduced immunological functional response; Rat: reduced F_0 body weight, increased kidney weight PFOS: HED/UF, POD=HED; Rat: decreased F_0 pup wt (2-gen or 1- gen study)	PFOA: 300 PFOS: 30	PFOA: UF_H: 10, UF_A: 3, UF_L:10; PFOS: UF_H: 10, UF_A: 3;	PFOA: 5,300 ng/kg/day PFOS: 510 ng/kg/day
ATSDR* 2018[1]	PFOA	78 ppt (adult) Adult values use a 80 kg body weight and drinking water intake of 3.092 liters per day 21 ppt (child) Child values use a body weight of 7.8 kg (age birth to one year old) and drinking water intake of 1.113 L/day No relative source contribution is included (assumes all exposure is from drinking water)	3 ng/kg/day	LOAEL Mice: Gestation exposure, decreased motor activity (males only); Adult offspring (females) altered bone cell differentiation	300	UF_H: 10, UF_A: 3, UF_L: 10	820 ng/kg/day

Table 4. (continued)							
Source	Chemical	Drinking water values and parameters used for development	Reference Dose (RfD) or Minimal Risk Level (MRL)	RfD or MRL Basis	Total Uncertainty Factor (UF)	Uncertainty Factor Basis	Human Equivalent Dose
ATSDR* 2018[2]	PFOS	52 ppt (adult) *Adult values use a 80 kg body weight and drinking water intake of 3.092 liters per day* 14 ppt (child) *Child values use a body weight of 7.8 kg (age birth to one year old) and drinking water intake of 1.113 L/day No relative source contribution is included (assumes all exposure is from drinking water)*	2 ng/kg/day	NOAEL *Rat:* delayed eye opening in offspring, lower pup weight	300	UF_H: 10, UF_A: 3, MF: 10	515 ng/kg/day
ATSDR* 2018[3]	PFHxS	517 ppt (adult) *Adult values use 80 kg body weight and drinking water intake of 3.092 liters/ day* 140 ppt (child) *Child values use body weight of 7.8 kg (age birth to one year) and drinking water intake of 1.113 L/day. No relative source contribution is included (assumes all exposure is from drinking water)*	20 ng/kg/day	NOAEL *Rat*: thyroid follicular cell hypertrophy, hyperplasia in offspring (male only); increased liver weight and centrilobular hepatocellular hypertrophy	300	UF_H: 10, UF_A: 3, MF: 10	4,700 ng/kg/day

Table 4. (continued)							
Source	Chemical	Drinking water values and parameters used for development	Reference Dose (RfD) or Minimal Risk Level (MRL)	RfD or MRL Basis	Total Uncertainty Factor (UF)	Uncertainty Factor Basis	Human Equivalent Dose
ATSDR* 2018[4]	PFNA	78 ppt (adult) *Adult values use a 80 kg body weight and drinking water intake of 3.092 liters per day* 21 ppt (child) *Child values use a body weight of 7.8 kg (age birth to one year old) and drinking water intake of 1.113 L/day* *No relative source contribution is included (assumes all exposure is from drinking water)*	3 ng/kg/day	NOAEL *Mice*: decreased pup wt and delayed eye opening	300	UF_H: 10, UF_A: 3, MF: 10	100ng/kg/day
NH, ME, 2016	PFOA and PFOS in combination or individually	70 ppt Same as EPA	20 ng/kg/day	Same as EPA			
VT 2016	PFOA PFOS, PFHxS, PFHpA, and PFNA in combination or individually	20 ppt Water ingestion to 0-1 yr old child, 51 approximately. 0.175 L/kg child; RSC= 20%	20 ng/kg/d	Same as EPA			
NJ 2016	PFOA	14 ppt Adult water ingestion (2 L/day) and body weight (70 kg) RSC = 20%	20 ng/kg/d	$BMDL_{10}$ *Mice*: increased relative liver weight	300	UF_H: 10, UF_A: 3, UF_D: 10;	14.5 ng/ml (target human serum level = $BMDL_{10}$/UF)

Table 4. (continued)							
Source	Chemical	Drinking water values and parameters used for development	Reference Dose (RfD) or Minimal Risk Level (MRL)	RfD or MRL Basis	Total Uncertainty Factor (UF)	Uncertainty Factor Basis	Human Equivalent Dose
NJ 2017	PFOS	13 ppt Adult water ingestion (2 L/day) and body weight (70 kg) RSC = 20%	18 ng/kg/d	NOAEL *Mice*: decreased plaque-forming cell response (immune)	30	UF_H: 3, UF_A: 10	22.5 ng/ml (target human serum level = serum NOAEL/UF)
NJ 2015	PFNA	13 ppt 200:1 serum to water ratio, which represents a central tendency estimate RSC = 50%	4.9 ng/ml (target human serum level)	$BMDL_{10}$ *Mice*: increased maternal liver weight at GD17	1000	UF_H: 10, UF_A: 3, UF_S: 10; UF_D: 3	4.9 ng/ml (target human serum level)
MN 2017	PFOA	35 ppt The MDH toxicokinetic model included upper percentile water and breastmilk intake rates along with a breast milk transfer factor: 0.052 (of maternal serum); RSC=50%	18 ng/kg/d	*Mice*: reduced limb ossification, accelerated male puberty	300	UF_H: 10, UF_A: 3, UF_L:3; UF_D: 3	5,300 ng/kg/d
MN 2017	PFOS	27 ppt The MDH toxicokinetic model included upper percentile water and breastmilk intake rates along with a breast milk transfer factor: 0.013 (of maternal serum); RSC=50%	5.1 ng/kg/d	*Rat*: decreased F_0 pup weight (2-generation or 1- generation study)	100	UF_H: 10, UF_A: 3, UF_D: 3	510 ng/kg/d

Source	Chemical	Drinking water values and parameters used for development	Reference Dose (RfD) or Minimal Risk Level (MRL)	RfD or MRL Basis	Total Uncertainty Factor (UF)	Uncertainty Factor Basis	Human Equivalent Dose
MN 2017	PFBS	2 ppb (2,000 ppt; chronic) Chronic water intake rate: 0.044 L/kg/d; RSC=50%	430 ng/kg/day	; *Rat*: kidney epithelial and tubular/ductal hyperplasia	300	UF_H: 10, UF_A: 3, UF_D: 3, UF_S: 3	129,000 ng/kg/day
MN 2017	PFBA	7 ppb (7,000 ppt; short-term, subchronic and chronic values) Short-term intake rate: 0.285 L/kg/d; RSC=50%	3,800 ng/kg/day	*Rat*: 28-day, decreased cholesterol	100	UF_H: 10, UF_A: 3, UF_D: 3	380,000 ng/kg/day

Table 4. (continued)

*The ATSDR document is still receiving public comments and has not been finalized, but they have posted their MRLs and drinking water values at https://www.atsdr.cdc.gov/pfas/mrl_pfas.html. Abbreviations: UF_A, animal to human extrapolation for toxicokinetic differences: UF_H, variation in sensitivity among humans; UF_S, subchronic to chronic extrapolation; UF_L, LOAEL to NOAEL extrapolation' UF_D, incomplete database; MF, modifying factor based on expert opinion on scientific uncertainties; RSC, relative source contribution.

[1] Only MRL derived, no D-R (1-dose only), determination in offspring at 5-8 week (increased exploratory activity in dark), 17-month-old (decreased mineral density in tibia but no diff. in other biochemical or biomechanical properties).

[2] Only MRL derived, same driver as EPA: 2-generation study, same UF but RfD 10-times lower

[3] Only MRL derived, NOAEL: 3 g/kg/d (or 143,000 ng/ml PFHxS); thyroid changes likely in response to elevated TSH, but hormones not measured

[4] Only MRL derived, same driver as NJ study but different endpoint

Serum Concentrations Resulting from 70 ppt PFOA in Water

Much of the epidemiological evidence on PFAS health effects uses measured or modelled PFAS serum concentrations rather than exposure dose rates. Several PFAS health studies use "cumulative" serum concentrations, also known as area-under-the-curve (AUC) serum concentrations. The AUC serum concentration is the integral of the serum concentration versus time and represents the cumulative internal dose. It has been used as a chemical exposure metric in assessing risk of cancer or other chronic health conditions.

For interpreting health risks from drinking PFAS contaminated water based on the epidemiological literature with serum-based exposure metrics, it is necessary to determine the PFAS serum concentrations that are expected to result from consumption of contaminated water. Pharmacokinetic models (also called toxicokinetic or biokinetic models) are used to represent the quantitative relationship between specific water concentrations and the resulting human serum concentrations over time. These models require knowledge regarding several key physiological and behavioral characteristics including the excretion half-life of the chemical, the extent to which it is absorbed and distributed among various bodily tissues after ingestion, and the water ingestion rate. Because these characteristics may vary among individuals and are often difficult to measure, the models are most often used to represent the average relationship between environmental concentrations and serum concentrations for populations, rather than making specific predictions for individuals.

Although human half-life estimates are available for a handful of PFAS, based on follow-up of previously exposed populations after exposure ceases (Table 2), most PFAS do not have extensive information available on human pharmacokinetics. For legacy PFAS such as PFOA and PFOS, pharmacokinetic models are available and have predicted human serum concentrations with reasonable accuracy (e.g., Shin et al. 2011). One such model is available for PFOA as an on-line calculator (Bartell 2017); it predicts that chronic ingestion of 70 ppt PFOA in water by adults is expected, on average, to increase serum PFOA concentrations by about 8 ng/Ml above background concentrations that result from food, various consumer products, and general environmental sources. This model uses a one compartment pharmacokinetic model with a 2.3-year serum half-life (Bartell et al. 2010), and 114 steady-state serum to water concentration ratio (Hoffman et al. 2011). The median serum PFOA concentration for adults in the US was 2.07 ng/ml in 2013-2014 as reported in the most recent survey results reported for NHANES (CDC 2018). As less than 50% of the US population is reported to have measurable PFOA in their water supplies (Hu et al. 2016), the median serum concentration is presumably due to exposure sources other than drinking water. The total average serum concentration experienced by a population with both typical background exposures and chronic consumption of 70 ppt PFOA in drinking water is thus expected to be about 10 ng/ml, including contributions to serum from drinking water (8 ng/ml) and from other sources (2.07 ng/ml).

Average serum predictions from these models are based on average water consumption. As noted in the New Jersey report on PFOA (NJDWQI 2017), serum concentrations are expected to be higher for individuals consuming larger amounts of contaminated water. That report includes calculations for "upper percentile water ingestion," at a rate 81% higher than typical water consumption rates. Among these individuals consuming relatively high amounts of water (about 2 L/day) contaminated with 70 ppt PFOA, the expected serum PFOA concentration including background exposures is about 16.5 ng/ml.

Calculation of cumulative serum concentrations (AUC for serum concentration vs. time) is somewhat more complex but can be approximated by computing the expected serum concentration for each year after exposure starts, then summing those values over the exposure duration (i.e., the rectangle method). For example, consider a group of individuals whose mothers drank water with 70 ppt PFOA for years prior to pregnancy, and who subsequently consume 70 ppt PFOA for an average lifespan of 79 years. Because PFOA is passed from the mother to fetus with approximately the same serum concentrations, we might expect these individuals to have an average of about 10 ng/ml serum PFOA through their lifetimes, resulting in an average cumulative serum concentration of about 790 ng/ml—years. For upper percentile water ingestion, the estimated cumulative serum concentration is 1300 ng/ml-years. These calculations ignore an increase in early life exposure due to breastfeeding and assume that background contributions will continue to be about 2 ng/ml throughout the person's lifetime rather than declining, now that PFOA has been phased out of production in the US. Nonetheless, they serve as a first approximation for estimating the cumulative exposure and chronic disease risk faced by people chronically exposed at the EPA limit.

The parameters used for these calculations are somewhat uncertain, but published models appear to differ only slightly in their serum predictions for environmental exposures (NJDWQI 2017). The pharmacokinetic model used in the EPA and New Jersey assessments for PFOA relies on a different parameterization but appears to produce serum predictions that are identical to those from the above model. Nonetheless, if the parameters are wrong then these models may produce estimates that are somewhat too low or too high. For example, several publications have reported human half-lives slightly longer than 2.3 years for PFOA. Because the half-life and other parameters are intertwined, a longer half-life might result in a different estimate of the steady-state serum to water concentration ratio, and slightly different serum predictions. Nonetheless, a close agreement among different models suggests that the calculations can be useful in translating drinking water exposures to serum concentrations for comparison to the epidemiological literature.

Comparison of Epidemiological Study Results with Predicted Serum Concentrations at 70 ppt PFOA or PFOS in Drinking Water Consumption

These serum PFOA predictions for consumption of 70 ppt PFOA in drinking water have important implications. First, the predicted average value of 10 ng/ml serum PFOA exceeds the 90th percentile of measured serum PFOA in every reported survey cycle of NHANES (from 1999-2014) and exceeds the 95th percentile in every cycle since 2007 (CDC 2018). This is important because it indicates that this level of exposure would result in being in the top quartile, quintile, or decile of exposure in epidemiological studies of the general population. Thus, lifetime consumption of 70 ppt PFOA in drinking water is without health

consequences only if the general population studies that reported adverse health effects of PFOA exposure among those with serum PFOA concentrations of 10 ng/Ml or higher are not interpreted as indicating a causal effect of exposure. For example, a recent hospital-based case-control study on ulcerative colitis (one of the health conditions reported by the C8 Science Panel as "probably linked" to PFOA exposure) reported a statistically significant increase of 60% in the odds of ulcerative colitis per log unit increase in serum PFOA, with serum PFOA concentrations less than 10 ng/Ml for the vast majority of study participants (Steenland et al. 2018). If the observed increase in the ulcerative colitis was actually caused by PFOA exposure, rather than some other unmeasured or unidentified factor, then consumption of 70 ppt PFOA in drinking water is not safe.

Second, the 25th percentile of measured serum PFOA was 13.4 ng/ml for the large cohort examined by the C8 Health Project/C8 Science Panel studies (https://www.hsc.wvu.edu/media/5354/overall-c8-c8s-results.pdf). Thus, consumption of 70 ppt PFOA in drinking water would place typical people near the top of the first quartile of exposure for that population using measured serum, and the highest water consumers near the bottom of the second quartile of exposure. Thus, in order to judge chronic consumption of 70 ppt of PFOA in drinking water to be likely without an appreciable risk of deleterious effects in the human population (including susceptible subgroups such as those with more water intake), one must also interpret as non-causal all of the C8 Health Project/C8 Science Panel studies that reported an increase in adverse health effects with serum PFOA concentrations above the first quartile.

For some epidemiological studies, cumulative serum concentrations have been used to characterize exposure instead of serum concentrations at a single time point. For example, Barry et al. (2013) investigated cancer incidence in the C8 Science Panel cohort and reported a 23% and 48% increase in kidney cancer incidence for the second quartile and third quartile, respectively, versus the first quartile of cumulative exposure. For testicular cancer, incidence was increased by 4% and 91%, respectively, in the second and third quartiles. These two conditions were judged as having a probable link to PFOA exposure in the C8 Science Panel population. Thyroid cancer was similar elevated, but with less precise effect estimates and weaker evidence of a dose-response relationship. For the lifetime exposure scenario with consumption of 70 ppt PFOA in drinking water that was described in the previous section, cumulative serum PFOA is estimated to be 790 ng/ml-years for typical people and 1300 ng/ml-years for those with upper percentile water ingestion. These cumulative exposures fall near the top of the second quartile or bottom of the third quartile of exposure for the C8 Science Panel cohort; the second quartile was 219-812 ng/Ml-years for kidney cancer and 150-876 ng/ml-years for testicular cancer (http://www.c8sciencepanel.org/prob_link.html). Again, the implication of this comparison is that one must infer that the cancer associations reported in this study (and in the similar study by Vieira et al., 2013) are due to bias or some other error and not indicative of a causal relationship for long term consumption of 70 ppt PFOA in drinking water to be considered free of appreciable health risk.

Epidemiological effect estimates for ulcerative colitis at exposures corresponding to long-term consumption of 70 ppt PFOA in drinking water are summarized in the following table. Three such studies appear to be available, showing a remarkable consistency despite different primary exposure pathways, study designs, and methods of exposure quantitation (Table 5). Although the dose-response patterns across exposure categories within each of these studies are more variable, each suggests a trend of

increasing risk with increasing PFOA exposure. Because ulcerative colitis is an immune disorder, the evidence of other immune system effects of PFOA in laboratory animals may be viewed as evidence supporting the biological plausibility of causation. However, we are not aware of any direct studies of PFOA and ulcerative colitis in laboratory animals; such studies would better inform the biological plausibility of this association consistently observed in humans.

Table 5. Increased risk of ulcerative colitis with long-term consumption of 70 ppt PFOA in drinking water.

Study	Exposure Source; Quantification	Equivalent Exposure Category for 70 ppt	Effect Estimate (95% Confidence Interval)
Steenland et al. (2013)	Drinking water; modelled exposure	586 to 3,500 ng/ml-years (third quartile)	Rate Ratio = 2.63 (1.56, 4.43)
Steenland et al. (2015)	Occupational; modelled exposure	800 to 3,440 ng/ml-years (second quartile)	Rate Ratio = 3.00 (0.82, 11.0)
Steenland et al. (2018b)	Background; measured serum	> 5 ng/ml (fifth quintile)	Odds Ratio = 2.86 (0.94, 8.75)

These comparisons of serum or cumulative serum categories for consumption of 70 ppt PFOA in drinking water for ulcerative colitis and several cancers are selected examples, and not comprehensive in addressing all of the reported epidemiological associations with PFOA. However, because serum PFOA concentrations are similar across study populations with only background exposures (IARC 2017) and across the various C8 Science Panel Studies, the calculations suggest that chronic consumption of 70 ppt PFOA in drinking water would result in serum concentrations within the observed range of exposures and above the reference category in most of the epidemiological literature.

The limitations in this approach must also be acknowledged, starting with the inherent uncertainty in a limited body of research from a single study population as in the C8 Health Project. Random error and bias were addressed to the extent feasible, but nonetheless, some or all of the associations may not reflect causal effects. The quantification of risk is also subject to uncertainty, with some uncertainty in reconstructing exposure and inferring water consumption levels to derive risk estimates. Nonetheless, even if some of the inferred associations are not reflective of adverse effects of PFAS, 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.

Epidemiological studies of immune system dysfunction in children in a variety of study populations provide additional evidence for associations of PFOA or PFOS with adverse health effects at serum concentrations below those anticipated to result from long-term consumption of water with 70 ppt or higher (Grandjean et al. 2012; Granum et al. 2013; Mogensen et al. 2015; Stein et al. 2016). Benchmark dose modeling was conducted using vaccine titer response data from one of these studies, resulting in $BMDL_{05}$ values of 1.3 ng/ml serum PFOS and 0.3 ng/ml serum PFOA (Grandjean and Budtz-Jorgensen 2015). The authors noted that these serum concentrations are well below current background serum concentrations and imply a limit of about 1 ppt for PFOA in drinking water. Although they did not convert their serum PFOA $BMDL_{05}$ to a drinking water concentration, one could do so using a pharmacokinetic model for PFOS such as that used by the USEPA.

The decision of whether to rely on toxicological dose-response data or epidemiological dose-response data for setting drinking water limits is difficult, as each approach has serious limitations. High quality toxicology experiments use randomized experiments under carefully controlled laboratory conditions, which increases confidence for inferring causation, but laboratory animals are not humans (despite many similarities in mammalian physiology across species). There is no guarantee that quantitative dose-response relationships and safety limits derived from rodent experiments will be relevant to humans, even when known physiological differences such as the large differences in pharmacokinetics of PFAS are accounted for using the best available information.

Epidemiology studies, on the other hand, must rely on natural experiments or other observational data rather than randomized experiments, which makes it much more difficult to rule out confounding or other sources of bias and infer causation. Exposure measurement can also be difficult in epidemiology studies, though this appears to be less a limitation for PFAS than it is for many other chemicals, due to relatively long serum half-lives for PFAS in humans. Hertz-Picciotto (1995) proposed influential guidelines for determining when epidemiological data are sufficient for risk assessment, including criteria for individual-level exposure quantification, limited potential for confounding and other bias, and clearly elevated risk. These criteria appear to be met for some of PFAS epidemiology literature (e.g., PFOA and ulcerative colitis).

Finally, some authors have recommended that animal and human dose-response information be combined quantitatively using formal methods, rather than choosing one or the other, when high quality studies of both types are available (Samet et al. 2014; Bartell et al. 2017). This approach has not yet, to our knowledge, been used to set drinking water limits.

It should also be recognized that, at present, epidemiology-based risk estimates, and inferences apply directly only to PFOA and PFOS, not to other forms of PFAS where high quality epidemiologic evidence is much more limited or simply unavailable.

Conclusions and Recommendations

USEPA, ATSDR, and a variety of states have determined advisory levels equivalent to about 13 to 70 ppt for PFOA, PFOS, or the sum of PFOA and PFOS in drinking water, based on immunological, developmental, and other toxicity studies in laboratory animals. The differences in these recommended limits reflect selection of different health outcomes, or different assumptions regarding water consumption rates or lactational transfer. The pharmacokinetic models used to link serum concentrations in these animal studies to human doses can also be used to determine the serum concentration expected to result in humans. For example, chronic consumption of 70 ppt PFOA in drinking water is expected to result in an average serum PFOA concentration of about 10 ng/ml in adults, and about 16.5 ng/ml among those with high rates of water consumption. These serum concentrations fall above the range of values reported for a representative sample of the US population, and within the second or third quartile of exposure categories in several published epidemiological studies in highly exposed populations such as the

C8 Science Panel Studies. Increases in ulcerative colitis, some cancers, and other health effects have reported for those exposure categories. *If one accepts the probable links between PFOA exposure and adverse health effects detected in the epidemiological literature as critical effects for health risk assessment, then 70 ppt in drinking water might not be sufficiently protective for PFOA.*

Conclusions

Based on the available evidence for PFOA, in particular, the combined evidence from toxicology and epidemiology the Panel concludes that the research supports the potential for health effects resulting from long-term exposure to drinking water with concentrations below 70 ppt. The epidemiologic evidence that supports health effects from the serum levels produced by long-term exposure to 70 ppt pertains to developmental immunologic outcomes as well as adult diseases evaluated by the C8 Science Panel and are supported by the toxicology studies.

Recommendations

1. The panel recommends that the State of Michigan consider both animal and human data for quantification of risk for PFOA and PFOS. Newer advisory levels have been proposed for additional PFAS, for which there are fewer epidemiological studies but sufficient toxicological evidence indicating some common modes of action.

2. For PFAS other than PFOA and PFOS, since there is limited epidemiological evidence and a less firm scientific basis for defining a specific level of drinking water as acceptable or unacceptable, inferences from toxicologic studies with appropriate margins of safety may provide the only basis for making judgments. Nonetheless, the panel also recommends that the State of Michigan consider setting advisory limits for these additional PFAS in light of their similar chemical structures and toxicity.

3. The options for recommending drinking water standards that we recommend the State of Michigan consider are: (a) adopting one of the advisory values developed by various agencies that are based on toxicological outcomes exclusively; (b) adopting a more novel approach and developing the an advisory value solely based on epidemiological findings (such as one described above and one used by EFSA (draft document to be released by end of 2018); or, preferably, (c) developing a new set of values based on weight of evidence and convergence of toxicological and epidemiological data.

4. Given our incomplete understanding but quickly evolving scientific literature on the health effects of specific forms of PFAS, the Panel recommends that all judgments regarding acceptable levels in drinking water should be subject to periodic re-evaluation, with the potential for adopting more or less stringent criteria based on new insights.

SECTION 6 Mitigation/Remediation

PFAS are a class of compounds with widely varying properties (Table 6). While the most common PFAS chemicals contain 4 to 10 carbon atoms, they can contain from a single carbon atom to 16 carbon atoms. Their solubility in water ranges from insoluble at (3×10^{-15} mg/L) to being completely dissolvable in water (>2×10^7 mg/L) (Concawe Soil and Groundwater Taskforce (STF/33) 2016). Their vapor pressures range from <0.004 Pa to 5900 Pa (Table 6); chemicals with higher vapor pressures will tend to move from the liquid to air. Their log K_{oc} (organic carbon-water partitioning coefficient) values range from 1 to 230; chemicals with higher K_{oc} values will tend to move into the organic matter on soils and biosolids, whereas compounds with low K_{oc} will have stronger associations with (and will be more mobile in) water. Some of the PFAS are negatively charged, while others are positively charged, and others can be either positively or negatively charged, depending on pH of the water. The charge of the compound is important as it will affect whether it is in air, water, or on a solid surface, how it is transported into an organism, and the efficacy of a remediation strategy. The PFCAs and PFSAs are almost entirely ionized over the pH range encountered in natural waters and therefore have lower vapor pressure when in water-containing media than one would expect for the pure (protonated neutral) compounds. The shorter chain PFAS are typically more mobile owing to their greater solubility in water. There is some debate regarding the extent to which the PFSA compounds are sorbed relative to the PFCA compounds of perfluoroalkyl equivalent chain length. Earlier research (Higgins and Luthy 2006) suggested that PFSA sorption was 1.7-fold greater than PFCA sorption for compounds of the same chain length. However, more recent research suggests that the K_{oc} values for these compounds depend more on chain length than whether the chemical contains sulfonic acid or carboxylic acid groups (Rayne and Forest, 2009). **As a result of these highly variable properties, there is no single method for the treatment of contaminated water that is effective at removing all PFAS, but as is discussed below there are methods that are effective for some PFAS.**

Drinking Water Treatment

There are only a few treatment methods that have been demonstrated to be effective for removing PFAS from drinking water at the field or full-scale (community water system) level. These include sorption by granular activated carbon (GAC) or anion exchange resin (AIX), membrane filtration(M-FIL), reverse osmosis (RO), and coagulation/flocculation/sedimentation (COAG/FLOC/SED). Compounds with a high log K_{oc} (usually those with longer chains) are more effectively removed by adsorption onto activated carbon thank those with a low log K_{oc}. Longer chain compounds (i.e. those with a relatively high molecular weight) can be potentially removed by nanofiltration or reverse osmosis. Charged compounds are more suitable for removal by ion exchange. Oxidation/reduction (OXID) processes show promise; however, none of these have been employed beyond the bench-scale. Few PFAS can be removed by biodegradation. Among the challenges in measuring efficiencies are an inability to quantify these chemicals or to identify their byproducts analytically along with unknown or unmeasurable losses of the chemical to the air and solid. Despite these challenges, the removal efficiencies for field/full scale operation have been quantified (Table 7). The most feasible processes for immediate/rapid deployment are discussed herein.

Table 6. Chemical characteristics of representative PFAS (Reference is ATSDR unless otherwise noted).

Chemical	Aqueous solubility (mg/L) at 25 °C	pKa	Vapor pressures for pure compounds (Pa) at 25 °C (unless noted)	Organic carbon-water partitioning coefficient (log K_{oc})
PFBA (C4)	2.14×10^5, Miscible[©]	0.08[b] 0.4-0.7[d]	5900[a]	1.88[©]
PFHxA (C6)	1.57×10^4	-0.16	457[©]	1.91[©]
PFHpA (C7)	4.37×10^5	-0.15[b]	80; 158[©]	2.19[©]
PFOA (C8)	9.5×10^3	-0.5[d]	2.3 [b]	2.06[f], 17-230
PFDA (C10)	No data	-0.17[b]	0.10	No data
PFBuS (C4)	No data	0.14[b]	631[e]	1.0[©]
PFOS (C8)	5.7×10^2	0.14[b]	3.3×10^{-3}[©]	2.5-3.1[©]
PFOSA (C8)	0.14[b]	6.24[b]	No data	2.5-2.62[©]
Me-PFOSA-AcOH (C11)	No data	3.92[b]	No data	No data
Et- PFOSA-AcOH (C12)	No data	3.92[b]	No data	No data
12:2 diPAP (C14)	3×10^{-15}[d]	No data	0.000[d]	No data
HFPO-DA (Gen X)	No data	<1[g]	No data	1.92[g]

a) at 56 °C; b) estimated; c) at 20 °C; d) (Goss 2008) Ionized form of PFOA; e) (Concawe Soil and Groundwater Taskforce (STF/33) 2016) Data are for the protonated forms of the acid; f) (Danish Ministry of the Environment 2015) Data are for the potassium salt of PFOS and the free acid for PFOA; g) (Xiao 2017) pK$_a$ is predicted using Marvin 15.10.26 and ACD/Labs 12.0; Log K$_{oc}$ is predicted from EPISuite 4.1

Sorption processes involve the attachment of molecules to a solid surface, for example, soil and sediment. There are two broad categories of PFAS sorption treatment: granular activated carbon and ion exchange. In both cases, after the carbon or ion exchange material reaches its capacity for removal, it must be removed and replaced. In larger scale systems this material can be regenerated either on-site or off-site. With granular activated carbon, carbon regeneration using thermal desorption has the potential to release PFAS to the atmosphere unless off-gas treatment is utilized to capture and destroy the released fluorinated products. Regeneration of ion exchange sorbents produces regenerant solutions that will contain high concentrations of PFAS that must be removed prior to discharge. With point-of-use or point-of-entry residential systems, the solid material containing PFAS is typically disposed of to a landfill (Interstate Technology Regulatory Council 2018), which does not destroy PFAS.

Table 7. PFAS Treatment efficiency as measured by percent removal at field or full-scale operation.

Treatment Type	PFOA	PFOS	Other compounds
coagulation/flocculation/sedimentation	1-20%[b]	1-80%[b]	1-5%[b]
Granular Activated Carbon – frequent replacement	>48% - >90%[c]	>89 to >98%[a]	>22% - >90%[c]
Anion Exchange	51-90%[c]	90-99%[a]	Faster breakthrough of shorter chain compounds[b]
Membrane Filtration	0%[b], 10-50%[c]	0-23%[a]	<10% for most compounds
Biological treatment (including slow sand filtration and river bank filtration)	<10%[c]	0-15%[a]	Highly variable, in some cases concentrations increased[©]
Reverse Osmosis	>90%[c]	93-99%[a]	>90%[c]
Oxidation (ozone)	<10%[c]	0-7%[a]	<10%[c]
Advanced oxidation (UV-TiO$_2$)	<10%[c]	15%[a]	<10%[c]
Powdered activated carbon	No data	10-97%[a]	No data

a) Speth, et al., 2018; b) Interstate Technology Regulatory Council 2018; c) Dickenson & Higgins, 2016

Granular activated carbon is presently the most commonly used treatment technique for PFAS removal. Removal efficiencies of between 90 and > 99% have been reported in the literature; the lower values are likely due to the inefficient removal of the shorter chain PFAS (Interstate Technology Regulatory Council 2018). In 2007, granular activated carbon was used to remove PFOA from two public water supplies in West Virginia (Dickenson and Higgins, 2016). The system, which is designed with dual filters and is monitored carefully, has been highly effective at removing PFOA. Granular activated carbon has been implemented successfully at several other sites. In Penns Grove, NJ, GAC treatment is achieving PFOA removal to below 40 ppt. At a 3 million gallon per day plant in Oakdale, MN, granular activated carbon treatment is achieving effluent with PFOS levels below 8 ppt (Cummingset al. 2015). As removal efficiencies typically decrease as the length of carbon chain decreases, granular activated carbon may not be amenable to the removal of these compounds. Irrespective of the target PFAS, laboratory and field studies are essential to the proper design and implementation of granular activated carbon treatment systems for community water supplies.

Ion exchange is a process whereby one ion is exchanged for another, similar to that which occurs in a home water softener, where calcium is removed, and sodium is released into the water. Ionized PFAS may be removed using ion exchange, however reported removal efficiencies are highly variable. Additionally, competition with common anions, such as bicarbonate, nitrate, and phosphate, for binding sites on resins can impact effectiveness. Organics, total dissolved solids, minerals can clog resins and reduce efficiency (Cummings, et al. 2015). Anion exchange appears to be more effective for the removal of smaller chain PFAS than granular activated carbon and is being implemented at several sites (Amex et al. 2016 and ect2 2018).

Reverse osmosis and nanofiltration systems have been shown to be effective for the removal of many types of molecules and ions. With reverse osmosis, PFAS are retained in the reject stream on the pressurized side of the membrane, which must be further treated to prevent the release of PFAS back into the environment. Reverse osmosis has been shown to be effective at the flowrates typical of that in community water systems (Interstate Technology Regulatory Council 2018) (Cummings et al 2015); however, reverse osmosis is costly and responsible treatment and disposal of the PFAS-enriched reject stream is necessary. Nanofiltration, which is less expensive than reverse osmosis, as it operates at lower pressures, is still at a developmental stage and has not be used at the pilot or full-scale operation (Interstate Technology Regulatory Council 2018). PFOS removal efficiencies of 93-99% have been reported for reverse osmosis and nanofiltration membranes (Speth et al. 2018). Dickenson and Higgins (2016) reported removals > 90% for PFOA and PFOS and several other PFAS including PFPeA, PFHxA, PFHpA, PFNA, PFDA, PFBS, and PFHxS.

Point-of-use (POU) and point-of-entry (POET) household filters can be used for the removal of PFOA and PFOS. However, it is recommended that only filters certified for such use be employed. The certifying body in the U.S. is NSF International. To date, NSF has certified some point-of-use granular activated carbon and reverse osmosis filters for PFOA and PFOS reduction. A list of filters that have received this certification can be found on the NSF International website (http://www.nsf.org/). The New Hampshire Department of Environmental Services recommends point-of-use systems, over point-of-entry systems where PFAS contamination is an issue as exposure to PFAS is associated with drinking water. All filters are certified to achieve removal of PFOA/PFOS to below 70 ppt. Spent filter cartridges are not considered hazardous waste and can be disposed of with household trash (Michigan Department of Environmental Quality 2017).

Wastewater Treatment

The presence of PFAS in wastewater has been well documented. For example, Xiao et al. (2012) found elevated levels of PFHxA, PFOA and PFOS in wastewater influent in 18 out of 37 Minnesotan wastewater treatment plants (WWTPs). The concentrations of PFHxA and PFOA were observed to increase in 59% of the WWTPs surveyed; further evidence that PFOS and PFOA are generated by biological processes in wastewater treatment (Xiao 2017). Yu et al. (2009) concluded that the mass flows of PFOS and PFOA increase during conventional activated sludge treatment due to the transformation of PFOS, PFOA, and other PFAS.   Pan et al. (2016) similarly reported the increase of mass loadings of PFOS and PFOA during biological wastewater treatment. They also reported the production of PFNA, PFDA, PFHxS, PFHxA, and PFUnDA during biological treatment. Dauchy et al. (2017) reported that mass flow of PFCA increased after secondary treatment, likely due to the degradation of polyfluorinated chemicals. Several precursors and transformation products have been identified during wastewater treatment (Table 4).

Arvaniti and Stasinakis (2015) reported that sorption could be an important removal mechanism for PFAS during wastewater treatment, particularly for the longer chain compounds. Dauchy et al. (2017) reported that PFCA adsorbed to flotation sludge. Both studies demonstrate the potential for PFAS to accumulate in the biosolids produced during conventional wastewater treatment.

Table 8. PFAS generated during wastewater treatment.

PFAS Chemicals	Transformation product	Process/Organism	Reference
8:2 FTOH	PFOA	Activated sludge	Wang et al. 2005
6:2 FTOH	Shorter chain PFCAs, including PFPeA, PFHxA	Activated sludge	Zhao et al. 2013
6:2 FTS			Wang, et al. 2011
PFOA	None – biologically inactive	Anaerobic microorganisms	Liou et al. 2010
N-EtFOSE, N-ETFOSAA	PFOS	Activated sludge	Yu et al. 2009
Unknown	PFOS	Activated sludge	Yu et al. 2009

Landfill Transformation and Leachate treatment

The presence of PFAS in landfill leachate is not surprising given the ubiquitous use of these compounds. PFOA has been detected in US landfill leachate at concentrations up to 9.2 µg/L. The levels depend on climate, as precipitation is a major source of infiltration into landfills, waste age, and seasonal variability (Lang et al. 2017). Allred et al. (2014) identified more than 70 PFAS in their study of the leachate from 18 U.S. landfills. The 5:3 fluorotelomer carboxylate was dominant in all 95 samples and concentrations varied with waste age. The C4-C10 PFCAs and C4, C6, and C8 PFSAs were found above detection limits in more than 50% of the samples. Biodegradation of polyfluorinated chemicals in landfills is thought to be significant (Hamid et al. 2018), resulting in the concentration of perfluoroalkyl acids (PFAAs). The mass flow of PFAS in US landfill leachate in 2013 was estimated to be ~600 kg/yr. This estimate is likely an underestimate since it is unclear how many more unidentified PFAS are in landfill leachate. Benskin et al. (2012) monitored landfill leachate and found that PFPeA and PFHxA were the dominant PFAS throughout the year, except for March and April. In March and April, the concentrations of PFOS, PFOA, and numerous PFAA precursors increased by factors of 2-10. They estimated that the single municipal landfill released ~16 kg/yr of PFAS to the wastewater treatment plant.

Hamid et al. (2018) reported that biological leachate treatment results in an increase in PFAA concentrations. Activated carbon treatment was reported to achieve removal efficiencies of 68-99% for the sum of the 43 PFAS measured (Busch et al. 2010). The variability is likely due to differences in the distribution of PFAS found at the three landfill sites, along with differences in the activated carbon utilized and in the characteristics of the landfill leachate. The same authors reported that reverse osmosis and nanofiltration resulted in the lowest concentrations of the PFAS quantified. Both biological treatment and wet air oxidation using ozone resulted in little removal. These processes are discussed in more detail in the section on drinking water treatment.

Soil treatment (including phytoremediation)

At present, the only technologies that are sufficiently mature for the treatment of PFAS-contaminated soils are excavation with off-site disposal in a landfill or incineration, capping or covering and monitoring infiltration, and soil washing (Ross et al. 2018). While the off-site disposal of contaminated soils in a landfill is feasible, it is a less desirable option due to long-term liability and restrictions regarding disposal of PFAS

in landfills. The incineration of excavated soils requires temperatures in excess of 1,100 °C and is, therefore, very expensive. Capping of contaminated soils requires long-term monitoring and management. Soil washing of excavated soils results in the creation of highly contaminated leachate, which then requires subsequent, often complex and expensive treatment (Ross et al. 2018).

There are a number of technologies that are in various stages of development. The *in situ* stabilization of contaminated soils involves the mixing of soils with adsorbents to protect groundwater from leached PFAS. Activated carbon, organo-modified clays, and proprietary blends of activated carbon/clay/aluminum hydroxides have been used for lab testing but have not been demonstrated in the field (Ross et al. 2018). *In situ* oxidation using peroxone activated persulfate (OxyZone) was employed at the pilot-scale for the remediation of soils contaminated with chlorinated volatile organic compounds (cVOCs) and PFAAs. Statistically significant decreases in PFAA groundwater concentrations were observed in post-treatment samples (Eberle et al. 2017). The formation of lower molecular weight and more mobile PFAS is of concern (Yao et al. 2015). Phytoremediation of PFAS contaminated soil has been tested at a fire training site at the Stockholm Arlanda airport. PFAS were taken up by several plant species, with the highest concentration of contaminants in the foliage and twigs (Gobelius et al. 2017). However, the amount of PFAS extracted per tree is low (Ross et al. 2018). The only other study of the use of phytoremediation for mitigation of PFAS contaminated soils was conducted at an established wetland and no significant removal of these compounds was achieved (Ross et al. 2018).

Excavated soils and spent granular activated carbon could also be treated by high temperature incineration. However, this treatment technology is costly and consumes large amounts of energy. The Concawe (2016) report recommends incineration temperatures of between 1,000 and 1200°C for complete destruction of PFOS. MDEQ (2018) states that incinerators operating in Michigan function at temperatures between 590 and 980°C. As such, incomplete destruction and the formation of reaction byproducts is likely (Concawe Soil and Groundwater Taskforce 2016) and stack treatment to remove fluorinated chemicals would be required. While GAC has been shown to be effective for the removal of PFOS and PFOA in waters, there are no known studies demonstrating its use for stack gasses. Wet scrubbers are used at three Michigan incinerators. The use of this technology for stack gas treatment has the potential of transferring PFAS and byproducts to wastewater.

Conclusions and Recommendations

Conclusions

Because of the widely varying properties (e.g., persistence, water solubility, polarity, volatility) no one treatment method will be effective for the removal of all PFAS. Anion exchange and granular activated carbon show promise for the removal of PFAS from drinking waters. Reverse osmosis also has significant potential, however, as with anion exchange and granular activated carbon, the efficacy of removal of short-chain PFAS chemicals is less than that obtained for the longer-chain compounds. However, laboratory-scale and pilot-scale studies are recommended before implementation since the efficacy of removal varies significantly with PFAS and matrix. In the case of anion exchange and reverse osmosis, there are concentrated liquid waste streams that must be further treated prior to their discharge. With granular activated carbon, carbon regeneration has the potential to release PFAS to the atmosphere.

Anion exchange, granular activated carbon and reverse osmosis can also be used to remove PFAS from wastewater effluent and landfill leachate. However, the presence organic matter, inorganic chemicals, and particulates will reduce removal efficacy of PFAS as compared to that in most drinking waters.

For private drinking water supplies, certified point-of-use filters are commercially available for the removal of PFOA and PFOS.

High temperature incineration has been used for the oxidation of PFAS from solid material.

Recommendations
1. Water systems facing PFAS contamination should be required to evaluate all possible remedial approaches, including the use of alternative non-contaminated sources. Once potentially suitable options are identified, then these choices will need to be tested at the bench and pilot scale using the contaminated water. Numerous factors, including initial concentrations of PFAS, specific PFAS present, background organic and inorganic concentrations, and pH will need to be considered in the design. In addition, operation and maintenance costs, ease of operation, ability to treat multiple compounds, and disposal options need to be considered. Based on these tests, full-scale options can be implemented on a case- by-case basis.

2. 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.

3. The use of NSF International-certified filters is recommended where private well water is contaminated with PFOA and PFOS and an alternative water source is unavailable.

4. Laboratory-scale and pilot-scale studies are recommended before the implementation of treatment technologies to remediate landfill leachate and wastewater effluent contaminated with PFAS chemicals. The efficacy of treatment technologies should be evaluated based on the efficiency of destruction and completeness of converting PFAS chemicals to nonhazardous substances.

5. As anion exchange, granular activated carbon, and reverse osmosis result in the production of waste streams that contain PFAS, it is recommended that these streams be treated prior to discharge. Additional research is necessary to more effectively destroy the PFAS chemicals and avoid simply transferring them from one medium to another.

SECTION 7 Other Types of PFAS for Consideration

Our awareness of contamination of water, soil, foods, and air by PFAS is emerging now, in part, due to the development of analytical instrumentation capable of detecting and quantifying PFAS in environmental matrices. Most priority pollutants, such as trichloroethene, benzene, toluene, xylenes are volatile contaminants that are detected by gas chromatography/mass spectrometry. However, the majority of PFAS of interest are ionic in nature and are inherently non-volatile; hence, they are not captured when screening groundwater, soil, and sediment for priority pollutants by gas chromatography/mass spectrometry. Until the development of modern liquid chromatography-tandem mass spectrometry now used for PFAS analysis, the only clues we had to suggest high concentrations of PFAS were reports of foaming groundwater and foaming of soil during heavy rains. Modern liquid chromatography-tandem mass spectrometry is ideal for quantifying known and prioritized ionic PFAS and is a commercially available technology now used by contract, state, federal, and academic labs for PFAS analysis. High quality measurements of some of the most common PFAS are obtained using Method 537 now that analytical grade standards, including stable-isotope labeled internal standards are commercially available. However, it is anticipated that the range of PFAS of potential concern may change as new replacement substances are produced when other PFAS are regulated or banned from production.

PFAS (14 going to 24) in USEPA Method 537

Of the thousands of PFAS, 14 of the most studied are currently measured using Method 537 Rev 1.1, including C6-C14 perfluoroalkyl carboxylates (PFCAs); C4, C6, and C8 perfluoroalkyl sulfonates (PFSAs), N-methyl perfluorooctane sulfonamide acetic acid (N-MeFOSAA) and N-ethyl perfluorooctane sulfonamide acetic acid (N-EtFOSAA). Method 537 is a drinking water method modified by labs for analyses of PFAS in other matrices such as groundwater. Because the solid phase extraction sorbent used in Method 537 in its current form does not capture short-chain PFBA and PFPeA, it yields data that lack information about the PFAS that are most readily transported in water.

To address these shortcomings, recent information from EPA indicates that Method 537 will be modified to measure a total of 24 PFAS including C4 and C5 PFCAs and C5, C7, C9, and C10 PFSAs, perfluorooctanesulfonamide (PFOSA), along with 4:2, 6:2, and 8:2 fluorotelomer sulfonates (FTSAs) (Impellitteri et al. 2018). The EPA will also introduce Methods 8327 (direct injection modern liquid chromatography-tandem mass spectrometry, which avoids PFAS capture technologies that are inefficient capturing short chain compounds) and 8328 and will extend the analyte list to include the perfluoropolyethers GenX, Adona, and F53-B (Impellitteri et al. 2018). In addition, there is a proposed American Society for Testing and Materials Method that is likely to include additional PFAS.

The PFAS being added to the current list of 14 PFAS to bring the total to 24 offers the following attributes that may confer advantages when characterizing sites or waste streams:

- Measurements of short chain (e.g., PFBA, PFPeA, and 4:2 FTSA) PFAS are useful for evaluating drinking water treatments because they are the most water soluble PFAS and tend to be the most difficult to remove from water, for example by granular activated carbon (Appleman 2014). They are also those that most readily escape from contaminated sites and are transported in groundwater.
- Odd-carbon chain length PFSAs (e.g., C5, C7, and C9) occur at AFFF sites and contribute significantly to the mass of PFAS (Backe et al. 2013).
- Long-chain PFSAs (e.g., PFNS (unpublished data) and 8:2 FTSA)(Schultz et al. 2004) are also found at aqueous film forming foam-contaminated sites and are expected to more bioaccumulative than PFOS).
- The various telomer sulfonates (4:2, 6:2, and 8:2 FTSAs) are potentially important since they are electroplating substitutes (Fath et al. 2016, Yang et al. 2014, and Wienand et al. 2013) and can occur at concentrations that exceed that of PFOS and PFOA in AFFF-contaminated groundwater (Schultz et al. 2004).
- The 8:2 telomer sulfonate associates with groundwater but also with soil sediment and can transform to PFOA (Harding-Marjanovic et al. 2015) and is found at aqueous film forming foam-contaminated sites.
- GenX and Adona are PFAS not currently found on lists of measured PFAS but, in the case of GenX, it is known to occur in drinking and river water near manufacturing sites (Hopkins et al 2018 and Gebbink et al. 2017).
- FTCAs and FTUCAs are found in relatively high abundance in landfill leachate (Allred et al. 2014) since they are biodegradation intermediates of fluorotelomer precursors, including FTOHs.

Branched and linear isomers of PFSAs and PFCAs

Branched and linear isomers are always potentially present for PFAS produced by electrofluorination. At present, there are analytical-grade branched and linear standards available for PFOS and PFHxS, but not for PFOA. PFCAs can be branched and linear and the presence of branching will depend on the synthesis used to generate the PFCAs and their precursors. For example, PFCAs generated by the 3M electrofluorination reaction are branched (25%) and linear (75%) (Benskin et al. 2010 and 3M 1999). However, PFCAs made by telomerization are only linear and, for this reason, telomer-based precursors will degrade to only linear PFCAs. Unless the branched isomers are correctly identified, they will go unidentified in samples. In that case, the reported concentrations will be lower than the actual concentrations. Technical mixtures are one source of branched and linear isomers that can be used to identify branched isomers until analytical-grade standard are available.

The environmental process of partitioning between sediment/soil and water impacts the apparent branched and linear ratios of PFAS. Branched isomers are more compact and, for this reason, partition less relative to the linear isomers to environmental solids, including biosolids. For example, biosolids are relatively enriched in linear isomers whereas primary effluent of WWTPs are relatively enriched in the

branched isomers. Depth profiles in groundwater indicate a greater proportion of branched isomers at depth relative to linear isomers due to the relatively faster transport of branched compared to linear isomers (Jennifer Field, personal communication, unpublished data).

Volatile PFAS

To date, there are no EPA methods that measure volatile PFAS in water or air, which include the fluorotelomer alcohols (FTOHs) and N-methyl perfluorooctane sulfonamido alcohol (N-MeFOSE) and N-ethyl perfluorooctane sulfonamido alcohol (N-EtFOSE). The volatile FTOHs are associated with gas-phase emissions from municipal wastewater treatment plants and landfills (Ahrens et al. 2011). One report of FTOH, N-MeFOSE, and N-EtFOSE in aqueous film forming foam formulations is reported, but to the best of our knowledge, no data are publicly available for these volatile PFAS at aqueous film forming foam-contaminated sites.

Future Directions: Analytical Methods for Closing PFAS Mass Balance

At present, there is no single methodology for isolating, identifying, and quantifying all PFAS in environmental media. For this reason, it is challenging to close the mass balance on PFAS, but this should be of high priority if we are to understand transport of PFAS in environmental media and the extent of human exposures. What does exist is a number of analytical tools that provide quantitative data on a select number of individual PFAS and PFAS classes (Table 9). Analytical methodology is used by commercial (contract), state, federal, and academic laboratories for generating quantitative data on PFCAs and PFSAs in drinking water (USEPA Method 537), groundwater, surface water, soil, sediment, and biota. However, for classes other than the C4-C14 PFCAs and C4, C6, and C8 PFSAs, methodologies are generally not available outside academic settings. Alternative methods for detecting and quantifying a broader array of PFAS, including 'precursors' that have the potential to degrade to persistent PFCAs and PFSA, are described briefly below with the advantage and limitations. Closing mass balance with high confidence is not yet possible and will depend on the commercial availability of high-quality analytical standards.

Liquid Chromatography-Tandem Mass Spectrometry

As a commercially available tool, liquid chromatography-tandem mass spectrometry is the current industry standard for PFAS quantification in environmental and biological media, including human blood. In many laboratories, liquid chromatography-tandem mass spectrometry can measure target PFAS down to low part-per-trillion levels. Method 537 for drinking water is based on liquid chromatography-tandem mass spectrometry and is used to quantify a discrete number of individual PFAS for which high quality standards and stable-isotope labeled standards are commercially available. Liquid chromatography-tandem mass spectrometry is sensitive and selective, and laboratories are required to perform extensive quality analysis and quality control to provide measurements of high confidence. The instrumentation requires skill to operate and the analyses are typically several hundred US dollars per analysis.

Total Oxidizable Precursor Assay

Precursors are defined as PFAS that can under biotic or abiotic transformation to dead-end PFCAs and PFSAs. The total oxidizable precursor assay is a method whereby precursors are quantified by the net production of PFCAs after oxidation of a sample (Houtz et al. 2013). Hydroxyl radicals are generated under basic conditions using persulfate and the radicals convert polyfluorinated precursors to PFCAs upon oxidation. For the total oxidizable precursor assay, PFCAs are quantified in sample extracts before and after oxidation by LC-MS/MS. The net production of PFCAs is a quantitative estimate of precursors. The total oxidizable precursor assay does not identify individual precursors and the assay does not preserve the precursor's original fluorinated chain. The total oxidizable precursor assay does offer some chain length information in the form of the "n+1 effect." The "n+1 effect" is the observation that the highest PFCA chain length produced (e.g., PFNA), which is typically in only a small fraction of the resulting PFCA distribution after oxidation, is one carbon atom greater than the initial fluorinated chain length (e.g., C8). It is possible to assess whether precursors are branched and/or linear because the oxidation does not rearrange the fluorinated backbone (Robel et al. 2017). The total oxidizable precursor assay was developed for storm water runoff and for aqueous film forming foam-contaminated groundwater, soil, and sediment (Houtz and Sedlak 2012 and Houtz et al. 2013). The assay is now available from several contract laboratories in the US and Canada. Because two liquid chromatography-tandem mass spectrometry analyses and a reaction are required, the total oxidizable precursor assay is more expensive than a conventional single analysis for a given sample. Because the total oxidizable precursor assay relies on the difference between PFCA concentrations before and after oxidation, measures of uncertainty in the two analyses are needed to confidently report a significant difference, which is challenging at low PFAS concentrations if replicate analyses of the total oxidizable precursor assay are not conducted. The total oxidizable precursor assay is unlikely to detect GenX, Adona, and F-53B, which are considered replacement chemicals since the fluorinated chains lengths of the replacement chemicals are typically < C4 (Hopkins et al. 2018) and would likely to oxidized to forms not detected by the total oxidizable precursor assay, which is based on the net production of C4 and greater PFCAs."

The total oxidizable precursor assay is useful for determining whether precursors that are not captured using USEPA and other analytical methods are present. Given that it does not require identities of individual PFAS (e.g. various fluorotelomer-derived compounds) that are oxidized in the assay conditions and can exploit targeted instrument methods that measure PFSAs and PFCAs, the total oxidizable precursor assay is a useful tool for sample and site characterization, as opposed to using it for monitoring.

Total Fluorine by Particle Inducted Gamma Ray Emission

Total fluorine by particle inducted gamma ray emission is an approach for quantifying total fluorine atoms in a solid sample (Ritter 2017). To date, total fluorine by particle inducted gamma ray emission is used for solid materials including food wrappers (Schaider et al. 2017), papers and textiles (Robel et al. 2017). Total fluorine by particle inducted gamma ray emission quantifies fluorine atoms and cannot provide information on individual PFAS, chain length information, or information on the presence or absence of branching. The total fluorine by particle inducted gamma ray emission approach remains under development for water samples and soils/sediments. Water analysis by total fluorine by particle inducted

gamma ray emission requires extraction onto a sorbent media, typically in a laboratory environment. Total fluorine by particle inducted gamma ray emission has the promise of being faster and the rate-limiting factor for water analysis, is the extraction/concentration step. At present, total fluorine by particle inducted gamma ray emission has a quantification limit in the low ☐g/L range, so it is far less sensitive than LC-MS/MS for individual PFAS and less sensitive than the TOP assay. Thus, when PIGE analyses report total fluorine levels below the low limit of quantification, LC-MS/MS is required to avoid false negatives. Another limitation is that PIGE is not yet validated for environmental matrices and is not yet commercialized. Current instrumentation for PIGE is quite large and is not yet field portable. PIGE has promise as a screening tool for groundwater, sediment, and soil which may prove useful in providing feedback to drillers at a site.

Total Fluorine by Other Methods

Other methods for total fluorine include the extractable (EOF) (Yeung et al. 2008) or absorbable (AOF)(Wagner et al. 2013) organic fluorine assays. Both techniques rely on high temperature combustion to convert organic fluorine to fluoride, which is then measured using ion chromatography. Limits of detection are similar to what is achieved with PIGE (low µg/L), far above the low ppt detection of PFAS achieved using liquid chromatography-tandem mass spectrometry. However, these total fluorine methods are not yet available in North America. Both techniques give information on the presence of precursors, but like total fluorine by particle inducted gamma ray emission, do not offer information on the identities of precursors, chain lengths, or information about branching. Due to limited availability, there are limited comparative data at this time.

Liquid Chromatography and High-Resolution Mass Spectrometry

Many PFAS remain unidentified since sophisticated analytical techniques and time are required to identify unknown PFAS and because new PFAS are continually being developed without much information available to the public about their chemistry. Minimal information is available about these new chemicals or their degradation products including levels in drinking water or environmental media. Other types of mass spectrometers can be employed for the analysis of the non-target PFAS and are needed for discovery of unknown PFAS. Mass spectrometers that offer high accuracy mass measurements are used to identify PFAS (e.g., non-target analysis). Quadrupole time-of-flight and orbital trap types of high mass accuracy instruments are commercially available and are in use by academic laboratories, but they are likely to be needed for PFAS analysis in the future by commercial laboratories and regulatory agencies. One advantage of these types of mass spectrometers is the large dataset that can be analyzed now and can be archived for future analysis as more PFAS are identified. The instruments are more expensive and require a higher technical skill for both operation and data interpretation compared to tandem quadrupole mass spectrometers (e.g., liquid chromatography-tandem mass spectrometry). The high mass accuracy instruments are well suited for identifying unknown in microcosm studies of PFAS biodegradation (Yi et al. 2018), characterizing influents to granulated activated carbon treatment system, and for site characterization. A more complete understanding of human exposures to PFAS chemicals would require occasional surveys capable of detecting a broader range of substances than the current and planned targeted methods.

Table 9. Advantages and limitations of various analytical approaches to quantifying individual PFAS and precursors.

Method	Advantages	Limitations
Liquid Chromatography-Tandem Mass Spectrometry LC-MS/MS Method 537 V 1.1	• commercially available • QA/QC extensive • quantifies individual PFAS • UCMR3/Method 537/SW-846 8327&8328/ASTM based on instrument • differentiates branched/linear	• expensive • limited number of PFAS • 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 • caution at low levels • limited value for forensics
Suspect screening (LC-HRMS)	• unlimited number of PFAS • stored data can be searched in future • value as a forensics tool	• 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 • available through only one academic lab that may have a commercial partner	• only quantifies total fluorine (the atom) • no information on individual PFAS • small database (few comparative data) • not as sensitive (yet) as LC-MS/MS or LC-HRMS • limited value for forensics
Total adsorbable organic fluorine	• total adsorbable fluorine (what the title says) • 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

Source Area Characterization

The environmental forensics of PFAS is in its infancy. The analytical tools available from contract laboratories and under development in academic settings are being developed to assist in answering questions about the release histories of PFAS and to identify sources of PFAS contamination in the environment. The application of increasingly sophisticated tools will be useful for reconstructing historical PFAS releases to answer questions about when release events occurred, the chemical nature and amount of PFAS released, and the sources of the PFAS released to the environment. Fingerprinting is an established technique in environmental forensics, but fingerprinting is in its early stages for PFAS. Attempts to characterize sources with a limited number of analytes (e.g., those listed in Method 537) offer limited insight since the suite of PFCAs and PFSAs occur in most environmental media, as has been described earlier in this report. Once developed, fingerprinting approaches can be combined with the growing literature on the fate and transport of PFAS, modeling, site hydrogeological investigation, and existing information on operational practices at sites to reconstruct site history and to explain the disposition of PFAS at sites.

More information is available on the PFAS at AFFF-impacted sites compared to municipal wastewater and landfill leachates. However, existing data for PFAS in wastewater effluent (Gobelius et al. 2018, Schultz et al. 2006, and Loganathan et al. 2007) and landfill leachates (Allred et al. 2014, Benskin et al. 2012, Allred et al. 2015, and Gallen et al. 2017) provides evidence that these various systems have some unique aspects to their PFAS composition. For example, the fluorotelomer acids and short-chain PFCS and PFSAs are abundant in landfill leachates compared to municipal wastewater effluent and AFFF-contaminated groundwater (unpublished data). Groundwater from AFFF-contaminated sites has zwitterionic PFAS, but no data for these species in municipal wastewater effluent and landfill leachate are yet available so it is too premature to determine if cationic and zwitterionic PFAS are unique to AFFF and AFFF-impacted systems. More extensive fingerprinting of various types of sources is needed, including manufacturing sites.

Another 'secondary' level of information that may prove useful in discerning sources of PFCAs is by evaluating their branched and linear isomer ratios. PFCAs produced by 3M are branched (25%) and linear (75%) (Benskin et al. 2010) although the ratio is influenced by environmental processes such as partitioning during transport in aquifers and between solids and liquids during waste water treatment. PFCAs produced by telomerization are only linear such as the degradation of fluorotelomer sulfonates to PFCAs produces only linear PFCAs. Thus, one can potentially distinguish if PFCAs derive from a 3M source, a telomer source, or a combination of the two. For example, PFCAs that are characterized by a low percentage or absence of the branched isomers is potentially indicative of PFCAs that arise from the degradation of telomere precursors. Information on the relative proportions of branched and linear isomers is available from analytical data and obtaining information may be as simple as asking the analytical laboratory for that information.

The proprietary nature of the PFAS composition of products and goods in the marketplace is problematic for states like Michigan in impeding the ability to monitor and plan mitigation of exposure where needed. While concealing the identity of PFAS and other components in products may be important to

protect intellectual property and patents, it is problematic when chemicals like PFAS end up in the environment, impacting soil, water, food quality, and ultimately ecosystem and human health. In order to understand the composition of products (e.g., AFFFs) released into the environment and their potential human and ecotoxicological effects, extensive effort is required although chemical manufacturers and product producers already know about the chemical composition of their products. Many PFAS were discovered serendipitously and, recently, some were discovered through a concerted, multi-year, team-based 'reverse engineering' efforts. Such 'reverse engineering', using modern 'non-target' mass spectrometric approaches, incurs a significant financial burden to support the human expertise and instrumentation needed to put together pieces of a complex puzzle. The result is an incomplete patchwork of understanding of the type, number, and potential effects of PFAS now circulating in the marketplace, the environment, and in humans. States such as California and Washington have restricted the use of various chemical classes; Michigan could consider adopting policies put in place by other states but should consider monitoring for such chemicals independent of the restrictions.

Conclusions and Recommendations

Conclusions

Many stakeholders, including those in Michigan, recognize that PFAS contamination is comprised of more than just the two most well-known PFAS, PFOS and PFOA. Analytical methods are being developed to capture PFCAs, PFSAs, and sulfonamide acetic acids from Method 537 but will also include newer PFAS (e.g., GenX) as high-quality analytical standards become available for PFAS. Using analytical methods that offer data for a wide range of individual PFAS and the TOP assay are likely to aid in characterizing and differentiating sources and for evaluating treatment technologies. Knowledge of the branched and linear isomers of PFAS can also offer diagnostic information to differentiate PFCA sources and to interpret the impact of environmental processes (e.g., partitioning) on PFCA and PFSA transport. At present, USEPA methods do not capture gas-phase PFAS that are known to occur in municipal wastewater and landfill leachates. Additional methods including particle induced gamma ray emission, total absorbable organic fluorine, and high mass accuracy mass spectrometry offer advantages and limitations but are not yet commercially available. Forensic approaches for PFAS are under development but it is likely to be years before the techniques are fully validated. As fingerprinting capabilities become available, indicator PFAS are likely to be identified and pushed into analytical methods in the commercial market.

Recommendations
1. Detection of PFAS should move beyond the legacy chemicals of PFOS and PFOA, to include a suite of other PFSAs and PFCAs (p. 24), as well as replacement chemicals (such as GenX) and constituents of aqueous film forming foam (AFFF) that are being identified, when sensitive analytical methods are feasible.

2. For initial waste or site characterization, the Panel recommends use of analytical methods that measure the greatest number of PFAS as well as quantify the branched and linear PFSAs and PFCAs.

3. In cases where water is being treated for use as a drinking water source, the Panel recommends use of analytical methods that quantify short-chain PFAS because they are more difficult to remove under traditional methodologies.

4. The Total Oxidizable Precursor assay is commercially available methodology and should be used by analytical laboratories to characterize environmental media including groundwater, wastewater, sediment, soils, and biosolids. The Total Oxidizable Precursor assay signals the presence of precursors, which is useful information when designing and evaluating remedial systems.

5. Agency staff in Michigan should keep abreast of progress in the area of PFAS forensics as techniques undergo validation for stakeholder use.

Concluding Comments

The Panel recognizes the importance and complexity of the issues facing Michigan and has strived to provide a clear description of the available evidence. **Michigan leadership should be commended for their efforts to address environmental and health concerns with PFAS conscientiously by developing policies that do justice to the current state of knowledge. The questions posed to the Panel are the appropriate for drawing out the information needed to make sound, evidence-based policy decisions. However, by asking these pointed, critical questions, they have also obligated us to reveal how far short the scientific evidence is in providing clear answers to many of them.** The Panel believes that it is beneficial to make use of the evidence that is available, even when it is incomplete, tentative, and subject to change as more research is done on PFAS. It is also important for the many stakeholders concerned with these issues to appreciate that even after assembling and providing a full description of current knowledge, which we have strived to do, the gaps in that knowledge require informed judgment regarding regulation and mitigation. The research does not provide direct indications of the "right" choices but with continuing progress, the uncertainties will be reduced enabling more informed decisions in the future. Although the evidence is still evolving and weak in some important areas, there is sufficient evidence from the toxicologic and epidemiologic findings to justify regulatory efforts to manage exposure for protecting human health. As scientists, the Panel welcomes the opportunity to share our understanding and insights in the service of guiding these critical policy decisions facing the State of Michigan.

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Definitions and Acronyms

Terminology	Definition
Adona	3H-perfluoro-3-[(3-methoxy-propoxy) propanoic acid]
AFFF	Aqueous film forming foam
AIX	Anion Exchange (water purification method)
Anion	A negatively-charged molecule
AOF	Adsorbable organic fluorine assay
Biosolids	Sewage sludge, usually generated by water treatment plants
BMDL	Benchmark dose lower confidence limit
Branched chain	A connection of carbon atoms arranged in a non-linear arrangement (with branching points)
Cation	A positively-charged molecule
Chain length	Number of carbon atoms linked together in a chain
Constitutive Androstane Receptor (CAR)	A nuclear receptor that regulates gene expression and metabolic processes.
diPAP	Polyfluoroalkyl diphosphate esters
EFSA	European Food Safety Authority
Electrofluorination	Older procedure used for PFAS manufacture that can yield both branched and linear chain perfluorinated substances
EOF	Extractable organic fluorine assay
ERK1/2	Extracellular regulated kinases
Estimated glomerular filtration rate (eGFR)	Measure of kidney function
Et-PFOSA-AcOH	2-(N-Ethyl-perfluorooctane sulfonamido) acetic acid
FTOH	Fluorotelomer alcohol (a group of chemicals, usually polyfluorinated)
FtS (FTS)	Fluorotelomer sulfonate (a group of chemicals, usually polyfluorinated)
GAC	Granular activated carbon (for water purification)
GenX	2,3,3,3-tetrafluoro-2-(perfluoropropoxy)propanoic acid (also known as HFPO-DA; hexafluoropropylene oxide dimer acid)
Half life	the time required for the concentration of a substance in the body to decrease by half
K_{oc}	Organic carbon-water partitioning coefficient

LC-HRMS	Liquid chromatography-high resolution mass spectrometry
LC-MS/MS	Liquid chromatography-tandem mass spectrometry (an instrumental method for analysis)
LHA	Lifetime Health Advisory
LOAEL	Lowest observed adverse effect level
M-FIL	Membrane filtration
MAPK	Mitogen-activated protein kinase
MCL	Maximum contaminant level
MDEQ	Michigan Department of Environmental Quality
Me-PFOSA-AcOH	2-(*N*-Methyl-perfluorooctanesulfonamido) acetic acid
Method 537	Targeted USEPA analytical method for measuring 14 targeted PFAS chemicals using LC-MS/MS
Methods 8327 and 8328	A draft method under development for targeted measurement of an extended group of PFAS chemicals using LC-MS/MS
mg/L	Milligrams per liter (parts-per-million)
µg/L	Micrograms per liter (parts-per-billion)
MRL	Minimal risk levels
N-EtFOSA	*N*-Ethyl-perfluorooctanesulfonamide
NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
ppt	Nanograms per liter (parts-per-trillion)
NOAEL	No observed adverse effect level
NSF	NSF International, a product testing, inspection, and certification company based in Ann Arbor, MI
Obesogenicity	Promotion or contributing to obesity
PAPs	Polyfluorinated phosphate esters
PFAA	Perfluorinated aliphatic acids
PFAS	Per- and poly-fluoroalkyl substances
PFBA	Perfluorobutanoic acid (C4; a PFCA)
PFBS	Perfluorobutanesulfonic acid (C4; a PFSA)
PFCA	Perfluorocarboxylic acids (class of compounds)
PFDA	Perfluorodecanoic acid (C10; a PFCA)
PFHpA	Perfluoroheptadecanoic acid (C7; a PFCA)
PFHxA	Perfluorohexanoic acid (C6; a PFCA)

PFHxS	Perfluorohexanesulfonic acid (C6; a PFSA)
PFNA	Perfluorononanoic acid (C9; a PFCA)
PFNS	Perfluorononanesulfonic acid (C9; a PFSA)
PFOA	Perfluorooctanoic acid (C8; a PFCA)
PFOS	Perfluorooctanesulfonic acid (C8; a PFSA)
PFPeA	Perfluoropentanoic acid (C5; a PFCA)
PFSA	Perfluorosulfonic acids (class of compounds)
PIGE	Particle-induced gamma ray emission assay for fluorine
pKa	A measure of acid strength
POET	Point-of-entry treatment
POU	Point-of-use treatment
PPARα	Peroxisome proliferator activated receptor-alpha
ppb	Parts-per-billion (micrograms per liter)
ppm	Parts-per-million (milligrams per liter)
ppt	Parts-per-trillion (nanograms per liter)
QTOF	Quadrupole time-of-flight mass spectrometer
RfD	Reference dose considered to be without adverse effects
RO	Reverse osmosis (water purification)
Telomer	A process for synthesis of linear oligomeric molecules
TOP assay	Total oxidizable precursor assay based on oxidation and LC-MS/MS
Zwitterion	A molecule with both positively-charged and negatively-charged groups