Water Analysis: Emerging Contaminants and Current Issues
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CONTENTS

■ BACKGROUND

This biennial review covers developments in water analysis for emerging environmental contaminants over the period of October 2013-October 2015. Analytical Chemistry's policy is to limit reviews to a maximum of 250 significant references and to mainly focus on new trends. Therefore, only a small fraction of the quality research publications are discussed. The previous Water Analysis review (with Thomas Ternes) was published in 2014.¹ This year, Susana Y. Kimura joined me to cover the section on Pharmaceuticals and Hormones. We welcome any comments you have on this Review (richardson.susan@sc.edu).

Numerous abstracts were consulted before choosing the best representative ones to present here. Abstract searches were carried out using Web of Science, and in many cases, full articles were obtained. A table of acronyms is provided (Table 1) as a quick reference to the acronyms of analytical techniques.
and other terms discussed in this Review. Table 2 provides some useful Web sites.

**Major Analysis Trends.** High-resolution-mass spectrometry (HR-MS) continues growing exponentially as a hot trend for use with liquid chromatography (LC) for identifying unknown contaminants, especially environmental transformation products (TPs) and disinfection byproducts (DBPs). For these analyses, Orbitrap, time-of-flight (TOF), quadrupole (Q)-TOF, and sometimes Fourier transform (FT)-ion cyclotron (ICR) mass spectrometers are used. Another growing trend is the combination of TOF-MS screening for large multianalyte analyses followed by target quantification. For example, a study cited in this Review performed an initial screening of 69 pharmaceuticals using ultraperformance liquid chromatography (UPLC)-TOF-MS and followed this analysis

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with a target quantification analysis for the analytes that were detected. This approach streamlines research efforts and minimizes the use of analytical standards.

Nuclear magnetic resonance (NMR) spectroscopy has also grown significantly as a complementary analytical technique to confirm tentative structures proposed by LC−HR-MS and LC−MS/MS. Because of NMR’s lack of sensitivity compared to MS and difficulty in analyzing mixtures, preparative LC coupled to fraction collection is often used to collect enough material to obtain an NMR spectrum. NMR techniques include traditional 1D techniques, such as 1H NMR and 13C NMR, as well as 2D techniques, such as nuclear Overhauser effect spectroscopy (NOESY) and correlation spectroscopy (COSY). Examples in this Review include the identification of TPs and DBPs from pharmaceuticals and the identification of new algal toxin cyanopeptides.

Another growing trend is the use of metabolomics tools. The METLIN database (a free online database of metabolite MS/MS data) and statistics-based profiling tools used in metabolomics are starting to be used more frequently for environmental research to assist with identification of TPs and to discriminate TPs from background signals. An example provided in this Review includes the identification of TPs from the reaction of iopromide (a pharmaceutical medical imaging chemical) with UV−H₂O₂.

Novel analytical applications that may become trends in the future include the use of compound-specific isotope analysis (CSIA) and single-crystal-X-ray analysis. For example, CSIA was used to identify the pharmaceutical diclofenac in environmental samples, based on carbon and nitrogen isotope measurements with gas chromatography (GC)-isotope ratio (IR)-MS, and it was also used to identify transformation pathways. Single-crystal X-ray analysis was used as an additional, more rigorous unknown chemical confirmation technique (along with GC/MS, LC−TOF-MS, and NMR) for structural confirmation of chlorine DBPs from the antidiabetic drug, metformin.

Finally, interesting new sensors are being developed. These include a new molecularly imprinted photoelectrochemical sensor to measure PFOA under visible light irradiation and a new nanochannel-based electrochemical sensor for real-time detection of the pharmaceutical ibuprofen in water.

**Sampling and Extraction Trends.** Solid phase extraction (SPE) with Oasis HLB cartridges continues to be the most popular means of extraction and concentration for emerging contaminants in water. However, new SPE sorbents continue to be developed, with the synthesis of new polymers reported in this Review, which improve the retention of illicit and licit drugs and their metabolites, while removing interfering compounds. Solventless extraction techniques, such as solid phase microextraction (SPME), continue to be used in many applications, with examples of perfluroinated compounds (PFCs) and DBPs cited in this Review. Dispersive liquid−liquid microextraction (DLLME) is another new extraction technique that minimizes solvent and requires very small water samples (∼10 mL) that has been used for emerging contaminants, including benzotriazoles cited in this Review.

Ionic liquids (ILs) also continue to be explored for extraction of emerging contaminants. An example in this Review includes IL-based DLLME coupled with micro-SPE for extracting antidepressant drugs from water.

**Chromatography Trends.** UPLC continues in popularity. Because it uses small diameter particles (∼1.7 μm) in its stationary phase and short columns, which allow higher pressures, narrow LC peaks (5−10 s wide) are obtained, which improves chromatographic separation with dramatically shorter analysis times (10 min or less). Two-dimensional GC (GC × GC) is also increasing in popularity and can now be coupled with HR-MS. GC × GC allows enhanced 2D separations of complex mixtures and enhanced detection of trace contaminants that may have been obscured by coeluting compounds in traditional GC. TOF-MS is often used as the detector for GC × GC because of its rapid acquisition capability. Furthermore, a new instrument will now allow both rapid scanning and high resolution-MS capabilities.

**Emerging Contaminant Trends.** The trend in identifying environmental TPs continues, with increasing studies of TPs produced by photolysis and advanced oxidation processes (AOPs). There has also been a substantial increase in studies of DBPs formed from emerging contaminants when they react with disinfectants (oxidants) used in drinking water and wastewater treatment, including chlorine, chloramines, ozone, and chlorine dioxide. More researchers are proposing complete (and often complex) reaction pathways, with detailed mechanisms deduced by LC−MS/MS and LC−HR-MS and sometimes confirmed by NMR.

Studies combining chemistry with toxicology continue to increase significantly, with the goal typically to determine whether TPs or DBPs formed are toxic. Combined chemistry-toxicology is also sometimes used to determine the forcing agents of toxicity in a complex mixture, as in effects-directed analysis (EDA). Examples in this Review include a study using bioassays with chemical analysis to identify chemicals that produced steroid-like activities in river water; a study that investigated UV−chlorine and UV−chloramine treated drinking water; and another study that investigated DBPs in outdoor, indoor, and baby swimming pools.

Research in the PFC area continues to move beyond perfluoroalkyl sulfonates and perfluorocarboxylic acids like PFOS and PFOA to identify and explore new classes of PFCs. This Review includes new ones, such as polyfluorinated sulfates, chlorine-substituted perfluorocarboxylates, hydro-substituted perfluorocarboxylates, and a new chlorinated polyfluorinated ether sulfonate. New PFCs are being identified in the environment and in PFC products, such as aqueous film forming foams (AFFFs), used for extinguishing fires. New flame retardants also continue to be identified as companies shift from polybrominated diphenyl ethers (PBDEs) and other brominated flame retardants to newer ones, including more chlorinated species. In addition, a DBP was reported from a flame retardant for the first time. Interesting new human exposure studies are examining existing and new flame retardants, including studies of gymnasts who are exposed to flame retardants through contact with flame retardant-containing gymnastics equipment and campers who are exposed through contact with tents treated with flame retardants.

**New Emerging Contaminant.** This year, microplastics are added as a new emerging contaminant. While they were first reported in the environment as early as the 1970s, our global use of plastics has made them a considerable problem, especially in ocean gyres, where water circulation accumulates these plastics into “plastic islands”. Estimates indicate that 5.25 trillion particles weighing >250 000 tons have accumulated in the world’s oceans. Research has shown substantial impacts on wildlife, including seabirds, seals, sea lions, dolphins, whales,
marine reptiles, zooplankton, and many other species. On average, albatross chicks that hatch on Midway Island each year are fed 5 tons of plastic. Microplastics also sorb and concentrate persistent organic pollutants (POPs), including polychlorinated biphenyls (PCBs), polyaromatic hydrocarbons (PAHs), dichlorodiphenyldichloroethylene (DDE), dichlorodiphenyltrichloroethane (DDT), and nonylphenols, which can increase exposure to contaminants when these plastics are ingested.

General Reviews, Large Occurrence Studies, Multicontaminant Methods, and Emerging Areas of Focus

This section includes general reviews relating to water analysis and emerging contaminants (ECs) as well as analytical methods involving the measurement of large numbers of ECs, large occurrence studies involving ECs, and new emerging areas of focus. Reviews that relate to specific areas (e.g., PFCs, pharmaceuticals, DBPs) can be found in those specific sections. Several reviews and special issues of journals have been published over the last 2 years that relate to water analysis, and several focus specifically on emerging contaminants. Because of the high number of these, only a few could be cited here.

Emerging Contaminant Reviews. Pal et al. published an excellent review of ECs of public health significance as water quality indicators in the urban water cycle. Because of stresses on water resources, new supplies from impaired sources, such as wastewater effluents, wastewater-impacted rivers, brackish waters, and stormwater runoff are being used for drinking water. This review discusses these kinds of waters and how drinking water plants are treating these waters, along with sources of ECs, occurrence of ECs in urban source waters, potential health impacts of specific ECs, and research needs. Petrie et al. reviewed ECs in wastewaters and the environment, including a discussion of understudied areas, including spatial and temporal variability of ECs in wastewater and surface waters, partitioning to sludge in wastewater treatment, and fate of ECs in environmental waters and their toxicological impacts. The authors discussed intraday and interday variability of EC concentrations, seasonality, and occasional events, such as increased drug inputs to wastewaters following music festivals, direct disposal during police raids, and pandemics, which involves extreme use of antibiotics and antiviral medications.

Large Occurrence Studies of ECs. A European Union (EU)-wide occurrence study of 156 polar organic chemicals in 90 European WWTPs was published by Loos et al. Target ECs included pharmaceuticals and personal care products, veterinary drugs, PFCs, organophosphate flame retardants, pesticides and their degradates, industrial chemicals like benzotriazole, iodinated X-ray contrast media (ICM), and gadolinium magnetic resonance imaging agents. Methods included those using LC–MS/MS (positive and negative ion) and GC-HR-MS methods. Results showed the detection of 125 chemicals (80% of the target chemicals) in European wastewater effluents at concentrations ranging from low ng/L to mg/L. Among the compounds present at the highest levels were artificial sweeteners, benzotriazoles, flame retardants, and ICM. Acesulfame maximum levels reached 2.5 mg/L. Mean levels for ascorbic acid, sucrose, methylbenzotriazole, 1H-benzotriazole, tris(2-chloroisopropyl)phosphate (TCP), tris(2-butoxyethyl)phosphate (TBEP), and isopropyl were >1 μg/L.

Lopez et al. published an extensive nationwide screening of 411 ECs and other regulated compounds in 494 groundwaters in France. LC–MS/MS and GC-HR-MS methods were used. Approximately 44% of the target chemicals were found in at least one sample. Among the unregulated chemicals found in >10% of the samples were acetaminophen, carbamazepine, PFCs, dioxins and furans, tolyltriazole, bishphenol A, triazine transformation products, and caffeine. Concentrations exceeding toxicity thresholds included tolyltriazole, bishphenol A, and triazine transformation products. One interesting discovery was the presence of pesticides that were no longer on the market.

Kong et al. published an extensive study of 1300 micro-pollutants in surface waters from northern China. Results showed the presence of 227 chemicals, with bis(2-ethylhexyl)-phthalate, siduron, lidocaine, antipyrine, caffeine, cotinine, phenanthrene, metformin, diethyl phthalate, quinoxaline-2-carboxylic acid, 2-(methylthio)-benzothiazole, and anthraquione found the most often and at the highest levels. Three highly polluted sites were found to contribute significantly to the chemical load in these waters, with inputs from industrial wastewater, domestic discharges, tire production, and atmospheric deposition.

Large Multianalyte Methods. More than 400 ECs were measured in a new SPE-LC-TOF-MS method developed to measure pharmaceuticals, illicit drugs and their metabolites, pesticides and their degradates, nitrosamines, flame retardants, plasticizers, and PFCs in surface water and wastewaters. A large proportion of the analytes could be detected below 10 ng/L, with recoveries between 50 and 130%. Bletsou et al. developed a target and nontarget LC–MS workflow procedure for identifying TPs from ECs in environmental waters. HR-MS was key for this workflow, due to the high resolving power and mass accuracy in MS and MS/MS modes and sophisticated software available.

New Emerging Area of Focus. By far, the new emerging area of focus the last 2 years has been hydraulic fracturing (HF), with many studies focusing on potential risks to the environment. HF (also called hydrofracking) involves the injection of high pressure water, surfactants, sand, and chemicals (including biocides) deep into the ground to fracture shales and extract natural gas into horizontally drilled wells. Most shale gas development is occurring in the U.S., with >7000 shale gas wells drilled in Pennsylvania alone, but HF is also expanding to Canada and will soon be launched on a global scale, with significant reservoirs in South America, northern and southern Africa, Europe, China, and Australia. Vengosh et al. published an excellent review of the risks to water resources from unconventional shale gas development and hydraulic fracturing in the U.S. The authors identified four potential risks for environmental waters, including contamination of shallow aquifers with fugitive hydrocarbon gases (e.g., methane, ethane, and propane), contamination of surface water and shallow groundwater from spills, leaks, and/or disposal of inadequately treated shale gas wastewater, accumulation of toxic and radioactive elements in soil or stream sediments near disposal of spill sites, and overextraction of water resources for high-volume HF that could cause water shortages.

Biocides in HF fluids were the focus of another review by Kahrilas et al., who discussed their usage, mobility, degradation, and toxicity. Biocides currently in use include glutaraldehyde and quaternary ammonium compounds. HF activities use biocides to prevent biofilm formation, which can inhibit gas extraction. Degradation pathways for biocides include hydrolysis, photodegradation, and biodegradation. Uncharged species
were found to degrade and mobilize in HF waters, whereas charged species sorbed to solids and were less bioavailable. Harkness et al. investigated iodide, bromide, and ammonium ions in HF and oil/gas wastewaters. Brines are colocated with natural gas in many shales, and they can be released in produced waters, which can impact waters downstream and drinking waters that use these sources. The authors investigated 44 produced waters from conventional oil and gas wells in the Appalachian Basin, including HF flowback and produced waters, effluents of treated oil and gas wastewater discharged to surface waters, surface waters collected downstream from disposal sites, and fluids from an accidental spill. In these waters, high levels of chloride, bromide, and iodide (up to 56 mg/L) and ammonium (up to 420 mg/L) were found. A follow-on study by Parker et al. investigated the enhanced formation of DBPs (iodo-trihalomethanes (THMs), bromohaloacetonitriles, and nitrosamines) from shale gas wastewater-impacted drinking water supplies. Levels as low as 0.01% of the HF wastewater was found to alter the speciation of DBPs formed, such that bromo- and iodo-DBPs dominated. This is a concern because brominated and iodinated DBPs are much more toxic than chlorinated ones. Levels of 0.1% of HF wastewater increased the formation of N-nitrosodimethylamine (NDMA) during chloramination, particularly with high iodide present (54 ppm).

Hladik et al. also investigated the formation of DBPs (THMs, iodo-THMs, halonitromethanes, haloacetonitriles, 2 halodehydes, and 1 haloopropanone) from oil and gas wastewaters. Waters were collected downstream of a WWTP in Pennsylvania that treats oil and gas as well as other locations along this river. WWTPs accepting produced waters showed elevated levels of DBPs, especially brominated and iodinated THMs.

Finally, Loh et al. developed a clever method for rapidly measuring bromide in HF wastewater. This method involved a microfluidic paper-based analytical device called a μPAD, which allows the colorimetric detection of bromide in water using a smartphone. These devices were cheap to make, are intended as a one-time disposable use, and could detect 3.2 ppm of bromide (which is a relevant level in the HF wastewaters).

## NEW REGULATIONS/REGULATORY METHODS
Recent U.S. Rules and Regulations are listed in Table 3. These include the new draft Contaminant Candidate List (CCL)-4.

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<th>Table 3. Recent U.S. Rules/Regulations</th>
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<tr>
<td>Stage 2 D/DBP Rule</td>
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<tr>
<td>Draft Contaminant Candidate List (CCL)-4</td>
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<tr>
<td>Proposed Unregulated Contaminant Monitoring Rule-4 (UCMR-4)</td>
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<td>UCMR national occurrence data</td>
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and the third Unregulated Contaminant Monitoring Rule (UCMR-3), for which national data for priority drinking water contaminants is available.

The Fourth Unregulated Contaminant Monitoring Rule (UCMR-4). As with previous UCMRs, the upcoming UCMR-4 will require drinking water utilities to monitor for a small number of contaminants and will provide national occurrence data for priority unregulated contaminants for future regulatory consideration. This Rule supports the Safe Drinking Water Act and Amendments, which requires every 5 years, a list of no more than 30 unregulated contaminants to be monitored nationally. The next UCMR (UCMR-4) was just proposed by the U.S. Environmental Protection Agency (EPA) in November 2015 (www2.epa.gov/dwucmr). The current contaminants proposed include triclosan, 14 pesticides, 4 haloacetic acids (HAAs), 4 commercial chemicals, 2 aldehydes (formaldehyde and acetaldehyde), 2 algal toxins, 2 metals (germanium and manganese), nitrate and nitrite, butylated hydroxyanisole (BHA), and Legionella bacteria. The UCMR-4 is expected to be finalized in January 2016, and monitoring will occur during 2016–2018. National occurrence data from the previous UCMR-3 collected from 2013 to 2015 is available at http://www2.epa.gov/dwucmr/occurrence-data-unregulated-contaminant-monitoring-rule#3.

The New Draft Contaminant Candidate List-4 (CCL-4). In February 2015, the U.S. EPA published the draft CCL-4, the new drinking water priority contaminant list for regulatory decision making and information collection. The contaminants listed either occur or are anticipated to occur in drinking water systems and will be considered for potential regulation. The draft CCL-4 contains 100 chemicals or chemical groups and 12 microbial contaminants (Table 4), including chemicals used in commerce, pesticides, biological toxins, DBPs, pharmaceuticals, and waterborne pathogens. Many of the chemicals and all of the pathogens on this list are the same as what was previously on the CCL-3. The U.S. EPA made a few changes to the list based on available occurrence and health effects data, which included the addition of two nominated contaminants (manganese and nonylphenol), removal of perchlorate and strontium (which are scheduled for regulation), and removal of four contaminants that the U.S. EPA decided not to regulate (1,3-dinitrobenzene, dimethoate, terbufos, and terbufos sulfone). Additional information on the draft CCL-4 and the process used to create this new list can be found at http://www2.epa.gov/ccl/draft-contaminant-candidate-list-4-ccl-4.

As with the previous draft CCL-3, it is possible that the final CCL-4 may differ substantially from what is originally proposed, due to feedback from stakeholders and the general public. In particular, when the current CCL-3 was finalized, pharmaceuticals, hormones, DBPs, and perfluorinated compounds (PFOA and PFOS) were added to what was originally proposed in the draft CCL-3. The new CCL-4 is scheduled to be finalized in the fall of 2016.

New Regulatory Methods for Drinking Water. Six new drinking water methods were developed by the U.S. EPA (Table 5): Method 530 (semivolatile organic chemicals), Method 541 (small polar organic compounds), Method 542 (pharmaceuticals and personal care products), Method 543 (selected organic chemicals), Method 544 (microcystins and nodularins), and Method 545 (cylindrospermopsin and anatoxin a). These methods are mostly directed toward the measurement of CCL, UCMR, or regulated chemicals in drinking water. The U.S. EPA’s National Exposure Research Laboratory and the U.S. EPA’s Office of Ground Water and Drinking Water created these new methods and have also produced many other excellent drinking water methods, which can be found at http://www2.epa.gov/water-research/epa-drinking-water-research-methods.

EPA Method 530: Semivolatile Organic Chemicals. In January 2015, a new EPA method was created for measuring
### Table 4. Draft Contaminant Candidate List-4 (CCL-4)

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<td>Perfluoroctanoanic acid (PFOA)</td>
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<tr>
<td>Permethrin</td>
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<tr>
<td>Profenofos</td>
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<td>Quinoline</td>
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<tr>
<td>RDX (Hexahydro-1,3,5-trinitro-1,3,5-triazine)</td>
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<tr>
<td>sec-Butylbenzene</td>
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<td>Tebuconazole</td>
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<td>Tebufenozide</td>
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<td>Tellurium</td>
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<td>Thiadicarb</td>
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<td>Thiophanate-methyl</td>
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<td>Toluene diisocyanate</td>
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<td>Tribufos</td>
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<td>Triethylamine</td>
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<td>Triphenyltin hydroxide (TPTH)</td>
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<td>1,1,1,2-Tetrachloroethane</td>
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<tr>
<td>1,2,3-Trichloropropane</td>
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<tr>
<td>1,3-Butadiene</td>
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**Microbial Contaminants**

- Adenovirus
- Caliciviruses
- Campylobacter jejuni
- Enterovirus
- Escherichia coli (0157)
- Helicobacter pylori
- Hepatitis A virus
- Legionella pneumophila
- Mycobacterium avium
- Naegleria fowleri
- Salmonella enterica
- Shigella sonnei

**Chemical Contaminants**

- 1,1-Dichloroethane
- 1,1,1,2-Tetrachloroethane
- 1,2,3-Trichloropropane
- 1,3-Butadiene
- 1,4-Dioxane
- 17α-estradiol
- 1-Butanol
- 2-Methoxyethanol
- 2-Propen-1-ol
- 3-Hydroxyacarbofuran
- 4,4’-Methylenedianiline
- Acephate
- Acetaldehyde
- Acetamide
- Acetochlor
- Acetochlor ethanesulfonic acid (ESA)
- Acetochlor oxanic acid (OA)
- Acrolein
- Alachlor ethanesulfonic acid (ESA)
- Alachlor oxanic acid (OA)
- alpha-Hexachlorocyclohexane
- Aniline
- Bensulide
- Benzyl chloride
- Butylated hydroxyanisole
- Captan
- Chlorate
- Chloromethane (Methyl chloride)
- Clethodim
- Cobalt
- Cumene hydroperoxide
- Cyanotoxins
- Dicrotophos
- Dimethipin
- Disulfoton
- Diuron
- Equilenin
- Equilin
- Erythromycin
- Estradiol (17-beta estradiol)
- Estriol
- Estrone
- Ethinyl estradiol (17-alpha ethinyl estradiol)
- Ethoprop
- Ethylene glycol
- Ethylene oxide
- Ethylene thiourea
- Fenamiphos
- Formaldehyde
- Germanium
- HCFC-22
- Halon 1011 (bromochloromethane)
- Hexane
- Hydrazine
- Manganese
- Mestranol
- Methamidophos
- Methanol
- Methyl bromide (bromomethane)
Table 5. New Regulatory Methods

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<tr>
<td>EPA Method 530</td>
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<td>small polar organic compounds</td>
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<tr>
<td>EPA Method 542</td>
<td>pharmaceuticals and personal care products</td>
<td><a href="http://www2.epa.gov/water-research/epa-drinking-water-research-methods">http://www2.epa.gov/water-research/epa-drinking-water-research-methods</a></td>
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<tr>
<td>EPA Method 543</td>
<td>selected organic chemicals</td>
<td>a</td>
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<tr>
<td>EPA Method 544</td>
<td>microcystins and nodularin</td>
<td><a href="http://www2.epa.gov/water-research/epa-drinking-water-research-methods">http://www2.epa.gov/water-research/epa-drinking-water-research-methods</a></td>
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<td>EPA Method 545</td>
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<td>water.epa.gov/scitech/drinkingwater/labcert/upload/epa815r15009.pdf</td>
</tr>
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</table>

“Not yet posted on the Web (as of November 2015).

four semivolatile organic chemicals in drinking water: EPA Method 530, Determination of Select Semivolatile Organic Chemicals in Drinking Water by Solid Phase Extraction and Gas Chromatography/Mass Spectrometry (GC/MS) (http://www2.epa.gov/water-research/epa-drinking-water-research-methods). This method is for quantifying o-tolididine, quinolone, butylated hydroxyanisole (BHA), and dimethipin, which are on the CCL-3 and draft CCL-4 and may be potentially used in future UCMRs. Method detection limits range from 7 to 44 ng/L.

EPA Method 541: Small Polar Organic Compounds. In November 2015, a new EPA method was created for measuring four small polar organic chemicals in drinking water: EPA Method 541, Determination of 1-Butanol, 1,4-Dioxane, 2-Methoxyethanol, and 2-Propen-1-ol in Drinking Water by Solid Phase Extraction and Gas Chromatography/Mass Spectrometry. These analytes are being considered for inclusion in the new UCMR-4, and 1,4-dioxane is currently on the UCMR-3 (and currently being measured using EPA Method 522) and on the CCL-3. Method detection limits range from 0.074 to 0.44 μg/L.

EPA Method 542: Pharmaceuticals and Personal Care Products. In November 2015, a new EPA method was created for measuring 12 pharmaceuticals and personal care products (PPCPs) in drinking water: EPA Method 542, Determination of Pharmaceuticals and Personal Care Products in Drinking Water by Solid Phase Extraction and Liquid Chromatography/Electrospray Ionization Tandem Mass Spectrometry (LC/ESI-MS/MS). This method is for quantifying carbamazepine, diazepam, diclofenac, enalapril, erythromycin, fluoxetine, gemfibrozil, naproxen, phenytoin, sulfamethoxazole, triclosan, and trimethoprim, which are currently being considered for the UCMR-4. Erythromycin is also currently on the draft CCL-4 and was on the previous CCL-3.

EPA Method 543: Selected Organic Chemicals. In March 2015, a new EPA method was created for measuring 12 selected organic chemicals in drinking water: EPA Method 543, Determination of Selected Organic Chemicals in Drinking Water by Online Solid Phase Extraction-Liquid Chromatography/Tandem Mass Spectrometry (Online SPE-LC/MS/MS) (http://www2.epa.gov/water-research/epa-drinking-water-research-methods). This method is for seven pesticides and updates EPA Method 540, which uses offline SPE. Compounds included are 3-hydroxy carbocofuran, bensulide, fenamiphos, fenamiphos sulfone, fenamiphos sulfoxide, tebuconazole, and tebufenozide. Method detection limits range from 0.13 to 0.99 ng/L.

EPA Method 544: Microcystins and Nodularin. In February 2015, a new EPA method was created for measuring the algal toxins, microcystins and nodularin, in drinking water: EPA Method 544, Determination of Microcystins and Nodularin in Drinking Water by Solid Phase Extraction and Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS) (http://www2.epa.gov/water-research/epa-drinking-water-research-methods). Included in this method are six microcystins, microcystin (MC)-YR, MC-RR, MC-LR, MC-LA, MC-LY, and MC-LF, and one nodularin, nodularin-R. Method detection limits range from 1.2 to 4.6 ng/L. This method is used to support the CCL-3 and the draft CCL-4 (microcystins are currently listed), and future efforts that may involve nodularin, another algal toxin commonly found in surface waters.

EPA Method 545: Cylindrospermospin and Anatoxin α. In April 2015, a new EPA method was created for measuring the algal toxins, cylindrospermospin and anatoxin α, in drinking water: EPA Method 545, Determination of Cylindrospermospin and Anatoxin-α in Drinking Water by Liquid Chromatography/Electrospray Ionization Tandem Mass Spectrometry (LC/ESI-MS/MS) (http://water.epa.gov/scitech/drinkingwater/labcert/upload/epa815r15009.pdf). This method does not require extraction or preconcentration, only the direct injection of the water sample (with internal standard) onto an LC column for LC−MS/MS analysis using multiple reaction monitoring (MRM). Minimum reporting levels were 0.063 and 0.018 μg/L for cylindrospermospin and anatoxin-α, respectively. This method is used to support the CCL-3 and the draft CCL-4.

### SUCRALOSE AND OTHER ARTIFICIAL SWEETENERS

Artificial sweeteners are widely used in diet soft drinks and foods, and many survive wastewater treatment and are present in environmental waters. These include sucralose, acesulfame, saccharin, cyclamate, aspartame, neotame, steviol, glycyr rhizic acid, and neohesperidine dihydrochalcone. Because of their stability in the environment, sucralose and acesulfame are often above 1 μg/L in surface waters, which is much higher than most emerging contaminants. While early ecotoxicology studies suggest low bioaccumulation potential and minimal acute/chronic toxicity to aquatic organisms, new studies indicate behavioral effects for *Daphnia magna* and gammarids, which may have ecological consequences.

While artificial sweeteners are generally recognized as good tracers of anthropogenic contamination, Engelhardt et al. discovered limitations for the use of acesulfame to trace surface waters...
water–groundwater interactions. In particular, acesulfame missed wastewater-impacted surface waters in the hyporheic zone (region of stream bed that contains at least 10% streamwater and less than 90% groundwater) under stream-gaining conditions (inflow of groundwater through the streambed), while under stream-losing conditions (outflow through the streambed), acesulfame led to overestimation of surface water volume in the riparian zone. This study was initiated to examine the suitability of acesulfame as a tracer of wastewater-impacted surface water fluxes from streams into the hyporheic and riparian zones over long periods and compared the use of acesulfame to traditional stable isotopes (δ18O or δ2H).

In a particularly interesting study, Roy et al. evaluated the use of artificial sweeteners (saccharin, acesulfame, and cyclamate) as tracers for municipal landfill leachates. IC-MS/MS (negative ion) was used for their detection, which allowed low ng/L detection limits. Two MRM transitions were monitored for each analyte. The artificial sweeteners were detected in leachate or leachate-impacted groundwaters at levels similar to untreated wastewater in 14 of the 15 municipal landfill sites sampled, including sites that were closed for more than 50 years. In old landfills (pre-1990), saccharin was the dominant sweetener; in newer landfills, saccharin and acesulfame were dominant; cyclamate was detected less frequently. Using these sweeteners, the impact of landfill leachate on a groundwater plume discharged to a stream was investigated. Results indicate that artificial sweeteners can be used for current and legacy landfill contamination, and relative abundances can be used to distinguish landfill and wastewater sources.

A number of new methods have been developed for artificial sweeteners. Wu et al. created a new direct, large-volume injection UPLC−MS/MS method for measuring sucralse and acesulfame in well water. Acesulfame is inherently sensitive by negative-ion-ESI-MS due to its anionic structure. The use of formic acid to form (M + HCOO)− ions of sucralose increased its sensitivity, and large-volume injection further increased the sensitivity for both, allowing 0.2 and 5 ng/L method detection limits, respectively, for acesulfame and sucralose. These are the lowest detection limits reported to-date for either sweetener. Using this new method, acesulfame was detected in 24 wells in Alberta, Canada, at levels ranging from 1 to 1534 ng/L; sucralose was detected less often, at 65–541 ng/L. Results reveal the potential for groundwater contamination by wastewater and indicate that acesulfame may be a better tracer than sucralose, due to its greater sensitivity and lower detection limits.

Ferrer et al. evaluated LC−QTOF-MS and LC−triple quadrupole-MS/MS for detecting sucralose in environmental waters. Positive and negative ion modes were compared. Because sucralose contains three chlorine atoms, TOF-MS was advantageous in providing accurate mass information for the chlorine isotopes, providing extra selectivity. Positive ion mode was better for both techniques. LC−triple quadrupole-MS/MS provided 15 ng/L detection limits, compared to 400 ng/L with LC−TOF-MS.

Arbelaez et al. created a new method for eight sweeteners, saccharin, cyclamate, aspartame, acesulfame, neohesperidin dihydrochalcone, sucralose, stevioside, and glycyrrhizic acid, in river water and wastewater. This method used SPE and LC−MS/MS with Oasis HLB cartridges and was able to achieve method detection limits of 1−40 ng/L (river water) and 10−50 ng/L (wastewater influent and effluent). This is one of the first methods created for stevioside, a popular natural sweetener. This method was subsequently used to measure these sweeteners in waters from Catalonia, Spain, where acesulfame and sucralose were found at the highest levels in rivers (1.62 and 3.57 μg/L, respectively).

Several interesting occurrence studies have been published, including one by Spoelstra et al., who measured three artificial sweeteners, sucralose, cyclamate, and saccharin, at 23 sites along the Grand River in Ontario, Canada, which is impacted by agricultural and urban contamination. Tap water was also sampled. Levels included the highest reported concentrations in the world for sucralose (21 μg/L), saccharin (7.2 μg/L), and cyclamate (0.88 μg/L) in surface waters. Acesulfame was found to persist over a distance of 300 km and behaved conservatively in the river.

Qi et al. investigated the occurrence, seasonal variation, and annual loads of 117 organic micropollutants in the Yangtze River in China. Using sucralose as a tracer for domestic wastewater, a daily disposal of 47 million m³ of sewage was estimated, corresponding to 1.8% of its average hydraulic load. Tran et al. published the first quantitative data for artificial sweeteners in Southeast Asia. Acesulfame, cyclamate, saccharin, and sucralose were ubiquitous in wastewaters from Singapore, and acesulfame, cyclamate, and saccharin were present in most groundwater samples. Surface waters from Finland were surveyed by Perkola and Sainio, who reported measurements of acesulfame, sucralose, saccharin, and cyclamate in boreal lakes and rivers.

Several interesting fate studies have also been published the last 2 years. For example, Subedi and Kannah investigated the fate of artificial sweeteners (sucralose, saccharin, aspartame, and acesulfame) in WWTPs in New York State. This was the first study to investigate their mass loadings, removal efficiencies, and environmental emission based on wastewater influent, primary effluent, suspended particulate matter, and sludge. Significant sorption was found for many, with the following rank order: sorbed onto suspended particulate matter: aspartame (50.4%) > acesulfame (10.9%) > saccharin and sucralose (0.8%).

Sang et al. evaluated the distribution, photodegradation, and toxicity of acesulfame, cyclamate, saccharin, and sucralose. Geographical, seasonal, and hydrological interactions were measured in coastal areas at the boundary of estuarine and marine waters from Hong Kong. Acesulfame and sucralose resisted microbial degradation in these coastal waters and persisted in regions linked to polluted estuarine waters and local wastewater. UV photolysis studies revealed the formation of new transformation products (TPs) from these two sweeteners, one of which was 6X more persistent than the parent compound (acesulfame). Acute toxicity (as measured in the Microtox test) increased by factors of 575 and 17.1 for acesulfame and sucralose, respectively. TiO2/UV degradation was also investigated, which produced 4 TPs for sucralose and 12 TPs for acesulfame. In a later study, Scheurer et al. investigated the UV photolysis of acesulfame, identifying a hydroxylated acesulfame and iso-acesulfame as the major TPs, using HR-MS.
NANOMATERIALS

Nanomaterial (NM) research continues to expand, with numerous reviews and papers on new methods, environmental occurrence, environmental fate, and toxicity. As before, most nanomaterial research focuses on new uses and new products with unique properties, but there is also significant research on impacts to the environment, due to their widespread use in commercial products. Nanosilver (nAg) is the dominant NM currently in use and is the most studied the last 2 years. More than 400 tons of Ag nanoparticles (NPs) are produced every year, with 30% being used in medical applications, due to their antibacterial properties. For example, they are used in medical bandages. Ag NPs are also used in some gym socks and t-shirts as antimicrobials to prevent musty odors. Other metal NMs are also popular, such as nano-TiO$_2$, CeO$_2$, ZnO, Au, and Fe(0), as well as carbon-based NMs, such as fullerenes, nanotubes, and graphene.

Analytical techniques for their measurement include size-based techniques, such as transmission electron microscopy (TEM), scanning electron microscopy (SEM), atomic force microscopy (AFM), flow field-flow fractionation (FIFFF), dynamic light scattering (DLS), quartz crystal microbalance, energy dispersive X-ray spectroscopy (EDS), X-ray absorption spectroscopy, X-ray photoelectron spectroscopy, static light scattering (SLS), particle electrophoresis, LC–UV, Raman spectroscopy, and NMR spectroscopy. Mass spectrometry techniques used for measuring nanomaterials include inductively coupled plasma (ICP)MS and single particle (sp)-ICPMS (for metal-containing nanomaterials) and ESI- and atmospheric pressure ionization (APPI)-MS and matrix-assisted laser desorption ionization (MALDI)-MS. Examples cited include (1) the use of NMs as molecular wires to enhance proton transfer or to catalyze chemical reactions; (2) their use as optical probes for novel detection systems; (3) their use as stationary phases or sorbents (due to their large surface areas and specific affinity for contaminants); and (4) the use of magnetic NMs for solid-phase extraction, which saves time in sample preparation.

Kunhir Krishnan et al. reviewed the sources, distribution, environmental fate, and ecological effects of NMs in wastewater streams. This review included discussions of ENM applications, the major types of ENMs used today, their origin and distribution in wastewater, removal in wastewater treatment, and uptake in biota. Recommendations were made for future research efforts, including identification of the sources of ENMs in wastewater, development of analytical methods to quantify and identify them in wastewater, monitoring their transport and impact on ecosystems and human health, characterization of exposure routes of ENMs, development of guidelines for the allowable concentrations of ENMs in discharged water and biosolids, long-term persistence of ENMs in the environment, development of models to predict their fate and impact in aquatic and terrestrial environments, screening of biological organisms to test for bioaccumulation and reprocessing of NMs, and temporal fate of ENMs in products.

Modeling and analytical measurements of ENMs in surface waters, WWTP effluents, biosolids, sediments, soil, and air was reviewed by Gottschalk et al., who focused on 6 ENMs: nano-TiO$_2$, ZnO, Ag, CeO$_2$, fullerenes, and carbon nanotubes. Use of models to predict their concentrations, along with limitations of these models, was also discussed. While models have only been validated to a minor extent, the authors believe they provide useful data for environmental risk assessment of ENMs.

While most toxicity and fate studies are carried out in controlled laboratory environments, Colman et al. published a very interesting study on the impact of silver NPs on ecosystems, using wetland mesocosms with aquatic plants. In this study, two types of nAg were investigated (12 and 49 nm) and compared to ionic silver (Ag$^+$) in 19 wetland mesocosms. All 3 silver treatments were toxic to the aquatic plants over the 30 days of exposure, which led to a significant release of dissolved organic carbon and chloride. Dissolved methane levels also increased 40× relative to controls, and despite widely different toxicities observed in controlled laboratory tests, toxicities in these outdoor mesocosms were very similar.

Several new interesting methods have been published the last 2 years for NMs. For example, Lee et al. created a new method using spICPMS to estimate the size detection limit observed minimum detectable sizes are consistent with the calculated as fertilizer in agriculture, allowing re-entry into the environment.

Liu et al. published an interesting alternative review by reporting on the use of NMs for analysis and monitoring of other emerging chemical pollutants. As mentioned earlier, most work with NMs involves new uses and new products, and some of these new uses involve the creation of new analytical methods for other emerging contaminants. The NMs discussed in this review included the use of carbon nanotubes, graphene, metal NPs, magnetic NPs, and quantum dots for sample preparation, extraction, electrochemical sensing, fluorescence detection, colorimetric detection, surface-enhanced Raman spectroscopy, and matrix-assisted laser desorption ionization (MALDI)-MS. Examples cited include (1) the use of NMs as molecular wires to enhance proton transfer or to catalyze chemical reactions; (2) their use as optical probes for novel detection systems; (3) their use as stationary phases or sorbents (due to their large surface areas and specific affinity for contaminants); and (4) the use of magnetic NMs for solid-phase extraction, which saves time in sample preparation.
(estimated) $D_{\text{min}}$ values, and they demonstrated that spICPMS can detect at <20 nm diameter for some element-based NPs, including Rh, Ce, Pb, Pt, Ag, and Au. However, for others, such as TiO$_2$, detection of particles <90 nm was not possible. Bourgeault et al. created another method by synthesizing TiO$_2$ NPs labeled with the stable isotope, Ti-47. The use of this stable isotope with ICPMS enabled the detection of TiO$_2$ NP bioaccumulation in zebra mussels (7–120 μg/L of $^{47}$TiO$_2$ NPs), despite the high natural Ti background.

A new rapid LC–ICPMS method created by Zhou et al. enabled the separation and detection of Ag(I) and Ag-containing NPs in antibacterial products and environmental waters, with only 5 min required for separation. This method allowed the separation of a range of 1100 nm by using a 500 Å porous size amino column. Mwilu et al. developed a new method using magnetic NPs coated with dopamine or glutathione to separate and preconcentrate Ag NPs followed by ICPMS detection. These magnetic particles could selectively capture Ag NPs in a mixture containing both NPs and ionic silver. Recoveries of >97% were achieved for tap water, surface water, and seawater. Finally, Khaskar et al. developed a new method to study the chemical transformation of Ag NPs along the water–sediment continuum. For this method, functionalized Ag NPs were immobilized onto plasma-polymerized solid substrates to form “nano in situ deployment devices”. This allowed the retrieval and analysis of Ag NPs after exposure to freshwater-sediment and saltwater-sediment environments. Chemical transformation was investigated using synchrotron radiation X-ray absorption spectroscopy. Results showed the effect of redox conditions on the chemical transformation of Ag NPs in both freshwater and saltwater sediments.

Several interesting fate studies have been published the last 2 years on NMs. Mitrano et al. used spICPMS to track the dissolution of Ag NPs at environmentally relevant concentrations in laboratory, natural, and processed waters. Ag NPs (60 and 100 nm) coated with citrate, tannic acid, or polyvinylpyrrolidone were examined, and results showed the importance of chloride, sulfate, and dissolved organic carbon (DOC) on their dissolution, with higher concentrations resulting in negligible Ag NP dissolution over 24 h. The benefits of using spICPMS for this work included the direct measurement of NP size, even in the presence of known sinks for Ag$^{+}$.

Tugulea et al. published an interesting study of nAg in drinking water and source waters. Results showed that DOC stabilizes Ag NPs, while the high ionic strength of groundwater favors their agglomeration and precipitation. Also, interestingly, while nAg was not stable in Ottawa River water, it survived for several days after being added to water treated with chlorine or chloramines. The DBPs formed with and without the addition of nAg differed significantly, with reduced formation of some brominated DBPs and a small increase in cyanogen chloride. The reduced formation of brominated DBPs was explained by the decrease in available bromide due to the presence of Ag$^{+}$ ions.

Marine snow, along with natural seawater, artificial seawater, and Milli-Q water, was the focus of an interesting study of TiO$_2$ NPs by Doyle et al. Dynamic light scattering, zeta potential, field-emission scanning electron microscopy, and ICPMS were used to investigate the particles over time. All three types of TiO$_2$ NPs studied (rutile, anatase) were found to readily incorporate into the marine snow, with incorporation efficiencies increasing over 72–120 h, reaching a maximum of 95% after 168 h. This study has important implications for exposure to benthic organisms in marine environments.

Sunscreens were the focus of another study by Sanchez-Quiles who found that TiO$_2$ and ZnO NPs used as UV filters could produce significant amounts of hydrogen peroxide when exposed to solar radiation. The H$_2$O$_2$ produced could, in turn, cause stress for marine phytoplankton. Results showed that 1 g of commercial sunscreen product could produce hydrogen peroxide at rates up to 463 nM/h, directly affecting the growth of phytoplankton. It was estimated that 4 kg of TiO$_2$ NPs are released during the summer on a given day at a Mediterranean beach, producing up to 270 nM H$_2$O$_2$ per day. These results indicate that TiO$_2$ NPs are a major oxidizing agent entering coastal waters, with potential for adverse ecological effects.

Mixtures of NPs are now being recognized as being important for environmental behavior and effects. For example, Tong et al. examined the effects of mixtures of NPs by investigating chemical interactions between nZnO and nTiO$_2$ in water. Results showed that the combined effects of ZnO dissolution and Zn adsorption to TiO$_2$ NPs controlled the concentration of dissolved Zn. X-ray absorption spectroscopy revealed that Zn partitions between nZnO and Zn$^{2+}$ adsorbed onto TiO$_2$ NPs. As a result, it is clear that mixtures of NPs can be important, and fate and toxicity are likely to be influenced by the presence of other stable ENMs. Another study by Tong et al. investigated the combined toxicity of nZnO and nTiO$_2$ under solar radiation conditions. Results showed that nTiO$_2$ and nZnO can damage bacterial cell membranes under simulated solar radiation but the phototoxicity was not additive. The presence of nZnO (1 mg/L) eliminated the damaging effect of nTiO$_2$ at 10 mg/L. Therefore, NP interactions and surface complexion reactions can alter the original toxicity of individual NPs.

Brunetti et al. used X-ray absorption spectroscopy to investigate the fate of Zn and Ag NPs during their transit through sewer systems on their way to wastewater treatment. Results showed that both ZnO and Ag NPs underwent significant transformation during their transit through the sewer network, with reduced sulfur playing a major role, converting ZnO to ZnS; Ag sorbed to cysteine and histidine. In addition, both Ag$^{+}$ and Ag NPs formed secondary Ag–S NPs, and Ag–cysteine was found to be a major species in biofilms. Finally, Furtado et al. used filtration with ICPMS to investigate the environmental fate of polyvinylpyrrolidone and citrate-coated Ag NPs in boreal lake ecosystems. Sediments and periphyton on the mesocosm walls were found to be important sinks for Ag, and results indicated that Ag NPs were relatively stable in this boreal lake environment.

**PFOA, PFOS, AND OTHER PERFLUORINATED COMPOUNDS**

Perfluorinated compounds (PFCs) are unusual chemically, being both hydrophobic (repel water) and lipophobic (repel lipids/grease), and containing one of the strongest chemical bonds (C–F) known. PFCs are used to make stain, grease, and water repellent coatings that are widely applied to fabrics, carpets, and paper, including microwave popcorn bags. They are also used in the manufacture of paints, adhesives, waxes, polishes, metals, electronics, film forming foams (for extinguishing fires), and caulks. PFCs are highly stable in the environment and in biological samples and have unique profiles of distribution in the body. While two 8-carbon PFCs have received the most attention, perfluorooctanesulfonate (PFOS)
and perfluorooctanoic acid (PFOA), many other PFCs are found in the environment, including new 4-carbon PFCs (e.g., perfluorobutanoic acid (PFBA) and perfluorobutanesulfonate (PFBS)) that are in replacements for PFOS and PFOA. New classes of PFCs continue to be discovered: perfluoroalkyl-sulfonamides, -ester phosphates, -phosphonates, -ethoxylates, -acylates, -amino acids, -sulfonamide phosphates, -thioacids, and thioamidosulfonates, as well as four new classes just reported the last 2 years (polysulfonated sulfates, chlorinated-substituted perfluoro-carboxylates, hydro-substituted perfluorocarboxylates, and a chlorinated polysulfonated ether sulfate), whose discoveries are reported below.

Health concerns for PFCs include cancer, reproductive and developmental effects, bioaccumulation, immunotoxicity, ulcerative colitis, and thyroid disease. Research questions include understanding the sources of PFOA and other PFCs, their environmental fate and transport, pathways for human exposure and uptake, and potential health effects. The widespread occurrence of PFOA and other fluoro-acids is believed to be due to their direct atmospheric and oceanic transport and also the transport of their more volatile precursors, fluorinated telomer alcohols (FTOHs), which can transform into PFOA and other fluoro-acids via metabolism and biodegradation. The National Health and Nutrition Examination Survey (NHANES), conducted by the Centers for Disease Control and Prevention (CDC), has information on levels of PFOA, PFOS, and other PFCs in blood from the U.S. population (www.cdc.gov/nchs/nhanes.htm). This survey is carried out on a continual basis, with blood and urine collected from thousands of participants. The most recent report (September 2013) can be found at http://www.cdc.gov/exposurerating. The National Toxicology Program is also studying PFOA and several other perfluorocarboxylic acids (PFCAs) and perfluorosulfonates (PFSAs) to better understand their toxicity and persistence in human blood (http://www.niehs.nih.gov/health/materials/perflourinated_chemicals_508.pdf). PFCs have unusual mechanisms for bioaccumulation in the body by binding to serum proteins and accumulating in blood, rather than fatty tissues.

PFOA has been phased out of use in North America since 2002, and environmental levels are decreasing. However, it is still being made in China. PFOA will be phased out completely in the U.S. in 2015. The U.S. EPA has listed PFOA and PFOS on the draft CCL-4 (http://www2.epa.gov/ccl/draft-contaminant-candidate-list-4-ccl-4), and six PFCs are listed on the UCMR-3: PFOA, PFOS, perfluorononanoic acid (PFNA), perfluorohexanesulfonic acid (PFHxA), perfluorooctanoic acid (PFHpA), and perfluorobutanesulfonic acid (PFBS) (http://water.epa.gov/lawsregs/rulesregs/sdwa/ucmr/ucmr3). As a result, drinking water utilities in the United States are required to measure these contaminants in finished drinking water. In Europe, there are restrictions on the use of PFOS as part of the European Union’s Registration, Evaluation, and Authorization of Chemicals (REACH) program (http://ec.europa.eu/enterprise/sectors/chemicals/files/reach/restre_inventory_list_pfos_en.pdf). Moreover, the Stockholm Convention recently recommended PFOA be listed as a persistent organic pollutant (POP) (http://chm.pops.int/Implementation/PublicAwareness/PressReleases/OutcomesofPOPRC11/tabid/4692/Default.aspx).

Two health effects studies published the last 2 years are worthy of note. First, Winquist and Steenland reported positive associations between PFOA exposure and thyroid disease (hyperthyroidism and hypothyroidism) among plant workers and women in exposed communities from the mid-Ohio River Valley. Some results indicate an increase of hypothyroidism among men. Previous toxicological studies and some human studies had suggested that PFOA could disrupt thyroid function, and this study of people exposed for >50 years supports those earlier findings. In a separate toxicological study, Das et al. discovered that PFNA, the 9-carbon PFC related to PFOA, can cause developmental toxicity in mice. Similar to PFOA and PFOS, PFNA produced hepatomegaly in pregnant dams at ≤5 mg/kg doses but did not affect the number of implantations, fetal viability, or fetal weight. However, 80% of the newborn pups died by the time they were 10 days old. Surviving pups showed other effects, including delayed eye opening and puberty and increased liver weight, which persisted into adulthood.

Several good reviews have also been published for PFCs. Ruan et al. reviewed analytical methods for studying the biotransformation of polyfluoroalkyl precursors in the environment. Sample extraction, concentration and cleanup, derivatization, and analysis by LC–MS and GC/MS were reviewed, along with MS elucidation of biotransformation products. Current knowledge gaps and challenges were discussed as well as future trends in analytical techniques. Future needs that were highlighted included (1) expanding current analytical methodologies to address short-chain precursors (4 and 6 carbons) that are becoming more widely produced and testing more types of environmental matrices and biota; (2) new sample preparation and instrumental methods for PFC alternatives that have novel functional groups like functionalized perfluoropolyethers and zwitterionic, cationic, and anionic fluorooxalic acids that are used in AFFs; (3) new automated processing tools, such as automated data deconvolution, chromatographic peak detection, feature filtering, and scaling to help identify TPs that might be missed with current HR-MS approaches; (4) more effective sample pretreatment to trap and derivatize possibly unstable intermediates to provide insights into transformation mechanisms; and (5) omics studies of polyfluoroalkyl-precursor biotransformation with increased instrument sensitivity and throughput to help discern defluorination mechanisms. Raham et al. reviewed the behavior and fate of perfluoralkyl and polyfluoroalkyl substances in drinking water. While PFCs are generally not removed by most drinking water treatment processes (e.g., coagulation, flocculation, sedimentation, filtration, biofiltration, oxidation, UV irradiation, and low pressure membranes), studies show that activated carbon, ion exchange, and high pressure membrane filtration can be effective for removing many of them. However, the authors emphasized the need to investigate removal of shorter chain replacements, for which little is known. These shorter chain PFCs may not sorb as well to activated carbon as the longer chain PFCs. In addition, while it is possible to oxidize a few PFCs like FTOHs and perfluorooctyl sulfonamides, they typically just transform into other PFCs.

One of the biggest trends in PFC research is the discovery of new PFC precursors and substances. Previous research has indicated that a significant portion of the total organofluorine in environmental and biological samples is currently unidentified. As a result, several research groups have been trying to identify the missing PFCs. In one of these more significant studies, Liu et al. reported the discovery of C6−C16 poly- and perfluoroalkyl substances in water using in-line SPE–LC–Orbitrap-MS with
in-source fragmentation flagging.50 In this procedure, high-volume injection-ultrahigh resolution-MS and in-source fragmentation was used, in which scans were flagged for marker fragment ions including \((\text{C}_x\text{F}_y)^-\), \((\text{C}_x\text{F}_y\text{H})^+\), \((\text{SO}_3\text{H})^+\), and \(\text{Cl}^-\). For flagged PFCs, molecular formuлас were generated from accurate masses, isotopic patterns, and fragment ions, after which a HR-MS/MS analysis of suspect PFC ions was carried out, allowing tentative identification of chemical structures. Using this procedure, 36 new PFCs were discovered, including 26 confidently assigned to 3 new PFC classes not previously reported: polyfluorinated sulfates, chlorine-substituted perfluorocarboxylates, and hydro-substituted perfluorocarboxylates.

Another paper by Wang et al. gave the first report of a Chinese PFOA alternative that was overlooked for 30 years: a chlorinated polyfluorinated ether sulfonate \((\text{C}_x\text{Cl}_y\text{O}_z\text{S})^+\).51 This new PFC has been applied as a mist suppressant in the chrome plating industry in China for decades but had not been identified in the environment until now. Using LC−MS/MS, it was found at high concentrations (up to 78 \(\mu\text{g/L}\)) in wastewater effluents from the chrome plating industry in Wenzhou, China. It was also detected at significant levels (up to 50 ng/L) in surface waters, at levels similar to PFOS. Toxicity experiments showed that it is moderately toxic to zebra fish and is resistant to degradation, like PFOS.

A large portion of the unknown PFCs not yet identified is believed to reside in the proprietary fluorinated surfactants used in AFFFs. To this end, D’Agostino and Mabury reported the identification of novel fluorinated surfactants in AFFFs and commercial surfactant concentrates.52 For this work, fluorinated AFFF concentrates were obtained from fire sites in Ontario, Canada, and two commercial fluorinated surfactant concentrates were characterized using fractionation by mixed-mode ion exchange SPE, LC−HR-MS, and MS/MS. In total, 12 novel and 10 rarely reported PFC classes were identified, with C3−C15 chain lengths, for a total of 103 compounds.

New methods continue to be developed for PFCs. For example, Deng et al. coupled SPME with ambient mass spectrometry, using a surface-coated wooden tip probe for rapid analysis of PFCs in complex environmental and biological samples.53 Silanization was used to modify n-octadecyl(dimethyl[3-(trimethoxysilyl)propyl]ammonium chloride on the surface of a sharp wooden tip which allowed ambient ESI and selective enrichment of PFCs in these samples (4000−8000-fold in aqueous samples and 100−500-fold in blood and milk samples). Detection limits ranged from 0.06 to 0.59 ng/L. This method was demonstrated on surface waters, blood, and milk samples. Boone et al. created a new method for measuring 17 PFCs in environmental and drinking waters using isotope dilution and SPE-LC−MS/MS.54 This method reports the lowest levels to-date, with detection limits ranging from 0.034 to 0.60 ng/L for surface water and 0.033 to 0.640 ng/L for drinking water. This method was also able to address problems with recovery of PFBA and other shorter chain PFCs and was subsequently used to detect PFC levels in the Mississippi River water, New Orleans drinking water, and well water from a fire training area where AFFFs are used.

A new molecularly imprinted photoelectrochemical sensor was developed by Gong et al. to detect PFOA under visible light irradiation.55 This sensor was made using modified AgI nanoparticles and bismuth oxyiodide (BiOI) nanoflake arrays and allowed high sensitivity and selectivity. PFOA could be rapidly detected, down to 0.01 \(\mu\text{g/L}\), as demonstrated on real water samples. LC−fluorescence was the focus of a new method by Meng et al. for measuring perfluorooctanesulfonyl fluoride (PFOSF).56 In this method, PFOSF was first derivatized using 1-naphthyl to form 1-naphthylperfluorooctanesulfonate (NPFOS), which provided rapid detection using LC-UV and LC-fluorescence detection, down to 1.5 \(\mu\text{g/L}\).

Several interesting new studies have been conducted for PFCs the last 2 years. Two studies focused on PFC measurements resulting from natural disasters, including the earthquake in Japan in 2011 and a major flood event in Australia. Miyazawa et al. used a simulation model to understand the abrupt increase in PFC concentrations in the ocean east of Japan following the Japanese earthquake of 2011.57 Simulation results confirmed a spike-like input of PFOA into the Western North Pacific Ocean after the earthquake, and advection and diffusion played a key role. However, the models were not able to explain the observed distribution of PFOA, suggesting differences in oceanic transport processes between PFOA and PFOS. Gallen et al. conducted a spatiotemporal assessment of PFCs in the Brisbane River system in Australia following a major flood event.58 PFOA and PFOS were the dominant PFCs released, as measured by LC−MS/MS, with mean levels ranging up to 6.1 and 15 ng/L, respectively. This study was one of the first to examine urban floodwater, found to be a major source of PFCs to the surrounding environment. In particular, the amount of PFOS relative to other PFCs was higher in samples closest to urban areas, indicating flooded properties are a potential source of PFOS.

PFCs continue to be measured in large regions of the oceans. For example, Gonzalez-Gaya et al. analyzed PFCs in 92 seawater samples collected in tropical and subtropical surface waters from the Atlantic, Pacific, and Indian Oceans.59 The Atlantic Ocean showed a broader range of concentrations of total PFCs, up to 10.9 ng/L, compared to other oceans; the Pacific Ocean yielded concentrations up to 2.5 ng/L; and the Indian Ocean, up to 2.0 ng/L. PFOS was the dominant PFC, accounting for 33% of the total PFCs globally, followed by perfluorodecanoic acid (PFDA) and PFHxA. LC−MS/MS was used for detection. Factors affecting their distribution included the distance to coastal regions, oceanic gyres, currents, and biogeochemical processes. Solar radiation, temperature, and chlorophyll a concentrations showed significant correlations with some PFCs but only explained small to moderate percentages of the variability observed.

Sanchez-Vidal et al. investigated the delivery of unprecedented amounts of PFCs to great depths in the Mediterranean Sea.60 In this study, a dense shelf water formation triggered the flushing of large amounts of PFCs through a submarine canyon to depths >1000 m. The finding of PFOA, PFOS, PFNA, and high levels of PFBA and PFHxA indicate that these PFCs sorb onto particulate matter and are quickly and directly transferred to the sea’s interior. This was the first study reporting PFC fluxes. Storms and dense cascading shelf water resulted in PFC fluxes that increased by an order of magnitude, with maximum values of 584, 106, 42, 10, and 6 ng/m²/day for PFHxA, PFBA, PFOS, PFNA, and PFOA, respectively.

The Lake Victoria Basin in Kenya was the focus of another study by Chirikona et al., who used UPLC−MS/MS and LC−MS/MS to measure daily discharge loads of PFCs.61 Domestic, hospital, and industrial wastewater varied in PFC composition, with higher levels coming from domestic wastewater. Hospitals also contributed significantly to the amounts released to the municipal wastewaters and the lake catchment. A mass load of...
1013 mg of PFCs was discharged into the Lake Victoria Basin per day, with predominantly long-chain PFCs (≥8). PFOA and PFOS concentrations ranged from 1.3 to 28 and 0.9–9.8 ng/L, respectively, in wastewater.

In a special issue of *Chemosphere* highlighting PFCs, Filipovic et al. investigated historical usage of AFFFs at a former military airport in Stockholm, Sweden, that had been abandoned since 1994.62 Despite no recent introductions of PFCs at this site, PFOA and PFOA were present at significant levels in groundwater and surface waters, with the sum of PFCs up to 51.0 μg/L and 79.0 ng/L, respectively. Significant levels were also found in soils and fish from the area. Results provided evidence that abandoned airfields may still pose an environmental and human health risk. Ye et al. investigated the spatial distribution of potential perfluorooalkyl acid (PFAA) precursors in urban rivers and WWTPs in Japan.63 This was done by converting the perfluorocarboxylic acid and perfluorosulfonic acid precursors into PFCAs by chemical oxidation. Higher ratios of PFCAs formed by oxidation, as compared to PFAAs originally present, were found in rivers vs wastewater effluents, suggesting a decomposition of some precursors into PFAAs during wastewater treatment. At the same time, higher ratios were found in water samples upstream of WWTPs, indicating other emission sources.

A special issue of *Science of the Total Environment* also focused on PFCs, with Campo et al. reporting PFC contamination of the Llobregat River ecosystem in NE Spain.64 SPE with LC−MS/MS was used for the detection of 21 PFCs (C4−C14, C16, C18 carboxylates; C4, C6−C8, and C10 sulfonates; and C8 sulfonamide) in water, sediment, and biota. The most frequently observed PFCs were PFBA, PFOA, and PFOS, with an extraordinarily high level of PFOS (2.71 μg/L) found near industrial activities. Wang et al. measured 17 PFAAs in 12 coastal rivers in the south Bohai coastal region, where 8 fluoropolymer manufacturing facilities are located.65 Extremely high concentrations of PFOA were found, up to 4.5 μg/L, with highest levels in the Xiaqing River which receives effluents from these manufacturing facilities.

Sources and fate of PFCs in wastewater effluents, rivers, and drinking waters from a highly urbanized and industrialized region of Italy was the focus of another excellent study by Castiglioni et al.66 Nine PFCAs and three PFSAs were measured using SPE with LC−MS/MS and UPLC−MS/MS. Industrial wastes contributed up to 50X the loads of PFCs in WWTPs compared to plants receiving only domestic waste. The Lambro River was found to be a major source of contamination to the Po River, and the mass balance across the Lambro River Basin showed continuously increasing contamination from north to south and differences in PFC composition in the west and east sides of the basin. While groundwaters and drinking waters were contaminated in industrial areas (maximum of 137 ng/L for the sum of the PFAAs), PFCs were well removed in treatment in Milan.

Finally, Washington et al. published an ambitious study examining the degradation rates of commercial, side-chain fluorotelomer-based polymers (FTPs) in soils and water over a 376-day period.67 Fifty PFCs were measured using GC/MS and LC−MS/MS, including fluorotelomer alcohols and acids and PFCAs. One commercial FTP showed half-life estimates of 65−112 years, and the other showed estimates of 33−112 years. These results confirm that commercial FTPs, which are the primary products of the fluorotelomer industry, are sources of the fluorotelomer and PFCs in the environment.

### PHARMACEUTICALS AND HORMONES

Pharmaceuticals and hormones are contaminants of growing concern due to their presence in the environment and potential risk to induce adverse ecological and health effects to wildlife and humans. Possible outcomes include effects of endocrine disruptors in fish, the creation of antibiotic resistant bacteria caused by exposure to antibiotics in the environment, and wildlife poisoning from the consumption of animals exposed to pharmaceuticals. About 3000 different compounds are used as ingredients in pharmaceuticals, including painkillers, antibiotics, steroids, antiinfectives, betablockers, contraceptives, lipid regulators, antidepressants, and illicit, impotence, and cytostatic drugs. Pharmaceuticals are released to the environment by various routes, including human excretion, direct waste disposal to sewage, and from veterinary use for livestock, poultry, and fish. Veterinary drugs are fed to farm animals to prevent disease and to maximize the size of the animals. Antibiotic resistant bacteria or "Super Bugs" that are capable of transferring the resistance to other neighboring bacteria were recently reported in farm animals, which raises a great concern because the possible effects that can follow still remain unknown.68 Further, it is not well understood whether exposure to low levels of other pharmaceuticals (typically at ng/L concentrations) poses a health risk to humans and wildlife in the long term. Monitoring efforts of several pharmaceuticals and hormones by the U.S. EPA and the European Union (EU) are being conducted to evaluate and support possible future regulations. The U.S. EPA draft CCL-4 list includes erythromycin, nitroglycerin, 17α-ethinylestradiol (EE2), 17α-estradiol, estrone (E1), 17β-estradiol (E2), estriol (E3), equilenin, equinol, mestranol, and norethindrone. The EU (Commission Implementing Decision EU 2015/495 of March 15) recently added hormone E1 and the antibiotic erythromycin to their watch list, which already included diclofenac and two hormones EE2 and E2.

Analytical instrumentation, such as hyphenated techniques in mass spectrometry, can quantify and identify pharmaceuticals, hormones, and their transformation products (TPs) in water samples and other environmental matrices in the pg/L and pg/kg range. Transformation products are the result of reactions that occur in the environment, caused by biological degradation in WWTPs, oxidation by strong oxidants including chlorine, ozone, and OH radicals, or through natural photolysis by sunlight. TPs can sometimes have higher toxicity than the parent compounds.

While LC−tandem mass spectrometry is the method of choice for the quantification of pharmaceuticals, a trend for more advanced techniques using HR-MS for the identification and quantification of the transformation products at trace levels is occurring. Jakimska wrote a review that summarizes the current mutiresidue methods used to detect pharmaceuticals in environmental samples.69 This review highlights a current trend toward UPLC or fused-core columns with tandem mass spectrometry because of the faster elution of multiple analytes and increased chromatographic resolution. However, with narrower peaks, mass spectrometers must acquire spectra rapidly without losing mass accuracy. LC−QTOF-MS provides high mass resolution accuracy and is typically used as an identification method in combination with LC−QqQ-MS. Even though HR-MS can provide exact masses and mass fragments that lead to the identification of unknown compounds in samples, it is not sufficient to confirm chemical
structures. High purity and isolated analytical standards are needed for confirmation either by MS or other analytical methods including NMR and infrared (IR) spectroscopy. In the case where no analytical standards are available and only MS spectra are obtained, the unknown compounds are “tentative identifications”.

For example, Schymanski et al. analyzed wastewater samples, where only 1.2% of the detected peaks (with 376 standards available) corresponded to target analytes. Of the 30 most intense peaks, only 4 corresponded to target analytes; of the 26 remaining, 7 were tentatively identified and 1 peak was confirmed.

Environmental Impacts. Pharmaceuticals are found in the environment at concentrations ranging from ng/L to low μg/L, which are significantly lower than most of the lowest observed effect concentrations (LOECs) for aquatic or other organisms. However, the chronic toxicity LOECs of a few pharmaceuticals, including salicylic acid, diclofenac, propranolol, clofibric acid, and fluoxetine, are comparable to concentrations found in wastewater. For example, maximum concentrations of propranolol and fluoxetine measured in wastewater effluents were within the range of their toxic LOEC in zooplankton and benthic organisms, respectively. Similarly, diclofenac LOECs in fish were within the same concentration range found in wastewater effluents and it can bioaccumulate in the bile of fish. The antibiotic ciprofloxacin can induce effects on plankton and algae growth at concentrations found in the environment. The contraceptive EE2 at very low concentrations in WWTPs, with concentrations up to 2 and 4 μg/L in WWTP effluents, respectively. Other TPs were also detected.

Predicting the possible environmental effects caused by pharmaceutical exposure remains a challenging goal. A review article summarizes the effects of pharmaceuticals on higher vertebrates, including birds and mammals, and highlights environmental exposure routes and methods that can be used to monitor environmental effects. Two recent studies link possible pharmaceutical input sources, occurrence, and their effects on bacteria and fish. Zhang et al. provided a profile of antibiotic concentrations in a river basin in China, investigated possible influent sources, and measured the effects associated with antibiotic resistant bacteria. This study quantified three classes of antibiotics in wastewater effluents and impacted rivers and identified a slight correlation with the presence of antibiotic resistant E. coli. Martinovic-Weiglet et al. used transcriptomic and metabolomic technologies to determine the effects of pharmaceutical-containing WWTP effluents on fish. It was found that male fathead minnows exposed to wastewater effluents up-regulate genes related to cholesterol and steroid metabolism and were linked to endocrine active chemicals, including E2.

Progestins are used as an ingredient in oral contraception and also for hormone replacement therapy, endometrial cancer, and uterine bleeding. Kumar et al. summarized the chemical and biological properties of progestins, their biological effects on aquatic organisms, concentrations in sewage and rivers, and identified knowledge gaps needed to conduct risk assessment studies. The review highlights that only five progestins of the 20 currently being used in the medical field have been found in the surface waters and wastewaters. Similar to estrogens, low levels of levonorgestrel, norethisterone, and gestodene (0.8–1.0 ng/L) have the ability to reduce egg production in fish. Further, it is predicted that bioaccumulation of ethynodiol diacetate and desogestrel in fish could potentially reach human therapeutic doses but still needs to be investigated.

Biological Transformation Products. Anticonvulsants carbamazepine (CBZ) and oxcarbazepine (OXC) and their main human metabolites were biodegraded with activated sludge and sand filter material to 7 TPs. TPs were identified with LC–linear ion trap (LTQ)-Orbitrap-MS, and their chemical structures were confirmed with NMR and reference standards. Three transformation pathways were proposed, which include oxidation, α-ketol rearrangement, or benzylic acid rearrangement reactions. 1-(2-Benzoic acid)-(1H,3H)-quinazoline-2,4-dione (BaQD), 9-carboxylic acid-acridine (9CA-ADIN), and acridone were found in WWTP effluents, rivers, and streams. 9CA-ADIN was quantified in WWTP effluents, rivers, and drinking water up to 920, 304, and 189 ng/L, respectively. Similarly, BaQD was quantified up to 135, 74, and 26 ng/L, respectively. Bahlmann et al. also investigated the occurrence of CBZ, OXC, their main metabolites, and other 3 TPs in Portuguese and German WWTP influents and effluents. Analytes were quantified with LC–LTQ-Orbitrap-MS. Results suggest that CBZ and its main metabolite dihydroxy-carbamazepine (DiOH-CBZ) are not degraded well in WWTPs, with concentrations up to 2 and 4 μg/L in WWTP effluents, respectively. Other TPs were also detected.

Llorca et al. investigated the biodegradation of the antibiotics tetracycline (Tc) and erythromycin (ERY) by enzymes with online turbulent flow LC–LTQ-Orbitrap-MS. This online configuration can analyze the parent and TPs without further sample manipulation. Tc was degraded by laccase enzyme up to 78% after 18 h, forming 3 TPs. Proposed reactions that led to the TPs include dehydroxylation, (bi)demethylation, and oxidation of two rings. ERY degradation after 16 h exposure was 52%, forming 5 TPs.

Fluoroquinolone antibiotics ofloxacin (OFL), norfloxacin (NOR), ciprofloxacin (CPF), and moxifloxacin (MOX) were biodegraded with a mixed bacteria culture that have shown to degrade other fluorinated compounds. After 19 days, all four antibiotics degraded 98.3%, 96.1%, 94.7%, and 80.5% for OFL, NOR, CPF, and MOX, respectively. Intermediate TPs were identified with LC–MS/MS and new chemical structures were proposed with LC–QTOF-MS. Allopurinol, an antigout drug, is readily metabolized to oxypurinol (80%) and riboside conjugates (10%), and oxypurinol is detected in WWTP influents and effluents up to 26.6 μg/L and 21.7 μg/L, respectively. Allopurinol was not observed in either type of samples. Kinetic degradation experiments of allopurinol-9-riboside with activated sludge showed the formation of allopurinol and oxypurinol followed by a complete transformation of allopurinol to oxypurinol. Oxypurinol was observed to be stable during controlled experiments and through wastewater treatment and was detected in rivers, streams, and groundwater in the range of 0.09–22.6 μg/L, which could make it a good marker for wastewater contamination. High correlations were observed between oxypurinol and two other wastewater biomarkers carbamazepine ($r^2 = 0.89$) and primidone ($r^2 = 0.82$).

Certain pharmaceuticals are not detected in WWTP influents, even though they are highly consumed, as in the case of omeprazole, a drug used for gastric diseases. Boix et al. identified 24 omeprazole metabolites in urine from patients that took the drug by LC–QTOF-MS. An omeprazole isomer that shared a major common fragment was detected, which highlights the importance of good chromatographic separation.
to differentiate isomers. The metabolites were screened in environmental waters, and 14 were detected.

Selected pharmaceuticals, alkylphenols, and their corresponding halogenated DBPs were screened in a sampling campaign of 10 WWTP effluents in southern California.\textsuperscript{82} WWTP effluents are typically disinfected and quenched prior to their discharge to the environment. Chlorination of pharmaceutical-containing effluents can produce chlorinated and brominated DBPs (in the presence of Br\textsuperscript{−}). Chlorinated and brominated DBPs and their isotopically labeled internal standards were synthesized to accurately quantify salicylic acid, bisphenol A, gemfibrozil, naproxen, diclofenac, technical 4-nonylphenol, 4-tert-octylphenol, and their halogenated DBPs with LC-QqQ-MS. Salicylic acid was readily halogenated in all effluents, with dichlorinated species most prevalent, followed by monochlorinated and dibrominated compounds. Bisphenol A had no measured halogenated DBPs despite high concentrations of the parent compound.

A new approach, known as compound-specific isotope analysis (CSIA), identifies diclofenac in the environment based on carbon and nitrogen isotope measurements with GC-isotope ratio (IR)-MS.\textsuperscript{83} This method includes a derivatization step with on-column injection. Oxidation and reduction transformation are evaluated with bulk enrichment factors (ε) that relate the isotope ratios at the beginning and after time t to the remaining substrate fraction (Ct/C0). Oxidative transformation of diclofenac reveals a strong nitrogen isotope fractionation (εN = −7.1\%) whereas reductive dechlorination was associated with carbon isotope fractionation (εC = −2.1\%). CSIA can also identify transformation pathways as well as diclofenac degradation. Biochemical and chemical reactions can be analyzed with this new approach.

Elimination/Reaction During Oxidative Water Treatment. Iodinated X-ray contrast media are inert compounds that are excreted nonmetabolized and are not well removed by WWTPs. Two recent studies investigated the DBPs and TPs of iodinated X-ray contrast media with chlorine, chloramine, chlorine dioxide, and an AOP, UV–H2O2.\textsuperscript{84,85} From the three chlorinated oxidants and five X-ray contrast media tested at pH between 6.5 and 8.5, free chlorine was the only oxidant to react substantially with iopamidol.\textsuperscript{84} No significant degradation was observed for iopromide, iohekol, iomeprol, or diatrizoate. DBPs were identified with LC–LTQ-Orbitrap-MS and NMR data supported two TP chemical structures. Hypochlorite (OCl\textsuperscript{−}) was the reactive chlorine species with the highest observed rate at pH 8.5. Iodine was released during iopamidol oxidation, with transformation primarily to iodate. Only 2\% of the reacted iopamidol was transformed to low molecular weight iodinated DBPs (iodo-trihalomethanes and iodo-acids). However, chlorinated iopamidol was much more cytotoxic than unreacted iopamidol. In another study, iopromide was reacted with UV–H2O2 and 14 TPs were identified with LC–QTOF-MS.\textsuperscript{85} The complexity of iopamide-spiked wastewater samples after treatment led to the identification of only 4 TPs. The METLIN database and statistics-based profiling tools used in metabolomics were effective in discriminating between background signals and TPs. TPs were also predicted for structurally similar iopamidol after UV–H2O2 treatment. Predicted TPs were subsequently observed in unspiked AOP-treated wastewater.

Other pharmaceuticals can also act as precursors and react with commonly used disinfectants in water treatment to form DBPs. Postigo et al. summarized DBPs formed by the reaction of pharmaceuticals with chlorine, chloramines, ozone, chlorine dioxide, and AOPs and outlined their main reaction pathways.\textsuperscript{86} Recently, two studies involving the reaction of methadone with chloramines and free chlorine have shown the possible formation of highly toxic DBPs.\textsuperscript{87,88} For example, chlorination (1–150 mg/L) of methadone can yield between 23 and 70\% of NDMA, a known carcinogen in animals and a DBP of concern.\textsuperscript{87} Chlorination (10 mg/L) of methadone (0.2 mg/L) led to the formation of 8 DBPs, including the human metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidinone (EDDP).\textsuperscript{88} Methadone undergoes intramolecular cyclation, dehydrogenation, oxidation, and chlorination to produce DBPs that were identified with LC–QTOF-MS in MS/MS mode. It was observed that methadone (0.05 mg/L) reactions with chlorine (10 mg/L) are faster at neutral to high pH, with complete removal (>98\%) after 10 min in ultrapure and creek water. Potential ecotoxicological impacts for two aquatic organisms were predicted using a computer model (based on predicted LC50), which suggested possibly higher effects for several DBPs compared to the parent methadone.

Miao et al. investigated the transformation and degradation of the analgesic aminopyrine by ozonation and AOPs.\textsuperscript{89} Aminopyrine oxidation with O3/H2O2 was more effective than O3 alone, followed by O3/HCO3\textsuperscript{−} (HCO3\textsuperscript{−} is an OH radical scavenger), suggesting that indirect OH radicals play an important role in the degradation of aminopyrine. Twenty-one TPs were identified with LC–QTOF-MS, and a reaction pathway was proposed that includes pyrazole ring cleavage, demethylation, defenylation, and hydroxylation reactions. Experiments that tested inhibition of bioluminescence of photobacteria were conducted, and results suggested that TPs have a higher toxicity than aminopyrine. Furthermore, as aminopyrine is increasingly being mineralized with increasing oxidant dosages, lower toxicity levels were observed. A pilot-scale experiment with spiked aminopyrine in surface water showed that 3 TPs were formed after O3 and O3/H2O2 but were later effectively removed with biologically active carbon (BAC). Similarly, ozonation of the analgesics phenazone and propyphenazone and its metabolites, acetamido antipyrine (AAA) and formyl aminooantipyrine (FAA), were studied by Favier et al.\textsuperscript{90} Ring opening and oxidation of carbon–carbon double bonds led to the identification of 17 TPs by LC–LTQ-Orbitrap-MS. Target analytes were found to be very reactive with ozone. Quantitative structure activity relationships (QSARs) estimate that the toxicity to aquatic organisms of some TPs can be higher than the parent compounds.

Chlorination of cefazolin, a β-lactam antibiotic, its DBPs, reaction mechanisms, and toxicity were characterized by Li et al.\textsuperscript{91} Two main reactions were identified where the thioether-sulfur moiety is oxidized to sulfoxide and disulfide, and the amide α-carbon undergoes a base-catalyzed electrophilic substitution by chlorine. One chlorinated and 4 oxidation DBPs were identified with UPLC–QTOF-MS. A SOS/umu bioassay was used to test for toxicity of the parent compound and its DBPs. Results suggest that at neutral pH, DBPs have slightly higher toxicity than the parent, but toxicity was reduced with increasing oxidant dosage.

The quinolone antibiotic levofloxacin reaction with birnessite (δ-MnO2), a common soil metal oxide, and its TPs were characterized with LC–QTOF-MS.\textsuperscript{92} Levofloxacin degradation was slow and needed an oxidant molar ratio excess of 200:1 to degrade up to 90\% of the parent compound in 35 days. Ten TPs were identified.
Olvera Vargas et al. investigated the transformation of ranitidine, a gastrointestinal drug, by electrochemical AOPs that produce OH radicals, including (1) in situ electrogenerated H2O2 and electro-Fenton processes and (2) anodic oxidation by testing three different anodes.99 The boron-doped diamond (BDD) anode proved to be the most oxidative power, with almost complete mineralization of ranitidine under the tested conditions. Eleven TPs were identified with LC–QTOF-MS and were mineralized with further treatment. A reaction pathway was proposed. A comparative toxicity test that uses bioluminescence inhibition of photobacteria revealed that the TPs are relatively more toxic than the parent compound. However, toxicity was reduced after mineralization of ranitidine.

Photodegradation. The anticonvulsant lamotrigine’s degradation with UV, ozone, and hydroxyl radicals were investigated by Keen et al.86 It was observed that lamotrigine was stable under UV and ozone treatments, but degraded in the presence of hydroxyl radicals, so advanced oxidation processes would be the most optimal choice for treatment. The transformation pathway and products were determined with LC–TOF-MS. The main transformation pathways include hydroxyl group addition to the benzene ring.

The phototransformation of EE2 by UVC–H2O2 or solar/Fe2+ was evaluated at levels close to environmentally relevant concentrations (100 μg/L) in secondary-treated wastewater by Frontitis et al.95 Treatment conditions were optimized to achieve complete EE2 removal in 15 min for UVC–H2O2, and 86% removal was achieved after 60 min of solar/Fe2+ treatment. Several TPs were identified by UPLC–QqQ-MS including quinone methide and 1,2-quinone derivatives through a proposed reaction pathway.

De Laurentiis et al. investigated acetaminophen’s transformation by direct and indirect photolysis.96 Indirect photolysis with intermediate species, such as the carbonate radical (CO3−••), and under certain water quality conditions, the triplet state chromophoric dissolved organic matter (†CDOM*) were found to be the main transformation pathways. Acetaminophen degradation leads to hydroxylated derivatives, ring-opening compounds, dimers, and trimers.

The antibiotic ciprofloxacin was treated with UV and xenon lamps, and 11 TPs were identified using LC–QqQ-MS and LC–LTQ-Orbitrap-MS.97 TPs were stable and retained the core quinoline structure and did not undergo full mineralization. Therefore, it is expected that the TPs will persist in the environment. Another study evaluated ciprofloxacin oxidation by the electro-Fenton process.98 The reaction rate constant for ciprofloxacin oxidation by OH radicals was determined to be 1.01 × 10−10 M−1 s−1. An optimized current of 400 mA and Fe2+ concentration of 0.1 mM were found to mineralize >94% (0.15 mM of ciprofloxacin) in 6 h.

Phototransformation products of two of the most common erectile dysfunction drugs, vardenafil and sildenafil, were found to undergo cleavage of the piperazine ring and hydroxylation to make two stable sulfonic acid isomers with a molecular mass of 392 Da.99 Another study photolyzed four unapproved analogues of sildenafil; their TPs were identified using UPLC–Orbitrap-MS.100 All four sildenafil analogues were degraded to the stable sulfonic acid TP (392 Da) observed from sildenafil decomposition.

Methamphetamine degradation by UV–TiO2 was investigated by Kuo et al.101 The authors found that 100 ppb methamphetamine treated with UV–TiO2 (4.5 mW/cm², 0.1 g/L) in wastewater treatment decomposed by 67% after a 30 min exposure time. Nine TPs were identified, and they completely mineralized after 3 h. Two main pathways were proposed, where one involves cleavage of a side chain to smaller fragments and the other pathway includes an initial hydroxylation of the aromatic ring, which then undergoes cleavage to smaller fragments.

Sun et al. investigated the photolysis of two veterinary ionophore antibiotics, monensin (MON) and salinomycin (SAL), and found that only SAL degraded under simulated and natural sunlight.102 However, both compounds showed increased degradation in the presence of nitrate, where indirect photolysis plays a major role.

A review paper summarizes the application of UV-TiO2 treatment of different pharmaceuticals and the parameters that affect their degradation, including catalyst loading, initial pharmaceutical concentration, pH, and other interferences that compete for oxidative species produced by UV-TiO2.103 Moreover, the authors highlight the different TiO2 modes of application (either suspended in solution or fixed to a medium), reactor type, and reaction kinetics used in these studies.

Antivirals. Wood et al. investigated the occurrence of 12 commonly used antivirals used to treat HIV-positive patients in South Africa, one of the highest consumers of antiviral compounds per capita.104 The authors developed a SPE and LC–MS/MS method and used the standard addition method for quantification of samples from every major dam and river across the country. Nevirapine, lopinavir, and zidovudine were the most frequently detected, with average concentrations of 360, 239, and 319 ng/L, respectively. Stavudine was found with the highest average concentration of 431 ng/L. The majority of the target antivirals were detected in the Rooielpaart Dam system, which received effluents from 2 WWTPs.

A study investigated the source of anti-influenza drugs, oseltamivir and its metabolite oseltamivir carboxylate, amantadine, and zanamivir, in the Yodo River system in Japan.105 The major contributors of anti-influenza drugs originated from WWTP effluents. Additionally, it was observed that WWTP effluents treated with ozone (n = 2) had significantly lower levels of antivirals than those treated with free chlorine (n = 6). Photolysis of three prevalent antivirals, acyclovir, zidovudine, and lamivudine, were investigated.106 Zidovudine was transformed via direct photolysis and inhibited by Cl− and Br− found in seawater. Acyclovir and lamivudine were transformed primarily by indirect photolysis in the presence of dissolved organic matter and in the presence of bicarbonate for acyclovir. However, in seawater, lamivudine degradation was enhanced.

Antidiabetic Drugs. Metformin is an antidiabetic drug that is not efficiently removed by WWTPs. An interesting study characterized the fate of metformin and guanyurea in the water cycle that could potentially become a risk to human health.107 An analytical method was developed to quantify target analytes with limits of quantification (LOQs) ranging between 2 and 10 ng/L using LC–Qtrap-MS. Results suggest that metformin (86–142 μg/L) predominantly enters WWTPs and is 93–97% biodegraded to predominantly form guanyurea (28–67 μg/L) in the effluent. Metformin and guanyurea were detected in surface waters with concentrations up to 150 ng/L and 27 ng/L, respectively. Further, metformin was quantified in drinking water (2 ng/L and 61 ng/L) where Lake Constance (102 ng/L) is used as the source water. Metformin loads into the North Sea were calculated to be 15.2 kg day−1 and 6.4 kg day−1 from de Laurentiis et al. 561

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rivers Elbe and Weser. Another study by Kosma et al. characterized the occurrence of metformin and main biological TP guanylurea in eight Greek WWTP influents and effluents over the course of a year. Metformin was present in 97% of the samples in WWTP influents (up to 1167 ng/L) and was predominant over guanylurea with a ratio of metformin/guanylurea of 0.88 to 81.3. However, WWTP effluent guanylurea (up to 627 ng/L) predominated over metformin with a ratio of 0.005–0.78.

Oxidation of metformin by free chlorine can lead to the formation of toxic nitrogen-containing DBPs (N-DBPs) as characterized by Armbruster et al. Two main products, a cyclic dehydro-1,2,4-triazole-derivative and a chloro-organic nitrile, were synthesized from the reaction and characterized with LC–QTOF-MS, X-ray crystallography, NMR, UV–vis, and IR spectroscopy. A reaction pathway was proposed. At trace levels of metformin (100 ng/L) and chlorine (0.2 mg/L), the chloro-organic nitrile was quantified between 0.3 and 0.7 ng/L, where molar conversion rate was ≤1%

Cytostatic Pharmaceuticals. The fate of 13 cytostatic drugs and 4 metabolites in wastewater effluents from WWTPs and a hospital was investigated by Negreiro et al. An automated SPE followed by LC–LTQ-MS analysis was developed. Methotrexate (MET), ifosfamide (IF), cyclophosphamide (CP), irinotecan (IRI), doxorubicin (DOX), capetabine (CAP), tamoxifen (TAM), and three metabolites, endoxifen, hydroxytamoxifen, and hydroxyplactaxel, were detected at levels between 2 ng/L (for MET) and 180 ng/L (TAM). MET, DOX, and IRI were efficiently removed by WWTPs; however, TAM, CP, and IF were not. In another study by Gomez Canela et al., the authors observed higher concentrations ranging between 0.02 and 86.2 μg/L in hospital effluents, where IF, IRI, and megestrol acetate (MEG) were the most prevalent. However, in WWTPs influents, only CP and MEG where detected, suggesting that cytostatic drugs are environmentally degraded before they reach WWTPs.

The phototransformation of MET and DOX by UV and UV–TiO2 was investigated by Calza et al. TP s were tentatively identified with LC–LTQ-Orbitrap-MS by analyzing MS* data of individual chromatographic peaks. DOX degradation by UV treatment alone led to 8 TPs and an additional 6 TPs with UV–TiO2. A proposed reaction pathway included (poly)hydroxylation, oxidation, and cleavage of the sugar moiety. MET degradation led to the formation of 15 TPs from both photolytic treatments. Proposed reactions include decarboxylation, hydroxylation, and bond cleavage.

Negreiro et al. investigated the chemical degradation of etoposide (ETP) by chlorination, a commonly used disinfectant. TPs were identified with UPLC–LTQ-Orbitrap-MS from a time course chlorination experiment. EPT degradation was observed to be fast, forming oxidation byproducts (BP1 and BP2), with BP1 formed under low chlorine doses and BP2 in the presence of free chlorine in excess. BP1 was confirmed with an analytical standard to be 3′-O-desmethyl etoposide and was quantified in raw wastewater and river waters with concentrations of 33 ng/L and 14–31 ng/L, respectively. ETP was not detected in any samples.

Drugs of Abuse. Illicit drugs and metabolites, produced by phase I and II metabolic transformation reactions in humans were targeted and identified in sewage samples by Heuett et al. An LC–QExtractive-Orbitrap instrument operated in two modes (targeted MS/MS and data-dependent screening) were compared. However, targeted MS/MS provided enough data points across each chromatographic peak and was subsequently used in the study. Identification of TPs was done by considering 17 phase I and 7 phase II reactions the parent compounds might undergo. A total of 54 TPs were tentatively identified.

Enantiomeric profiling of amphetamines and MDMA (3,4-methylenedioxy-methamphetamine) was investigated in two Dutch cities by Emke et al. MDMA has two enantiomers, R(−) and S(+), where S(+) is preferentially metabolized to R(−) and excreted by MDMA consumers. However, a racemic mixture was observed in one sampling campaign, whereas an enriched R(−) enantiomer was only previously observed. The racemic sampling campaign might be explained by a direct disposal of MDMA that possibly occurred as a result of a recent police raid on a nearby illegal production facility.

Cannabis consumption is estimated by measuring the main metabolite 11-Nor-9-carboxy-Δ9-tetrahydrocannabinol (THC-COOH) in sewage effluents. Boit et al. tentatively identified 19 THC-COOH TPs formed by chlorination, hydrolysis, and photolysis (UV and simulated sunlight) using LC–QTOF-MS. THC-COOH was found in all influent and effluent WWTP samples with a removal efficiency of 86%. One hydrolysis and five photolysis TPs were found in effluent and surface waters.

Enantiomers. Separation of chiral pharmaceuticals and illicit drugs is of growing interest in the biomedical and environmental areas, due to the different reactivity enantiomers can have in the human body. Ribeiro et al. provides a nice review of chiral analytical methods developed for both areas. Only a few drug classes have been analyzed for their enantiomers, including beta-blockers, antidepressants, antifungals, nonsteroidal anti-inflammatory drugs, and amphetamines. The authors highlight the challenges in multiresidue method development due to the lack of simultaneous enantioselective separation of different classes of chemicals with the same chromatographic conditions. Additionally, current trends for fast multiresidue trace analysis of environmental samples with UPLC requires sub-2 μm chiral stationary phases which are not yet widely available.

A multiresidue study analyzed 18 chiral drugs in wastewater and sludge samples, including beta-blockers, antidepressants, and amphetamines. The study used two separate extraction methods for wastewater effluents and sludge, followed by two independent LC columns and ESI-QqQ-MS analysis. The method was validated for 10 compounds in all matrices, 7 compounds in liquid matrices only, and 1 compound in solid samples only. Wastewater influent, effluent, and digested sludge had different enantiomeric composition, which suggests different biological transformation inherent to the microbial communities present in WWTPs.

Multiresidue Methods. A multiresidue method was developed by Robles Molina et al. for the determination of 430 emerging pollutants in water and wastewater. The method included the quantification of 105 pharmaceuticals, caffeine, nicotine, 21 drugs of abuse and their metabolites, 279 pesticides and metabolites, nitrosamines, flame retardants, plasticizers, and perfluorinated compounds. Analytes were extracted with SPE Oasis HLB cartridges and analyzed with LC–TOF-MS in positive and negative modes. Recoveries ranged between 50 and 130% for 281 compounds, and LOQs were below 10 ng/L for 190 compounds. Petrović et al. developed a method for 81 pharmaceuticals in water in Serbia. The method included SPE extraction and analysis...
with UPLC-Qq-linear ion trap (LIT)-MS. A total of 47 compounds were detected and quantified, with ibuprofen, two carbamazepine metabolites, and acetaminophen at the highest concentrations.

Another study developed a large volume injection UPLC–TOF-MS method that first screened 69 multiclass pharmaceuticals as suspects, followed by a target quantification analysis in surface water samples. The screening process takes into account the signal intensity-dependent accurate mass error in TOF-MS that limited the false negative rate (FNR) to 15% and false positive rate (FPR) to 5%. The advantage of this approach is that fewer analytical standards are needed and research efforts are streamlined. The proposed methodology identified 37 suspects and later confirmed 30 analytes with analytical standards. Target and quantification analysis detected 17 compounds at concentrations ranging between 17 ng/L and 3.1 μg/L. A critical review by the same research group summarizes trends in LC–HR-MS for multiresidue analysis of contaminants in aquatic environments. Among the most detected pharmaceuticals and their TPs in groundwater include 4-hydroxy-propanolol, enalaprilat, salicyclic acid, anhydroerythromycin, and the carbamazepine metabolite epoxycarbamazepine. Even though hormones in groundwater are rarely detected, aquifers impacted by land irrigation of reclaimed water can have high concentrations, with up to 1745 ng/L of estriol reported. This review also highlights that caffeine, nicotine, and their main TPs are typically found in groundwater in the range of a few hundred ng/L, while artificial sweeteners can generally go up to μg/L. In addition, the fate and transport of contaminants of concern and their physical, biological, and chemical processes that affect groundwater quality are discussed. Bradley et al. investigated the fate and transport of 110 pharmaceuticals from wastewater effluents to a shallow groundwater in Fourmile Creek, Iowa. Carbamazepine, sulfamethoxazole, and immunologically related compounds were detected at concentrations >0.02 μg/L. About 43–55% of target pharmaceuticals were detected in surface waters and 6–16% were detected in groundwater. Results suggest the potential risk that wastewater reuse could have to groundwater sources.

Efforts to characterize contaminants present in European WWTPs led to a sampling campaign of 90 WWTPs to analyze 156 polar organic contaminants. A total of 125 substances were detected with five different analytical methods that include SPE or liquid–liquid extraction (LLE) and LC–ESI-MS/MS or GC-HR-MS analysis. Relevant compounds with the highest mean concentrations include artificial sweeteners acesulfame and sucralose, benzo triazoles, several organophosphate esters, and antibiotics trimethoprim, ciprofloxacin, sulfa methoxazole, and clindamycin. Bioassays used to test for estrogenic and dioxin activities in WWTP effluent samples found 36% and 84% positive, respectively.

In another study, UPLC–ESI-QTOF-MS was used to screen for more than 1000 licit and illicit drugs (215 standards available) in WWTP influents and effluents and 10 surface waters sampled around the region of Bogotá, Colombia. The most frequently identified analytes (using the retention time and 2 accurate masses) include acetaminophen, carbamazepine and metabolites, clarithromycin, diclofenac, ibuprofen, gemfibrozil, lincomycin, losartan, valsartan, two metabolites of metamizol, sucralose, lidocaine, and cocaine and its main metabolite benzoylco choline. Other analytes tentatively identified (2 accurate masses only) were caffeine, saccharin, metformin, and two metabolites of losartan.

The occurrence of 64 pharmaceuticals was investigated in six drinking water treatment plants (DWTPs) and two industrial water purification plants in Japan. The authors analyzed the samples with three different analytical methods that included LC–MS, LC–MS/MS, and trimethylsilyl derivatization followed by GC/MS. A total of 37 target analytes were detected with maximum concentrations below 50 ng/L except for 13 compounds. Iopamidol exceeded 1000 ng/L at most facilities. DWTPs that had advanced drinking water treatment, including ozonation and granular activated carbon filtration, were able to efficiently remove most of residual pharmaceuticals vs DWTPs that had only conventional treatment. However, amantadine, carbamazepine, diclofenac, epinastine, fenofibrate, ibuprofen, iopamidol, and oseltamivir acid were detected in finished water samples, and removal of several of them was not sufficient even with ozonation and activated carbon filtration.

Casado et al. investigated the occurrence of antimycotics in surface waters and WWTP influents and effluents. Fluconazole, ketoconazole, miconazole, and clotrimazole were measured in wastewater samples up to 200 ng/L. Fluconazole was the highest quantified antimycotic and was poorly removed by wastewater treatment. A post-target analysis of LC–QTOF-MS data were screened for additional antimycotics present in the samples. Climbazole was identified and confirmed by its MS spectrum and an analytical standard.

**Novel Sample Extraction Materials and Methods.** Recent efforts to improve pharmaceutical and illicit drug extraction from water samples have led to the synthesis and modification of polymers. One study synthesized eight cation-exchange resins using two polymerization methods (nonaqueous dispersion and precipitation polymerization), followed by hyper-cross-linking, and treated with varying concentrations of sulfuric acid to increase sulfonic groups in the material. Each resin had different ionic exchange capacity, specific surface area (SSA), and mean particle size. Resins with higher SSA had better percent recoveries (75–100%) for most tested drugs. Ion suppression (20–30%) was observed for some analytes, including morphine, trimethoprim, caffeine, and atenolol. In another study, two sorbents were synthesized to improve pharmaceutical and illicit drug extraction from wastewater effluents. One sorbent consisted of copolymerization of three monomers, while the second sorbent was a copolymer that was modified with sulfuric acid. The later had a superior retention of analytes and removal of interfering compounds. Analytical methods were optimized for 8 drugs of abuse and their metabolites and 9 pharmaceuticals to provide low MDLs ranging between 2 and 40 ng/L.

A novel method that uses ionic liquid (IL)-based dispersive liquid–liquid microextraction (DLLME) coupled with micro solid phase extraction (μSPE) was developed by Ge et al. to extract antidepressants drugs from water samples. The IL 1-
hexyl-3-methylimidazolium tris(pentafluoroethyl)trifluorophosphate and μSPE zeolite imidazolate framework were used. Relative recoveries from canal water ranged from 94.3 to 114.7%.

An innovative passive water sampler, known as o-DGT (diffusive gradients in thin-films for organics), was tested for 40 target antibiotics in WWTP influents and effluents. The water sampler allows for analyte diffusion onto thin-films, which accumulates on a binding phase. Antibiotic diffusion coefficients were characterized, and o-DGT samplers were deployed for 4–18 days. Forty-four antibiotics were detected in o-DGT devices when used for 7 days; however, due to biofouling, a 7 day deployment is recommended where 10 of the 14 antibiotics were detected. A comparison between o-DGT and a 24 h autosampling composite shows very similar results, whereas, o-DGT and grab sampling showed very different results, due to the high variability and dependence on the time of the grab sample.

**Quality Control of Pharmaceutical Quantification and Identification.** Llorca et al. investigated the stability of 56 antibiotics (macrolides, tetracyclines, fluoroquinolones, quinolones, penicillins, cephalosporines, lincosamides, sulfonamides, and nitroimidazoles) in water samples under three conditions: stored at −20 °C, stored with ethylenediaminetetraacetic acid (EDTA) at −20 °C, and extracted with SPE cartridges and stored at −20 °C. Results showed that 37 of the 56 antibiotics were stable within 1 week in at least one of the three storage methods. However, macrolides, tetracyclines, and fluoroquinolones exhibited the least stability (<80%) compared to the other antibiotics. It is recommended that when measuring these compounds, they should be analyzed immediately after sampling.

High-resolution mass spectrometry is advantageous for screening suspect analytes and even when no standards are available. However, there is the possibility of obtaining high false negative (FNR) and false positive (FPR) rates. A recent study developed a method based on a multivariate statistical model that can control the FNR to an acceptable level by considering the mass error of one to three isotopes, isotope ratios, and signal-to-noise. With increasing number of isotopes (from one to three), the FPR decreased from 22%, 2.8% to <0.3%; however, the limits of detection increased from 200 ng/L, 2000 ng/L to 2062 ng/L. A wastewater sample was analyzed for 77 pharmaceuticals with a criteria of <5% FNR and two isotopes. The analysis led to the identification of 25 suspect analytes. Reference standards confirmed 19 of the 25 pharmaceuticals.

Another study tested analytical method accuracy across 25 research and commercial laboratories. The test consisted of single-blind surface water and drinking water samples with 22 spiked analytes, including pharmaceuticals, personal care products, and hormones at relevant concentrations in the environment. False positives for all the compounds were typically <5%, but bisphenol A, caffeine, 4-nonyn phenol, tert-octylphenol, and triclosan had rates >15%. False negatives were also observed with an overall rate of <5% for most compounds; however, steroid hormones and ciprofloxacin had higher rates. The method that had highest accuracy consisted of LC–QqQ-MS calibrated with isotope dilution.

**Microfluidic Devices and Real-Time Monitoring.** Gracioso Martins et al. developed an innovative microfluidic device that can perform rapid in-line quantification as low as 20 ng/L of l-proline. The authors use surface acoustic waves (SAW) to efficiently mix the sample and indicator reagent that are fed into a 100 μL chamber cast in polydimethoxysiloxane atop a microfluidic chip consisting of a single crystal piezoelectric material. A continuous flow injection into a microfluidic device is typically diffusion-limited; therefore, by achieving efficient mixing, it enhances the detection of a chemiluminescent species, tris(2,2’-bipyridyl)-dichlororuthenium(II) hexahydrate, a common reagent used to detect pharmaceuticals, illicit drugs, and pesticides. Power, duration, and orientation of the SAW input were optimized.

A nanochannel-based electrochemical sensor was developed for real-time detection of the pharmaceutical ibuprofen in water. A nanoporous alumina membrane placed over a gold sensor where nanochannels (200 nm in size) provided a confined environment for ibuprofen to bind specifically to antibodies. Antibodies were fixed onto the gold sensor, where molecules can bind and produce a disturbance in the charged layer. The change in the charged layer is then amplified by the summation of individual perturbations, allowing detection of molecules at very low concentrations (0.25 ng/L). This sensor was able to detect ibuprofen in river waters. However, it might be possible that chemicals that are added during drinking water treatment may interfere with the sensor, as in the case for drinking water measurements.

**Bioassays.** A chemical and bioanalytical study investigated the presence of synthetic steroids in river water that receives pharmaceutical and WWTP discharges. Polar organic compound integrative samplers (POCIS) were used upstream, between pharmaceutical and WWTP discharges, and downstream. In vitro bioassays showed the occurrence of xenobiotic and steroid-like activities, including high glucocorticoid, antimineralocorticoid, progestogenic, and pregnant X receptor-like activities. Chemical analysis identified dexamethasone, spironolactone, and 6-alpha-methylprednisolone as major contributors to corticosteroid activities and levonorgestrel as the main contributor to progestogenic activities. In contrast, estrogenic activity in river samples was very low, suggesting the importance of understanding the effects of corticosteroids and progesterogens on fish. Bioassays also detected known and other unknown compounds that were not identified with chemical analysis.

Escher et al. tested in 10 different laboratories more than 103 in vitro bioassays for a common set of 10 water samples collected in Australia, including WWTP effluents, recycled water, stormwater, surface water, and drinking water. Interestingly, the most responsive bioassays were related to xenobiotic metabolism (pregnane X and aryl hydrocarbon receptors), hormone-mediated modes of action (related to estrogen, glucocorticoid, and antiandrogen activities), reactive modes of action (genotoxicity), and adaptive stress response pathways (oxidative stress).

**Drinking Water and Swimming Pool Disinfection Byproducts.**

**Drinking Water DBPs.** DBPs are an unintended consequence of killing harmful pathogens in drinking water, and they are formed by the reaction of disinfectants (chlorine, chloramines, ozone, chlorine dioxide, UV) with natural organic matter (NOM), bromide, and iodide in source waters. Many anthropogenic pollutants can also form them. For example, in this Review, DBPs are reported from iodinated X-ray contrast media (ICM) and other pharmaceuticals and personal care products as well as a flame retardant. Potential health risks from...
DBPs include cancer (bladder and colorectal), miscarriage, and birth defects, with bladder cancer showing the most consistency in human epidemiologic studies from several countries. In addition to the study of DBPs arising from the disinfection of pollutants, new research continues to focus on toxicologically important DBPs (iodo-DBPs, bromo-DBPs, nitrosamines, halobenzoquinones), and some researchers are integrating chemistry with toxicology. Recycled water is also becoming an important focus as freshwater resources are becoming more limited, and treatment of seawater, whether for desalination for potable drinking water or for treating ship ballast water, which has also become important due to an international treaty that will soon go into effect. Swimming pool research continues to be a hot area of research, with swimming in pools being a significant source of exposure to DBPs (some can be inhaled or permeate the skin), and asthma has been frequently observed in human epidemiology studies of elite swimmers. Finally, new analytical methods continue to be developed, both for newly identified DBPs and for other toxicologically important ones.

Several DBPs are included on the new Draft CCL-4, including 5 nitrosamines: NDMA, N-nitrosodiethylamine (NDEA), N-nitrosodipropylamine (NDPA), N-nitrosodiphenylamine (NDPhA), and N-nitrosopyrrolidine (NPRY), two aldehydes (formaldehyde and acetaldehyde), and chlorate (http://www2.epa.gov/ccl/draft-contaminant-candidate-list-4-ccl-4).

**New Health Effects Information.** While the focus of this Review is on chemistry, there are a few highly significant health effects studies published the last 2 years that are important to highlight. First, Zeng et al. published a study on the effects of DBPs on semen quality for a population of >2000 men in Wuhan, China. Trichloroacetic acid (TCAA) was measured as a biomarker of exposure in urine using liquid–liquid extraction with MTBE and GC-electron capture detection (ECD) analysis. Results showed 253 men (13%) with sperm motility below the World Health Organization (WHO) reference level (<20 million/mL), 1128 men (56%) with sperm motility below the WHO reference level (<50% motile), and 206 men (10.2%) had sperm counts below the reference (<40 million). Significant positive associations were found between urinary TCAA levels (above the lowest quartile, 6.0 µg/L) and each adverse outcome, suggesting that DBPs may contribute to decreased semen quality in humans. These results were consistent with previous toxicological data, including a recent U.S. EPA study of drinking water concentrates in rats.

A new toxicology study by Yang et al. answered a lingering question regarding whether chloraminated waters with high bromide and iodide might have higher toxicity than chlorinated waters with high bromide and iodide. As mentioned earlier, iodo-DBPs are generally much more genotoxic than chlorinated and brominated DBPs, and they are increased in formation with chloramination. However, chloramination will also significantly lower the levels of regulated THMs and HAAs (and other DBPs) when compared to chlorination. So, it was not known whether the formation of iodo-DBPs would offset the lowered levels of other toxic DBPs, causing the relative toxicities of chlorinated and chloraminated water to switch places. Results from this study showed just that. With low levels of bromide and iodide in source waters, chloraminated drinking water was significantly more genotoxic than these same waters treated with chloraminates. However, with high levels of bromide and iodide (consistent with higher levels in real source waters), the genotoxicity dose–response curves switched, with chloraminated water significantly more toxic than chlorinated water. Also both waters (chloraminated and chlorinated) were much more genotoxic with higher levels of bromide and iodide present as compared to treated source water with low levels of bromide and iodide, indicating that iodinated and brominated DBPs are the forcing agents for genotoxicity.

A new study also showed an increase in antibiotic resistance with exposure to mutagenic DBPs. In this study by Lv et al., exposure of *Pseudomonas aeruginosa* to dibromoacetic acid, dichloracetonitrile, bromate, and 3-chloro-(4-dichloromethyl)-5-hydroxy-2(5H)-furanone (MX) resulted in resistance to 10 individual antibiotics and to multiple antibiotics. Resistance to norfloxacin and polymycin B was increased >10X compared to controls, MX increased resistance the most, consistent with its higher mutagenicity. Results showed that mutagenic activities of these DBPs could induce antibiotic resistance, even multidrug resistance.

Lyon et al. published a very nice integrated chemical and toxicological investigation of UV–chlorine and UV–chloramine treated drinking waters. For this study, medium pressure–UV followed by chlorine or chloramine was used to treat NOM concentrations with and without nitrate and iodide spiking. The use of concentrated NOM allowed the volatile DBPs to be conserved and provided a concentrated aqueous DBP mixture that could be used directly in the *in vitro* cytotoxicity assay conducted with normal, non-neoplastic human colon cells. Results showed that the nitrate-spiked UV–chlorine treated waters had higher cytotoxicity than either nitrate-spiked chlorinated water (without UV) or with UV–chlorine treated waters without nitrate added. This suggests that nitrate was responsible for the formation of cytotoxic DBPs during UV–chlorine treatment, which the authors suggested that trichloronitromethane may have contributed to this increase in cytotoxicity because its formation was increased by 150X with the use of UV. Samples treated with UV–chloramine were more cytotoxic than those treated with chloramine only, and this was further increased in the presence of iodide, due to formation of iodo-DBPs.

**Recycled Water.** Because of continued population growth and limited water resources, there is growing interest in the use of recycled wastewater for potable use. For example, the world’s largest indirect potable reuse system in Orange County, California, uses advanced treatment with microfiltration, reverse osmosis (RO), and UV–C with hydrogen peroxide, following conventional treatment, to extensively purify wastewater. Recycled water is also an expanding area of research, due to interest in understanding and improving the removal of contaminants in these systems, as well as DBPs that can be formed in them. Recycling wastewater presents challenges for DBPs because effluent organic matter can be very different and more complex that typical NOM in conventional drinking water and can also contain many more anthropogenic contaminants to form different levels and types of DBPs upon disinfection. Also, because many DBPs are not well removed by RO membranes, the control of their formation prior to membrane treatment is important. Doederer et al. published an excellent study that examined factors affecting the formation of DBPs in the production of high-quality recycled water from secondary wastewater effluents in Queensland, Australia. The effect of reaction time with disinfectants was investigated as well as temperature and disinfectant (chlorine or chloramines). Contact time with chlorine was recognized as the major factor influencing DBP formation during chlorination,
except for brominated THMs and dibromoacetanitride, for which pH had more effect. Temperature had the least effect. Using a pH of 8.5, concentrations of most DBPs were lower for waters treated with chloramines; reaction time was a significant factor for the formation of trichloronitromethane, chloroform, trichloroacetanitride, dichloroacetanitride, and bromochloroacetanitride, while pH was the major factor for other DBPs.

Dai et al. reported the discovery of a new nitrosamine, N-nitrosodiethanolamine (NDELA) as a significant component of total nitrosamines in recycled wastewater. 146 NDELA was measured using a new method using isotope dilution (with NDELA-d₈) and LC−MS/MS. NDELA was targeted because triethanolamine is widely used for pH control in cosmetics and shampoos, and NDELA has been previously found in cosmetics. It accounted for ~6% of the total nitrosamines and, in some cases, exceeded levels of NDMA and other nitrosamines measured in these waters. Four water recycling facilities using advanced treatment (microfiltration, RO, and UV or advanced oxidation) were included in this study. Ozone and chloramines were found to increase NDMA concentrations up to an order of magnitude, while chloramines increased NDELA levels in some cases. Total nitrosamine concentrations (as measured by the total nitrosamine (TONO) assay) increased by only 38–89% during ozonation and 23–65% during chloramination, suggested that nitrosamines upstream of disinfection may be more significant than their formation as DBPs. Among the advanced treatments studied, RO and UV−H₂O₂ were found to reduce the levels of specific nitrosamines to below detection.

**Seawater DBPs.** An excellent review on DBP formation from seawater desalination was published by Kim et al. 147 Because chemical disinfection is used in pretreatment at desalination plants to control biofouling and also for postdisinfection of desalinated water, DBPs can form. This review discussed DBP formation in pretreatment and postdisinfection using chlorine and other disinfectants as well as DBP rejection by RO membranes and formation in the distribution system. Future research needs to be discussed included systematic DBP studies for unregulated, emerging DBPs, characterization of the seawater organic matter, reactions of disinfectants with antiscalants, total organic halogen (TOX) changes during desalination treatments, DBP formation in blended waters (seawater blended with other waters), DBPs produced from innovative membrane technologies, and toxicology of desalinated waters.

Werschkun et al. published a review outlining emerging risks from ship ballast water treatment. This is important because the International Ballast Water Management Convention will soon require the disinfection of ship ballast water to control the spread of invasive species across the world. 148 Approved disinfection systems based on chlorine (generated in situ by seawater electrolysis or from hypochlorite) predominate, followed by ozone, peracetic acid, and chlorine dioxide (in this order). DBPs formed in these scenarios may pose a risk to aquatic life in ship harbors as well as to ship workers. Because seawater contains high levels of bromide, chlorination will result in high levels of brominated DBPs. While there is not yet much research on DBPs from ballast water, some DBPs have been identified in land-based disinfection studies, including halo-methanes, acetonitriles, amines, phenols, acetic acids, and inorganics.

Gonsior et al. used ultra-HR-MS (with a FTICR mass spectrometer) to investigate the bromination of marine DOM following full-scale electrochemical ballast water disinfection. 149 Results showed 462 distinct bromo-DBPs. New DBPs were identified for the first time, including 2,2,4-tribromo-5-hydroxy-4-cyclopentene-1,4-dione and tribromoethenesulfonate, whose core structure of tribromoethene has important toxicological implications. On the basis of these results, the authors suggested that electrochemical and direct chlorination of ballast water in estuarine and marine systems should be approached with caution. Peracetic acid (PAA) treatment of saline waters in the presence and absence of hydrogen peroxide was the focus of another study by Shah et al., who studied natural brackish waters and synthetic seawater in controlled laboratory experiments. 150 Hydrogen peroxide was found to reduce HOCl and HOBr to Cl⁻ and Br⁻, respectively, which resulted in limited formation of bromo- and chloro-DBPs when concentrations of H₂O₂ were greater than those of PAA. For PAA-treated waters with concentrations of PAA > H₂O₂ and high bromide levels, bromo-DBPs were formed primarily. In natural brackish waters, under this same scenario, bromoform, bromoacetic acid, dibromoacetic acid, and tribromoacetic acid were formed at levels up to 260 μg/L with doses of 150 mg/L PAA; however, these same brackish waters produced no THMs and only low levels of HAAs when [H₂O₂] > [PAA].

Iodinated DBPs resulting from disinfection of saline wastewater effluents were the focus of another paper by Gong and Zhang. 151 This study was initiated because Hong Kong uses seawater for toilet flushing, and disinfection of these saline wastewaters is carried out to prevent the introduction of harmful pathogens to coastal waters, which might form DBPs that might pose a risk to aquatic organisms. Precursor ion scan with LC−MS/MS was used to identify new polar iodo-DBPs generated in both the primary and secondary wastewater effluents, including a new class of DBPs: iodo-trihydroxybenzenesulfonic acid, which was also quantified. Organic precursors for this new class were found to be 4-hydroxybenzenesulfonic acid and 1,2,3-trihydroxybenzene. Formation pathways for these DBPs were also proposed. A new group of bromopyrrole DBPs was also reported for chlorinated saline wastewaters in Hong Kong by Yang and Zhang. 152 These new DBPs included tetrabromopyrrole, tribromochloropyrrole, tribromiodopyrrole, and tribromopyrrole, with tetrabromopyrrole as the predominant species. While 2,3,5-tribromopyrrole was reported in drinking water previously, this is the first time that this group of DBPs have been found in disinfected wastewater. A precursor ion scan with LC−MS/MS was used for their identification, and tetrabromopyrrole was found to cause significant developmental toxicity to the marine polychaetes, P. dumerilii. In another study, Liu and Zhang also found that new halophenol DBPs formed in chlorinated saline wastewater were toxic to marine algae. 153 In fact, these new DBPs, including bromo-, iodo-, and chloro-phenols, nitrophenols, -aldophenols, and carbboxylated phenols, were more toxic to *Tetraselmis marina* than haloacetic acids.

Chlorination and chloramination of aquarium seawater was the focus of another study by Zhang et al., who used GC-ECD to measure THMs, HAAs, and haloacetamides, including chlorinated, brominated, and iodinated species. 154 Raw seawater samples were collected from the big fish tank and the sea lion tank at the Beijing Aquarium and treated under controlled conditions in the laboratory. In the real situation in this large aquarium, preozone is used for treatment, followed by postchlorine dioxide treatment for the mammal tanks. For this study, the effect of organic precursors, Br⁻, and...
preozonation were investigated. An increase in bromide concentration from 3 to 68 mg/L enhanced formation of most DBPs (except HAAs) and increased bromine substitution. Preozonation reduced formation of all DBPs in chlorinated water and also iodo-THMs in chloraminated water.

**Formation and Fate.** Changes in dissolved organic matter during drinking water treatment was the focus of another study by Gonsior et al., who used ultra-HR-MS (resolution of 500 000 at m/z 400) with a FTICR-mass spectrometer and NMR to measure DBPs formed following flocculation, sand filtration, and chlorination at a drinking water plant in Sweden.\(^{155}\) While half of the chromophoric DOM was removed in flocculation, 4−5 mg/L of DOC remained. Approximately 800 MS ions containing halogen atoms were detected; molecular formulas were assigned using HR-MS. The most abundant peaks had formulas of C\(_5\)H\(_{10}\)O\(_3\)Cl\(_6\)Br\(_2\), CHO\(_2\)Cl\(_2\)Br\(_2\), and C\(_5\)H\(_{10}\)O\(_3\)Cl\(_3\)Br\(_2\). \(^{1}H\) NMR showed a 2% change in the overall signals following chlorination, which supported a significant change in DOM in the formation of DBPs.

Chu et al. investigated the impact of UV−H\(_2\)O\(_2\) preoxidation on the formation of haloacetonamides and other nitrogenous (N-)DBPs formed during chlorination.\(^{156}\) This study was important because advanced oxidation processes using UV and hydrogen peroxide are being explored for treatment of trace pollutants, particularly for recycled wastewater. Results showed that UV−H\(_2\)O\(_2\) treatment at typical doses (585 mJ/cm\(^2\) and 10 mg/L, respectively) for contaminant removal was successful for controlling haloacetonamides and other N-DBPs in chlorinated drinking water. However, low pressure−UV and H\(_2\)O\(_2\) preoxidation alone did not significantly change total haloacetamide formation following chlorination, and H\(_2\)O\(_2\) preoxidation of iodide-containing waters resulted in the formation of diiodoacetamide and increased utilization of bromide.

The importance of dissolve organic nitrogen (DON) and monochloramine as nitrogen sources were reported in a study by Chuang and Tung.\(^{157}\) This study investigated precursors and kinetics for the formation of two DBPs, trichloronitromethane (TCNM) and dichloroacetonitrile (DCAN), using \(^{15}\)N-labeled monochloramine and GC/MS. Results showed that aromatic NOM was an important precursor in their formation, TCNM and DCAN that originated from DON followed second order kinetics, formation was faster with DON precursors as compared to monochloramine, and 4-hydroxybenzaldehyde was recognized as an important precursor during chloramination of natural waters.

An interesting study by Pan et al. evaluated the effect of boiling drinking water on DBPs and the resulting toxicity of the water.\(^{158}\) UPLC−MS/MS with precursor ion scanning was used for analysis as well as a volatile total organic halogen (TOX) analysis. Results showed a reduction of halogenated DBPs and accompanying mammalian cell cytotoxicity following 5 min of boiling simulated chlorinated tap water. In this boiled water, bromo-DBPs were reduced by 63%, of which 40% volatilized and 23% was converted to Br\(_2\); chloro-DBPs were reduced by 61%, of which 44.4% was volatilized and 16.7% was converted to Cl\(_2\). Most polar brominated DBPs were thermally unstable during the boiling process, degrading by decarboxylation or hydrolysis. A few aromatic brominated DBPs increased after boiling through decarboxylation of their precursors.

Effects of wildfire on the reactivity of terrestrial-derived DOM with chlorine and chloramines was evaluated by Wang et al.\(^{159}\) DOM was collected from burned forest detritus following the 2013 Rim Fire in California and reacted under controlled laboratory conditions. Overall, lower extractable organic carbon and organic nitrogen were present in the burned DOM, and DBP formation was greatly reduced for THMs and HAAs. However, both white (highly burned) and black ashes (moderately burned) showed higher reactivity in forming more toxic N-DBPs, haloacetonitriles and NDMA. In another interesting study, chironomid larvae were examined as precursors in the formation of chloramination DBPs.\(^{160}\) These larvae were recognized for the first time as potential precursors of DCAN, trichloroacetonitrile (TCAN), chloroform, dichloroacetic acid (DCAA), Trichloroacetic acid (TCAA), chloropicrin, and chloral hydrate. Increased NH\(_4\)Cl dosage and reaction time resulted in increased formation of most DBPs, and the formation of TCAN, DCAN, and chloral hydrate initially increased over time before reaching a plateau that was likely due to hydrolysis of functional groups (e.g., formation of the amides from the acetonitriles).

Heeb et al. published a critical review on the oxidative treatment of bromide-containing waters and the formation of bromine and its reactions with inorganic and organic compounds.\(^{161}\) Different oxidant species and their reaction kinetics were discussed, including Br\(_2\), BrCl, and Br\(_2\)O that have been recently recognized as important in some scenarios. Of the organic compounds, phenols and sulfur-containing compounds show a very high reactivity with bromine, and many inorganic species also show high reactivity with bromine, including ammonia, Fe(III), As(III), and many inorganic anions.

**Nitrosamines.** Leaching of NDMA precursors has been previously observed from virgin nanofiltration (NF) membranes, and Ersan et al. conducted a systematic study to examine this phenomenon from different types of NF membranes and determine whether cleaning techniques could reduce the leaching.\(^{162}\) All 5 NF membranes studied showed leaching of NDMA precursors (up to 450 ng/L NDMA formation potential), along with variability from different sections of the same membrane. It was suggested that precursor leaching is caused by incomplete reaction of polymers or additives in the manufacturing process of these membranes. Even after membranes had been washed with ~3900 L of purified water, leaching of precursors still continued. Washing with 1 mg/L chlorine solution was found to be the most effective for reducing NDMA precursors.

Park et al. investigated the NDMA formation potential of amine-based water treatment polymers, examining the effects of in situ chloramination, breakpoint chlorination, and preoxidation.\(^{163}\) Polymers included those containing polyamine and poly-DADMAC (diallyldimethylammonium chloride). Results revealed that dichloramine formation was a critical factor in NDMA formation during in situ chloramination, and the highest levels occurred near the breakpoint chlorination. Polymer chain degradation and transformation of released dimethyamine and other intermediates were important factors affecting NDMA formation from the polymers in preoxidation followed by postchloramination.

A particularly innovative idea was pursued by Teng et al. to synthesize a new quaternary phosphonium cation polymer that could be used in the place of DADMAC in drinking water treatment, to eliminate the formation of NDMA.\(^{164}\) This new polymer, poly(diallyldimethylphosphonium chloride) (poly-DADEPC), involved the substitution of the nitrogen atom of poly-DADMAC with a phosphorus atom. As predicted, the use of
this new polymer resulted in no NDMA or other nitro-DBPs formed even under strong nitrosation conditions. In addition, this polymer achieved coagulation performance comparable to poly-DADMAC for particle and DOM removal. In another study, Kosaka identified a new NDMA precursor in sewage containing industrial effluents.\textsuperscript{165} This precursor, 1,1,5,5-tetramethylcarbohydrazide (TMCH), was found using UPLC−MS/MS, UPLC−TOF-MS, and NMR spectroscopy. This work is important because wastewater DOM is recognized as an important source of nitrosamines, but few organic precursors have been identified. Upon ozonation, TMCH formed a mean molar yield of 140% NDMA from 4 different waters, and its contribution to total NDMA precursors following ozonation was 43−72%, 51−72%, and 42−60% in primary, secondary, and final wastewater effluents.

In another significant development, tobacco-specific nitrosamines were identified as a new class of DBPs formed in chloraminated drinking water.\textsuperscript{166} In this study by Wu et al., a new, sensitive SPE-LC−MS/MS method was developed to investigate their potential occurrence in wastewater and as DBPs in drinking water. 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) was detected in controlled laboratory experiments as a DBP, while (methylnitrosamino)-1-(3-pyridyl)-1-butaneone (NNK) was found as a DBP and also as a wastewater contaminant. Both were found in formation potential tests of wastewater-impacted drinking water plant influents, but only in one of the seven drinking water plants sampled (a plant that had high ammonia in its source waters and did not achieve breakpoint chlorination). These new nitrosamines were found at levels 100× lower than NDMA, so they are believed to have a lesser contribution to nitrosamines in drinking water. In a follow-up study, Chen et al. identified precursors and mechanisms of formation for these tobacco-specific nitrosamines.\textsuperscript{167} Results showed that the tobacco-specific nitrosamines were formed by specific tobacco alkaloids during chloramination, including nicotine. Experiments included chloraminating water-leached samples from three brands of cigarettes. In addition to NNAL and NNK being formed from nicotine, N-nitrosornicotinone was found to form from normonocotine, and N-nitrosobasabasine from anabasine. Pathways of formation were also proposed.

Finally, Marti et al. investigated the formation of NDMA from the ozonation of model compounds and discovered 6 new NDMA precursor compounds not previously reported.\textsuperscript{168} Of the 31 N-containing compounds investigated, those with hydrazine and carbamate groups were particularly reactive, with molar yields of 61−78% for three of them. Bromide concentrations also played a role for three compounds: 1,1-dimethylhydrazine, acetone dimethylhydrazone, and dimethyl-sulfamide but did not enhance NDMA formation for other precursors.

Swimming Pool DBPs. Swimming pool DBPs continue to be an active area of research. Two excellent reviews were written the last 2 years on DBPs and other contaminants in pools. Teo et al. reviewed the occurrence, implications, and control of chemical contaminants in pools, including DBPs.\textsuperscript{169} Chowhury et al. reviewed the occurrence, implications, and future needs for DBPs in swimming pools.\textsuperscript{170} Yeh et al. published an excellent study combining chemistry and toxicology for investigating DBPs in outdoor, indoor, and baby pools in Brisbane, Australia, along with their dynamics after a complete water renewal.\textsuperscript{171} Overall, DBP levels were higher in other countries, with DCAA and TCAA the dominant DBPs, up to 2600 μg/L, exceeding Australia drinking water guidelines (100 μg/L). Chlorinated DBPs were higher in pools vs tap water and brominated DBPs decreased with pool water age. Quantified HAAs accounted for 35−118% of the absorbable organic halogen (AOX), but <4% of the cytotoxicity measured and <1% of the oxidative stress response and genotoxicity observed.

Manasfi et al. investigated the formation of DBPs from the popular UV filter, benzophenone-3 (BP-3) in chlorinated seawater swimming pools.\textsuperscript{172} BP-3 is a common ingredient in sunscreens and has been shown to be an important contaminant in pools. In seawater pools, high levels of bromide will result in the formation of aqueous bromine (HOBr) when chlorine is added (either with bleach or by electrolysis of the seawater). This study showed the formation of bromoform and 9 other DBPs formed by the reaction of BP-3 with chlorine in artificial seawater. UV treatment of swimming pool water was the focus of another study by Spiliotopoulou et al., who found that medium pressure-UV with and without chlorine resulted in changes in 7 of the 11 volatile DBPs studied.\textsuperscript{173} In particular, DCAN and dichloropropanone showed small but significant increases. UV irradiation was found to accelerate THM formation (after postchlorination), but their overall concentrations did not increase.

DBPs of Pollutants. As mentioned earlier, pollutants can also often serve as precursors to DBPs, and they are typically introduced into drinking water sources due to their incomplete removal in wastewater treatment. DBPs have been reported from pharmaceuticals, antibacterials, pesticides, hormones, UV filters, bisphenol A, parabens, surfactants, musks, textile dyes, and algal toxins. The first report of a DBP from a flame retardant is also included for the first time in this review (see below). Transformation of pharmaceuticals in drinking water treatment was the focus of a detailed review by Postigo and Richardson.\textsuperscript{86} Examples included the formation of NDMA from the popular antibiotic azithromycin, formation of iodoacetic acid from the X-ray contrast media iopamidol, formation of hydroquinone from penicillin, and formation of NDEA from lidocaine. These reactions occur with the disinfectants, monochloramine, chlorine, chloride dioxide, and monochloramine, respectively. DBPs are also reported from ozone. Detailed reaction mechanism pathways are shown for many.

Wendel et al. reported the transformation of iopamidol during chlorination, detailing the formation of high molecular weight (MW) DBPs identified using LC−HR-MS/MS, MS\textsuperscript{a}, and NMR spectroscopy, with NMR data collected for several DBPs isolated using preparative-LC.\textsuperscript{34} Other iodinated X-ray contrast media (ICM) did not show appreciable reactivity with chlorine, and chlorine was more reactive than monochloramine (which is different from what is observed with reactions of iodide salt). Side chain cleavage was observed as well as the exchange of iodine by chlorine, and an overall transformation pathway was proposed. Mammalian cell cytotoxicity measurements revealed that the presence of iopamidol enhances the toxicity of chlorinated waters, likely due to the formation of toxic iodo-DBPs. Ye et al. investigated the formation of iodo-THMs during chlorination or chloramination of five ICM in the presence of NOM.\textsuperscript{174} Consistent with what has been found in earlier studies, reactions of ICM in the absence of NOM produces only trace-level iodo-THMs, but the presence of NOM resulted in much higher levels. This study involved the investigation of two ICM not investigated previously, histodenz and iodixanol, and the reactivity order observed was iopamidol
are commonly observed in drinking water. Methadone could contribute significantly to NDMA levels that are reported in the literature for surface waters. As a result, NDMA in molar yields of 23–70% upon chloramination. Methadone is a drug that mitigates heroin withdrawal symptoms and is also used for chronic pain. It was found in surface water samples, ranging from 1 to 2256 ng/L, and was responsible for 1–10% of NDMA formation potential from surface waters and up to 62% in wastewater. Low ng/L NDMA formation potential was predicted from levels of methadone reported in the literature for surface waters. As a result, methadone could contribute significantly to NDMA levels that are commonly observed in drinking water.

Bulloch et al. reported DBPs from select pharmaceuticals and personal care products (PPCPs) in secondary and tertiary treated wastewaters from Southern California. This study involved the sampling of 10 WWTPs with 4 different treatment regimens for PPCPs, alkylphenols, and 21 of their halogenated DBPs. Chlorinated and brominated standards and isotopically labeled standards were synthesized and purified to confirm DBPs from salicylic acid, bisphenol A, gemfibrozil, naproxen, diclofenac, technical 4-nonylphenol, and 4-tert-octylphenol using LC–MS/MS. Concentrations of parent compounds ranged from <10 to 3830 ng/L, and DBPs from <4 to 370 ng/L, with the highest being dibromo-nonylphenol. The highest concentrations of parent compounds were in wastewater with no tertiary treatment. DBPs were found in all plants sampled, with significant formation of dichloro-salicylic acid, dibromo-salicylic acid, bromo-naproxen, dichloro-nonylphenol, dibromo-nonylphenol, and chloro-gemfibrozil. Salicylic acid was the most readily transformed compound.

Armbruster et al. reported the formation of DBPs from the chlorination of the antidiabetic drug metformin. Two new DBPs were reported, one being a cyclic dehydro-1,2,4-triazole derivative with a molecular formula of C₈H₈Cl₂N₃ with intense yellow color and the other a chloroorganic nitrile that was a decomposition product of the first DBP. GC/MS, LC–TOF-MS, ¹H NMR, and single-crystal X-ray analysis were used for structural determination. To the best of our knowledge, this is the first time that single-crystal X-ray analysis has been used to confirm a structural assignment of a DBP from a pollutant. This work represented the most complete confirmation of a tentative assignment possible without an authentic standard, which would have been very difficult in this case. The transformation of metformin was observed at trace levels of reactants during reactions relevant to drinking water treatment. While the first product did not persist, the second one is likely to persist in drinking water distribution systems. Reaction mechanisms for both are proposed.

The first DBPs reported from a flame retardant were published in another study by Pang et al. The most widely used brominated flame retardant, tetrabromobisphenol A, was found to react appreciably with potassium permanganate to form two major DBPs, 4-(2-hydroxyisopropyl)-2,6-dibromophenol and 4-isopropylene-2,6-dibromophenol, and 5 minor DBPs, including 2,6-dibromophenol, 2,6-dibromo-1,4-benzoquinone, and three dimers. Permanganate is sometimes used in drinking water treatment as a preoxidant to control taste and odors and remove color, iron, and manganese. These DBPs were identified using precursor ion scanning with ESI-MS/MS, and reaction pathways for their formation are proposed. Another study by the same research group investigated the oxidation of bromophenols with potassium permanganate, where they found the formation of brominated dimeric products, including hydroxylated polybrominated diphenyl ethers and hydroxylated polybrominated biphenyls.

New Methods. Kolkman et al. reported a particularly creative method using stable isotope labeling (¹⁵N) of nitrate combined with HR-MS. This method was used to trace N-DBPs after medium pressure (MP)-UV treatment. The motivation for this study came from the observation of increased mutagenicity following MP-UV treatment of drinking water, which was believed to be possibly due to reaction of photolysis products of nitrate with NOM and its photolysis products. MP-UV treatment of water containing NOM and nitrate was found to form 84 different N-DBPs, ranging from 1 to 135 ng/L benzotrid-d₄ equivalents, with a summed concentration of 1.2 μg/L benzotrid-d₄ equivalents. Structures for 3 of these DBPs were confirmed: 4-nitrophenol, 4-nitroanisole, and 2-methoxy-4,6-dinitrophenol, and 22 of these N-DBPs were later found in real drinking water samples from The Netherlands that used MP–UV–H₂O₂ and granular activated carbon (GAC) treatment.

Wang et al. reported a new method using SPE with UPLC–MS/MS for quantifying halobenzoxoquine and hydroxyhalobenzoquinone DBPs at sub ng/L in drinking water. Recoveries of 68–96% were achieved, and this method was used to confirm that hydroxylated halobenzoquinones were formed from the less stable halobenzoquinones in distribution systems. In addition, their in vitro toxicity was investigated with CHO-K1 cells, and their IC₅₀s ranged from 15.9 to 72.9 μM. Deng et al. reported a new ESI-MS/MS method for differentiating chlorine substitution in DBP formation from model compounds. This method uses precursor ion scanning for m/z 35 (chlorine) and relies on different collision energy ranges (5–7 eV and >15 eV) for a chlorine atom substituted on an aliphatic group and on an aromatic group, respectively. It was used to predict the structures of intermediates, and it revealed transformation pathways during the chlorination of 4-amino-2-chlorobenzoic acid and phenylalanine.

Fourteen chlorinated and brominated haloalkanes were the focus of a SPME–GC/MS method developed by Serrano et al. This “green” method was solvent-free, only requires 12 mL of water with a 15 min extraction, and provides low detection limits (15–600 ng/L), good linearity from 0.05 to 2 μg/L and 100–2000 μg/L, and good repeatability (relative standard deviation [RSD] < 7%). SPME was also used with GC/MS and GC-ECD in a new method proposed by Domínguez-Tello et al. for quantifying iodo-THMs and regulated THMs in drinking water. A two-phase hollow fiber was used for extraction. Detection limits of 1–3 ng/L and 3–44 ng/L were achieved, respectively, and relative recoveries ranged between 97 and 105%. This method was applied to the measurement of these DBPs in drinking water from southwest Spain, which used different treatment processes. Fourteen nitrosamines, including traditional nitrosamines and tobacco-specific nitrosamines, were the focus of another study.
method by Qian et al. This method used custom-built SPE cartridges with a vinyl/divinylbenzene polymer for extraction and LC−MS/MS for detection. A lower volume of water (100 mL) was required for this method as compared to EPA Method 8310 and other methods for nitrosamines, and it provided extremely low detection limits of 0.01−2.7 ng/L. This method was subsequently demonstrated in drinking water systems in the U.S. and Canada, in which NDMA, NDEPhA, and the tobacco-specific nitrosamine NNAL were identified and quantified. Finally, Spahr et al. reported a new GC-isotope ratio–MS method for measuring compound-specific isotope analysis of $^{13}$C/$^{12}$C, $^{15}$N/$^{14}$N, and $^2$H/$^1$H ratios of NDMA in aqueous solutions. This method has relatively high detection limits (45 μg/L), but it can be used to pinpoint precursors of NDMA and understand mechanisms of formation in controlled laboratory reactions. To that end, the authors used this method to determine whether the dimethyamine group in the commonly found pharmaceutical ranitidine is directly involved in forming NDMA.

**SUNSCREENS/UV FILTERS**

Sunscreens, cosmetics, and other personal care products, such as shampoos and hair dyes, contain UV filters that are used to protect against sun damage to skin or hair. Organic UV filters (e.g., benzophenone-3) work by absorbing UV light, and inorganic UV filters (e.g., TiO$_2$, ZnO) work by reflecting and scattering UV light. Most of these are lipophilic compounds (low water solubility) with conjugated aromatic systems that absorb UV light at 280−315 nm (UVB) and/or 315−400 nm (UVA). Sunscreen products often contain a mixture of several UV filters, often in combination with inorganic micropigments.

They are frequently found in environmental waters, introduced directly from activities such as swimming and sunbathing in coastal seawaters, lakes, and rivers or indirectly, through treated wastewater following showering, bathing, washing clothes, and other such activities. Levels can reach μg/L in the environment. Toxicity concerns include estrogenicity (some can have estrogenic effects similar to E2), developmental effects, and toxicity to marine organisms. Increasing research is also pointing to UV filters used in sunscreens being responsible for the bleaching and death of coral reefs in many locations around the world. Evidence supports that this bleaching is through induction of viral infections, which kills the symbiotic microalgae zooxanthellae.

Sanchez-Quiles and Tovar-Sanchez published an excellent review entitled, “Are sunscreens a new environmental risk associated with coastal tourism?” The authors discuss the main components of sunscreens, analytical methods used for their measurement in environmental samples, sources of UV filters in the marine environment, photolysis, photoreactivity, and phototoxicity of UV filters, concentrations and toxicity of organic and inorganic UV filters, role of sunscreens as sources of pollutants in coastal waters, coastal tourism trends and use for sunscreens, and future perspectives. In total, 51 UV filters are permitted for use in the U.S., the EU, Canada, Australia, New Zealand, China, India, Japan, Korea, South Africa, Southeast Asia, and South America. Levels of UV filters reported in water samples range from low ng/L to μg/L levels.

Ramos et al. published an excellent review on analytical methods, properties, and occurrence of organic UV filters in the environment. Physicochemical properties discussed included their boiling points, solubilities, and log $K_{ow}$, which is an important parameter to predict whether these UV filters will be present in the water (low $K_{ow}$) or partition to sediments (high log $K_{ow}$) and potentially bioaccumulate in biota. Analytical methods summarized include several different SPE techniques, various derivatization procedures, and analysis using GC/MS, GC/MS/MS, LC−UV, LC−MS/MS, and UPLC−MS/MS. This article provides a handy table that lists the specific methods, their limits of detection, and recoveries. The toxicity of organic UV filters is also discussed as well as their occurrence in surface waters, groundwater, seawater, tap water, swimming pool water, sediments and soils, and biota. Highest levels have reached 0.3 mg/L in rivers for the most studied class, the benzophenones. Organic UV filters have been found in all water matrices studied, with levels ranging from ng/L to μg/L. Swimming pools are also a sink for UV filters as well as a source of exposure to their chlorinated DBPs.

Interesting occurrence studies continue to be published. Tsui et al. published a large international study of 12 UV filters in 8 cities from 4 countries (China, the U.S., Japan, Thailand) and from the North American Arctic. UV filters were widely found, including waters from the Arctic, with median concentrations <250 ng/L. Highest concentrations were found in surface waters from Hong Kong, with up to 2812, 4043, 5429, and 6812 ng/L for homosalate (HMS), ethylhexyl methoxycinnamate (EHMC), BP-3, and octocrylene (OC). SPE with LC−MS/MS was used for their measurement. The number of UV filters detected generally correlated with higher populations, and their presence in the Arctic was linked to a combination of insufficient wastewater treatment and long-range oceanic transport. Overall, BP-3 and EHMC had the highest detection frequencies and concentrations in recreational areas. A risk assessment concluded that these levels pose an ecotoxicological risk to marine ecosystems, including coral bleaching and reproductive effects on fish. In particular, BP-3 and EHMC posed 21% and 11% of the estimated risk for bleaching of hard corals at beaches in Hong Kong located near popular snorkeling areas.

Antarctic coastal environments were the focus of another interesting occurrence study by Emnet et al, who measured 4 UV filters as well as other personal care products and hormones in wastewater effluents, coastal seawater, sea ice, and biota. SPE, along with florilis cleanup, and GC/MS were used for their analysis in water, accelerated solvent extraction (ASE), along with SPE and florilis cleanup and gel permeation chromatography prior to GC/MS analysis, was used for biota measurements. Three UV filters (4-methylbenzylidine camphor (4-MBC), BP-3, and octyl methoxycinnamate (OMC)) were found in the sewage effluents, 4 UV filters (4-MBC, BP-3, 2,4-dihydroxybenzophenone-1 (BP-1), and OMC) were found in coastal seawaters and sea ice, and one UV filter (BP-3) was found in biota, with preferential accumulation in clams (up to 112 ng/g dry weight). Of all the contaminants measured, 4-MBC, BP-3, and OMC were among the 5 most detected compounds. UV filters and other emerging contaminants were found in seawater and biota at distances up to 25 km from the Research Station WWTP discharges, and these effluents, along with disposal of raw waste through sea ice cracks, were the sources of these contaminants to the Antarctic coastal environment.

Tsui et al. investigated the seasonal occurrence and removal efficiency of 12 organic UV filters in 5 WWTPs in Hong Kong. Using a newly developed LC−MS/MS method, 4-tert-butyl-4′-methoxyldibenzylmethane (BMDM), BP-1, BP-3,
Crista et al. reported the formation of two chlorinated DBPs. Phenolic ring to form a third DBP with two chlorines. Finally, found to undergo an additional chlorine substitution on the atom at position-3 on the phenolic ring (DBP 1), and (2) DBPs were formed by (1) chlorine substitution for a hydrogen in the presence of NOM. Unlike similar chlorination studies for a hydrogen on the methoxy-benzene ring and a dichloro- a monochloro-substituted product with a chlorine substituted into water. Following 24 h reactions, two DBPs were identified: Accurate mass measurement provided by the Q-TOF instrument, along with fragmentation obtained by MS/MS was important in their identification. Two DBPs were formed by (1) chlorine substitution for a hydrogen atom at position-3 on the phenolic ring (DBP 1), and (2) chlorination of the phenolic ring with simultaneous elimination of the ethyl group of the amine moiety (DBP 2). Product 1 was found to undergo an additional chlorine substitution on the phenolic ring to form a third DBP with two chlorines. Finally, Crista et al. reported the formation of two chlorinated DBPs formed by the reaction of the UV filter, BMDM with chlorine in the presence of NOM. Unlike similar chlorination studies that have been conducted in the past, these authors used two real commercial sunscreens (rather than the pure, isolated UV filters) for their chlorination studies. Both sunscreens had a sun protection factor (SPF) of 30, and they contained complex mixtures of other ingredients, including other organic and inorganic UV filters and preservatives. Reaction products were analyzed using UPLC with ethyl acetate, followed by solvent exchange into methanol and analysis using LC−MS. In contrast to pure BMDM, the sunscreen formulations were not readily soluble in water (as designed). As a result, there is a protective effect of the other constituents for the dissolution of BMDM into water. Following 24 h reactions, two DBPs were identified: a monochloro-substituted product with a chlorine substituted for a hydrogen on the methoxy-benzene ring and a dichloro-substituted product with two chlorines on this ring.

**BROMINATED AND EMERGING FLAME RETARDANTS**

Brominated flame retardants have been common ingredients in many commercial products, including children’s sleepwear, foam cushions in chairs and sofas, computers, plastics, and electronics. In particular, polyurethane foam can contain up to 30% by weight brominated flame retardants. They work by releasing bromine free radicals when heated, which scavenge other free radicals in the flame propagation process. Flame retardants are believed to have reduced fire-related deaths, injuries, and property damage. However, they are environmentally persistent and are present in locations far from where they were produced or used. Polybrominated diphenyl ethers (PBDEs) have been a popular ingredient in flame retardants since polybrominated diphenyls were banned ~30 years ago. They are lipophilic and bioaccumulate in animals and humans. PBDEs are composed of 209 possible congeners with 1–10 bromine atoms; 23 of these congeners are of environmental significance. The most significant health concern is development of neurotoxicity, but hormonal disruption and cancer are also of concern. In 2004, the European Union banned the use of the penta- and octa-BDEs and later, in 2008, banned deca-BDEs. In addition, the Stockholm Convention recently recommended deca-BDE be listed as a persistent organic pollutant (POP) (http://chm.pops.int/Implementation/PublicAwareness/PressReleases/OutcomesOfPOPRC11/tabid/4692/Default.aspx).

Following a voluntary halt in production of PBDE-based flame retardants in the U.S. in 2004, several U.S. states banned the penta- and octa-BDEs, and in December 2009, two U.S. producers of deca-BDE agreed to voluntarily phase it out in the United States because the deca-BDE had been shown to debrominate to form the more toxic penta and octa-BDEs. However, despite the halt in manufacture of most of these PBDEs in North America and Europe, they are still present in many consumer products previously sold and can be released into the environment during use and disposal. In addition, products containing them can still be imported from other countries. Four PBDEs, 2,2′,4,4′-tetrab-BDE (BDE-47), 2,2′,4,4′,5-penta-BDE (BDE-99), 2,2′,4,4′,5,5′-hexa-BDE (BDE-153), and 2,2′,4,4′,6-penta-BDE (BDE-100), and another brominated flame retardant, 2,2′,4,4′,5,5′-hexabromobiphenyl (HBB), were previously on the UCMR-2 in the U.S., and national occurrence data are available (http://water.epa.gov/lawsregs/rulesregs/sdwa/ucmr/data.cfm#ucmr2010).

New “emerging” flame retardants are also being discovered in the environment, e.g., bromophenols, bromophenyl ethers, brominated phenyl esters, other bromoaromatic compounds, and brominated and chlorinated cyclic aliphatic compounds, organophosphates, and chloro-organophosphates. Global production of brominated flame retardants is estimated at 100 000 to 180 000 tons per year. Some of these “emerging” flame retardants have been used for many years but were only recently discovered in the environment and some are new products that manufacturers have shifted to.

A few interesting human exposure studies are worthy of mention. In a study by Carignan et al., collegiate gymnasts in the U.S. were found to contain 4–6.5 times higher BDE-153 levels in their blood than the general population. Handwipe samples showed median levels of penta-BDE, 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (TBB), and (2-ethylhexyl)-2,3,4,5-tetrabromophthalate (TBPB) that were 2–3 times higher after practice compared to before practice. In addition, mean levels of penta-BDE, TBB, and TBPB were 1–3 orders of magnitude higher in gym air and dust than in private residences. Gymnastics training facilities contain a large amount of polyurethane foam in equipment, such as landing mats and loose foam pits. Also, as mentioned earlier, this polyurethane foam can contain high amounts of flame retardant material. Other new results show that contact with flame retardant-treated textiles, like in camping tents, can also be a source of exposure to flame retardants. In this study by Keller et al., paired samples of tent wipes and hand wipes from 27 individuals after tent setup were collected. Of the 11 tent fabric samples analyzed, 10 contained flame retardants, including tris(1,3-dichloroisopropyl)phosphate (TDCPP), BDE-209, triphenyl phosphate, and tetrabromobisphenol A, up to 37.5 mg/g (3.8% by weight). TDCPP and BDE-209 were the most frequently occurring, and a significant association between TDCPP in tent wipes and hand wipes was found, suggesting that contacting the tent material leads to transfer of the flame retardants to skin.

Wei et al. published an excellent review of the sources, occurrence, toxicity, and human exposure of organophosphorus flame retardants. Sources discussed include water, dust, air, sediment, soil, and biota, with routes of exposure through
dermal contact, dust ingestion, inhalation, and dietary intake. Release from consumer products and potential transport pathways are also discussed.

Several new methods have also been published. For example, Teo et al. created a new isotope dilution GC-electron ionization (EI)-MS/MS method for measuring five organophosphate flame retardants and plasticizers in water.198 Run time was only 15 min, and analytes included tributyl phosphate (TBP), tris(2-chloroethyl)phosphate (TCEP), tris(1-chloro-2-propyl)-phosphate (TCP), tris(1,3-dichloro-2-propyl)phosphate (TDCP), and triphenylphosphate (TPP). SPE was used for extracting 500 mL samples, and method detection limits ranged from 0.3 to 24 ng/L in purified water, tap water, seawater, surface water, secondary wastewater effluent, and swimming pool water. A new GC-ICPMS method was created by Novak et al. to measure six PBDEs in environmental waters.195 BDE-28, BDE-47, BDE-99, BDE-100, BDE-153, and BDE-154 were measured in 300 mL water samples extracted using tris-citrate buffer to desorb the PBDEs from suspended particles and humic acid and 2 mL of iso-octane. Limits of quantification were 0.109 ng/L. This method was subsequently demonstrated on river water and seawater samples.

Liu et al. created a new UPLC–Orbitrap-MS method to measure two novel brominated contaminants, tetrabromobisphenol A mono(2-hydroxyethyl ether) (TBBPA-MHEE), and TBBPA mono(glycidyl ether) (TBBPA-MGE), which are impurities of TBBPA derivatives used as flame retardants.196

In particular, TBBPA is an important brominated flame retardant that is widely found in the environment, and many impurities associated with their synthesis are becoming a concern for humans and wildlife. A previous study had identified these new brominated contaminants and showed their potential to bioaccumulate. For this new method, these two compounds (TBBPA-MHEE and TBBPA-MGE) were synthesized, and a new HR-Orbitrap method was developed to measure them at 0.9 and 0.8 ng/L method detection limits, respectively, in river water. Using this method, these compounds were detected in river water samples for the first time, including 3 factory wastewaters, domestic wastewaters, and seawater from China. UPLC–MS/MS was the focus of another method created by Kim et al., who measured 13 organophosphorus flame retardants and other contaminants in environmental waters.197 SPE was used for extraction, and limits of quantification ranged from 1.9 to 16 ng/L and 2.3–45 ng/L in river water and WWTP effluents. The method was subsequently used to determine these flame retardants in river water and WWTP effluents from Japan.

Several interesting occurrence studies have been published. For example, before they became more widely recognized and studied, the last 2 years has seen a large increase in the numbers of publications, with new methods developed and new occurrence and fate studies. Benzotriazoles have bicyclic heterocyclic structures with a five-membered ring containing three nitrogen atoms fused to a benzene ring. They are widely used as corrosion inhibitors (e.g., in engine coolants, antifreeze liquids, aircraft deicers, metal processing) and for silver protection in dishwashing detergents, due to their ability to form a thin protective film on the surface of metals.205 Benzotriazoles also prevent yellowing and degradation of polymers and other

Drinking water was the focus of another occurrence study by Li et al., who used UPLC–ESI-MS/MS to measure nine organophosphorus flame retardants in drinking waters from eight diverse cities in China.199 Cities included coastal, inland, developed, and less developed ones. Total levels ranged from 85.1 to 325 ng/L, with tris(2-butoxyethyl)phosphate (TBBPE), triphenylphosphate (TPP), and TCPP the most frequently observed. Boiling the tap water was found to increase some flame retardant concentrations (e.g., TBBPE) or decrease others (e.g., tributylphosphate). In addition, bottled water was also found to contain many of these flame retardants, with levels 10–25% lower than observed in tap water. Estebar also measured organophosphorus flame retardants (TBBPE, TCP, and TCEP) and other endocrine disrupting chemicals in tap waters from Madrid, Spain.200 Organophosphorus flame retardants were found at the highest levels, up to 165 ng/L.

Kim et al. measured hydroxylated, methoxylated, and parent PBDEs in water, soil, air, and vegetation from Busan, Korea.201 In total, 55 analytes were measured up to 87 ng/L in environmental waters, 0.22 ng/g in vegetation, 7.7 ng/g in soil, and 16 pg/m³ in air. Levels of hydroxylated BDEs were much higher in water samples than parent PBDEs, and methoxy-BDEs were much greater in air samples.

Interesting fate studies include one by Lin et al., who examined the formation of hydroxylated PBDEs from bromophenols.202 OH-PBDEs are of concern because they have elevated toxicity relative to the parent PBDEs, and while previous studies indicate they may be naturally produced in the environment to some extent, the mechanisms are not known. These results showed that bromophenols could oxidize with MnO₂ to form these hydroxylated PBDEs, revealing that they can be formed abiotically in the environment. In a related study, Lin et al. discovered that an enzyme (bromoperoxidase) found in marine red alga can also catalyze the formation of hydroxylated PBDEs from 2,4-dibromophenol and 2,4,6-tribromophenol when bromide and H₂O₂ are present.203 Reactions were pH dependent, with pH 6.5 yielding the highest levels. Finally, leaching from simulated landfills was the focus of another fate study conducted by Kajiwara et al.204 The authors measured PBDEs, tetrabromobisphenol A, tribromophenols, and hexabromocyclododecane in leachate samples collected from lysimeters during a 3.5-year study. Brominated flame retardant elution was immediate, and the presence of air reduced the levels observed. However, outflows were only 0.001–0.58% of the total brominated flame retardants in the waste, such that most remained in the lysimeters.

Benzotriazoles and Benzothiazoles

Benzotriazoles are one of the more recent emerging contaminant discoveries, and they have been included in this review on water analysis since 2007. While it took a few years before they were more widely recognized and studied, the last 2 years has seen a large increase in the numbers of publications, with new methods developed and new occurrence and fate studies. Benzotriazoles have bicyclic heterocyclic structures with a five-membered ring containing three nitrogen atoms fused to a benzene ring. They are widely used as corrosion inhibitors (e.g., in engine coolants, antifreeze liquids, aircraft deicers, metal processing) and for silver protection in dishwashing detergents, due to their ability to form a thin protective film on the surface of metals.205 Benzotriazoles also prevent yellowing and degradation of polymers and other
products, so they are used in common plastics, automobile parts, building materials, paint, skin creams, and shampoos. Benzotriazole (BTri) and tolyltriazole (a mixture of 4- and 5-methyl-1H-benzotriazole) are the most common ones used and found in the environment, but others such as S,6-dimethylbenzotriazole, S-methylbenzotriazole, 4-methylbenzotriazole, and S-chlorobenzotriazole are also used. Benzotriazoles are highly water-soluble, resistant to biological degradation, and only partially removed in wastewater treatment, which allow them to be found among the highest levels of emerging contaminants in the environment (up to mg/L levels in extreme cases). Evidence suggests that benzotriazole may be a human carcinogen, and it has been shown to be estrogenic. Australia recently established a drinking water guideline limit of 7 ng/L for tolyltriazole and a maximum allowable concentration of 2.4 μg/L.

Benzothiazoles have chemical structures similar to benzotriazoles, but with the five-membered ring containing one nitrogen and 1 sulfur. Like the benzotriazoles, benzothiazoles are used as corrosion inhibitors and in the manufacture of rubber and other products. Benzothiazoles can be present in rubber materials, herbicides, slimmicides, algaecides, fungicides, photosensitizers, azo dyes, drugs, deicing/anti-icing fluids, and food flavors. Both benzothiazoles and benzotriazoles are high volume production chemicals. It was recently reported that benzotriazole usage exceeds 9000 tons per year in the United States alone. Estimates show that ~80% of deicing fluids used at airports remains onsite after airplanes take off, which is believed to represent a major route for its contamination to the environment. In particular, groundwaters can become significantly contaminated, with reports of benzotriazole (BTri) as high as 126 mg/L in groundwater underneath a large airport and S-methylbenzotriazole (5-MeBT) as high as 17 mg/L. These concentrations exceed levels that would be lethal to fish, invertebrates, and bacteria. Water is also a major route for them to surface waters, and one study determined that ~99% of benzotriazoles found in wastewater was due to dishwasher effluents. Analytical methods typically involve LC−MS and LC−MS/MS. Studies indicate that benzotriazoles and benzothiazoles are ubiquitous contaminants in the aqueous environment.

Along with the increased number of research papers, there was also an abundance of review articles published on benzotriazoles and benzothiazoles the last 2 years. Alotaibi et al. published an excellent review on the occurrence, toxicity, degradation, and analysis of benzotriazoles in the aquatic environment. Physicochemical properties are discussed (including log $K_{\text{ow}}$, log $K_{\text{oc}}$, $pK_a$, solubility, and Henry’s Law constants) as well as the occurrence of BTri and S-MeBT in rivers, groundwater, drinking water, wastewater, soils, and dust. Toxicity to bacteria, aquatic organisms, mammals, and plants is discussed as well as removal mechanisms, including sorption and biodegradation. A summary of analytical methods is also provided, including solid phase extraction strategies and different LC−MS and LC−MS/MS methods for analysis that provide a range of detection limits, down to 0.3 ng/L in wastewater. Analytical methods were the focus of another review by Herrero et al. who discussed GC/MS, GC/MS/MS, GC×GC-HR-MS, LC−HR-MS, and LC−MS/MS methods for benzotriazoles, benzothiazoles, and benzenesulfonamides. While GC/MS methods are sometimes used for benzotriazoles and benzothiazoles, they are not as popular, due to the difficulty in finding a GC column that can separate a large number of these compounds. GC × GC-TOF-MS is a useful option for improving separations. Unlike other polar analytes that must be derivatized prior to analysis by GC/MS, the benzotriazoles and benzothiazoles do not require derivatization. Occurrence of these compounds in environmental waters was also reviewed in this article, including a mention of a pan-European study of contaminants in groundwater, in which benzotriazole was the fourth most commonly detected compound at concentrations >100 ng/L. Careghini et al. reviewed the occurrence, environmental fate and transport, and toxicity of benzotriazoles, along with other emerging contaminants in groundwater, surface water, and soils. Sorption and biodegradation of benzotriazoles are minimal, but some photolysis can happen in the presence of UV light, with degradation following two primary routes: nitrogen elimination (and production of aniline), followed by hydroxylation and dimerization. Montedieoca-Espanda et al. reviewed extraction and analysis methods for benzotriazole UV stabilizers in environmental and biological samples. Dummer presented a review of the life-cycle of tolyltriazole. Toxicity, biodegradability, occurrence, and treatment and removal strategies are discussed. GAC filtration, ozonation, and photolysis were among the more effective removal approaches.

New methods were recently developed for benzotriazoles. For example, Casado et al. created a new method using derivatization-dispersive liquid−liquid microextraction (DLLME) followed by GC/MS for measuring five benzotriazoles in water. This method required only 10 mL of sample and involved an acylation reaction occurring simultaneously with extraction into dispersed droplets of toluene. Quantification limits for BTri, 4-MeBT, 5-MeBT, 4-tolyltriazole (4-TTri), and 5-TTri ranged from 7 and 80 ng/L, with RSDs < 10% and good linearity and reproducibility. Recoveries ranged between 86 and 112%. Using this method, BTri was found at concentrations up to 1.9 μg/L in raw wastewater. Sulej et al. evaluated several different analytical procedures for measuring antifouling compounds, deicing compounds, and fuel combustion products in airport runoff water samples. Analytes included benzotriazoles, PAHs, and glycols. LLE and SPE were both used for the group of analytes, with SPE used for the benzotriazoles and GC/MS for detection. Limits of detection ranged from 0.3 to 10 ng/L for the benzotriazoles (BTri, 4-MeBT, and 5-MeBT). Benzotriazoles were subsequently measured in runoff waters from three airports in Poland and the U.K. and were found in most samples, up to 89.3 μg/L. Highest levels were found in locations where deicing was conducted and also in the machinery parks and technical roads in the airports.

Nodler et al. published an interesting occurrence study of benzotriazoles and other micropollutants in coastal environments of different marine systems. A total of 153 samples were collected from the shorelines of the Baltic Sea in Germany, the Northern Adriatic Sea in Italy, the Aegean Sea and Dardanelles in Greece and Turkey, San Francisco Bay and the Pacific Ocean in the United States, the Mediterranean Sea in Israel, and the Balearic Sea in Spain. BTri and tolyltriazole were detected in >50% of the samples, up to 177 ng/L in the Baltic Sea (Germany) and 240 ng/L in San Francisco Bay (for tolyltriazole). Levels of benzotriazoles followed this order: San Francisco Bay > Baltic Sea > Northern Adriatic Sea ~ Venice ~ Aegean Sea/Dardanelles > Pacific Ocean ~ Mediterranean Sea ~ Balearic Sea.
New fate studies include an interesting one from Huntscha et al., who used an innovative procedure to investigate the biotransformation of benzotriazoles. LC–HR-MS/MS was used with GC-isotope ratio-MS to study the range of aerobic biological degradation mechanisms in activated sludge in wastewater treatment. Biotransformation of BTri was accompanied by measurable C and N isotope fractionation and results showed preferential reactions of $^{12}\text{C}$ and $^{14}\text{N}$ isotopologues. Results provided the first evidence that biotransformation of benzotriazoles is associated with observable isotope fractionation and that this process may alter benzotriazole isotope signatures in the environment. The formation of hydroxy-benzotriazoles contributed significantly to the observed isotope fractions. Other degradation pathways including alkylation were observed.

Mazioti et al. examined the sorption and biodegradation of benzotriazoles and hydroxybenzotriazole in activated sludge in wastewater treatment. Batch experiments of BTri, 5-chlorobenzotriazole (CBTri), xylitriazole (XTri), 4-MeBT, 5-MeBT, and 2-hydroxybenzothiazole (OH-BTri) under aerobic and anaerobic conditions showed sorption ranges of 87–220 L/kg and significant degradation under aerobic conditions for 4 of these, with half-lives ranging from 23 to 45 h (BTri), 18–47 h (CBTri), 14–26 h (XTri), and 6.5–24 h (OH-BTri). Greatest removal was due to biodegradation, with sorption being minor. Biodegradation likely occurred through cometabolism by microorganisms using molecular oxygen or nitrates as electron donors and scavenging a wide range of carbon sources. Partial removal of these benzotriazoles is expected in actual WWTPs, with removals ranging from 29% for BTri to 46% for OH-BTri.

Recycled water was the focus of another interesting study by Aloabi et al., who investigated the fate of BTri and 5-MeBT in large-scale laboratory columns mimicking a managed aquifer recharge replenishment system in Western Australia. Sorption behavior demonstrated mobility of these compounds and biodegradation half-lives of 29 and 26 days, respectively. Results suggested that if these compounds were present in the recycled water that biodegradation would be likely, given sufficient aquifer residence time or travel distance between recycled water injection and groundwater extraction. Janssen et al. investigated the aquatic photochemical kinetics of BTri, 4-MeBT, 5-MeBT, and 4-OH-BTri under simulated sunlight. LC–UV was used to monitor their degradation. Half-lives ranged from 1.3 to 1.8 days, and DOM was found to be a sensitizer in sunlit aqueous environments for the degradation of the benzotriazoles. Ozonation of BTri and methyldiethanol was studied by Benitez et al., who found 6 TPs formed by the ozonation of BTri. LC–HR-TOF-MS was used to identify these TPs, which were hydroxylated forms of BTri, containing one, two, or three hydroxyl groups. HR-MS was key to their identification.

### DIOXANE

1,4-Dioxane is high production chemical used as a solvent stabilizer in the manufacture and processing of paper, cotton, textile products, automotive coolants, cosmetics, and shampoos. It can be found in environmental waters at levels exceeding water quality criteria and guidelines and has been found in drinking water. Dioxane is considered a probable human carcinogen, and the U.S. EPA has listed it on the previous CCL-3 list as well as the new draft CCL-4. As mentioned earlier, a new EPA Method (S41) was recently developed for its measurement as well as an EPA Method (S22) used previously. Because of its high water solubility, dioxane is problematic to extract and measure; it is also difficult to remove from water by carbon adsorption or air stripping and is not readily biodegradable. A new study by Stepie et al. investigated the mobility and persistence of 1,4-dioxane in wastewater, surface water, and drinking water from Germany.

### SILOXANES

Siloxanes are used in a number of products, such as cosmetics, deodorants, soaps, hair conditioners, hair dyes, car waxes, baby pacifiers, cookware, cleaners, furniture polishes, and water-repellent windshield coatings. Structures include the cyclic siloxanes, hexamethyldisiloxane (D3), octamethylcyclotrisiloxane (D4), decamethylcyclopentasiloxane (DS), dodecamethylcyclohexasiloxane (D6), and tetradecamethylcycloheptasiloxane (D7), and linear siloxanes. Because of concerns about potential toxicity and transport into the environment, a number of cyclic siloxanes are currently under review for priority pollutant classification in North America and Europe.

Siloxanes have been found in wastewater, river water, and landfill biogases. Xiao et al. investigated the kinetics and mechanism of oxidation of cyclic methylsiloxanes (D3, D4, and D5) in the gas phase to assess their persistence and long-range transport potential. For this work, a GC/MS instrument was modified for online sampling of a custom-built reaction chamber. The fate of these siloxanes was investigated in the presence of oxygen, ozone, UV light, and OH radicals, mimicking atmospheric conditions. Several transformation products were observed.

### NAPHTHENIC ACIDS

Napthenic acids (NAs) are natural contaminants found in crude oil (up to 4% by weight) and coal and are bitumen-derived substances composed of alkylsubstituted acyclic and cyclic-aliphatic carboxylic acids. NAs are endocrine disrupting and are toxic to aquatic organisms and mammals. The Athabasca oil-sands in Alberta produce >25% of Canada’s oil, and most research on NAs has been conducted in this region. Caustic hot water is used to extract crude oil from oil-sands, which results in high volumes of toxic tailing waters with high levels of NAs (80–120 mg/L levels are common).

Pereira and Martin created a new method using supercritical fluid chromatography (SFC)-Orbitrap-MS to characterize unknown species in oil-sands process-affected water. Positive and negative-ion atmospheric pressure chemical ionization...
(APCI) was used, and packed column SFC (with 4 columns in series) allowed a high number of theoretical plates on a 1-m column. A simple fluid restrictor was used to couple the SFC effluent directly to the Orbitrap mass spectrometer. This method allowed partial or full chromatographic separation of isomers for a wide array of chemical species, including NAs and sulfur- and nitrogen-containing molecules. Isomer-specific MS/MS allowed determination of functional groups for new compounds not previously characterized. For example, up to 16 isomers of C₅H₇NO were shown to have amide and amino functional groups.

Ortiz et al. developed another new method using GC-FTICR-MS, using EI and chemical ionization (CI). Methane and ammonia were used as CI gases. High resolution enabled visualization of the data using Kendrick mass defect plots. The method offered information complementary to previous atmospheric pressure ionization-based methods for characterizing the complex NA mixtures. Passive sampling was the focus of a new method by Harman et al., who used Oasis HLB-based polar organic chemical integrative samplers (POCIS) to measure NAs near offshore oil platforms. POCIS accumulated a range of mono- to tetracyclic NAs, with different degrees of alkylation. Monocyclic acids were found at the highest levels. POCIS showed an exposure pattern similar to the integrated biomarker ratio in blue mussels.

Interesting fate studies include one by Wang et al., who investigated the occurrence and fate of NAs in a refinery WWTP in northern China. UPLC–QTOF-MS was used for measurement. Concentrations ranged from 113 to 392 μg/L in wastewater, with aromatic NAs estimated at 2.1−8.8%. Biological treatment resulted in 65 and 86% reductions of total NAs and aromatic NAs, respectively. The major mechanism of removal for aliphatic and aromatic NAs was biodegradation via activated sludge. Temperature played a significant role, with much higher removals in summer (73%) than winter (53%). Misić et al. investigated the effect of algal side chain location and cyclicity on the aerobic biotransformation of NAs in wastewater treatment. Batch biotransformation assays of model compounds revealed that compounds with a quaternary carbon at the α or β position or a tertiary carbon at the β position are recalcitrant or only minimally degraded. Branched-chain structures were less degradable than nonbranched or cyclic structures. Klamerth et al. investigated the effect of ozonation on NAs from oil sands process water. Following ozonation, fractions of transformation products were extracted at different pH using dichloromethane. Higher pH (pH >7) fractions contained NAs with a higher number of carbons (14−22), and lower pH fractions (<7) had smaller carbon numbers (7−13). All extracts showed similar hydrogen deficiency (Z-number), with Z = 6, the most abundant. Despite significant degradation of NAs by ozonation, the fractions showed significant levels of toxicity toward goldfish macrophages and measurable toxicity toward Vibrio fischeri.

■ ALGAL TOXINS

Algal toxins have increased in interest, due to increased incidences of algal blooms throughout the world, including one in 2014 on western Lake Erie that shut down the drinking water supply in 2014 for the City of Toledo, Ohio (http://www.accuweather.com/en/weather-news/lake-erie-suffering-from-harm/31210317). Runoff of agricultural nutrients and wastewater discharges are mostly to blame for these events, which cause large fish kills, shellfish poisoning, livestock and wildlife death, and illness in humans. Toxins produced by these algae are implicated in the adverse effects, and these include microcystins, nodularins, anatoxins, cylindrospermopsin, and saxitoxins, which are found in fresh waters, and brevetoxins, which are found in coastal waters. Microcystins and nodularins have cyclic peptide structures; anatoxins, cylindrospermopsin, and saxitoxins have heterocyclic alkaloid structures; brevetoxins have heterocyclic polyether structures. These algal toxins are either neurotoxic or hepatotoxic. Microcystins are the most frequently reported of the algal toxins, and they have many variants, including a common type containing the amino acids leucine and arginine in their structures. Most regions of the world that uses surface water as a drinking water source have faced problems with cyanobacteria and their toxins. Algal toxins have been listed on all of the U.S. EPA’s Contaminant Candidate Lists, and they are currently listed on the new draft CCL-4. Several countries, including Australia, Brazil, Canada, France, Italy, Poland, and New Zealand, have guideline limits for microcystins, anatoxin a, and cylindrospermopsin (levels from 1.0 to 1.5 μg/L).

A new study from Switzerland (Sutton et al.) has revealed the trophic transfer of microcystins through the lake pelagic food web. Evidence shows that zooplankton can be a vector for microcystin uptake in fish. In a 24-h survey, the presence of P. rubescens algae filaments in the gut of various aquatic organisms (e.g., Daphnia, Bosmina, and Chaoborus) was verified by targeting the cyanobacterial nucleic acids (DNA). Results showed that cyanobacterial cells constitute a food source for herbivorous zooplankton during algal bloom periods. Moreover, the presence of microcystins in Chaoborus larvae revealed the trophic transfer of microcystins between zooplankton and their invertebrate predators, which can be eaten by whitefish. Chaoborus and Daphnia were the major vector of microcystin uptake in the whitefish diet at 74.6 and 20.5% of the microcystin-LR equivalent concentrations, respectively.

Corbel et al. published an excellent review on modes of action, fate in aquatic and soil ecosystems, phytotoxicity, and bioaccumulation of cyanobacterial toxins in agricultural crops. Modes of action in humans and mammals are discussed as well as concentrations in fresh waters and fate. In particular, it is clear that cyanobacterial cells and toxins can be associated with crop plants after spray irrigation, and these toxins and cells cannot only inhibit growth of the plants but can also introduce contamination to the food chain. Previous studies have shown absorption in the roots, transport to plant shoots, and translocation to grains and fruits. However, the concentrations observed to-date for microcystin-LR in rice grains is very low and may not pose a threat to human health at this time.

A brand new family of cyanobacterial peptides was discovered this year by Isaacs et al. These new micropeptin cyanopeptidases were discovered to be released by Microcystis aeruginosa blooms in North Carolina’s Cape Fear River and were discovered while carrying out a detailed chemical analysis of microcystins following two large algal blooms. These new micropeptins were identified using LC–MS and had molecular weights of 1105.6 and 1119.7 Da, respectively. Upon purification by preparative LC, 1D and 2D NMR revealed additional structural information, including a 3-amino-6-hydroxy-2-piperdione group, an oxymethine group correspond-
ing to a depsipeptide link through threonine, a butyric side chain, and additional amino acids (N,N-disubstituted valine, N-methyl-phenylalanine, isoleucine, threonine, arginine, glutamic acid, and tyrosine). Like microcystins, micropeptins are nonribosomally produced, but they have a cyclic ester linkage in their structures. Along with these new micropeptins, microcystin-LR and RR were also present, with the RR form found at 3 times that of LR. Levels of the new micropeptins were comparable to the microcystins. While their biological activity and potential environmental effects are not yet fully determined, their high levels suggest they should be further investigated.

Beversdorf et al. published a new study indicating that microcystin gene abundances are not good indicators of microcystin levels in lakes.228 The authors used quantitative polymerase chain reaction (qPCR) to quantify genes within the microcystin operon and found that toxin gene abundances were anticorrelated with microcystin in U.S. lakes.

New methods include a LC−ESI-MS/MS method for measuring domoic acid in seawater.229 Detection limits of 0.3 ng/L (positive ion mode) and 0.6 ng/L (negative ion mode) were achieved. This method was subsequently used to measure domoic acid in the Venice Lagoon (Italy), where the first reports of domoic acid were reported, up to 16.2 ng/L. Kaloudis et al. developed a SPE-LC−ESI-MS/MS method to measure microcystins and nodularin in environmental waters, at 2 ng/L detection limits.230 This method was used to measure these algal toxins for the first time in Lake Marathonas, which serves as a water resource for drinking water in Athens, Greece. Microcystin-YR, -LR, and -RR varied seasonally with the subject of the first occurrence study in Egypt for microcystins.234 This study was initiated to evaluate levels of microcystins in lakes.228 The authors used quantitative polymerase chain reaction (qPCR) to quantify genes within the microcystin operon and found that toxin gene abundances were anticorrelated with microcystin in U.S. lakes.

Finally, He et al. investigated the destruction of microcystins with UV-254 nm photolysis and AOPs.235 Addition of an oxidant to UV significantly improved reaction efficiency, with the following order: UV−S₂O₈− > UV−HSO₅⁻ > UV−H₂O₂. Moreover, microcystin-LR removal with UV−H₂O₂ was faster than for cylindrospermopsin. Transformation products were observed, which were formed by hydroxylation and diene-Adda double bond cleavages for UV−H₂O₂ reactions. Results showed that the variable amino acids in the chemical structures of microcystins influenced both the degradation kinetics and the reaction mechanisms.

CONTAMINANTS ON THE HORIZON: IONIC LIQUIDS AND MICROPLASTICS

Ionic Liquids. Organic salts with low melting points (<100 °C), ionic liquids (ILs), are being promoted as “green chemistry” replacements for traditional industrial solvents. While they have low vapor pressures and flammability, there is limited toxicity and environmental data for these new “green solvents”, and they could possibly pose a threat to aquatic and terrestrial ecosystems. In fact, recent data show that ILs are toxic, and their toxicities vary considerably across organisms and trophic levels.2 Most ILs are highly water-soluble and chemically and thermally stable, which creates potential for entry and persistence in the environment. ILs possess unique properties that make them useful for many applications, including organic synthesis and catalysis, production of fuel cells, batteries, coatings, oils, and nanoparticles. Structures of ILs typically involve a cationic or anionic polar headgroup with an alkyl side chain. Cationic head groups include imidazolium, pyridinium, pyrrolidinium, morpholinium, piperidium, quinolinium, quaternary ammonium, and quaternary phosphonium moieties. Anionic head groups include tetrafluoroborate (BF₄⁻), hexafluorophosphate (PF₆⁻), bis(trifluoro-methylsulfonyl)-imide [(CF₃SO₂)₂N⁻], dicyanamide [(CN)₂N⁻], chloride, and bromide. Addition of polar groups to the alkyl chains can decrease their toxicity and increase biodegradation, which suggests the possibility of tailoring their structures to produce more environmentally friendly compounds.

Markiewicz et al. made an important discovery regarding the ability of an ionic liquid to dissolve and mobilize PAH contaminants in soil at levels well below their critical micelle concentrations (CMCs).236 With increasing use and production of ILs, there is increased chance they will enter the environment, so these authors investigated how ionic liquid contamination can affect soil properties and sorption of pre-existing contaminants. The common ionic liquid 1-methyl-3-octyl imidazolium chloride was added to landfill soil contaminated with PAHs. PAH release into pore water revealed that while levels were highest above the CMC of the ionic liquid, significant levels were still released at levels well below the CMC. As a result, this study highlights how an ionic liquid can mobilize and enhance the release of sorbed contaminants into the aquatic environment.

Microplastics. The world’s consumption of plastic has led to significant microplastic contamination around the world. In 2012, 288 million tons of plastic were produced worldwide.237 Discarded plastics are subject to wind and river-driven transport, where they wind up in oceans and can wash up on beaches. They have been accumulating for the last 4 decades, with a current estimate of 5.25 trillion particles weighing >250 000 tons in the world’s oceans.237 Microplastics are
defined as 5 mm in size and can be either the original plastic produced (primary) or a degradation product of larger plastics (secondary). Microplastics are a growing problem in oceans, particularly in gyres, where water circulation accumulates them and larger plastics in "plastic islands". Levels of 32.76 particles/m³ and 250 mg/m³ were recently reported for the North Pacific Subtropical Gyre.238 Industrial coastal areas are also hotspots, where concentrations of 100 000 plastic particles/m³ have been reported.237 Sediments from heavily populated areas can also be contaminated with microplastics.

The impact of plastic pollution on marine organisms, whether through ingestion or entanglement, is well documented, with impacts on seabirds, seals, sea lions, dolphins, whales, marine reptiles, zooplankton, and many other species.238 The U.S. Fish and Wildlife Service has estimated that 320 000 albatross chicks that hatch on Midway Island each year are fed 5 tons of plastic.239 The accumulation of plastic debris also presents a new marine habitat where biological interactions are taking place.238 Fibers are the most commonly encountered form or microplastics in the marine environment, and some aquatic species will selectively ingest microplastics, favoring the fibers. Moreover, the presence of microplastics in fish, sea lions, and fur seal scat suggest microplastic trophic transfer through the pelagic food chain, such that lower trophic organisms can be a vector for microplastic transfer, along with their sorbed contaminants.238 In addition to the microplastics themselves, other organic chemical contaminants can also sorb on microplastics, presenting concentrated levels of organic contaminants to biota.

Wright et al. summarized the physical impacts of microplastics on marine organisms, including factors contributing to the bioavailability of microplastics, an assessment of relative susceptibility of different groups of species, factors that influence the physical impacts of microplastics, such as accumulation, translocation, and trophic transfer.238 Another study by Lusher et al. examined the occurrence of microplastics in the gastrointestinal tract of fish in the English Channel.240 More than 500 fish were collected, and all five pelagic species and all five demersal species had ingested plastic, with 36.5% of fish containing plastic. Average numbers of ingested plastic was 1.90 per fish. FT-IR spectroscopy showed that polyamide and rayon were the most common. Syberg et al. reviewed ecological risks of microplastics, including a discussion of sampling techniques, properties of microplastics, environmental fate, interaction with biological receptors, and mechanisms of toxicity.241 Parallels were drawn between microplastics and nanoplastics.

Eriksen et al. conducted a very ambitious study measuring plastic pollution in the world’s oceans from 24 expeditions (2007–2013) across all five subtropical gyres (North Pacific, North Atlantic, South Pacific, South Atlantic, and Indian Ocean), along with coastal Australia, the Bay of Bengal, and the Mediterranean Sea.237 This was the first study to compare all sizes of floating plastic in the world’s oceans. Nets with 0.33 mm mesh size were used to collect microplastics and other plastic debris from sea surfaces. Using a dissecting microscope, microplastics were manually separated from natural debris and were sorted into 4 sizes (0.33–1.00 mm, 1.01–4.75 mm, 4.76–200 mm, and >200 mm), counted individually, and weighed together. On the basis of these measurements, 5.25 trillion plastic particles weighing 268 940 tons were estimated to be currently floating at sea. A surprising discovery was that the total amount of plastics from the Southern Hemisphere oceans was within the same range as for Northern Hemisphere oceans, despite the fact that plastic inputs are much higher in the Northern Hemisphere. This indicates that plastic pollution may be able to move more easily between the oceanic gyres than previously assumed or it could be due to an increased, disproportional loss of plastics from the sea surface in the Northern Hemisphere. Higher amounts of plastics washed up on coastal beaches in the Northern Hemisphere support this alternate hypothesis.

Estimates suggest that two Northern Hemisphere ocean regions contain 55.6% of the particles and 56.8% of the plastic mass. In the Southern Hemisphere, the Indian Ocean had a higher number and weight of plastic particles compared to the South Atlantic and South Pacific oceans combined. More than 92% of the net tows contained plastic; locations without plastic were outside the central areas of the subtropical gyres. Of the larger macroplastics measured, foam polystyrene was dominant, with derelict fishing buoys accounting for most (58%) of the total macroplastic weight. Results also indicate significant removal processes of microplastics at the sea surface, including UV degradation, biodegradation, ingestion by organisms, decreased buoyancy due to fouling organisms, entainment in settling detritus, and beaching. In particular, brittle microplastics may break down into smaller particles, which are not captured by the 0.33 mm mesh nets.

A special issue on microplastics was published in Archives of Environmental Contamination and Toxicology, which highlighted high levels in the North Pacific Ocean, both on shorelines and the sea surface, along with particularly high levels on the western and southern coasts of South Korea.242 Microplastic sources included wastewater discharge, aquaculture, and shipyards. Surface winds and currents played an important role in shoreline patterns of distribution. Ingestion of microplastics by small plankton at the base of the food chain was also indicated as well as a broad array of chemicals that are associated with plastic debris.

The present and future of microplastic pollution in the marine environment was reviewed by Ivar do Sul and Costa.243 This review begins with a compelling reference to the first early alarm sounded by E. J. Carpenter and K. L. Smith in 1972 regarding the presence of plastic pellets on the surface of the North Atlantic Ocean, which stated that "The increasing production of plastic, combined with present waste-disposal practices, will probably lead to greater concentrations on the sea surface...At present, the only known biological effect of these particles is that they act as a surface for the growth of hydroids, diatoms, and probably bacteria."244 Within a few months, Carpenter et al. reported the ingestion of these plastic pellets by fish.245 This review includes a discussion of microplastics in plankton and sediments, ingestion by vertebrates and invertebrates, and interactions with chemical pollutants. Because of the larger surface area of microplastics compared to macroplastics, they are more susceptible to contamination by airborne and water pollutants, including persistent organic pollutants (POPs) and metals. Plastics are made of hydrophobic materials, which can sorb a number of contaminants, acting as reservoirs of toxic chemicals in the environment. Polychlorinated biphenyls (PCBs), PAHs, organochlorine pesticides (e.g., dichlorodiphenyldichloroethylene (DDE) and dichlorodiphenyltrichloroethane (DDT)), and nonylphenols have been associated with microplastics, and their levels are sometimes used to assess distribution of POPs in the environment.244 Different plastic materials can selectively
concentrate different chemicals, with PAHs and PCBs adsorbed onto high density polyethylene (HDPE), low density polyethylene (LDPE), and polypropylene (PP) more than polyethylene terephthalate (PET) and polyvinyl chloride (PVC). PE, PP, and PVC plastics are the most used and released. Colors of the microplastics can influence adsorption of contaminants, with black pellets having higher adsorption of PCBs than white or colored pellets.244

A new occurrence study by Davis and Murphy measured plastic in surface waters from the Salish Sea in Washington State and the Inside Passage to Skagway, Alaska.246 Foam, primarily from polystyrene, was found to be the dominant pollutant from both locations. Plastic was found over the full length of the Inside Passage but more concentrated in the harbors. On the sandy beaches in Washington State, an average square meter contained 61 pieces of anthropogenic debris. Surface sea waters were sampled using a 0.335 mm mesh net, dried, counted, and weighed to 0.01 g. and laboratory analysis of samples followed a wet peroxidase oxidation method, which allowed the digestion of most organics and facilitated floating plastic to the surface. Plastic material was dried, counted, and weighed to 0.01 g.

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Notes
The authors declare no competing financial interest.

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