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From Pesticides to Per- and Polyfluoroalkyl Substances: An Evaluation of Recent Targeted and Untargeted Mass Spectrometry Methods for Xenobiotics

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Environmental analysis of xenobiotics is a challenging yet necessary undertaking to characterize pollution levels, assess the effectiveness of remediation interventions, and prevent adverse environmental and health outcomes. Xenobiotics are concerning from an environmental perspective due to their chemical persistence, toxicity to humans and wildlife, and prolific use in agricultural and industrial applications.¹ Many xenobiotics are persistent organic pollutants (POPs), and the number of POPs listed in the Stockholm Convention is

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considerable and ever increasing (12 compounds/classes were initially defined at the historic Stockholm Convention on Persistent Organic Pollutants in 2001).² Chemical classes of environmental concern include but are not limited to per- and polyfluoroalkyl substances (PFAS), pesticides, polychlorinated biphenyls (PCBs), dioxins, disinfection byproducts (DBPs), microplastics, polycyclic aromatic hydrocarbons (PAHs), and pharmaceuticals and personal care products (PPCPs).³ While the assessment of xenobiotics in environmental and biological samples is a broad field of study encompassing a plethora of analytical methods, the combination of a chromatographic separation (gas chromatography, GC; liquid chromatography, LC; supercritical fluid chromatography, SFC) with mass spectrometry (MS) detection is rapidly becoming the preferred method of analysis.⁴

This Review will focus on four xenobiotic classes (PFAS, pesticides, PAHs, and PPCPs, Figure 1) and succinctly describe (1) the contextual background and chemical origin of each class, (2) the historically referenced methods for characterizing each group with a particular focus on those published from the U.S. Environmental Protection Agency (US EPA, Table 1), and (3) novel research methods for analyte extraction, separation, and detection published in the literature over the past two years (2018–2020). In general, the recent publications demonstrate either: (1) a targeted analysis approach for a predefined chemical class using a novel extraction procedure or an analytical method to enhance the selectivity or duty cycle or (2) an untargeted approach to characterize both known and unknown xenobiotics using high resolution MS instrumentation. Thus, the framework of this Review is broken down into these sections. While the selection of xenobiotic classes and cited references detailed in this Review are by no means inclusive of all current research efforts, our focus is to guide the reader toward a contextual framework of current environmental research and showcase future directions and applications.

PER- AND POLYFLUOROALKYL SUBSTANCES

Biochemical Context.

Per- and polyfluoroalkyl substances (PFAS) are a class of xenobiotics comprised of highly fluorinated aliphatic substances. The chemical and thermal stability of these compounds in addition to their hydrophobic and lipophobic nature renders them useful in a broad range of industrial and household applications.^{5,6} Examples of their use include nonstick cookware, stain-resistant materials, food-contact paper coatings, and aqueous film-forming foam (AFFF). Therefore, important sources of PFAS are industrial sites, firefighting training areas (e.g., military bases, airports, petrochemical plants), and wastewater treatment plants.^{6,7}

The production of long-chain perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) began in the United States in the 1950s and continued until the early 2000s. By that time, PFOS and PFOA had become an international concern due to emerging evidence of their environmental persistence, mobility, bioaccumulative nature, and toxicity. In 2018, PFOS was detected in the blood of nearly all (98%) Americans tested.⁸ PFOS was also detected in the blood of wildlife in remote regions including polar bears in the Arctic,⁹ and bioaccumulation in aquatic food webs was observed.¹⁰ Exposures to PFOS and PFOA have been linked to adverse health outcomes such as cancer, immune system dysfunction, liver damage, developmental and reproductive harm, elevated cholesterol, and thyroid disease.

^{11–14} Thus, PFOS and PFOA have been added to the Stockholm Convention's list of globally restricted POPs,¹⁵ and the production of PFOS and PFOA has been phased out in the U.S. There are no federal drinking water standards for PFAS; however, in 2016, the US EPA developed a lifetime health advisory level for the sum concentration of PFOA and PFOS at 70 ppt in drinking water.¹⁶

Some manufacturers in developing countries still produce and use what are now often referred to as "legacy PFAS" (PFOS, PFOA, and related compounds with longer aliphatic chains), but manufacturers in most countries have shifted to short-chain and structurally modified fluoroether replacement chemistries, such as per- and polyfluoroalkyl ether carboxylic acids (PFECAs) and other derivatives.¹⁷ While research on the impact of these "emerging PFAS" is ongoing, similar concerns about environmental persistence, mobility, and effects on human health have been raised.^{18–22} Therefore, understanding the mechanisms of toxicity, investigating remediation techniques, and monitoring global levels of both legacy and emerging PFAS are crucial.

Standardized Methods.

Concerns about the occurrence of PFAS in drinking water led the US EPA to publish Method 537 in 2008.^{23,24} This method relies on solid phase extraction (SPE) and liquid chromatography (LC) tandem mass spectrometry (MS/MS) to detect and quantify 14 PFASs (9 perfluorocarboxylic acids (PFCAs) containing 6 to 14 carbon atoms, 3 perfluorosulfonic acids (PFSAs) containing 4, 6, and 8 carbon atoms, and 2 perfluorooctanesulfonamidoacetic acids) in drinking water.^{23,25} In 2018, US EPA Method 537 was updated to Method 537.1, which targets the original 14 PFAS plus four fluoroethers (ADONA, GenX, and F-53B major and minor) for a total of 18 PFASs.^{23,25} Additionally, the US EPA released Method 533 in 2019 that targets 25 PFAS, including 3 fluorotelomer sulfonic acids, 2 short-chain PFCAs with 4 and 5 carbon atoms, 2 PFSAs with 5 and 7 carbon atoms, and 4 additional fluoroethers while dropping the 2 longest-chain PFCAs and the 2 perfluorooctanesulfonamidoacetic acids.²⁶

Emerging Methods and Applications.

While the standardized PFAS methods are widely used, recent research has largely focused on the identification, characterization, and quantitation of the increasing number of emerging PFAS.²⁷ Global interest in PFAS monitoring has also highlighted the need to develop new methods with higher throughput and lower limits of detection. Many targeted methods continue to rely on conventional extraction and separation protocols but now target a wider range of species spanning dozens of subclasses.^{22,28} Although their production has been widely phased out, legacy PFAS are still consistently detected due to their environmental persistence and possibly the continued use of precursor compounds that degrade to terminal products, such as PFCAs and PFSAs.^{29–31} Novel methods are also being explored for exposure studies that analyze PFAS in complex environmental and biological samples for an ever-increasing number of targeted analytes. Finally, the utilization of high resolution MS instrumentation (e.g., TOF, Orbitrap, etc.) in untargeted workflows continues to increase, allowing both known PFAS and PFAS that have not yet been documented in the literature to be profiled.³²

Targeted MS.—Widespread concern regarding the proliferation of PFAS led to an array of targeted analyses of drinking water to evaluate the compliance with drinking water guidelines that are being developed both in the U.S. and throughout the world (e.g., Interstate Technology and Regulatory Council (ITRC), US EPA HAL, guidelines in individual states in the U.S., European Food Safety Authority (EFSA), the National Health and Medical Research Council (NHMRC) in Australia, and many others). These methods provide both qualitative and quantitative information pertaining to PFAS concentration and occurrence and aid in assessing the amount of exposure in humans and the environment.³³ Typically, targeted methods are designed around standard extraction and separation approaches and often include SPE followed by LC-MS/MS.^{27,34–39} For example, Hu et al. recently used SPE-HPLC-MS/MS to analyze nurses' blood and tap water for 15 targeted PFAS and were able to detect 11.³⁵ This method was also used by Zhang et al. to detect PFASs in surface seawater samples and plankton.³⁴ In a more extensive study, Coggan et al. analyzed wastewater, surface water, and drinking water for 53 PFAS from 14 different subclasses via SPE-HPLC-MS/MS.²⁷ Though PFAS contamination of drinking water is a primary focus of regulatory agencies, consumption of food in contact with specific food contact materials, such as popcorn bags and other packaging, have also been correlated with increased PFAS exposure.^{40,41} Similarly, Gao et al. analyzed serum for 43 PFAS from ten different subclasses using SPE-HPLC-MS/MS to compare relative exposure rates of workers at a fluorochemical manufacturing facility compared to a control group. Of note, Gao et al.'s work utilized online SPE to reduce analysis time and increase sample throughput.³⁷ Miaz et al. also used this method to detect PFAS in blood samples of first-time mothers.³⁶ SPE concentration is however not always performed, and LC-MS/MS has been utilized without SPE to examine zebrafish tissue³⁸ and human serum samples.³⁹ Kotlarz et al. quantified 10 fluoroethers and 10 legacy PFAS in serum collected from adults and children in the Cape Fear River Basin (spatially located near a fluorochemical manufacturing plant) using LC-MS without SPE.²⁹ This study found that 3 fluoroethers were detected in over 85% of participants, and 4 legacy PFAS were detected in 97% of the population surveyed. Jin et al. performed an acetonitrile-based extraction method, consisting of spiking samples with an internal standard followed by the addition of acetonitrile for the characterization of both legacy PFAS and chlorinated derivatives.³⁹ Other analytical methods have also been utilized, such as when Ahmed et al. developed a rapid method to analyze PFAS and separate isomers via differential mobility spectrometry (DMS) followed by a linear ion trap quadrupole MS.⁴² One study of note from Favreau et al. analyzed liquid commercial products that typically contain PFAS such as aqueous film-forming foams and impregnating agents.³³ In the study, 11 different PFAS subclasses (41 molecules) were assessed in these substances using both LC and gas chromatography (GC) methods. Furthermore, the anionic PFAS were passed through weak anion exchange SPE prior to analysis, and neutral PFAS were analyzed via GC-MS/MS following a filtration step with a nylon syringe filter. This study resulted in the detection of at least one PFAS in 63% of the tested impregnation products and 92% of the tested aqueous film-forming foams.³³ While most legacy PFAS are effectively extracted through anion exchange, Nickerson et al. have developed a more comprehensive extraction method that demonstrates favorable recovery for both cationic and zwitterionic PFAS in AFFF affected soil samples.⁴³

Untargeted MS.—As manufacturers have shifted to replace and modify legacy PFAS classes with short-chain PFAS and fluoroether alternatives, PFAS research has become increasingly focused on untargeted discovery and the characterization of new species.^{18–21} A 2019 review reported that over 750 new PFAS belonging to 130 subclasses had been identified by untargeted analyses, while others have estimated >1000 new species.^{44,45} The annotation of PFAS features from untargeted studies is commonly achieved via homologue analysis and suspect screening. Prior to these evaluations, feature lists are filtered by mass defect, as PFAS have characteristically low or negative mass defect values due to the prevalence of fluorine.^{46,47} Since many PFAS are synthesized as mixtures containing homologues with the same core structure but varying numbers of repeat units, CF₂ Kendrick mass defect analyses easily separate the homologous series.^{48–50} Suspect screening then matches the observed exact mass, isotope pattern, generated molecular formula, and MS/MS spectra for each feature to databases or spectral libraries. This workflow provides some structural elucidation when standards are not available but is limited to the scope of the database entries.^{22,51}

Some recent studies have focused on identifying new volatile PFAS, which previously required complex sample preparation and long collection times. Riedel et al. developed an iodide adduct chemical ionization-MS method to examine gas-phase oxygenated PFAS including fluorotelomer alcohols. This method allows for real-time untargeted monitoring from direct volatilization of samples such as surfactants and AFFF.⁵² For the analysis of volatile PFAS on paper and textiles, Rewerts et al. developed a novel high-throughput, low-waste sample preparation method prior to large volume GC-MS analysis. Due to the large volume used, a comparable sensitivity to conventional methods was observed, and untargeted analysis revealed previously overlooked short-chain fluorinated sulfonamides.⁵³

To aid in the discovery of novel PFAS, Liu et al. recently implemented an in-source fragmentation flagging scan in parallel with a high-resolution full scan to flag the retention times of PFAS ions based on their diagnostic fluorine-containing fragments. The flagged ions are then further investigated with a second MS/MS scan.^{48,54} Previous flagging methods focused on fragments from the collision cell instead of the MS source region, disregarding this information.⁵⁵ In addition to identifying new PFAS homologues and isomers, four novel classes were reported when this method was applied to fish liver samples.⁵⁴ Yukioka et al. also integrated fragmentation flagging scans and ion mobility spectrometry (IMS), wherein drift time alignment was used to link the fragment flags to their molecular ions.⁵⁶ The incorporation of IMS separations into untargeted LC-MS workflows, including drift tube ion mobility spectrometry (DTIMS) and differential mobility spectrometry (DMS), has shown additional selectivity, annotation, classification, and isomer separation capabilities.^{56,57} These separations were utilized by Dodds et al.⁵⁷ and Yukioka et al.⁵⁶ for untargeted LC-IMS-MS analyses of water and fire extinguisher fluid. While these studies primarily focused on analyzing analytical standards, Dodds et al. also demonstrated the value of collision cross sections (CCSs) for both additional confidence in annotations and a new method of separating PFAS subclasses when plotted against *m/z* values due to differences in gas phase size (Figure 2).⁵⁷ While the addition of innovative workflow steps such as fragmentation flagging scans and IMS have aided in the discovery of novel PFAS,

traditional untargeted LC-MS/MS methods are still widely used for the detection and characterization of novel PFAS. For example, Washington et al. used untargeted LC-MS/MS to putatively identify ten chloroperfluoropolyether carboxylates and potential isomers in New Jersey soil samples.⁵⁸

The detection and characterization of novel PFAS are the first steps toward understanding the potential health and environmental hazards of these species. However, when one considers the increasingly large number of new PFAS species, the prioritization for further investigation is challenging, especially when commercial standards are not readily available.^{32,44,45,59} Therefore, methods have been developed to investigate the biological effects of PFAS by measuring biomolecules and PFAS simultaneously. One such method is for the ambient in situ microscale analysis of PFAS and lipids in biological tissues. A solid-phase microextraction (SPME) probe is utilized to collect analytes for untargeted nanoESI-MS analyses under ambient conditions. A high-resolution Fourier transform ion cyclotron resonance (FTICR) MS with fast polarity switching is then leveraged to simultaneously detect positive (mostly lipids) and negative (mostly PFAS) ions.⁵⁹ Another method utilizes size-exclusion column coelution (SECC) with untargeted LC-MS/MS analyses to screen for PFAS binding to human liver fatty acid binding protein (*h*L-FABP). *h*L-FABP plays a critical role in the toxicokinetics of PFAS, but this method can be adapted to screen PFAS binding to any protein of interest. Of 74 PFAS initially assessed, 20 were found to be binding ligands, with nearly 40 additional ligands identified when AFFF and AFFF-contaminated water were screened.⁴⁵ Although a comprehensive number of PFAS in the environment remains unknown, current trends in PFAS research suggest that enhanced method development is essential for all areas of analysis (extraction, identification, and quantitation) to effectively assess both known and unknown analytes in this class of xenobiotics.

PESTICIDES

Biochemical Context.

Pesticides are defined by the EPA as chemical substances used to regulate, prevent, or destroy pests.⁶⁰ The term pesticides encompasses well-known chemicals such as herbicides, fungicides, and insecticides as well as other lesser-known varieties such as nematocides, molluscicides, and rodenticides. Natural pesticides have been used in agriculture for thousands of years, but between 1940 and 1980, there was extensive growth in the production and use of synthetic pesticides.^{61,62} Organochlorine pesticides, such as DDT and lindane, were used widely at the beginning of this period until 1962 when Rachel Carson's book *Silent Spring* shed light on the environmental consequences associated with the widespread use of these pesticides.^{62,63} *Silent Spring* drew attention to the fact that pesticides are specifically designed to kill forms of life and, therefore, may also be toxic to animals and humans. In 1993, the U.S. Agricultural Health Study (AHS; <https://aghealth.nih.gov/>) was designed to help answer lingering questions of the impacts that pesticide usage may have on human health, specifically for farming populations.⁶⁴ Within the AHS, there are several studies focused on exploring the relationships that exist between pesticides and specific human health effects such as Parkinson's disease, neuro-behavioral

function, cancer, lung function, and asthma.^{64–67} One such study determined that the use of chlorinated pesticides was significantly associated with prostate cancer among applicators over 50 years old.⁶⁶ As the impacts on public health are better understood and toxic pesticides are phased out, the chemical structures of pesticides are continually manipulated.

Government regulation of pesticides in the United States began with the Insecticide Act of 1910, which was primarily established to regulate the sale and advertisement of pesticide products.⁶⁸ At this time, natural pesticides dominated the market, but when synthetic pesticides were popularized in the 1940s, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) of 1947 was established as a comprehensive update to the Insecticide Act of 1910. FIFRA required the registration of pesticide ingredients with the U.S. Department of Agriculture (USDA) prior to their sale.⁶⁸ In 1970, pesticide regulation shifted from the USDA to the newly established US EPA. Currently, in the U.S., pesticides must be registered with the US EPA prior to their distribution and use. Through this process, data on each pesticide's toxicity, risk to humans, and effects on the environment must be established.⁶² This process is primarily designed to regulate the active ingredients in pesticide products prior to the product's distribution commercially.

Standardized Methods.

Today, numerous organizations track the use and environmental presence of pesticides in the U.S., including the US EPA, USDA, and the U.S. Geological Survey (USGS). The National Water Quality Assessment (NAWQA) Program was created in 1991 under the USGS to better understand the human impact on water in the U.S. After its first decade, NAWQA published the most extensive and comprehensive national-scale study of pesticides in U.S. water sources.⁶⁹ To assess the quality of U.S. water sources, NAWQA developed analytical methods that targeted a limited number of pesticides suitable for analysis using GC-MS selected-ion-monitoring (SIM) mode combined with SPE.⁷⁰ Since that time, the methods used by NAWQA have evolved. USGS Method O-2437–15 was published in 2015. This new method expanded the analyte list to 257 pesticide compounds, utilized a new generation of commercially available LC-MS/MS instruments, and eliminated the need for SPE and intensive sample preparation techniques.⁷¹ Method O-2437–15 was one of the first implemented standardized methods to forego SPE and focus on a direct aqueous injection into the LC-MS instrument.

Similar to NAWQA, the US EPA has developed multiple methods intended to identify and quantify pesticides in environmental matrices. US EPA Method 1699 was developed in 2007 for the determination of approximately 100 selected organochlorine, organo-phosphorus, triazine, and pyrethroid pesticides in environmental matrices using GC-MS and SPE.⁷² In 2012, US EPA Method 525.3 was published for the determination of 125 semivolatile organic chemicals, including many pesticides, in drinking water using SPE and GC-MS.⁷³ US EPA Method 525.3 was followed up with various methods utilizing LC-MS, such as Method 540 which targets 12 pesticides in drinking water using SPE and LC-MS/MS.⁷⁴

Emerging Methods and Applications.

Understanding the prevalence of pesticides in the environment has become an almost impossible task using standardized, targeted methods thereby resulting in many challenges. The first challenge has been the ever evolving and growing list of registered pesticides. As more and more pesticides are registered with the US EPA and introduced to the market, the analyte list continually grows since historically used pesticides must remain due to their persistence in environmental samples. To meet this increase in xenobiotics, new analytical methods must also be developed at the same rate to assess the pesticides and their transformative products; however, this has currently not been the case. A second challenge is the vast spatial variation in pesticide use as the application of specific pesticides is dependent upon the type of crop, intended use, and geographic region. For example, pesticides intended to aid in the growth of tobacco are often very different from those for Christmas trees or corn. The third challenge is the temporal variation in pesticide concentrations in the environment.⁷⁵ To account for variations in concentration with respect to time, many longitudinally collected samples and resulting analyses must be completed. Thus, to address all of these challenges, new analytical methods often utilize HRMS and seek to (1) identify and quantify novel pesticides and/or transformation products, (2) identify temporal and spatial trends in pesticide concentrations, and/or (3) provide a holistic understanding of the presence or absence of pesticides.

Targeted MS.—Targeted methods have been specifically developed and utilized to address the challenges in pesticide analyses for a subset of interest. Specifically, to assess how pesticide concentrations vary with time and space, Nowell et al. utilized NAWQA Method O-2437–15 to determine concentration variations in Midwestern U.S. streams sampled from May–August of 2013.⁷⁵ In this study, water samples were taken weekly from various locations and analyzed using LC-MS/MS. Using this method, Nowell et al. detected and measured 94 pesticides and 89 transformation products in one or more of the samples taken. Using the concentration information obtained from the analysis, they determined that the measured pesticides reflected the land use and associated pesticide use patterns near the sample locations. Additionally, it was determined that, at various sampling time points, the total concentration of pesticides approached 10 000 ng/L.⁷⁶ Another study conducted by Spycher et al. sampled various small streams in Switzerland up to 360 times each from March–August of 2015.⁷⁷ Each of these samples were analyzed using online SPE LC-ESI-HRMS. Using reference standards, up to 213 pesticides in each of the samples were quantified. Spycher et al. determined that the pesticides present in the samples depended primarily on the type of crop grown, and their overall concentrations of pesticides increased with rain events.⁷⁷

Targeted studies to assess temporal variations in pesticide concentrations in Switzerland water were performed by la Cecilia et al. and utilized a mobile high-resolution mass spectrometer.⁷⁸ The mobile mass spectrometer, called MS² field, consists of a mobile trailer containing an LC-Orbitrap. la Cecilia et al. characterized nine rain events and identified peak pesticide concentrations during these events. During the study, the concentrations of fluopyram, cyprodinil, and napropamide were 30, 5, and 5 ppb, respectively. The temporal

resolution of the study enabled a better understanding of pesticide sources and pathways in the environment.^{78,79}

The second overall objective of the targeted analysis is to identify and quantify novel pesticides and transformation products. Kiefer et al. recently utilized a holistic targeted approach to detect a novel transformation product associated with chlorothalonil. Here, they used the untargeted data acquisition for the assessment of transformation products in 31 groundwater samples and quantified one novel transformation product using reference standards, isotope-labeled standards, and LC-ESI-HRMS.^{80,81} The quantification of this particular transformation product, chlorothalonil TP R471811, revealed that concentrations exceeded 100 ng/L in 20 of 31 water samples and had the highest maximum concentration of all the pesticides and transformation products assessed (2700 ng/L in one sample).^{80,81}

Untargeted MS.—To address the growing challenge of identifying new pesticides and transformation products, untargeted analytical methods have become a necessary starting point for a holistic understanding of the presence or absence of pesticides.^{82–85} Kiefer et al. were able to identify the novel transformation product, chlorothalonil TP R471811, mentioned above using untargeted analytical methods.⁸¹ In this study, an Orbitrap LC-MS in data-dependent acquisition mode was used to obtain data in both positive and negative ionization modes. Following data acquisition, target and suspect screening, feature prioritization, and target confirmation using reference materials were completed (Figure 3). While untargeted methods are powerful tools for discovering new pesticides and transformation products, isomeric and coeluting substances pose major challenges to these work-flows.⁸¹ To address this challenge, Chen et al. utilized IMS-MS and both ESI and APCI sources.⁸⁶ The peak for sulfotep, a pesticide included in method development, was overlapped by another neighboring peak that hindered its identification using only HRMS analysis. By obtaining IMS-MS data, Chen et al. were able to separate sulfotep from its neighboring peak and confidently identify it. Another recent study from Wu and coworkers utilized MALDI-FTICR to spatially probe pesticide residues from leaf sections and utilize HRMS analyses for both accurate mass annotation and MS/MS spectral matching of particularly challenging isomeric analytes, such as the pesticides tebuconazole and cletoquine noted in Figure 4.⁸⁷

To obtain a holistic understanding of the impact of pesticides on the environment, Moschet et al. sought to identify relevant micropollutants, including pesticides, by using both GC- and LC-HRMS as complementary tools.⁸⁸ The LC-HRMS data was acquired using an ESI source, while the GC-HRMS data was obtained using an electron ionization (EI) source. For decades, GC-MS has been a powerful tool utilized by both the US EPA and NAWQA to identify and quantify pesticides in environmental samples.^{72,73} While current methods primarily utilize LC, many pesticides are still best suited for GC analysis; of the prioritized pesticides in this study: 11 were best suited for GC, 7 could be analyzed using either GC or LC, and 6 were optimal for LC.

Overall, the assessment of the impact of pesticides on the environment requires the development of both untargeted and targeted analytical methods suitable for a wide range of chemical properties and environmentally relevant concentrations. Pesticide structures are

constantly being manipulated, requiring that researchers develop analytical methods using a variety of ionization sources and chromatographic separations. As novel pesticides and transformation products are identified in environmental matrices, untargeted methods must quickly be adapted to targeted methods for the quantification of these features. Finally, it is imperative that high-throughput methods be developed to further understand the temporal and spatial variability of the occurrence and exposure associated with pesticide use.

POLYCYCLIC AROMATIC HYDROCARBONS

Biochemical Context.

Polycyclic aromatic hydrocarbons (PAHs) are a chemical class of xenobiotics comprised of fused aromatic structures that consist of solely carbon and hydrogen atoms. PAHs originate from both natural and anthropogenic sources through the combustion of organic matter, including wildfires, volcanic eruptions, fossil or biofuel combustion, motor vehicle emissions, smoking, and indoor cooking.^{82–85} Human exposure to PAHs contributes to biological damage through several mechanistic pathways, though cancer is generally the prominent chronic manifestation of concern.^{85,89} While the primary PAH molecules can be dangerous, their metabolic byproducts (dihydrodiols, epoxides, and quinone derivatives, among other forms) are generally more concerning from a biological perspective.^{90,91} PAH metabolites form through enzymatic CYP processing and can form DNA adducts that promote transcriptional errors during replication.⁹¹ Because of their toxicity and ubiquitous production in the environment, quantitative monitoring and reduction of PAH levels is a major public health objective from a global perspective.

PAHs were first recognized as hazardous to human health in 1775 by Percivall Pott, an English clinician who noticed a correlation between the number of chimney sweeps who visited St. Bartholomew's hospital in London that were subsequently diagnosed with scrotal cancer. Pott suggested that the direct soot exposure encountered in this vocation was the instigator for the unnaturally high rate of contraction, and this observation is often suggested as one of the first instances wherein a specific substance is directly associated with a disease phenotype (though soot is technically a complex mixture of chemical entities).⁹² Pott published his medical observations for a broad public audience and generated much interest and sympathy for the unique danger faced by chimney sweeps. His efforts would ultimately contribute to the passing of the Chimney Sweepers Act of 1788 by the British Parliament,⁹³ which sought to limit child labor in this sector by establishing a minimum working age of 8 and mandating parental consent (though many sweeps were orphans). Pott's observation relating soot exposure to cancer would be subsequently expanded upon in a series of fascinating experiments by Cook et al.,^{94,95} which utilized topical applications of various coal tar extracts to vertebrates that would develop skin cancer. Each extract was characterized by fluorescence spectroscopy such that specific wavelengths were correlated with tumor development. After several years of synthesizing pure standards and comparing spectroscopic patterns against purified extracts, they eventually traced the origin of the primary carcinogen of coal tar to benzo[*a*]pyrene (BaP),⁹⁰ the relative toxicity of which most PAHs are still measured (known as toxicity equivalence factors or TEFs).^{96,97}

Standardized Methods.

Government monitoring and regulation of PAH concentrations in the environment began in the U.S. in 1976 by the EPA as a component of the Clean Water Act.^{98,99} 16 priority PAHs were highlighted in this initial effort (including BaP), and this list has endured for over 40 years as a preliminary benchmark to assess water quality both in the U.S. and abroad with further studies examining other matrices including soil⁹⁷ and air pollution,¹⁰⁰ among others.¹⁰¹ Following the establishment of the 16 prioritized PAHs, in 1979, the US EPA published Method 610, which utilizes either GC or LC with flame ionization or fluorescence detection to separate and quantify PAH targets in aqueous samples.^{102,103} Utilizing Method 610 as a common benchmark of analytical proficiency, research interest in improving the separation capabilities of commercially available columns led to significant enhancements in stationary phase design and method development. Noting the continuing prevalence of Method 610 and the related Method 625 for acids, bases, and neutral contaminants,¹⁰⁴ many commercial vendors now offer columns and corresponding SOPs specifically designed to characterize the 16 US EPA PAHs.¹⁰²

Emerging Methods and Applications.

While the 16 PAHs were instrumental in creating a unified list of accepted molecular targets for environmental profiling, emerging research efforts characterizing PAH pollution suggest that this list is unsurprisingly not inclusive of all molecules of concern. The European Union has established its own list of priority PAHs, which retains several molecules from the US EPA list yet also includes several larger molecular weight PAHs (302 Da).¹⁰¹ Large molecular weight PAH systems (generally classified as 302 Da and above) pose unique challenges to current approaches including decreased volatility for GC-based methods and limited selectivity for many isomeric contributors.^{105,106} In addition, recent studies suggest that alkylated PAH derivatives and heteroatom containing systems that incorporate nitrogen, oxygen, and sulfur also pose a substantial risk to public and environmental health and require further characterization.^{99,107} Hence, current studies are generally designed to either (1) improve analyte extraction and/or establish new methods for current PAH target lists or (2) develop untargeted assays to screen for many analytes in a single experiment.

Targeted MS.—Current research efforts to characterize PAHs from a targeted perspective are mostly focused on either simplifying extraction and sample preparation steps for predominantly the US EPA or EU lists or applying existing methods in new contexts. Szulejko et al. have published an extensive review covering all the primary methods for extracting PAHs from airborne particulates (Soxhlet, accelerated solvent extraction (ASE), QuEChERS, supercritical fluid extraction (SFE), and cold-fiber solid-phase microextraction (SPME)).¹⁰⁸ While the Soxhlet extraction is generally considered the reference standard technique,¹⁰⁹ other methods such as those described are being evaluated as potentially greener alternatives that may offer advantages such as reduced solvent consumption, simplicity through automation, and decreased cost.¹¹⁰ For example, Luo and Schrader conducted a detailed evaluation comparing the Soxhlet extraction using a range of solvents versus SFE for characterizing PAHs in sand samples spiked with crude oil. Their results demonstrate that Soxhlet extractions performed with toluene, dichloromethane, and a 1:1 mixture of acetone–hexane provided ~95% recovery of spiked targets, whereas SFE

extraction using only CO₂ provided ~47% recovery with decreased efficiency noted particularly for high molecular weight analytes.¹¹¹ Wicker et al. recently published a simplified method of sample preparation of soil samples using online extraction, separation, and detection for the US EPA PAHs by SFE coupled to SFC-MS.¹¹² Recently, Petrarca and Godoy demonstrated the utility of QuEChERS¹¹³ and liquid–liquid microextraction (LLME) to quantify PAHs in baby food.¹¹⁰ Pastor-Belda et al. recently published an article detailing extraction methods to characterize PAH content in human organs for forensic analysis.¹¹⁴ Similarly, Wang et al. used the 16 US EPA PAHs and two others (benzo[e]pyrene and benzo[j]fluoranthene) to characterize 73 cosmetic products by GC-MS/MS.¹¹⁵ In another study, Lee et al. utilized 15 of the 16 US EPA PAHs to characterize sediment pollution in two screening sites of Masan Bay, South Korea.¹¹⁶ In this work, the targeted PAHs and other selected compounds (styrene oligomers and alkylphenols) were used as a focused initial screen to compare the relative pollution levels and biological toxicity of each sampling site.

Untargeted MS.—Although targeted PAH studies have been instrumental in characterizing the severity of environmental pollution, emerging concern toward the toxicity of PAH derivatives and metabolites is moving analytical methods toward a more untargeted perspective, which includes alkylated PAHs and heteroatom byproducts, traditionally comprised of nitrogen, sulfur, and oxygen (NSO; referred to as “heterocycles” or more generally as polycyclic aromatic compounds, PACs).⁹⁹ The previously mentioned study from Luo and Schrader not only analyzed extraction efficiency for a targeted list of PAHs and heteroatom compounds but also characterized crude oil samples and their extracts in subsequent untargeted experiments using high resolution MS detection via Orbitrap FT-MS with a variety of ion sources (ESI, APCI, and APPI).¹¹¹ The increasing concern for heteroatom PACs presents an additional challenge to current analytical methods, wherein the acidic or basic residues benefit from additional methods of ionization, increasing experimental complexity. In addition, as more compounds are ionized, additional mass resolving power is necessary for quantitative analysis of each signal. For example, the analysis of crude oil samples by APPI in Luo and Schrader’s study shows 4 PAC signals in a narrow mass range of ~0.01 *m/z* (Figure 5). The resolution of these signals requires over 400 000 resolving power, which is currently only achievable by FT-MS. Tian et al. also noted the presence of NSO metabolites in a stable isotope labeling experiment assessing PAH derivatives in soil.¹¹⁷ The authors spiked both ¹²C and ¹³C labeled aliquots of fluoranthene, pyrene, and benzo[*a*] anthracene into contaminated soil from a wood treatment plant and analyzed the resulting LC-MS/MS data for signals with a predetermined abundance ratio of light ¹²C and heavy ¹³C as presumptive metabolites. This strategy has been extremely successful in untargeted metabolomics for elucidating mechanistic pathways,^{118,119} and the work by Tian et al. provides an excellent demonstration of utilizing this technique for environmental analysis. In addition, Zheng et al. recently demonstrated the application of ion mobility to facilitate the separation and characterization of PAHs, PCBs, and PDBEs in complex samples.¹²⁰ As with the study by Luo and Schrader, Zheng et al. also assessed the complementary utility of multiple sources of ionization (ESI, APCI, and APPI, Figure 6) wherein they noted APPI was particularly useful when characterizing a variety of PACs. Their work also shows distinct trend lines for individual chemical classes (e.g., PAH, PCB,

PDBE), which is indicative of the utility for this approach particularly when classifying unknowns in untargeted studies.

PHARMACEUTICALS AND PERSONAL CARE PRODUCTS

Biochemical Context.

Pharmaceuticals and personal care products (PPCPs) are a broad class of chemicals with a wide range of structures and physicochemical properties. PPCPs are used in daily life for a variety of purposes including veterinary medicine, human health, and personal/cosmetic care. Current estimates suggest there are more than 3000 active pharmaceutical ingredients and hundreds of active compounds for personal care products being produced.¹²¹ The increasing population and economic growth globally has resulted in the expanded production and use of PPCPs. As a result, there could be an increased discharge of PPCPs and potentially increased adverse human and environmental health effects. Currently, there is no U.S. or European Union (EU) legislation regulating PPCPs. The presence of PPCPs in the environment has put pressure on governing bodies to assess new regulatory policy for priority pollutants in the water sector as stated in Directive 2013/39/EU.¹²² In the U.S. under the fourth unregulated contaminant monitoring rule, the EPA is monitoring for several PPCPs in public drinking water systems. These PPCPs are currently not subject to any primary drinking water regulations but are known to occur in public water systems.¹²³

Continued scrutiny of PPCPs highlights the importance of sustained advancements in identifying and measuring these contaminants in the environment.^{124–126} Through the use of these PPCPs in households and health care settings, these chemicals ultimately end up in domestic wastewater. The current design of wastewater treatment plants does not include adequate processes to effectively remove PPCPs prior to being discharged to the environment. With improved sensitivity, accuracy, and selectivity of analytical instrumentation, research on the occurrence, fate, transport, and toxicity of PPCPs has increased drastically.

Emerging Methods and Applications.

Over the past decade, there has been a trending initiative to further understand the extent of PPCPs in the environment with numerous studies demonstrating widespread occurrence of PPCPs.^{121,127–129} The continued occurrence of previously undetected PPCPs may increase the risk of adverse human and environmental health issues. PPCPs are excreted from or washed off the body causing increased loading to wastewater treatment plants. Conventional wastewater treatment plants are not equipped to remove these PPCPs. In order to improve our understanding of the fate and transport of PPCPs ineffectively removed through treatment processes, analytical methods must be robust to measure the diverse classes of PPCPs quantitatively in a variety of matrices (e.g., water, biosolids, soil, biota).

Standardized Methods.

The US EPA has developed a few methods for the analysis of PPCPs in environmental samples. Both Methods 542 and 1694 can be used for targeted analysis in water samples.^{130,131} Method 1694 expands on the matrices in which PPCPs can be analyzed with a

method developed for analysis in soil, sediment, and biosolids. With advancements to extraction procedures, methods including 1694 will be improved, allowing for expanded detection and quantification of PPCPs in a variety of matrices.

Targeted MS.—PCPP targeted analyses are heavily focused on chromatographic approaches coupled with MS for the identification and quantitation of PPCPs in a variety of matrices. Inherently, we will never be able to analyze every PPCP with a single method for numerous reasons including chemical diversity and properties (Figure 7).¹³² The methods available therefore differ in several areas. First, sample preparation and preconcentration are altered in the methods resulting in differences in sensitivity, accuracy, and selectivity of PPCPs. Kachhawaha et al.¹³⁹ have provided a review of developed LC-MS/MS methods, which covers sample preparation approaches. Solid-phase extraction (SPE) has been the primary technique for extraction of PPCPs from water, sediment, and biota samples.^{133–136} For example, Miossec et al. coupled SPE with LC-MS/MS to analyze 44 pharmaceuticals in environmental samples.¹³⁷ Another study by Abou-Elwafa Abdallah et al. used SPE for cleanup and preconcentration prior to LC-HRMS analysis of 30 PPCPs.¹³⁸ Alternative methods for sample preparation have been suggested including: liquid–liquid extraction (LLE), solid–liquid extraction (SLE), ultrasound-assisted solvent extraction (USE), pressurized liquid extraction (PLE), solid phase microextraction (SPME), microwave-assisted extraction (MAE), QuEChERS, and other modifications.^{135,139} For example, Nannou et al. optimized and validated a modified QuEChERS method for the analysis of 25 pharmaceuticals in sediments by LC-Orbitrap HRMS.¹⁴⁰ With improvements to instrument sensitivity, researchers have been able to utilize direct injection as an approach for the analysis of PPCPs in water samples. Borrull et al. used a large volume direct injection approach to analyze PPCPs in river water.¹⁴¹

In terms of instrumentation, Carmona and Picó showed that roughly 92% of methods analyzing emerging pollutants, including PPCPs, utilized LC vs GC.¹³⁵ This critical review of methods found that for both abiotic and biotic samples, when comparing sensitivities and accuracies of targeted methods, triple quadrupole instruments performed better than Orbitrap, linear ion trap, time-of-flight, and single quadrupole instruments. Thus, HRMS systems are being used to initially identify key features/suspects in samples prior to verification by analytical standards.¹⁴²

Untargeted MS.—Since targeted analysis of PCPPs is limited by the availability of analytical standards used in these studies, untargeted methods are greatly needed. Furthermore, the continued development of new PPCPs and the potential for biotic and abiotic transformation of PPCPs means that untargeted techniques are required to identify features of interest in environmental samples that targeted analyses cannot. The application of HRMS instruments, including QTOF and Orbitrap, for untargeted screening is a promising tool for assessing water quality and treatment performance. Brunner et al. used the HRMS technique to assess the removal of a variety of organic micropollutants, including PPCPs, from drinking water treatment pilot systems.¹⁴³ These HRMS approaches provided more comprehensive assessments of the samples and expanded the view of water quality and human and environmental exposure. Old untargeted HRMS data sets are also being

reprocessed by retrospectively matching features to current compound libraries.^{144–146} For example, Alygizakis et al. conducted a retrospective analysis of archived HRMS data to identify temporal and spatial occurrences of previously unidentified contaminants, including surfactants and transformation products of drugs.¹⁴⁴ Additionally, taking advantage of archived data sets allows for the potential identification of new contaminants in a rapid and cost-effective manner. Alygizakis et al. also conducted untargeted profiling of data using LC-HRMS/MS at a riverbank filtration site in order to assess the potential for further occurrence of PPCPs and other organic contaminants during the sampling campaign.¹⁴⁵ Untargeted analysis has also garnered interest for prioritizing toxic, bioaccumulative, and persistent pollutant removal in wastewater systems. Purschke et al. developed a proof of concept method using two-dimensional LC with ultraviolet detection and HRMS to enhance untargeted analysis for tentative identification of unknown industrial wastewater contaminants.¹⁴⁷ Blum et al. conducted two-dimensional gas chromatography–mass spectrometry (GCxGC-MS) analysis of on-site sewage treatment facilities.¹⁴⁸ By using GCxGC, Blum et al. was able to improve compound separation from matrix interference without having to conduct expensive and time-consuming sample preparation. The approach of coupling untargeted screening and persistent, bioaccumulative, and toxic (PBT) prioritization could aid in identifying environmentally relevant PPCPs in wastewater systems while helping to understand the removal efficiency of PBT compounds. The authors do note that, to expand upon this approach, the workflow should be applied to both GC-MS and LC-MS to efficiently identify PBT compounds.

SUMMARY AND FUTURE OUTLOOK

The chemical persistence of xenobiotics and their propensity for adverse outcomes in both humans and wildlife suggest that the characterization of these chemical classes and quantitative assessment of their presence in the environment will be an ongoing endeavor. Analytical advances in sample preparation, chromatographic performance, and MS analysis are providing enhanced selectivity and higher throughput; however, the results collected from these screenings often suggest that an increasing number of uncharacterized systems are contributing significantly to pollution and adverse health outcomes. Even as the production of some xenobiotics are phased out in some countries (e.g., PFOS, PFOA, DDT, and others), other synthetic analogues are produced in their place and their novel structures may also generate adverse effects and require further study (e.g., GenX). Thus, for the foreseeable future, both targeted and untargeted assays will be required for both quantitative analysis of xenobiotics already known and qualitative information about emerging chemical threats requiring further investigation. While MS methods are vital to these efforts, the development of effective remediation strategies to reclaim polluted sites is also essential in actively addressing and mitigating the environmental damage. A recent review by Lu et al. provides an exemplary description of current strategies for PFAS removal and degradation including granular activated carbon (GAC), electrochemical methods, nanofiltration, and thermolysis, among many others.¹⁴⁹ Huang and Jaffé recently published an encouraging method describing the defluorination of PFOA and PFOS through biodegradation from a strain of soil bacteria, *Acidimicrobium* sp. A6.¹⁵⁰ For PAHs, Zhou et al. recently published an intriguing design that utilizes magnetic nanomaterials for the removal of PAHs in

aqueous environments.¹⁵¹ Activated carbon biochar has also been used by Sullivan et al. as a potential low cost option to remove PAHs from contaminated sources.¹⁵² Thus, to comprehensively address both the proliferation and severity of environmental contamination from xenobiotics, we must continue analytical techniques to detect and quantitate both known and emerging chemicals, while also generating effective methods to remediate the affected sites.

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Environmental Contaminants

Figure 1.
Illustrative characterization of selected environmental contaminants focused on in this Review.

Figure 2.

Mass spectrometry (m/z) versus IMS collision cross section (CCS) trend lines for the specific PFAS subclasses analyzed (e.g., FTSA, PFSA, etc.). Specific PFAS headgroups contribute significantly to the observed CCS for a given m/z in each PFAS subclass. The varying chain lengths of CF_2 then produce the linear trend lines observed within each subclass. Reproduced from Dodds et al. Rapid Characterization of Per- and Polyfluoroalkyl Substances by Ion Mobility Spectrometry-Mass Spectrometry (IMS-MS). *Anal. Chem.* **2020**, *92*, 4427–4435 (ref 57). Copyright 2020 American Chemical Society.

Figure 3.

Compiled list of pesticides and transformation products (TPs) from drinking water samples had 396 pesticides (43% targets, 57% suspects) and 1120 TPs (6% targets, 94% suspects). 1256 suspects (223 pesticides, 1033 TPs) had a monoisotopic mass of >99 Da; 95% of these suspects had a similar log *D* as the target compounds and 99.5% included a heteroatom (box 1). After the automated screening (box 2), the suspect hits were prioritized (box 3, blue color) and the most promising suspects were further examined with reference material if available (box 4, blue color). Reprinted from *Water Res.*, Vol. 165. Kiefer, K.; Müller, A.; Singer, H.; Hollender, J. New relevant pesticide transformation products in groundwater detected using target and suspect screening for agricultural and urban micropollutants with LC-HRMS (ref 81). Copyright 2019, with permission from Elsevier.

Figure 4.

(a) CID tandem mass spectra of two pure isomers (C₁₆H₂₂ClN₃O, MW = 307.83172), tebuconazole (marked in blue) and cletoquine (marked in pink), acquired with a dissociation energy of 20 eV. The pesticide isomers at a concentration of 5 mg/L were sprayed onto fresh leaves. (b) CID tandem mass spectrum of an isomer mixture of tebuconazole and cletoquine was acquired with a dissociation energy of 20 eV. The concentration ratio of tebuconazole (5 mg/L) and cletoquine (0.25 mg/L) was 20.1 to obtain a relatively uniform signal intensity of fragments. Reproduced from Wu et al. Rapid Trace Detection and Isomer Quantitation of Pesticide Residues via Matrix-Assisted Laser Desorption/Ionization Fourier Transform Ion Cyclotron Resonance Mass Spectrometry. *J. Agric. Food Chem.* **2018**, 66, 3966–3974 (ref 87). Copyright 2018 American Chemical Society.

Figure 5. Zoomed in mass spectra at m/z 400 for a crude oil sample using positive mode APPI FT Orbitrap MS. Some signals are highlighted with calculated elemental compositions and double bond equivalent (DBE) values, separated with a comma. Adapted/modified from Luo, R.; Schrader, W. Development of a Non-Targeted Method to Study Petroleum Polycyclic Aromatic Hydrocarbons in Soil by Ultrahigh Resolution Mass Spectrometry Using Multiple Ionization Methods. *Polycyclic Aromat. Compd.* **2020**, 1–16 (ref 111), with permission from Taylor and Francis.

Figure 6.

Different ionization techniques for polar and nonpolar molecules. Electrospray ionization (ESI) is mainly used for polar compounds, while atmospheric pressure chemical ionization (APCI) and atmospheric pressure photoionization (APPI) are needed for molecules of lower polarity. PAHs: polycyclic aromatic hydrocarbons; OH-PAHs: hydroxylated PAHs; PCBs: polychlorinated biphenyls; OH-PCBs: hydroxylated PCBs; PBDEs: polybrominated biphenyl ethers; OH-PBDEs: hydroxylated PBDEs. Reprinted from *Anal. Chim. Acta* Vol. 1037. Zheng, X.; Dupuis, K. T.; Aly, N. A.; Zhou, Y.; Smith, F. B.; Tang, K.; Smith, R. D.; Baker, E. S. Utilizing ion mobility spectrometry and mass spectrometry for the analysis of polycyclic aromatic hydrocarbons, polychlorinated biphenyls, polybrominated diphenyl

ethers and their metabolites. pp 265–273 (ref 120). Copyright 2018, with permission from Elsevier.

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Inherent Challenges in MS Workflows

Figure 7.

Potential reasons for the inherently incomplete molecular coverage in a generic analytical workflow using mass spectrometric (MS) detection. Adapted/Translated by permission from *Anal. Bioanal. Chem.* Springer. Recent trends in water analysis triggering future monitoring of organic micropollutants. Schmidt, T. C. Vol. 410, pp. 3933–3941 (ref 132) Copyright 2018 under a Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>).

Table 1.EPA Methods for Characterizing Environmental Pollutants^a

	EPA method	year(s)	number of analytes	extraction method	separation and detection	matrix
PFAS	537 (0.1)	2008 (2018)	14 (18)	SPE	LC-MS/MS	drinking water
pesticides	533	2019	25	SPE	LC-MS/MS	drinking water
	1699	2007	~100	SPE	GC-MS	water, soil, etc.
	525 (0.3)	1988 (2012)	125	SPE	GC-MS	drinking water
PAHs	540	2013	12	SPE	LC-MS	drinking water
	610	1979 (1984)	16	LLE	LC-UV/FL	wastewater
	625(.1)	1984 (2016)	84	LLE	GC-MS	wastewater
PPCPs	1694	2007	73	SPE	LC-MS/MS	water, soil, etc.
	542	2016	12	SPE	LC-MS/MS	drinking water

^aHighlighted analytical methods from the US EPA used for the environmental assessment of xenobiotic classes discussed in this work.