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Yale School of Public Health Symposium: An overview of the challenges and opportunities associated with *per*- and polyfluoroalkyl substances (PFAS)☆

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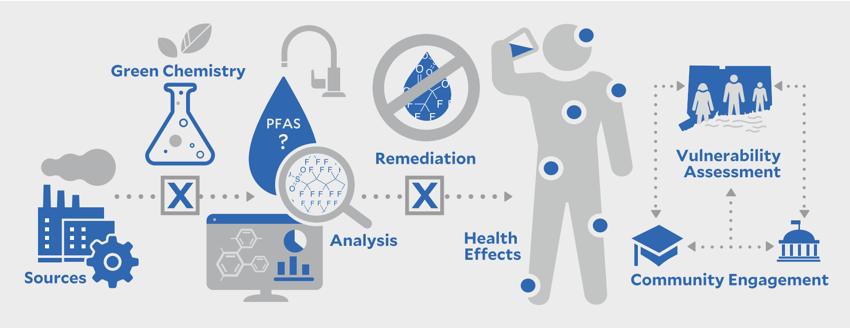
GRAPHICAL ABSTRACT



☆ The views expressed herein are those of the authors and do not necessarily reflect those of the Connecticut Department of Energy and Environmental Protection or the Connecticut Department of Public Health.

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ABSTRACT

On December 13, 2019, the Yale School of Public Health hosted a symposium titled “Per- and Polyfluoroalkyl Substances (PFAS): Challenges and Opportunities” in New Haven, Connecticut. The meeting focused on the current state of the science on these chemicals, highlighted the challenges unique to PFAS, and explored promising opportunities for addressing them. It brought together participants from Yale University, the National Institute of Environmental Health Sciences, the University of Massachusetts Amherst, the University of Connecticut, the Connecticut Agricultural Experiment Station, the Connecticut Departments of Public Health and Energy and Environmental Protection, and the public and private sectors. Presentations during the symposium centered around several primary themes. The first reviewed the current state of the science on the health effects associated with PFAS exposure and noted key areas that warranted future research. As research in this field relies on specialized laboratory analyses, the second theme considered commercially available methods for PFAS analysis as well as several emerging analytical approaches that support health studies and facilitate the investigation of a broader range of PFAS. Since mitigation of PFAS exposure requires prevention and cleanup of contamination, the third theme highlighted new nanotechnology-enabled PFAS remediation technologies and explored the potential of green chemistry to develop safer alternatives to PFAS. The fourth theme covered collaborative efforts to assess the vulnerability of in-state private wells and small public water supplies to PFAS contamination by adjacent landfills, and the fifth focused on strategies that promote successful community engagement. This symposium supported a unique interdisciplinary coalition established during the development of Connecticut's PFAS Action Plan, and discussions occurring throughout the symposium revealed opportunities for collaborations among Connecticut scientists, state and local officials, and community advocates. In doing so, it bolstered the State of Connecticut's efforts to implement the ambitious initiatives that its PFAS Action Plan recommends.

1. Introduction

Per- and polyfluoroalkyl substances (PFAS), a family of >9000 synthetic organic chemicals (EPAa), have captured the attention of people across the globe due to a growing concern about the health risks posed by widespread PFAS contamination in drinking water sources and other environmental media. While PFAS vary widely in their physical and chemical properties, they all contain at least one chain of carbon atoms in which one or more of the carbon atoms is perfluorinated, i.e., has fluorine atoms attached at all bonding sites not occupied by another carbon atom (Buck et al., 2011). Since their initial introduction in the 1940s, PFAS have become pervasive in consumer products and industrial processes because of the unique properties imparted by their chemical structures, including stability, heat resistance, friction reduction abilities, and oil and water repellence (Buck et al., 2012). However, as an unintended consequence of these same useful properties, many PFAS are now persistent pollutants that spread throughout the environment, contaminate food and drinking water sources, and ultimately bioaccumulate in animals and humans (Sunderland et al., 2019). Toxicological and epidemiological research has associated exposure to certain PFAS, particularly certain long-chain perfluoroalkyl acids, with a wide range of adverse health effects (reviewed in depth in Fenton et al., 2020), including thyroid disruption (Andersson et al., 2019; Ballesteros et al., 2017; Blake et al., 2018; Caron-Beaudoin et al., 2019), ulcerative colitis (Steenland et al., 2018; Steenland et al., 2013), high cholesterol (Lin et al., 2019; Nelson et al., 2010), pregnancy-induced hypertension (Starling et al., 2014), decreased immune responsiveness (DeWitt et al., 2019), and kidney and testicular cancer (Barry et al., 2013; Shearer et al., 2020). Measurable levels of some PFAS are present in the blood of over 95% of U.S. residents, and PFAS contamination has been discovered in drinking water nationwide (Hu et al., 2016). During the third Unregulated Contaminant Monitoring Rule (UCMR3; 2013–2015) water survey, the U.S. Environmental Protection Agency (EPA) found that 1.3% of the nation's largest public water systems, which provide drinking water to an estimated 5.5 million people, contained at least one PFAS compound in concentrations exceeding its reference concentration of 70 ng/L (ppt) (EPA, 2016).

In the absence of timely federal action to regulate PFAS or set enforceable drinking water standards and in response to community concerns, many U.S. states have taken independent action to safeguard their residents against the health risks posed by PFAS (reviewed in Blake and Fenton, 2020 and Post, 2020). In July 2019, Connecticut Governor Ned Lamont established the Interagency PFAS Task Force to advise his administration and formulate an action plan containing a comprehensive state strategy to address PFAS. The task force was led by the Commissioners of the Connecticut Departments of Public Health (CTDPH) and Energy and Environmental Protection (CTDEEP) and comprised representatives from 18 state agencies and entities. To enable all affected stakeholders to take part in the process, the task force established three subcommittees, each open to public participation, to discuss strategies to (1) minimize environmental exposure of Connecticut residents to PFAS, (2) minimize future releases of PFAS into the environment, and (3) identify, assess, and clean up historical releases of PFAS into the environment, respectively. This process brought together key academic, government, and private- and public-sector stakeholders from across the state. An action plan, developed by the Task Force and its subcommittees, was released in draft form in October 2019 for public comment. After revisions to reflect public input, the finalized PFAS Action Plan was delivered to Governor Lamont on November 1, 2019 and released to the public soon thereafter (The Connecticut Interagency PFAS Task Force, 2019). The plan laid out a series of actions that the State of Connecticut could take to protect public health, identify and remediate existing PFAS pollution, prevent future pollution, and enhance outreach and communication with the general public on the adverse health effects of PFAS exposure and strategies for mitigating exposure.

To foster continued collaboration between local scientists, government officials, public citizens, and other parties, the Yale School of Public Health hosted a daylong symposium on December 13, 2019 titled “Per- and Polyfluoroalkyl Substances (PFAS): Challenges and Opportunities.” This symposium drew participants from Yale, CTDEEP, CTDPH, the Connecticut Agricultural Experiment Station, the National Institute of Environmental Health Sciences (NIEHS), the University of Massachusetts Amherst, the University of Connecticut, and key stakeholders in the public and private sectors. Presentations during the symposium centered around several primary themes. The first reviewed the current state of the science on the health effects of PFAS and noted key research gaps that require further study. As research in this field relies on specialized laboratory analyses, the second theme considered commercially available methods for PFAS analysis as well as several emerging analytical approaches that support new health studies and facilitate the investigation of a broader range of PFAS. Since mitigation of PFAS exposure requires prevention and cleanup of contamination, the third theme highlighted new nanotechnology-enabled PFAS remediation technologies and explored the potential of green chemistry to develop safer alternatives to PFAS. The fourth theme covered a collaboration between Yale researchers and CTDEEP to assess the vulnerability of private wells and small public water supplies to PFAS contamination by adjacent landfills, and the fifth focused on strategies that promote successful community engagement. Discussions occurring throughout the symposium revealed opportunities for collaborations that would support ongoing CTDEEP and CTDPH efforts to implement the initiatives recommended in the Connecticut PFAS Action Plan. The highlights of these sessions' presentations are summarized herein. This summary provides a valuable snapshot of early dialogue between researchers, government officials, and representatives of local health and nonprofit organizations convened to share cutting-edge scientific advances and coordinate future multisector collaborations to help the state confront an environmental health issue of national and global importance.

2. Health effects

Decades of widespread PFAS use have led to pervasive environmental contamination and human exposure. Comprehensive research on PFAS-related health effects is therefore necessary to inform the risk assessment process used by government officials to derive health-based guidelines and standards that protect the public from potentially unsafe levels of exposure. As exposure occurs through various pathways, including consumer product use and ingestion of contaminated food and water, these officials face a daunting task. Many regulatory and research efforts have initially focused on human exposure through drinking water. In recent years, a growing number of epidemiological studies investigating populations with different levels of PFAS exposure have identified probable links between certain PFAS and various human health effects, which are generally supported by findings in toxicological studies conducted in laboratory rodent models. These studies have collectively demonstrated that pregnant mothers and developing offspring are the sub-populations most sensitive to low levels of PFAS exposure, which highlights the need to study adverse effects on maternal and infant health as particularly essential for risk assessment purposes (Goeden et al., 2019). Recent research has significantly enhanced our understanding of the health implications of PFAS exposure. However, major remaining data gaps make it challenging for officials to effectively assess the risks posed by PFAS and safeguard public health (Fenton et al., 2020). Moving forward, it is important for scientists to fill in these data gaps by investigating additional PFAS, geographical regions, and health effects, considering the implications of exposure to mixtures of PFAS, and elucidating the mechanisms responsible for adverse health effects.

Environmental epidemiological studies using data-rich prospective birth cohorts have provided valuable information on how PFAS exposure influences the health of pregnant women and of children in the earliest and most sensitive stages of development. Developing human fetuses can be exposed to PFAS *in utero* through active or passive transplacental transfer (Eryasa et al., 2019; Mamsen et al., 2019); after birth, infants can be exposed through breastfeeding and/or formula made with contaminated water, and by PFAS in the home environment. Studies using the Danish National Birth Cohort have provided evidence linking PFAS exposure to a range of pregnancy complications and neurodevelopmental effects (Ernst et al., 2019; Liew et al., 2020; Liew et al., 2018; Liew et al., 2014; Liew et al., 2015; Meng et al., 2018). Specifically, these studies have linked prenatal PFAS exposure with altered maternal thyroid hormone function during early pregnancy, an increased risk of cerebral palsy in male offspring (Liew et al., 2014), increased risks of miscarriage and preterm birth (Liew et al., 2020; Meng et al., 2018), and sex-specific effects on the onset of puberty (Ernst et al., 2019). Studies using the Faroe Islands birth cohorts have provided further evidence of associations between PFAS exposure and a broad range of health effects in children, including decreased birth weight (Xiao et al., 2020), impaired neurodevelopment (Oulhote et al., 2016), immunosuppressive effects (Grandjean et al., 2012), altered thyroid hormone levels (Xiao et al., 2020), childhood behavioral problems (Oulhote et al., 2016), and microbiome disruption (Oulhote et al., 2019). However, not all epidemiological studies examine the same set of PFAS, and the exposure levels may vary across populations. As such, it is challenging to corroborate findings across studies. To date, research efforts on the health risks of PFAS have predominantly focused on perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), both of which have already been largely phased out of nonessential uses in several parts of the world but remain widely detected in waste streams and the environment (Boiteux et al., 2016; Clara et al., 2008; Mussabek et al., 2019). The health impacts of the many other types of PFAS currently in use (including the shorter-chain compounds that have been used as replacements for PFOA and PFOS) are still poorly understood. Moreover, most studies rely on single-pollutant models that might not adequately capture the cumulative effects of exposure to multiple PFAS, let alone other coexistent environmental toxicants.

Epidemiological studies have also provided evidence of geographical variations in PFAS exposure and the health effects associated with such exposure. Levels of exposure vary widely on both local and global scales, likely because the level of PFAS exposure in a given population depends on a myriad of factors ranging from its proximity to individual point sources of pollution to the effects of regulatory action and industry phaseouts on PFAS levels in the marketplace. For instance, unlike many western countries, China has yet to phase out industrial use of PFOA and PFOS. However, epidemiological studies of PFAS exposure in China are relatively scarce and primarily focused on birth or pregnancy-related outcomes (Cao et al., 2018; Chen et al., 2013b; Chen et al., 2012; Chen et al., 2018; Huang et al., 2019; Li et al., 2017; Lien et al., 2016; Shi et al., 2017; Wang et al., 2016a; Wang et al., 2019a; Wang et al., 2018a; Wang et al., 2016b; Wang et al., 2015a; Wang et al., 2018b; Wu et al., 2012; Yao et al., 2019). Studies measuring levels of PFAS in cord blood indicate that PFOA and PFOS account for the majority of total PFAS exposure in mainland China, whereas longer-chain ($C \geq 9$) compounds are the dominant PFAS in Taiwan (Shi et al., 2017; Wang et al., 2016a). These studies have also revealed levels of PFAS in mainland China that are lower than those found in many western countries (Shi et al., 2017); this could change in the future as PFAS manufacturing shifts from the western world to China and developing countries (Land et al., 2018). Birth cohort studies in China have shown relatively consistent results linking PFAS exposure to decreased birth weight (Chen et al., 2012; Chen et al., 2018; Li et al., 2017; Wang et al., 2016b; Wu et al., 2012) and demonstrated that the length and structure of PFAS affect their toxicity. Whereas longer-chain PFAS in maternal blood were associated with adverse effects on birth weight (Wang et al., 2015a), those in cord blood were not (Chen et al., 2012). This may reflect size-dependent differences in the compounds' transplacental transfer efficiency (Wang et al., 2015a). In addition, branched PFAS were associated with stronger adverse effects than their linear counterparts (Li et al., 2017). Other results of these studies have proven less consistent, such as the effect of PFAS on birth length (Cao et al., 2018; Chen et al., 2018; Shi et al., 2017; Wang et al., 2019a; Wang et al., 2015a; Wu et al., 2012) and the influence of the sex of the infant on PFAS-related health effects (Cao et al., 2018; Li et al., 2017; Shi et al., 2017; Wang et al., 2016a). A few studies have also shown PFAS to have adverse effects on gestational hypertension disorders (Huang et al., 2019), some neurobehavioral development endpoints (Chen et al., 2013b; Wang et al., 2015a), and blood glucose levels (Wang et al., 2018b). Additional studies are necessary to reliably characterize the levels of PFAS exposure and resulting health impacts in China as well as understudied countries and regions around the world. Information on health effects in countries that manufacture and export PFAS-containing goods is particularly crucial for understanding the PFAS-related health risks of consumer products derived from globalized supply chains.

Animal-based studies are still regarded as necessary for deriving the “toxicity values” that are foundational to government officials' risk assessment processes (EPA, 2002). Such studies have directly linked PFAS exposure with numerous health effects, and their findings are generally concordant with those of epidemiological studies (Fenton et al., 2020). For instance, studies using the developing mouse model have shown PFOA exposure to decrease birth weight, increase excess weight gain in offspring and the pregnant mother, and impair lactation (Blake et al., 2020; Hines et al., 2009; Koustas et al., 2014; White et al., 2007). Similar effects in humans have been associated with PFOA exposure (Ashley-Martin et al., 2016; Halldorsson et al., 2012; Johnson et al., 2014; Karlsen et al., 2017; Romano et al., 2016; Timmermann et al., 2017; Xiao et al., 2020). Unlike epidemiological studies, toxicological studies in rodent laboratory models are able to provide evidence of causality, allow for investigation into modes of action, and enable scientists to test the dependence of a given health outcome on individual variables, including dose magnitude, dose timing, and specific PFAS compound(s). This has made it possible to establish, for example, that developing tissues are highly sensitive to PFAS, resulting in persistent effects (e.g., mammary gland development), and that since developing fetuses are more susceptible than adults, effective doses of PFAS are lower in developmental exposure situations (e.g., liver gene expression). For the few compounds whose toxicology has been extensively studied (such as PFOA), toxicologists at state and federal agencies have derived minimal risk levels (MRLs) using non-cancer reference doses based on a variety of different target effects, including increased liver weight, weakened immune response, delayed mammary gland development, delayed bone ossification, neurobehavioral effects, and accelerated male puberty (Post, 2020). It should be recognized that choice of target effect has major policy implications. Since some developmental effects may result from PFAS doses below those causing an increase in liver weight, selection of certain developmental target effects gives rise to lower MRLs. As reviewed by Post (2020), the range of different target effects that toxicologists at state agencies and the EPA have used to derive reference doses for PFOA contributes to the approximately four-fold range in the values of their PFOA drinking water guidelines. Recent toxicological studies have linked delayed mammary gland development (a particularly sensitive effect that persists into adulthood, affects lactation, and has a similar mode of action in mice and humans) to both PFOA and a short-chain replacement compound known as GenX (Fenton, personal communication). These results highlight the critical need for more studies focused on PFAS other than PFOA and PFOS.

Although many of the individual effects of PFAS exposure identified in toxicological and epidemiological studies reflect altered endocrine function, our understanding of how and the extent to which PFAS disrupt the endocrine system is far from complete (Braun, 2017). Endocrine-disrupting chemicals (EDCs) are inherently challenging to study due to their unique non-monotonic dose-response relationships, transgenerational effects, organ-type- and cell-type-specific responses, and potential for long latency periods between fetal exposure and disease onset (La Merrill et al., 2020). Studies that systematically evaluate the ability of PFAS to disrupt the various cell and organ types within the endocrine system are critically needed to more accurately characterize the health impacts of PFAS exposure and elucidate the various mechanisms by which endocrine disruption can occur (Burman et al., 2020; Gore et al., 2015; White et al., 2011). Certain EDC actions of PFAS have been well-described. For example, *in silico* analysis indicated the capacity of PFAS to disrupt thyroid hormone signaling by competing with thyroid hormone thyroxine for binding to thyroid transport protein transthyretin (Weiss et al., 2009). Consistent with this mechanism, PFAS exposure levels have been linked to changes in thyroid function and altered serum levels of thyroid-stimulating hormone (TSH) in affected communities, although the magnitude of this impact has varied by study population and sex (Blake et al., 2018; Byrne et al., 2018; Inoue et al., 2019; Kim et al., 2018; Preston et al., 2018; Xiao et al., 2020; Yang et al., 2016). PFAS exposure can also affect reproductive development and reproductive hormone production, giving rise to altered pubertal timing, impaired ovarian function, and infertility (Bach et al., 2016; Ding et al., 2020; Rappazzo et al., 2017). Exposures to PFOA, PFOS, and perfluorohexane sulfonic acid (PFHxS) have been associated with premature ovarian insufficiency and altered serum levels of estradiol (E2) and follicle-stimulating hormone (FSH) in women (Zhang et al., 2018). In agreement with these findings in humans, rodent models of PFOS exposure exhibit reduced serum E2 and progesterone levels (Feng et al., 2015). Importantly, the use of *in vivo* rodent models enabled investigators to attribute these alterations in hormone synthesis to targeted changes in both hypothalamic neurons and chromatin remodeling factors in the ovary regulating the expression of key steroidogenic enzymes, ultimately leading to impaired follicular development and ovulation. Moving forward, it is crucial to expand our understanding of how PFAS exposure can impact the endocrine system and to employ various testing models to establish the mechanisms by which these effects occur (Alofe et al., 2019).

3. Analytical methods

The scope and power of studies assessing PFAS exposure are inherently constrained by the analytical methods they employ to detect PFAS. Methods that pair liquid chromatography (LC) with tandem mass spectrometry (MS/MS) are well established for PFAS analysis in simple liquid media such as drinking water. The EPA has published multiple validated LC-MS/MS methods (i.e., Methods 537, 537.1, and 533) for the analysis of PFAS in drinking water, but has yet to do so for more complex liquid and solid matrices that are likewise important to monitor, such as serum and soil. Accurate PFAS analysis in such matrices can nevertheless be achieved by augmenting established methods with isotope dilution, appropriately tailored extraction and sample preparation procedures, and rigorous quality assurance and control measures to account for matrix effects. Most studies involving PFAS rely on targeted methods that measure tens of individual PFAS at best. Collectively, EPA Methods 537 (Shoemaker et al., 2008), 537.1 (Shoemaker and Tettenhorst, 2020), and 533 (Rosenblum and Wendelken, 2019) measure fewer than 40 compounds. Of the thousands of compounds in the PFAS class, analytical reference standards exist for fewer than 200. While non-targeted methods can be used to study much broader sets of PFAS, the resulting measurements are highly challenging to interpret. Emerging approaches in PFAS sampling and analysis present opportunities to use new data sources, broaden the range of PFAS that can be reliably measured, and predict the toxicity of PFAS that have yet to be studied in order to direct future health effects research and inform decision-makers working to develop health-protective policies.

PFAS analysis in new matrices requires investigation of suitable sample preparation and extraction methods. Advances in this area have made it possible to analyze PFAS in dried blood spots and thereby tap into new sources of prenatal PFAS exposure data. In an initial study, customized sampling, extraction, and analysis procedures were used to measure PFAS levels in dried blood spots collected through a newborn screening program in New York State between 1997 and 2010 (Spliethoff et al., 2008; Ma et al., 2013). This analytical method successfully quantified PFOS and PFOA concentrations in all blood spot samples and achieved detection limits in the ng/mL (ppb) range. While this initial investigation focused on targeted analysis of two specific compounds, its sampling and extraction procedures have more recently been adapted for analysis of an expanded list of PFAS (Kato et al., 2018; Poothong et al., 2019; Vorkamp et al., 2021) and could likely be further adapted for future use in non-targeted analyses. Given the sensitivity of the developing fetus to PFAS exposure, the ability to use archived repositories of newborn blood spots provides the opportunity to quantify exposures at a critical window of development and effectively explore the temporal relationship between PFAS exposure and onset of disease (Bell et al., 2018). This approach is expected to provide new opportunities for population-based PFAS epidemiological studies.

As a consequence of the multitude of PFAS used in commerce and of the chemical transformations they undergo in the environment, humans are exposed to a complex mixture of PFAS that extends far beyond the compounds measured by typical targeted analytical methods. Being able to study the full complement of PFAS present in humans and environmental media is crucial, particularly given that the EPA CompTox Chemicals Dashboard contains over 9000 PFAS (EPAa) and that the health and environmental effects of the vast majority of these compounds are completely unknown. Non-targeted analyses pairing LC or gas chromatography (GC) with high-resolution tandem mass spectrometry (HRMS/MS) analyses can help meet this need and allow for more comprehensive exploration of PFAS exposure. However, processing the large volumes of mass spectrometry data generated in these analyses to identify individual PFAS that have no analytical reference standards for mass spectral matching is a challenging task that requires extensive expertise and time. To facilitate interpretation of these data, Koelmel and colleagues developed FluoroMatch, the first automated open-source software for non-targeted assignment of PFAS structures (Koelmel et al., 2020; Nason et al., 2020). This software uses PFAS libraries with over 7000 *in silico* HRMS/MS spectra to process the mass spectral output of non-targeted analyses and automatically annotate and identify PFAS. In future updates, FluoroMatch will automate intelligent data acquisition (Koelmel et al., 2017; Koelmel et al., 2020), homologous series detection, fragment screening, and prediction of transformation products and HRMS/MS spectra from proposed PFAS structures (Innovative Omics). These advances will help users not only screen for the thousands of known PFAS, but also discover new PFAS previously uncharacterized.

A publicly available, NIEHS-developed online resource addresses, at least on a cursory level, the major challenge posed by scientists' limited knowledge of the biological effects of most PFAS. Borrel and colleagues developed PFASMap, a specialized application within ChemMaps.com (https://sandbox.ntp.niehs.nih.gov/chemmaps/), to plot and visualize >5000 PFAS from EPA databases in three-dimensional chemical space. Within PFASMap (Fig. 1a), spatial coordinates represent chemical structural properties of the compounds, making it possible to assess their structural similarity (Borrel et al., 2018). The platform also consolidates available information on the physicochemical properties, regulatory classifications, predicted activity against endocrine pathways, and acute oral systemic toxicity data of individual PFAS, along with links to more detailed information in the EPA CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard). While structural similarity does not automatically equate to similarity in toxicity, some correlations undoubtedly exist, and PFASMap provides the ability to visualize and explore the characteristics of chemicals clustered near PFAS of interest (Fig. 1b). In light of the relatively small number of PFAS characterized in toxicological and epidemiological studies and of the infeasibility of studying the health effects of every member of this ever-expanding class of compounds, PFASMap serves as a valuable tool that could be used to inform risk assessment and prioritize PFAS for further study.

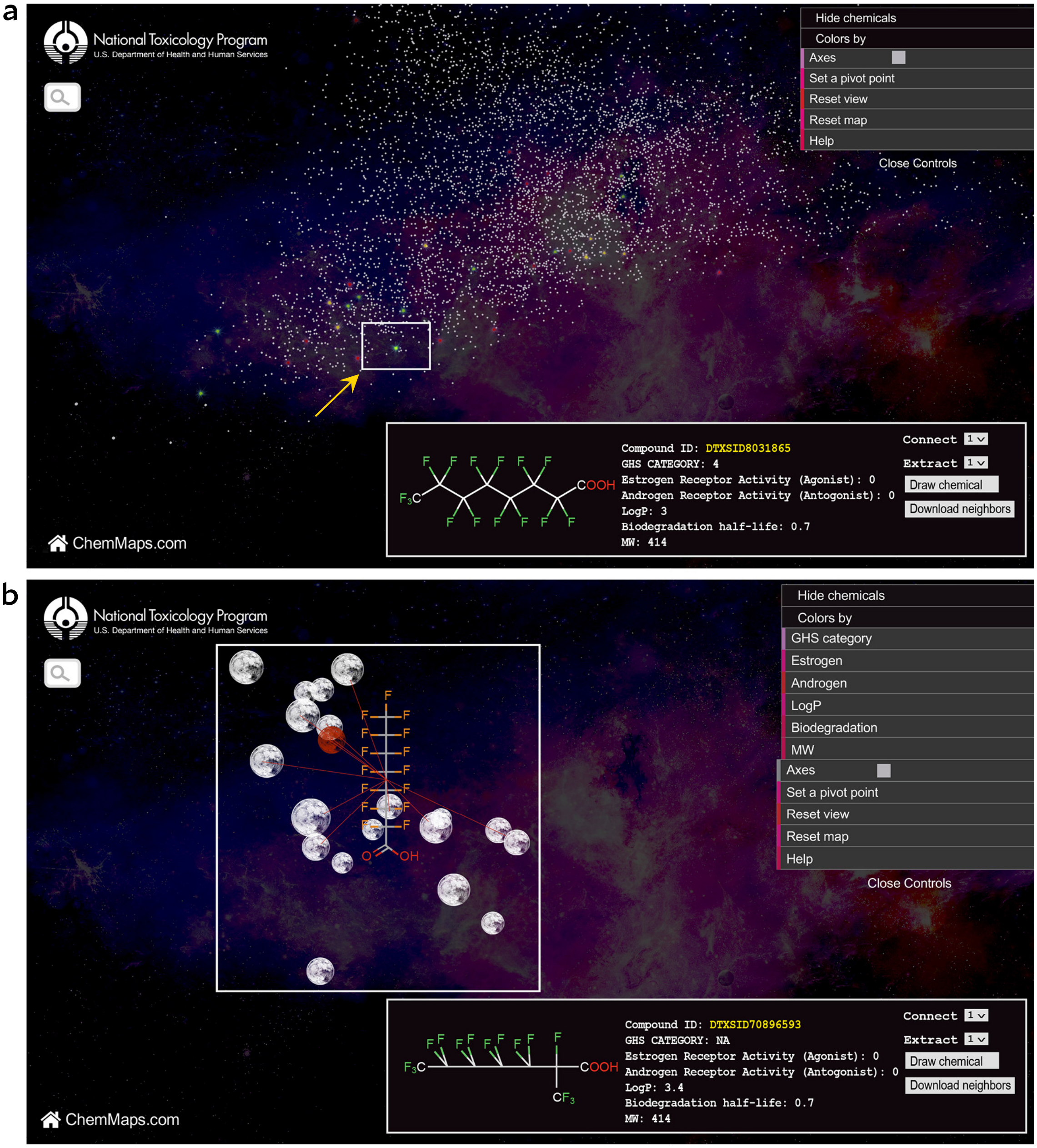
In the future, it would be highly beneficial to supplement complex laboratory techniques with technologies capable of rapid, sensitive PFAS detection in the field. Chromatographic techniques coupled with mass spectrometry (e.g., LC-MS/MS, GC-MS/MS) are accurate, sensitive, and increasingly powerful due to advances such as those discussed above. However, the accessibility of these technologies is limited by their high cost, and laboratory turnaround times give rise to an inevitable delay between the collection of samples and receipt of results. Field-deployable PFAS sensors that provide real-time results would enable environmental and public health professionals to immediately inform at-risk residents and thereby prevent ongoing exposures. While such sensors may not match the precision of the rigorous laboratory analyses used to investigate samples from PFAS-contaminated sites, they could be used as a screening tool to determine whether sites warrant additional, more in-depth studies. This would provide both time and cost savings. While several preliminary studies have successfully employed optical and electrochemical techniques to detect PFAS without the use of LC-MS/MS or GC-MS/MS systems (Cennamo et al., 2018; Chen et al., 2013a; Cheng et al., 2019; Li et al., 2019; Niu et al., 2014; Ranaweera et al., 2019), the utility of these techniques is constrained by their insufficiently low limits of detection and/or their inability to detect a wide range of PFAS, i.e., beyond PFOA and PFOS. Further research is necessary to advance such technologies for timely, in-field applications.

4. Remediation and pollution prevention

To minimize human exposure, it is necessary to remediate the PFAS-contaminated media that contribute to exposure (such as soil and drinking water sources) and concurrently act to prevent future pollution. Due to the energy input required to break their carbon–fluorine bonds (Sabater et al., 2013), PFAS are resistant to many traditional degradation treatments (Dickenson and Higgins, 2016b). As such, remediation of PFAS-contaminated water currently relies on PFAS removal using established filtration technologies, i.e., granular activated carbon, ion exchange resins, and reverse osmosis (RO; CDM Smith, Inc., 2018; Dickenson and Higgins, 2016a; Flores et al., 2013; Tang et al., 2006). These approaches, although effective, generate concentrated waste in the form of spent sorbent materials, RO concentrate, and the backwashing liquid used to clean RO membranes and regenerable ion exchange resins. Without further treatment, these PFAS-rich waste streams pose a potential threat to the environment surrounding their disposal sites. Responsible waste management poses a considerable challenge for environmental officials in states where PFAS contamination requires extensive drinking water treatment and/or environmental remediation. Connecticut officials have already begun grapple with this challenge, and their waste management needs will only increase as they carry out the widespread PFAS testing recommended in the PFAS Action Plan.

Researchers have recently leveraged advances in materials science to develop new state-of-the-art technologies for PFAS removal and destruction (Duan et al., 2020; Zhang et al., 2020; Huang et al., 2020; Le et al., 2019). For example, surface-tuned nanoscale composites have shown high potential for targeted PFAS separations (Saleh et al., 2019). Their high sorption capacities, a function of their specific surface area and tunable surface chemistries, present a distinct advantage over the larger granular activated carbon and ion exchange resin sorbents currently in use. Integrating superparamagnetic properties allows for low-energy recovery from complicated environmental matrices using a magnetic field (Li et al., 2016a; Li and Fortner, 2020). Specifically, nanoscale ferrite particles (diameter 8–20 nm) can be precisely synthesized using thermal decomposition processes, which provides precise control over their size and composition and thus over their magnetic susceptibility and (super)paramagnetic properties (Li et al., 2016b). These magnetic core particles can then be surface-functionalized with specific organic surfactants that have high selectivity and sorption capacity for PFAS. In a different approach also reliant on nanoscale engineering, Huang et al. have developed a method for fabricating cost-effective single-atom catalysts designed for PFAS destruction (Huang et al., 2018). The resulting catalysts, composed of single platinum atoms anchored onto silicon carbide substrates, photocatalytically hydrodefluorinate PFOA by breaking its carbon–fluorine bonds and immobilizing the resulting fluorine through covalent bonding to the substrate. More recently, Huang et al. developed a palladium-single-atom-loaded titanium oxide (Ti_4O_7) electrode that anodically oxidizes PFOA through an electrocatalytic process (Huang et al., 2020). These new materials not only outperform benchmark performance nanomaterials, but also enable selective destruction of carbon–fluorine bonds, and could eventually provide a new treatment option for the concentrated liquid waste streams generated during PFAS filtration. Further research is required to test the effectiveness of this method for degrading additional PFAS.

Mitigation would not be necessary if PFAS were prevented from being released into the environment in the first place. Although many industrial users and manufacturers have voluntarily phased out PFOS and PFOA, most have simply replaced these compounds with shorter-chain PFAS (Wang et al., 2015b; Wang et al., 2013; Zhou et al., 2013;



(a)

Compound ID: DTXSID8031865
GHS CATEGORY: 4
Estrogen Receptor Activity (Agonist): 0
Androgen Receptor Activity (Antogonist): 0
LogP: 3
Biodegradation half-life: 0.7
MW: 414

(b)

Compound ID: DTXSID70896593
GHS CATEGORY: NA
Estrogen Receptor Activity (Agonist): 0
Androgen Receptor Activity (Antogonist): 0
LogP: 3.4
Biodegradation half-life: 0.7
MW: 414

Fig. 1. PFASMap (https://sandbox.ntp.niehs.nih.gov/chemmaps/PFASMap). (**a**) PFASMap contains >5000 PFAS plotted in three-dimensional chemical space. For a selected compound (e.g., perfluorooctanoic acid, PFOA) in the map, the chemical information box (bottom right) provides a two-dimensional structure representation of the compound and user-selectable property/toxicity information. The local chemical neighborhood of the selected compound is shown in the white-outlined box (yellow arrow). (**b**) White-outlined box displays the 20 nearest neighbors of the selected compound, which can be extracted and downloaded. Individual compounds within the box can be selected (e.g., red sphere, a structural analogue of PFOA) to display their basic information (bottom right). Further chemical-specific details are provided via the DTXSID link to the EPA CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard/). The navigation pane (upper right corner) and search bar (upper left) are also shown. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Sun et al., 2016; Wang et al., 2019b; Brendel et al., 2018; Hopkins et al., 2018) whose health risks have not been comprehensively studied (Cheng and Ng, 2018). These replacement compounds are generally less bioaccumulative than their long-chain legacy predecessors but just as persistent and even more difficult to remediate (Gagliano et al., 2020), making their continued release into the environment difficult to reverse. Green chemistry provides a framework for designing chemicals that fulfill the function and match the performance of PFAS while eliminating or minimizing hazards throughout their life cycle. This design approach aims to address the hazards associated with PFAS at each stage of their life cycle, i.e., from feedstocks and manufacturing through use and end-of-life disposal concerns (Fig. 2). The processes used to manufacture PFAS typically rely on hydrofluoric acid, a highly hazardous chemical (Bertolini, 1992), to serve as either the direct fluorinating agent or the precursor to the fluorinating agent (Hekster et al., 2003). Hydrofluoric acid, in turn, is manufactured using sulfuric acid, another known hazard (Agency for Toxic Substances and Disease Registry, 1998). As such, its use as a feedstock poses serious risks to worker safety (Park, 2013). Moreover, PFAS themselves pose occupational safety risks. For example, in the early 2000s, the Centers for Disease Control and Prevention (CDC) found that the PFOS and PFOA blood levels of workers in PFAS manufacturing facilities were orders of magnitude higher than those of the general U.S. population (Agency for Toxic Substances and Disease Registry, 2017). These facilities have since shifted away from PFOA and

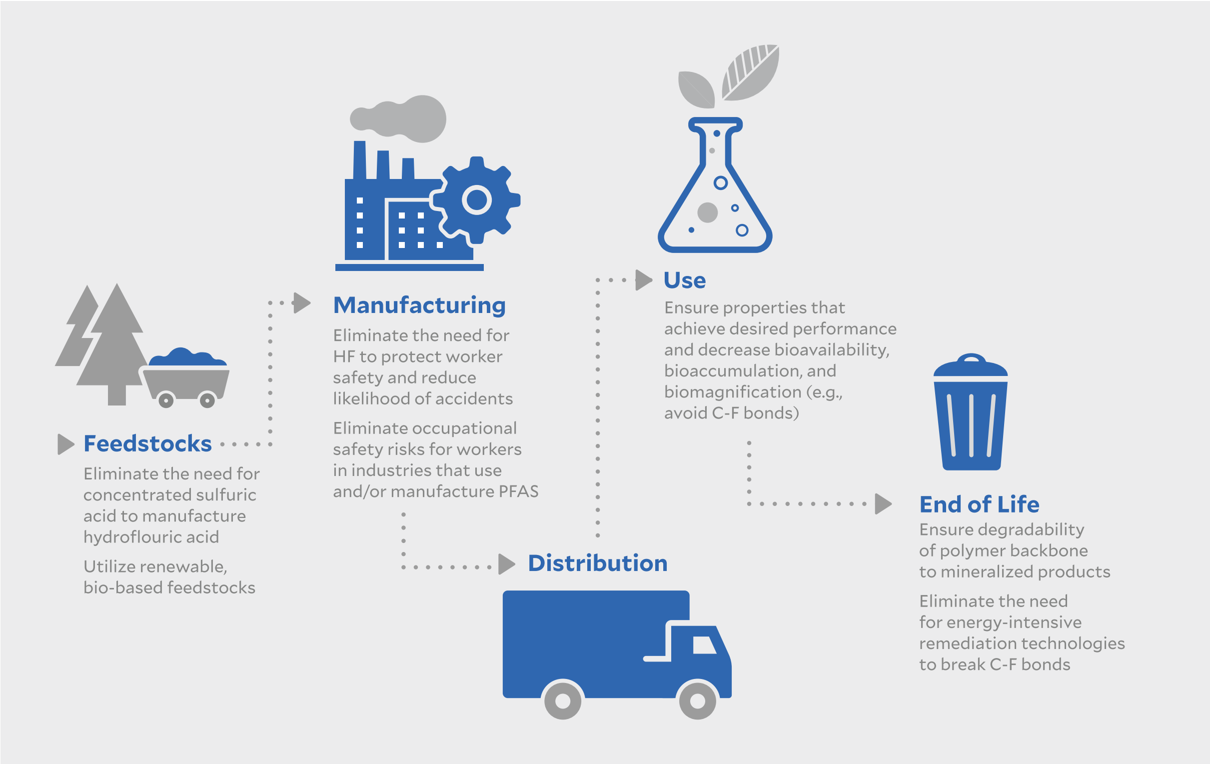


Fig. 2. Examples of the hazard reduction goals of green chemistry PFAS alternatives at each stage of the chemical life cycle. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

PFOS, but their workers (and the consumers of the products they manufacture) may now be exposed instead to shorter-chain replacement PFAS with potential health impacts that are poorly understood and persistence that is similarly problematic (Wang et al., 2019b).

Many green chemistry design approaches already show promise for the production of viable alternatives to PFAS. A variety of bio-based monomers, including stearic acid (Sharif et al., 2020), maleic acid (Yao and Tang, 2013), lactic acid (Zhang et al., 2017), and amines (Froidevaux et al., 2016), have been used as renewable feedstocks for fluorine-free polymers that could replace PFAS in flame-retardant coatings (Bourbigot and Fontaine, 2010) and in oil- and water-repellent coatings for fabric and paper (Hamdani et al., 2020; Kansal et al., 2020; Rabia et al., 2020). Ceramic-type coatings that create a barrier between a substrate and the surrounding environment (Lazar et al., 2020), typically based on silicates and alumina (Malucelli, 2016), have been demonstrated to be effective in similar coating applications (Colleoni et al., 2017; Hu et al., 2011; Liang et al., 2013; Shen et al., 2017). Biomimetic surface morphologies have been used to develop superhydrophobic surfaces that are non-fluorinated, inexpensive, mechanically strong, resistant to corrosion, and maintain water repellence despite weathering (Bhushan et al., 2009; Koch and Barthlott, 2009; Latthe et al., 2014; Lin et al., 2018; Sarkar and Saleema, 2010; Skoulas et al., 2017; Song et al., 2019; Xiu et al., 2010; Zorba et al., 2008). As many of the problems associated with PFAS stem from their persistence, degradable polymers such as biodegradable starch-based polymers are also being explored as potential replacements in water-repellence and flame-retardance applications (Albertsson and Hakkarainen, 2017; Chandra and Rustgi, 1998; Lu et al., 2009; Ma and Webster, 2018; Scott, 2002; Wu et al., 2009).

To mitigate current and future PFAS hazards, both approaches are clearly vital, i.e., to develop additional remediation technologies (especially destructive technologies) and to replace PFAS with safe and effective non-fluorinated green chemistry alternatives.

5. Fate and transport for local vulnerability assessment

In public health initiatives designed to minimize PFAS exposure, the testing of drinking water sources is a top priority. Detection of elevated PFAS concentrations in potable water enables further exposure to be prevented through remedial actions that remove PFAS or through provision of alternative water sources. However, the extent to which residents in Connecticut (and in many other states and nations) have been exposed to PFAS through drinking water ingestion is largely unknown. Public drinking water is regularly tested for numerous naturally occurring and anthropogenic contaminants, and this information is provided to CTDPH, the agency responsible for regulating the state's public drinking water systems. Between 2013 and 2015, as part of UCMR3 monitoring under the federal Safe Drinking Water Act, the EPA required large public water systems serving >10,000 people to test their finished drinking water for PFOA, PFOS, PFHxS, perfluorobutane sulfonic acid (PFBS), perfluoroheptanoic acid (PFHpA), and perfluorononanoic acid (PFNA). Of the 42 Connecticut public water systems in this category (which collectively provide drinking water to >2.3 million customers), none detected PFAS concentrations over the EPA reporting limits (EPAb). However, reporting limits at the time (20, 40, 30, 90, 10 and 20 ppt for PFOA, PFOS, PFHxS, PFBS, PFHpA, and PFNA, respectively) were higher than levels currently of concern to health officials in a number of states. In Connecticut, the current Action Level, an advisory level set by CTDPH in 2016 (CTDPHa), is 70 ppt for the summed concentrations of PFOA, PFOS, PFHxS, PFHpA, and PFNA. Continued monitoring of these large public water systems, as well as many smaller ones, is necessary to ensure that drinking water statewide is safe for human consumption. In 2018, CTDPH used its statutory authority to require (1) PFAS testing in all new sources of public drinking water and (2) public water systems serving >1000 people to evaluate their sources' vulnerability to PFAS contamination. CTDPH has also requested those water systems to test their finished drinking water for PFAS. While these initiatives made significant progress, many of the state's 2500 public drinking water systems (Fig. 3), which obtain their supplies from approximately 150 reservoir systems and 4000 groundwater sources, have not been assessed for PFAS vulnerability and have never been tested for PFAS. Moreover, nearly one quarter of Connecticut residents rely on water from an estimated 325,000 private wells (CTDPHb). This large quantity of wells presents a major challenge, and research assessing local PFAS sources and hydrogeology is necessary to prioritize the wells most vulnerable to PFAS contamination for initial rounds of testing.

Researchers at Yale are planning to study PFAS fate and transport near local landfills with the intention of developing vulnerability models for local drinking water resources and helping state officials assess the levels of PFAS exposure faced by residents. Investigation of landfills that pose potential threats to nearby residents was identified as a crucial need by regulators and researchers during the deliberations of the Interagency PFAS Task Force and highlighted in the resulting Action Plan. PFAS have already been detected in groundwater near two large landfills in Connecticut (Hladky, 2019), and although other landfills throughout the state are considered potential sources of PFAS contamination, few of these sites have been tested for groundwater contamination. Focusing on landfill sites prioritized by CTDEEP, Yale researchers intend to quantify the vulnerability of nearby wells using hydrologic models that simulate groundwater flow patterns and physicochemical factors governing PFAS migration away from a source. Drinking water from households with wells identified as vulnerable will be analyzed for concentrations of PFAS to enable evaluation of the models while providing immediate benefits to impacted residents through targeted interventions and focused monitoring. This work will provide a valuable model for further collaborations between university researchers and state officials to implement Action Plan recommendations and safeguard the health of Connecticut residents.

6. Community engagement

As testing for PFAS contamination in drinking water and the environment becomes more widespread, individual and community-based health concerns will require extensive research translation and risk communication by state and local leaders. Local health departments and municipal officials are often the first resources that concerned residents turn to with their questions about environmental health risks. During the development of the PFAS Action Plan, one of the primary topics raised by stakeholders was the importance of effective communication on PFAS by state agencies. This requires officials to stay abreast of the ever-evolving science of PFAS health effects, exposure pathways, analytical methods, treatment technologies, and the impacts of these scientific advances on their communities. Because PFAS have only recently begun to gain public attention in Connecticut, residents often hear about these chemicals for the first time when they learn that contamination has been discovered locally and their households have potentially been exposed. When this occurs, it is crucial for state and local officials to be able to communicate the health risks of PFAS exposure quickly, accessibly (i.e., using culturally and linguistically appropriate formats and outreach platforms), and in a manner that does not cause unnecessary panic.

Officials' PFAS communication strategies should leverage the expertise of local health officials and community organizers to engage Connecticut communities in active partnerships that facilitate effective science translation and risk communication. These local experts understand the needs and backgrounds of their individual communities and will be able to draw upon their experience with a range of community organization techniques to actively engage residents. For example, community forums enable state and local officials to share information and learn about their constituents' understanding of the science, exposure, and risk of PFAS, which enables the officials to better tailor their science communication moving forward. Community advisory groups encourage continual education, engage a variety of stakeholders (e.g., community members, environmental advocates, research scientists, and state and local officials), and give participants a collective voice that allows their opinions to be heard. Identifying and utilizing opportunities to connect community members and environmental advocates to local scientists and to engage them in the design and implementation of research studies offers them the agency to help generate data and contribute to solutions in their own communities. Such efforts are underway in the handful of Connecticut communities that have already had to grapple with the discovery of PFAS contamination in their local environment and/or drinking water. As the State works to carry out the extensive PFAS testing recommended in the PFAS Action Plan, these isolated PFAS engagement efforts will need to be extended statewide. Implementing PFAS-focused community engagement initiatives will enhance residents' understanding of the health risks posed by PFAS and encourage their participation in the development and implementation of policies to address PFAS at the local and state levels.

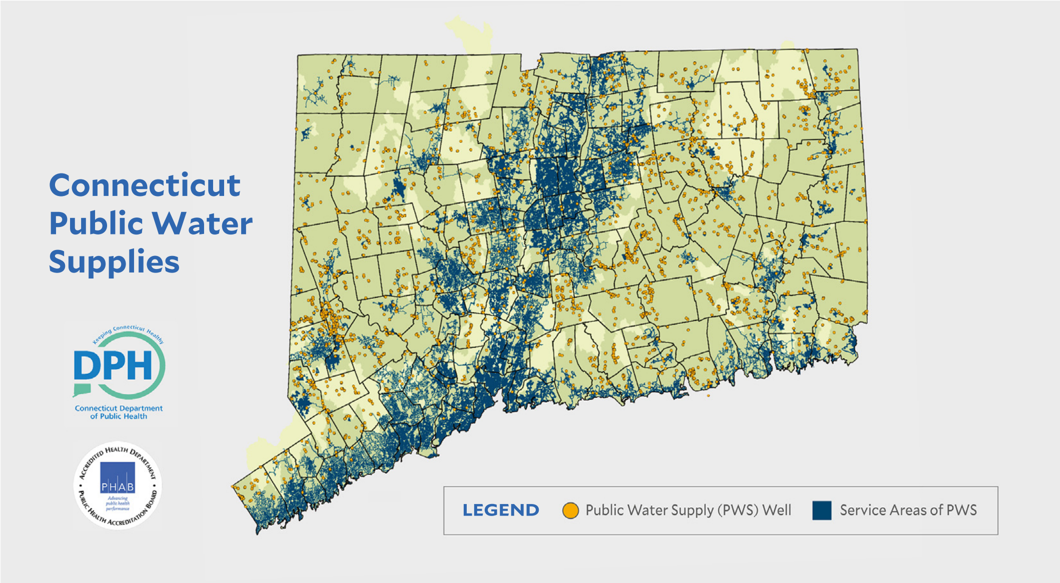


Fig. 3. Areas in Connecticut that are served by public drinking water supplies. It is presumed that outside of the service areas shown in dark blue, residents obtain drinking water from either private wells or the small public drinking water wells shown in gold. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Government researchers at the Connecticut Agricultural Experiment Station are currently collaborating with community member scientists to assess the potential of phytoremediation for removing PFAS from contaminated soil. The group is piloting this strategy at the former Loring Airforce Base, a former Superfund site in northern Maine where decades of firefighting drills and training with Class B firefighting foam (i.e., aqueous film-forming foam) contaminated the land in the vicinity of the burn house with high levels of PFAS, primarily PFOS. U.S. Air Force investigations between 2015 and 2017 measured PFOS concentrations up to 27 ng/g (ppb) in soil and 238 ng/L (ppt) in groundwater (Baker, 2018). The land is now owned by the Aroostook branch of the Micmac Nation, an indigenous people. Working with the Micmac Nation and a community organization called Upland Grassroots, a pilot test was conducted near the burn house using fiber hemp (*Cannabis sativa*), a crop that is suitable for phytoremediation due to its high water uptake, high biomass, and rapid growth. Hemp has previously been used for phytoremediation of both heavy metals (Ahmad et al., 2016) and organic contaminants (Campbell et al., 2002), although its use in the U.S. was legally restricted until recently (Smith-Heisters, 2008). Of the 19 PFAS quantified in soil at the test site, eight were taken up into hemp plants and four had significantly decreased soil concentrations at the end of the growing season. The group is currently exploring strategies to optimize hemp growth at the site and recently published their work on screening for additional PFAS in the soil (Nason et al., 2020). This work provides a model for citizen science initiatives in which members of PFAS-impacted communities can actively engage in research being conducted by scientists at local government laboratories and academic institutions.

7. Conclusion

As highlighted throughout this symposium, PFAS present unique challenges to scientists and policymakers alike. First and foremost, although the PFAS class comprises >9000 different chemicals, analytical chemists have reference standards for fewer than 200, and extensive epidemiological and toxicological data exist for only a handful of these compounds; there are even fewer studies evaluating the EDC potential of PFAS. Many of the PFAS prevalent in the global marketplace are short-chain replacement compounds whose health effects have yet to be studied. Furthermore, while many products and industrial process employ complex mixtures of PFAS, existing studies provide scant information about the health impacts of mixed PFAS exposures. These data gaps make it challenging for health officials to accurately assess the risks posed by PFAS and to develop sufficiently protective policies. For environmental officials, management of PFAS waste presents an immense challenge due the concentrated waste generated during the remediation of contaminated water and the lack of commercially available PFAS destruction technologies and remediation methods for PFAS-contaminated environmental media, e.g., soil.

These challenges present opportunities for scientists to conduct research with meaningful real-world implications. Ongoing epidemiological and toxicological research can help fill data gaps by exploring the pathophysiological effects of exposure to PFAS mixtures and short-chain PFAS, and by characterizing the mechanisms by which adverse health effects manifest. Progress in the understanding of these mechanisms could, in turn, inform green chemistry research to produce safer alternatives to PFAS. New sampling, data acquisition, and data analysis approaches should serve as valuable resources for large-scale epidemiological studies, increase the number of PFAS that can be easily identified during testing, and facilitate the prioritization of PFAS for future health studies. New remediation technologies that efficiently degrade PFAS could help manage the waste streams generated during drinking water remediation.

Moving forward, sustained connections between researchers, government officials, and community leaders (such as those fostered by this symposium) will be invaluable as states and regions work to implement ambitious PFAS management initiatives, such as those laid out in the Connecticut PFAS Action Plan (Fig. 4). It is clear that extensive

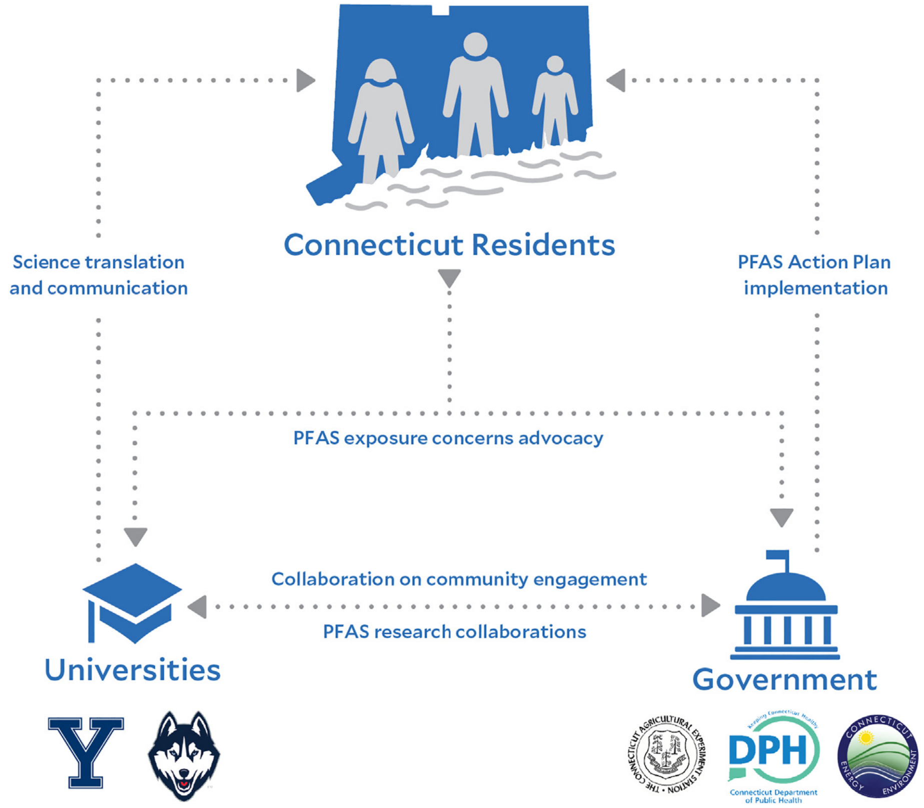


Fig. 4. Interactions between Connecticut residents, universities, and government entities that have taken place or could take place to address PFAS contamination and health concerns.

research will be necessary to assess the situation on the ground in Connecticut, i.e., to identify in-state PFAS sources and measure ambient PFAS concentrations in environmental media statewide. CTDPH efforts to identify public drinking water supplies potentially affected by PFAS contamination and CTDEEP efforts to inventory potential PFAS sources across the state provide an opportunity for a landfill-focused collaboration with Yale researchers to be broadened to apply a similar hydrological modeling approach on a larger scale. A statewide assessment of the vulnerability of community drinking water sources to PFAS contamination will help state government officials better identify and protect at-risk communities. In addition, connections with researchers will help ensure that messaging by state and local officials accurately represents the state of the science on PFAS. Collaborations between state officials, local officials, and community advocates will enhance existing communication channels and develop outreach practices that effectively meet the needs of Connecticut communities.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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