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Key Points:

- Contaminants of emerging concern (CECs) are an ever-evolving list of chemicals and microorganisms that are not currently regulated in water
- Advances in analytical technology have allowed the detection of individual and mixtures of CECs at ever decreasing concentrations
- Transdisciplinary research can be used to address science gaps in water monitoring, treatment optimization, and source water protection

Supporting Information:

Supporting Information may be found in the online version of this article.

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Water, Water Everywhere, but Every Drop Unique: Challenges in the Science to Understand the Role of Contaminants of Emerging Concern in the Management of Drinking Water Supplies

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Abstract The protection and management of water resources continues to be challenged by multiple and ongoing factors such as shifts in demographic, social, economic, and public health requirements. Physical limitations placed on access to potable supplies include natural and human-caused factors such as aquifer depletion, aging infrastructure, saltwater intrusion, floods, and drought. These factors, although varying in magnitude, spatial extent, and timing, can exacerbate the potential for contaminants of concern (CECs) to be present in sources of drinking water, infrastructure, premise plumbing and associated tap water. This monograph examines how current and emerging scientific efforts and technologies increase our understanding of the range of CECs and drinking water issues facing current and future populations. It is not intended to be read in one sitting, but is instead a starting point for scientists wanting to learn more about the issues surrounding CECs. This text discusses the topical evolution CECs over time (Section 1), improvements in measuring chemical and microbial CECs, through both analysis of concentration and toxicity (Section 2) and modeling CEC exposure and fate (Section 3), forms of treatment effective at removing chemical and microbial CECs (Section 4), and potential for human health impacts from exposure to CECs (Section 5). The paper concludes with how changes to water quantity, both scarcity and surpluses, could affect water quality (Section 6). Taken together, these sections document the past 25 years of CEC research and the regulatory response to these contaminants, the current work to identify and monitor CECs and mitigate exposure, and the challenges facing the future.

Plain Language Summary Contaminants of emerging concern (CECs) are included in an ever-evolving list of chemicals and microorganisms that are not currently regulated in drinking, recreational, or environmental waters but may be detrimental to human or ecological health. Advances in analytical technology have allowed the detection of these contaminants at ever decreasing concentrations. Additional techniques, such as nontargeted analyses and bioanalytical tools, have expanded our understanding on the occurrence of CECs both individually and in mixtures. Even with new analytical tools, little is known about the potentially tens of thousands of CECs that may be present in water. Models could be used to predict the fate and occurrence of these contaminants. Information on the toxicity to human and aquatic life, both for individual contaminants and mixtures, can follow environmental detection. Advancements in wastewater and drinking water treatment have increased the capacity for the reduction of contaminants in water. More research would be useful to determine human exposures that are occurring through all exposure routes to determine if, and where, additional treatment would be beneficial. If water resources become more limited due to population increases, climatic change, poor treatment performance, or other factors, CECs may become a larger concern for human and ecological health.

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1. Known and Suspected Drinking Water Contaminants

Research on water contaminants of unknown health consequences has been unfolding for centuries. In London, when John Snow recommended removing the Broad Street water pump handle in 1855 during a cholera epidemic, it was an intervention on a drinking water exposure of then-uncertain health significance (Cameron & Jones, 1983). When Rachel Carson (1962) wrote *Silent Spring* concerning the environmental risks of pesticides, she was writing about chemicals whose effects were then considered speculative (Griswold, 2012). The term contaminant of emerging concern (CEC) is currently used to describe chemicals and microorganisms that are not federally regulated in the United States, but that the scientific community suspects may have deleterious effects on humans or wildlife (Diamond et al., 2011). The CEC Interagency Workgroup describes CECs in drinking water as "newly identified or reemerging manufactured or naturally occurring physical, chemical, biological, radiological, or nuclear materials that may cause adverse effects to human health or the environment and do not currently have a national primary drinking water regulation" (National Science & Technology Council, 2018). While the concept is established, the term CEC has only been used for the past two decades. Other terms, such as organic wastewater contaminants, micropollutants, and trace organic chemicals have also been used to describe this wide-ranging class of contaminants. Today's CECs include pharmaceuticals, per-and polyfluoroalkyl substances (PFAS), exogenous and endogenous hormones, and microorganisms such as *Legionella* spp., mycobacteria, and cyanobacteria that produce cyanotoxins, and antibiotic-resistant bacteria and genes. Very recently, SARS-CoV-2, the causative agent of the COVID-19 pandemic, has emerged as a novel and pressing concern for water systems (Kitajima et al., 2020). The list of CECs will certainly continue to expand as improvements in detection technology, and with further experiments that reveal exposure related adverse health impacts. This is somewhat balanced by the implementation of regulations which truncates the list. For example, drinking water regulations on PFAS are forthcoming in the United States (USEPA, 2023), moving at least some contaminants in that class from a CEC to a regulated contaminant. But there is most likely a water sample being analyzed today that will find a previously undetected chemical or microorganism that will soon be included on the list of CECs.

1.1. U.S. Approach to Drinking Water Regulation

As understanding grew that some microorganisms and chemicals in drinking water had adverse health consequences, treatment systems and regulations emerged to limit these risks. The first Federal drinking water regulations in the United States arose in 1914, with Public Health Service standards set for bacteria with a goal of limiting contagious disease. These standards only applied to interstate carriers such as ships and trains (U.S. Environmental Protection Agency [USEPA], 1999). In 1925, they were recommended for all drinking water sources, even though federal standards were only mandatory for interstate systems at the time (Knotts, 1999). The recommendations were for population-based sampling rates and set limits for alkalinity, total solids, and select metal contaminants and phenolic compounds (Okun, 2003). The standards were revised in 1942, 1946, and 1962 (Knotts, 1999; USEPA, 1999). All 50 states used the 1962 standards as a basis for drinking water regulations or guidelines prior to the creation of the SDWA in 1974 (USEPA, 1999), which authorized the USEPA to set nationally enforceable standards for drinking water quality. The 1996 amendments to the SDWA (United States, 1996) created procedures to prioritize unregulated drinking water contaminants with potential health impacts (i.e., the contaminant candidate list; CCL), and to establish a list, once every 5 years, of unregulated contaminants to be monitored by public water systems (i.e., the unregulated contaminant monitoring rule; UCMR). These amendments also direct the USEPA to select no fewer than five contaminants from the current CCL and determine whether each contaminant should be regulated or not. These mandated activities allowed for the ongoing study and assessment of CECs. To date, over 90 national primary drinking water standards have been established by the USEPA.

Microorganisms have historically been the primary driver for water treatment (Knotts, 1999). For some microbial agents, USEPA sets a non-enforceable, recommended level below which there is no known risk to public health, or the maximum contaminant level goal (MCLG). For example, the MCLG for *Cryptosporidium* spp., *Giardia* spp., and *Legionella* spp. in drinking water is zero. As a zero concentration is not realistically possible under economic and technological constraints, treatment requirements need to balance ensuring public health with these considerations. Rather than setting an enforceable maximum contaminant level (MCL) for these contaminants, the SDWA requires treatment techniques that consider economic and technical feasibility in addition to adverse health effects. These requirements include maintenance of a disinfectant residual. The SDWA requires

Overview

The Safe Drinking Water Act (SDWA) defines "contaminant" as any physical, chemical, biological, or radiological substance or matter in water. Thus, by this definition, anything other than the water molecule itself (H_2O), is considered a contaminant. "Contaminants of emerging concern" (CECs) is a term that covers a wide variety of chemicals and microorganisms that are, typically, currently unregulated under the SDWA. Although the term "concern" is subjective, it is used here to refer to the scientific possibility that exposure may be associated with a toxicological or pathogenic disease or environmental harm. For example, inorganic contaminants generally are found more frequently than organic contaminants in untreated sources of private and public drinking water at concentrations with potential human-health concern (DeSimone et al., 2014; Focazio et al., 2006; Toccalino et al., 2012). However, these contaminants are regulated and would not fall under the operational definition of CEC used here. That is, they are of concern, but the science on their concentration and toxicity has "emerged" to the point that they have been regulated. Consequently, although some inorganic contaminants from natural as well as anthropogenic sources such as arsenic, lead, and radionuclides may pose the biggest concerns from a toxicity and exposure perspective, they are out of the scope of this paper. This approach acknowledges the uncertainties in our understanding of the thousands of potential water contaminants and their mixtures, does not exclude any CEC from the potential necessity for further research, and provides a variety of chemical, microbial, toxicological, epidemiological, and other integrated science actions to address whether the risk that initiated concern is real or perceived. Figure 1 shows the common sources of CECs in watersheds and aquifers, such as wastewater discharges and agricultural runoff and leaching, as indicated by yellow circles.

Population increases and relocation, storms, droughts, and other natural and human-caused events can negatively affect water supplies and degrade water quality. Some of these effects are illustrated in Figure 1, inside of the green circles. Drought can lead to an increase in wildfires where sequestered CECs may be mobilized, and chemical fire suppressants, a source of CECs, may contaminate source waters. Droughts can also lead to a decrease in aquifer recharge rates while groundwater pumping rates are increased. The resulting changes in groundwater flow patterns can lead to changes in aquifer geochemistry and degraded water quality as previously sequestered CECs are mobilized. Breaks in distribution-system pipes due to aging infrastructure and contracting soils during drought can also lead to degraded water quality and introduction of CECs into water supplies. In times of water surplus due to flooding, storms surges, or sea level rise, water quality may be affected as systems are inundated and contaminants are mobilized. The list of measured CECs in the environment continues to grow due to increased analytical capabilities, but thousands of CECs that could be present in drinking water sources remain unmonitored. Large-scale monitoring of watersheds and aquifers as well as at the point of exposures continue to be rare across the world for the full range of CECs. The health effects from CECs, as well as the effectiveness of treatments to reduce exposure, constitute substantial knowledge gaps.

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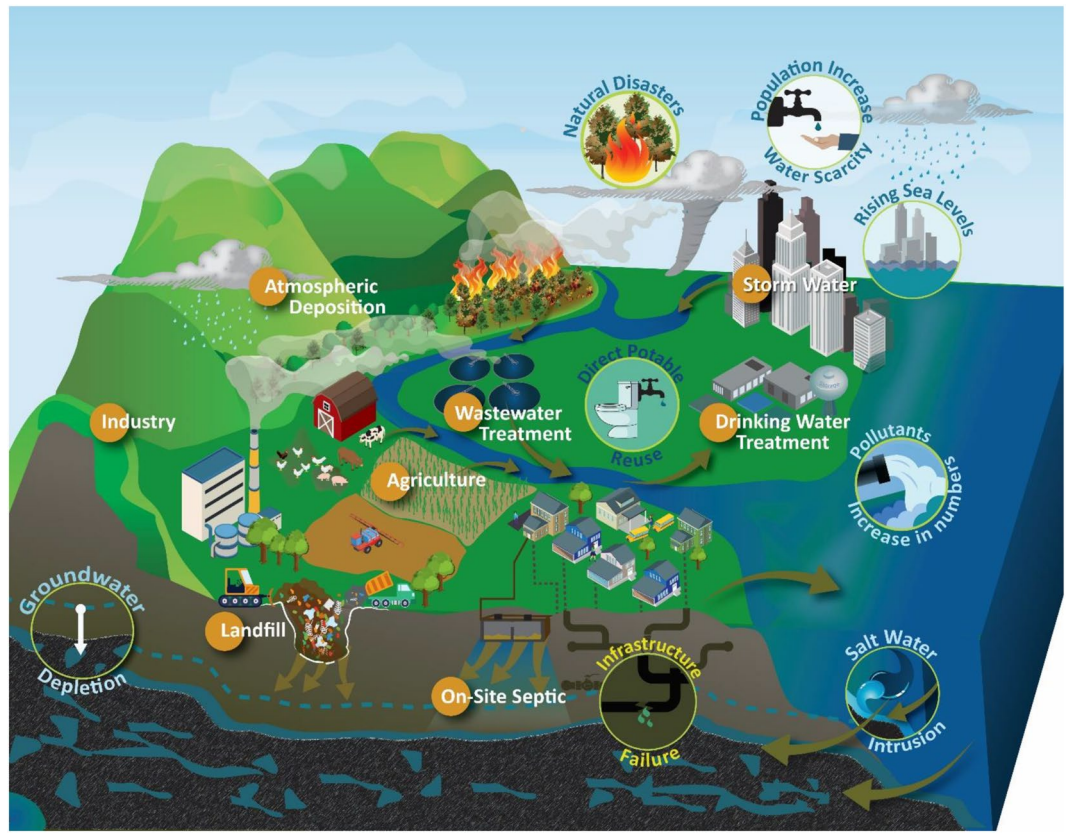

Figure 1. Common sources of contaminants of emerging concern (CECs) in watersheds and aquifers. Common sources of CECs to the environment are designated with orange circles. Changes in water quantity, from either scarcity or surpluses, can affect CEC concentrations in water. Some of these potential conditions are highlighted in the green circles.

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routine monitoring of drinking water for total coliforms, which is a broad group of bacteria naturally present in waters, including *Escherichia coli* (*E.* coli; USEPA, 2012b) as a surrogate for pathogenic microbial exposures. If a routine sample tests positive for total coliforms, then repeat samples are required. If repeat samples are total coliform-positive, then samples must be tested for *E. coli*. If samples are *E. coli*-positive, then the public water

Research Challenges

The scientific community continues to provide information on the presence, fate, and effects of contaminants of emerging concern within both the built and natural environments. Many questions arise as this information is used to balance public health protection with economic and other pragmatic constraints.

- What is the full list of contaminants that matter for the safety of water resources?
- What is the value of knowing the concentrations of contaminants at exceedingly low levels?
- What treatment options and mitigation strategies are effective for reducing contaminant concentrations in wastewater and drinking water to safe levels?
- What is the cost to society to implement those options and strategies?
- Do we have the right type and the appropriate amount of monitoring data that water-resource managers and public-health experts require?
- Are there biological effects on humans or on ecosystems induced by contaminants at environmentally relevant concentrations, singly or in mixtures?
- How and where can contaminants be monitored in the water supply to properly characterize exposures to the most important contaminants from a health perspective, or those exposures that are major drivers in degrading water quality?
- Can modeling be used to guide efforts to protect water quality along the lifecycle of a contaminant as it enters, is transported through watersheds or aquifers, and is changed by treatment and processes within conveyance, plumbing and other infrastructure to the point of exposure?
- Can those models identify the critical control points in the lifecycle of a water contaminant hazard where the most cost-effective mitigation or prevention can be focused to protect health?
- Where are the cross-cutting opportunities and force multipliers to monitoring, modeling, and process-based research for the full breadth of public, self-supplied, and bottled drinking water?
- How can science that is focused on ambient/ecological water resources be used to inform understandings of drinking water resources?

Answers to these and other questions would need the combined efforts of scientists from a range of disciplines working with engineers, managers, and other decision makers and stakeholders. However, the list of questions is presented here to help frame the scope of the science challenge that is addressed in more detail below.

system is in exceedance of the MCL and must report those results to SDWA primacy entities, typically the state. The public water system must then assess the sanitary defects and take corrective action.

1.2. Water Contamination as a Public Health Concern

Although it is widely recognized that water-associated exposures are important for many human health outcomes, and that drinking water can be a major route of exposure from many contaminants, less epidemiological research has focused on drinking water exposures than might be expected (Bradley et al., 2018). One reason for this research gap is the limited availability of occurrence, exposures, and associated health and outbreak data for drinking water systems and their customers in the United States. National primary drinking water regulations establish requirements for public water systems to monitor occurrence for the majority of regulated contaminants or indicators of contamination in public water supplies for regulatory compliance purposes (contaminants with treatment technique standards are not monitored). In contrast, every 5 years the USEPA determines a new list of up to 30 unregulated contaminants that are required to be monitored by some public water systems as part of the UCMR. However, for most contaminants, such data are collected at the point of compliance (e.g., entry to the distribution system) and might not accurately represent the water delivered to residential or other taps where exposures take place (Bradley et al., 2018, 2020). Notable exceptions are the monitoring of contaminants such as disinfection byproducts (DBPs) or metals that may increase in the distribution system and therefore monitored there, and lead which is monitored at the tap. There is also no specific federal monitoring of private well water used by ∼44.1 million people (Ayotte et al., 2017; Lee & Murphy, 2020; Rogan et al., 2009), and states differ in their water quality testing requirements for private wells (Bowen et al., 2019).

Waterborne disease surveillance efforts emphasize the tracking of acute disease outbreaks (Beer et al., 2015). For an event to be described as an outbreak, two or more people must be linked epidemiologically by time, location of exposure to water, and type of illness. The latest report describing outbreaks caused by exposure to treated drinking water in the United States covers years 2013–2014 (Benedict et al., 2017) and describes 42 outbreaks in 19 states consisting of 1,006 illnesses, 124 hospitalizations, and 13 deaths. *Legionella* spp. was responsible for 57% (24/42) of outbreaks, 130 cases, 109 hospitalizations, and all 13 deaths. Eight outbreaks were caused by *Cryptosporidium* spp., accounting for 279 cases, and *Giardia* spp. accounted for 10 cases. While *Legionella* spp. caused most of the outbreaks, most of the cases were caused by *Cryptosporidium* spp. or *Giardia* spp. (130 vs. 289). Community water systems were responsible for 75% of known drinking water outbreaks (Benedict et al., 2017). In the United States, community water systems are those systems having ≥15 service connections or serving ≥25 residents for more than 60 days/year (United States, 1996).

While known outbreaks represent only a small number of waterborne disease cases, the true burden of waterborne illness is likely greater, as there might be undetected or unconfirmed outbreaks and an unknown role in endemic transmission. Tracking and understanding the causes of waterborne disease outbreaks is essential to prevent future exposures, identify emerging pathogens, and inform the public and water system operators on proper treatment for intended use. The latest drinking water outbreak report (Benedict et al., 2017) was the first to include two outbreaks involving the CEC microcystin, a toxin produced and excreted into surface water during harmful algal blooms (HABs) by cyanobacteria. The two outbreaks involved 116 cases of acute gastrointestinal illness, one outbreak in September 2013 (6 cases) and one in August 2014 (110 cases), where levels in samples from a community water system exceeded state thresholds and resulted in “do not drink” advisories.

Long-term exposure to low levels of chemical contaminants also play an important role in shaping public health (Abdul et al., 2015; Vollet et al., 2016). Recent research has shown that environmental exposures may play an even greater role than genetic risk factors for some chronic diseases (Rappaport, 2012, 2016), but identifying the specific environmental exposures responsible for chronic disease is challenging. There are several reasons for these challenges, including (a) uncertainty regarding the “latency period” interval of time that elapses between the etiologically relevant exposure and the onset of the disease (Marshall et al., 2007), (b) lack of high-quality exposure data pertinent to the biologically relevant exposure-time, and (c) toxicity of low dose exposures to individual and mixtures of CECs and legacy contaminants (Kortenkamp et al., 2007).

1.3. 21st Century CECs

The sources and routes of CECs into the environment are as varied as the CECs themselves (Figure 1). For example, both industrial and household use and disposal of chemicals can result in the release of those materials into the atmosphere, surface water, and groundwater (Battaglin et al., 2018; Glassmeyer, 2007; Richardson & Kimura, 2017). Wastewater can be a source of both chemical and microbial CECs into the environment (Fairbairn et al., 2016). In some cases, such as agriculture and urban landscaping, contaminants (e.g., nitrate and phosphate) are released that exacerbate the production of HABs, a CEC. This section examines some of the current CECs in more depth.

1.3.1. Microorganisms and Microbial Products

Given that the healthy human body is heavily comprised of resident microorganisms (Sender et al., 2016; Stark, 2010), it is apparent that relatively few microorganisms regularly interacting with humans are pathogenic. However, the World Health Organization (WHO) estimates that 2.1 billion people around the world lack access to safe water at home (WHO, 2018a, 2018b); contaminated source water leads to approximately 750,000 children dying annually due to diarrhea (L. Liu et al., 2012).

Microbial CECs include microbes that may be newly apparent to public health practitioners, that appear to be associated with increasing disease incidence, or that appear to be expanding in geographic range. Although some microbial contaminants are known pathogens, many more are poorly characterized with additional evidence needed to establish a causal link to disease. Major known and potential emerging CEC pathogens in water are described in Table 1 (Ashbolt, 2015a, 2015b). *Waterborne* pathogens contaminate natural bodies of water through fecal matter but are generally removed through drinking water treatment and are not commonly found in treated drinking water (Ashbolt, 2015a). In contrast, *water-based* pathogens are non-enteric environmental microorganisms that may persist and grow in water, including in drinking water distribution systems. While waterborne pathogens cause substantial illness in the United States, direct healthcare costs due to illness caused by water-based pathogens, such as *Legionella* spp., are significantly higher (Collier et al., 2012; Strollo et al., 2015). Some microorganisms (e.g., cyanobacteria) produce toxins that cause more severe health impacts than do the microorganisms themselves (Díez-Quijada et al., 2019). Factors that may produce freshwater HABs include excess nutrient concentrations and availability of sunlight (Chaffin et al., 2019; Havens et al., 2019). Human contact with freshwater HABs and their toxins can cause a variety of symptoms (Otten & Paerl, 2015). In the most recent report on sources of drinking water-related disease outbreaks in the United States (Benedict et al., 2017), cyanotoxins were the only chemical agents listed as a known causative agent.

1.3.2. Antimicrobial Resistance and Antimicrobial Resistance Genes

Antimicrobial resistance (AMR) is the ability of microorganisms to defeat the effects of drugs used to combat them (Wellcome Trust et al., 2018). AMR is one of the greatest emerging public health challenges; AMR infections are associated with 4.95 million annual worldwide deaths and could result in an estimated 10 million annually by 2050, becoming the leading cause of global death (Antimicrobial Resistance Collaborators, 2022; O'Neill, 2016). In the United States, at least 2.8 million people acquire an AMR-derived infection each year, causing approximately 35,000 deaths (CDC, 2019). While these statistics emphasize AMR as a clinical healthcare concern, awareness is growing of the role the environment plays in the development and spread of AMR bacteria (ARB) and resistance genes (ARG; Table S1 in Supporting Information S1). The discharge of human and animal wastes has contributed to the exposure of environmental microbial communities to antibiotics, ARB, and ARG, providing new selective pressures and opportunities for genetic exchange (M. L. Chen et al., 2021; He et al., 2023; Hubbard et al., 2020). These waste discharges include both clinically-relevant AMR pathogens and genetic elements, with the environment then serving as a reservoir and conduit for further exposure and human health risks (Adegoke et al., 2017; Bengtsson-Palme et al., 2018; Cantas et al., 2013; Finley et al., 2013; Graham et al., 2019; Pruden et al., 2006; United Nations Environment Programme, 2023). Human feces and wastewater contain a high-strength mixture of antibiotics, ARB, and ARG, including those associated with clinical infections among the contributing population (Bouki et al., 2013; Rizzo et al., 2013). The wastewater from likely hotspots of AMR (e.g., hospitals and antibiotic manufacturing facilities) poses a particular concern (Gwenzi et al., 2020; Wellcome Trust et al., 2018). Likewise, domestic animal wastes are an important route for dissemination of antibiotics, ARB, and ARG to the environment. Large quantities of antibiotics are utilized in animal agriculture not only for disease treatment, but also for prophylaxis and (historically) growth promotion (Burkholder et al., 2007; Cromwell, 2002; Gaskins et al., 2002; Wegener, 2003). Such doses can be sublethal to microorganisms, providing ideal

GeoHealth

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Table 1
Known and Potential Emerging Waterborne and Water-Based Pathogens and the Diseases They Cause

Microbial group	Known waterborne (Enteric)[a]	Potential waterborne	Disease(s)	Known water-based (opportunistic)[a]	Potential water-based	Disease(s)
Bacteria	*Campylobacter* spp.	*Arcobacter butzleri*	Gastrointestinal	*Escherichia coli* O157:H7	*Acinetobacter baumannii*	Urinary tract
	Salmonella spp.	*Helicobacter pylori*		*Legionella* spp.	*Aeromonas hydrophila*	Respiratory
	Shigella spp.	*Clostridium difficile*		Non-tuberculous mycobacteria (NTM)	Toxigenic *E. coli*	Skin
	Vibrio cholerae	*Listeria monocytogenes*		*Pseudomonas aeruginosa*	*Listeria monocytogenes*	Wound
		Yersinia enterocolitica			*Staphylococcus aureus*	Soft-tissue
					Stenotrophomonas maltophilia	
Virus	Adenoviruses	*Mamastrovirus* 1	Gastrointestinal	None	*Mimivirus*	Gastrointestinal
	Astroviruses	*Orthoreovirus* C	Hand-foot-and-mouth		*Mamavirus*	
	Enteroviruses		Liver			
	Hepatitis A and E virus					
	Noroviruses					
	Rotaviruses					
	Sapovirus					
Fungi	None	*Candida albicans*	Gastrointestinal	None	*Aspergillus fumigatus* and *terreus*	Respiratory
					Exophiala dermatitidis	Skin
Protozoa	*Cryptosporidium hominis* and *parvum*	*Blastocystis hominis*	Gastrointestinal	*Acanthamoeba T4*	*Acanthamoeba* spp.	Keratitis
	Cyclospora cayetanensis			*Naegleria fowleri*	*Vahlkampfia* spp.	Encephalitis
	Giardia duodenalis				*Vannella* spp.	Meningoencephalitis
	Toxoplasma gondii				*Vermamoeba vermiformis*	

[a]Adapted from Ashbolt (2015a, 2015b) and WHO (2011).

conditions for the development, selection, and horizontal transfer of AMR (Aarestrup, 2015; ter Kuile et al., 2016). Because animal manures and process wastewaters are typically minimally treated or untreated prior to land application or these contaminant's disposal, the ARB and ARG that they contain can be discharged directly to receiving soils with subsequent transport to water resources. Affected waters can disseminate to subsequent receptors via irrigation, recreational use, or drinking water exposure. Although drinking water treatment processes (DWTP) are generally effective in reducing ARB and ARG, both are nevertheless detected in finished water (Sanganyado & Gwenzi, 2019).

Despite these concerns, the human health risk associated with environmental ARB and ARG is not fully understood. Important challenges include the lack of quantitative relationships between selective pressures and the development and spread of AMR; unknown rates of mutation and horizontal gene transfer, including between environmental bacteria and pathogens; and uncertain dose-response relationships of resistant strains (Ashbolt et al., 2013; Pires et al., 2018). Defining the risk associated with ARG detection in environmental samples is a considerable challenge, as it is generally unknown which bacteria harbor the genes; whether they are associated with mobile genetic elements; and whether they are capable of being expressed in viable cells (Martínez et al., 2015; Pires et al., 2018). It is also necessary to consider background levels of ARB and ARG in the natural environment and geospatial gradients of anthropogenic effects when assessing environmental AMR and associated risks (Pepper et al., 2018; Vikesland et al., 2017).

1.3.3. Pharmaceuticals

Pharmaceuticals were one of the first classes of CECs reported in the environment (Stan & Heberer, 1997; Ternes, 1998). Their ubiquity and environmental persistence (Kolpin et al., 2002) raised the interest and concern of the public, partially because these chemicals are explicitly designed to have biological effects on both humans and other forms of life, and because of their common use and visibility in daily life. Nearly 12,000 different chemicals have been identified as pharmaceutical drugs (Wishart et al., 2017) and the list of pharmaceuticals will continue to increase as the understanding of disease mechanisms and development of treatments continues to unfold. Changes in climate, disease vectors, and increases in contamination levels may alter the future use of pharmaceuticals in a region (Redshaw et al., 2013). A recent global-scale study investigated pharmaceuticals in 258 of the world's rivers, representing the environmental influence of 471.4 million people across 137 geographic regions (Wilkinson et al., 2022). Table S2 in Supporting Information S1 summarizes the concentrations of 326 prescription and over the counter pharmaceuticals that have been identified and measured in surface water, groundwater, and drinking water. This table also includes other commonly consumed chemicals such as caffeine, nicotine, and artificial sweeteners that are not technically pharmaceuticals. While this synopsis is not an exhaustive summary of the literature, it illustrates the range of environmental detections. The health hazards posed by pharmaceuticals may be direct or may be mediated by the effects of pharmaceuticals on the toxicity of other chemicals (Lepist & Ray, 2017) and on health risks posed by microbial pathogens (e.g., AMR (Section 1.3.2); Singer et al., 2019). Similarly, microbial processing of pharmaceuticals in the human gut may be affecting the dose of the original pharmaceuticals and of transformation products (TPs) with their own biological activities (Spanogiannopoulos et al., 2016). Thus, hazard characterization for pharmaceuticals, like many other CECs, is complicated by the influences of co-exposures.

1.3.4. Endocrine-Disrupting Chemicals

Endocrine-disrupting chemicals (EDCs) are another broad class of CECs occurring in drinking water. The publication of *Our Stolen Future* (Colborn et al., 1996) increased public awareness of the effects EDCs may have on wildlife and humans (Kwiatkowski et al., 2016). EDCs mimic the functions of hormones, which regulate many bodily functions such as metabolism and reproduction (Diamanti-Kandarakis et al., 2009). Disruption of natural hormone signaling may occur by blocking cellular receptors from receiving the endogenous hormone (suppression) or binding cellular receptors in the absence of hormones (enhancement). Approximately 1,000 chemicals are now believed to be EDCs (Bergman et al., 2013). Examples of EDCs include synthesized endogenous hormones, pharmaceutical hormone analogs, and industrial chemicals such as alkylphenol ethoxylate surfactants and plastics. Table S3 in Supporting Information S1 summarizes the concentrations of 151 EDCs found in the surface water, groundwater, and drinking water.

1.3.5. Per- and Polyfluoralkyl Substances

PFAS are unique chemical structures that contain both hydrophobic and hydrophilic properties. There are an estimated 12,000 PFAS chemicals (USEPA, 2021). While their physical and chemical properties make them ideal for

a variety of non-stick, water repellent, and stain resistant applications such as in cookware, clothing, and carpeting (Lang et al., 2017), their these properties also make PFAS resistant to some treatment approaches both for wastewater (Deng et al., 2010; Houtz et al., 2016) and drinking water (Crone et al., 2019), as well as making them extremely environmentally persistent (Boone et al., 2019). Some PFAS are a component of aqueous film-forming foams, commonly used to fight fires at airports, which is one way that PFAS may contaminate groundwater (Houtz et al., 2013). The presence of low levels of PFAS in some finished drinking water (Hu et al., 2016), combined with their persistence in the human body and potential adverse health impacts (Bruton & Blum, 2017), has raised public awareness of PFAS (SSEHRI, 2019). Table S4 in Supporting Information S1 summarizes some of the literature for 38 PFAS chemicals in surface water, groundwater, and drinking water.

1.3.6. Brominated and Organophosphate Flame Retardants

PFAS are not the only CECs with fire-fighting properties. Brominated and organophosphate chemicals are used to reduce the flammability of many household products such as clothing and furniture (Green, 1992). Approximately 200 chemicals are classified as flame retardants (Flame Retardants Europe, 2018). Concerns over the health risks of the brominated compounds, particularly to children (S. J. Chen et al., 2009; Small et al., 2009), has led to their phase out with a subsequent increase in organophosphate usage (Wei et al., 2015). Organophosphate flame retardants have been found to migrate through atmospheric transport pathways away from their areas of use (Salamova et al., 2014), and have been found in rainwater, surface water, and drinking water (U. J. Kim & Kannan, 2018). Table S5 in Supporting Information S1 summarizes the aquatic concentrations for 46 flame retardants.

1.3.7. Nanomaterials and Microplastics

Nanomaterials and microplastics differ from the other classes of chemical CECs in that they are classified due to their size rather than their chemical structure or commercial use (Boverhof et al., 2015; Cole et al., 2011). In fact, the determination of a consensus definition for nanomaterials is difficult, but most definitions include particles with at least one dimension measuring 1–100 nm (Boverhof et al., 2015). Environmental research on nanomaterials initially was focused on determining if they could have negative health effects on humans or aquatic life (Colvin, 2003; Daughton, 2004; Hoet et al., 2004). While this toxicological research has continued (Voelker et al., 2015), nanomaterials were found to have potential applications in water and wastewater treatment (Bishoge et al., 2018; Teow & Mohammad, 2019; Zhao et al., 2018). Some papers evaluated both the positive and negative aspects of nanomaterials (Zhu et al., 2019), contrasting the remediation potential against the environmental effects for individual nanomaterials.

Environmental concern regarding microplastics has dramatically increased in recent years (Burns & Boxall, 2018). Microplastics include a wide variety of materials such as polyethylene (PE), polypropylene (PP), polyamide (PA), polyvinyl chloride (PVC), polystyrene (PS), polyurethane (PUR), and polyethylene terephthalate (PET) (Rezania et al., 2018). Microplastics can take many forms including fibers discarded from cloth during laundering; particles generated from tire wear, particles originally designed to be microparticles; and breakdown products from larger materials, plastic films or sheets, and foams (Rezania et al., 2018). Microplastics can range in size from 1 to <5 mm, with mesoplastics ranging from 5 to <25 mm, and macroplastics exceeding 25 mm (Rezania et al., 2018). These materials get into surface water through a variety of pathways including wastewater effluent discharges and non-point source runoff. The methods for the collection and quantification of microplastics and associated quality control are still evolving (Koelmans et al., 2019; Li et al., 2018; Picó & Barceló, 2019; Silva et al., 2018; Whiting et al., 2022; S. Zhang et al., 2019). Microplastics are found in aquatic life throughout the food chain (Rezania et al., 2018), both ingested by and entangled with the organisms (Li et al., 2018). Microplastics may be introduced to agriculture through irrigation with treated wastewater or fertilization with biosolids (Nizzetto et al., 2016). Data are incomplete regarding the removal of microplastics during wastewater and drinking water treatment (Novotna et al., 2019).

1.4. Trends in Publications Regarding Environmental Concentrations of CECs

Research into these novel chemicals and microbes that are currently considered to be CECs have been rapidly and continually expanding. While it was once feasible to thoroughly summarize the literature on pharmaceuticals (Glassmeyer et al., 2008), the expanding number of analytes and the increasing number of publications investigating

these targets now makes this a Sisyphean task. Not only is the number of papers on CECs expanding, but so are the venues of publication and geographic locations where such research is conducted. Figure 2 characterizes the expansion of CEC publications from 2002 to 2022. In 2002, there were two papers published using the terms emerging contaminant (EC) or CEC (search term "contaminant* of emerging concern" or "emerging

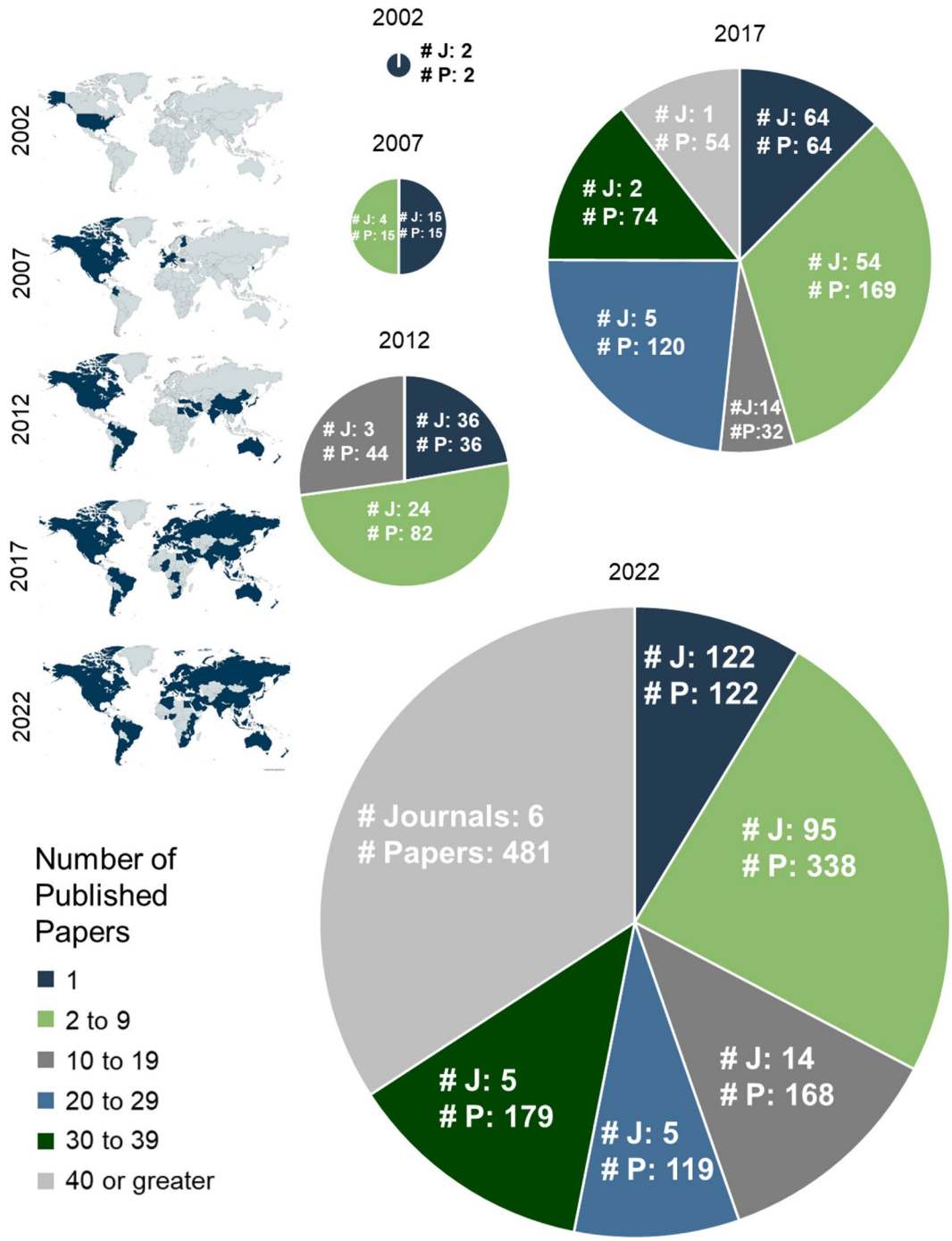

Figure 2. Evolution of contaminants of emerging concern (CECs) in the scientific literature 2002–2022. The numbers in each pie wedge are the number of journals and the number of CEC or emerging contaminant papers represented by each wedge as given by the color-coded legend (i.e., in 2012, 36 journals published one paper shown in the dark blue wedge, 24 journals published two to nine papers for a total of 82 papers represented by the light green wedge, and 3 journals published 10 to 19 papers, a total of 44 papers in the dark gray wedge). Size of the pie charts are proportional to the number of papers each chart represents.

contaminant*" in Current Contents Connect search of topics), one in *Analytical Chemistry* and one in *Electrophoresis*. The number of papers expanded to 30 in 2007, 162 in 2012, 513 in 2017, and topped out at 1407 in 2022. There were 247 journals that published at least one paper on CECs or ECs in 2022, with one journal, *Science of the Total Environment*, publishing 169 papers on the topic. While there are a wide number of journals that have published on CECs, more than half of the CEC papers published in 2022 were published in 16 journals. The locations of the research have also spread, expanding from primarily being conducted in North America and Europe to being truly global (i.e., Asia, South America, Oceana, and Africa; Wilkinson et al., 2022).

To further summarize the expansion of the literature, Figure 3 lists the number of publications for the 20 journals that each published at least 1% of the papers referring to CECs from 2010 to 2018 as indexed in Current Contents Connect. In total, these 20 journals published 61% of the CEC papers in this timeframe. In order of decreasing contribution, these journals are: *Science of the Total Environment* (9.3% of all CEC papers), *Chemosphere* (7.0%), *Water Research* (6.0%), *Environmental Science and Pollution Research* (5.0%), *Journal of Hazardous Materials* (4.7%), *Chemical Engineering Journal* (4.2%), *Environmental Science and Technology* (3.5%), *Journal of Chromatography A* (3.3%), *Environmental Pollution* (2.7%), *Analytical and Bioanalytical Chemistry* (2.5%), *Environmental Toxicology and Chemistry* (2.4%), *Water Environment Research* (1.5%), *Environment International* (1.4%), *Desalination and Water Treatment* (1.2%), *Analytical Chemistry* (1.1%), *Water, Air, and Soil Pollution* (1.1%), *Marine Pollution Bulletin* (1.0%), *Talanta* (1.0%), *TrAC Trends in Analytical Chemistry* (1.0%), and *Journal of Environmental Management* (1.0%). For comparison, the total number of papers published in the journals as well as the publication counts for legacy chemicals (chemicals such as polychlorinated biphenyls [PCBs], polycyclic aromatic hydrocarbons [PAHs], and dioxins and furans) were also tabulated in addition to the CEC classes discussed in Section 1.3. The search terms used were: CECs-*"contaminant* of emerging concern" or "emerging contaminant*"*; pharmaceuticals- *pharmaceutical* or drug* or antibiotic*or PPCP*; EDCs- *EDC* or E2 or EE2 or E1 or E3 or "endocrine disrupting compound*" or hormone* or "endocrine disrupting chemical*"*; PFAS- *"Per- and polyfluoroalkyl substance*" or PFAS* or PFC* or "Perfluorinated Chemical*" or "Perfluorinated Compound*" or PFOS or PFOA*; microorganisms- *bacteria or protozoa or virus* or microorganism* or pathogen* or fungus or fungi or mold**; AMR- *"antimicrobial resistance*" or "antibiotic resistance*"*; cyanotoxins- *"harmful algal bloom*" or cyanotoxin* or microcystin* or "algal toxin*" or cyanobacteria*; legacy chemicals- *PCB* or "polychlorinated byphenyl*" or dioxin* or PAH* or "polycyclic aromatic hydrocarbon*" or "persistent organic pollutant*"*; microplastics- *microplastic* or microfib* or microbead*or "plastic microparticle*"*; nanomaterials- *nanomaterial* or nanoparticle* or nanofib* or nanotube* or nanorod* or nanoribbon**; and brominated and organophosphate flame retardant- *flame retardant**. Separate panels in Figure 3 depict the number of publications for the various classes between 1998 and 2022. Proportionate percentile models were used to summarize the change in the number of papers across years, using Stata 14.2 S/E software (StataCorp LLC, College Station, Texas). The overall number of publications in these 20 journals increased 8% per year (shown in the upper right corner of each panel in Figure 3), presumably due to an increase in environmental research and improvements in electronic publishing. Legacy contaminants had a slightly slower increase of 5% per year. In stark contrast, the number of publications on CECs increased an average of 31% per year. Microorganisms and cyanotoxins increased at a slower average growth rate of 12% and 16% per year, respectively, but AMR publications increased at an average of 29% per year. These patterns reflect the continuing importance of AMR as a global health concern, as microorganisms become more resistant to the effects of current antibiotics (Section 1.3.2).

As one of the first classes of CECs investigated in the environment (Stan & Heberer, 1997; Ternes, 1998), pharmaceuticals lead all classes of CECs except nanomaterials in terms of number of publications (Figure 3). However, as was discussed in Section 1.3.7, the nanomaterial publication expansion is unique among the CECs due to the use of the materials in water treatment, rather than occurrence of the materials themselves. The number of pharmaceutical publications has continued to rise, with an average growth of 11% per year. The publication trends in Figure 3 illustrate the evolving nature of interest in various CEC classes. EDCs are the next most commonly reported class of CECs, followed by accelerating interest in PFAS and the organophosphate and brominated flame retardants. Nanomaterials and microplastics are more recent additions to the research lists, starting in the early 2000s. The average rates of increase of all classes of CECs (EDCs 13% per year, PFAS 25% per year, brominated and phosphorus flame retardants 19% per year, nanomaterials 32% per year, and microplastics 43% per year) far exceed the rate of growth for the journals. Halden (2015) noted that for 14 different CECs, research interest maximized an average of 14.5 years after the initial published reports of the contaminant, and interest

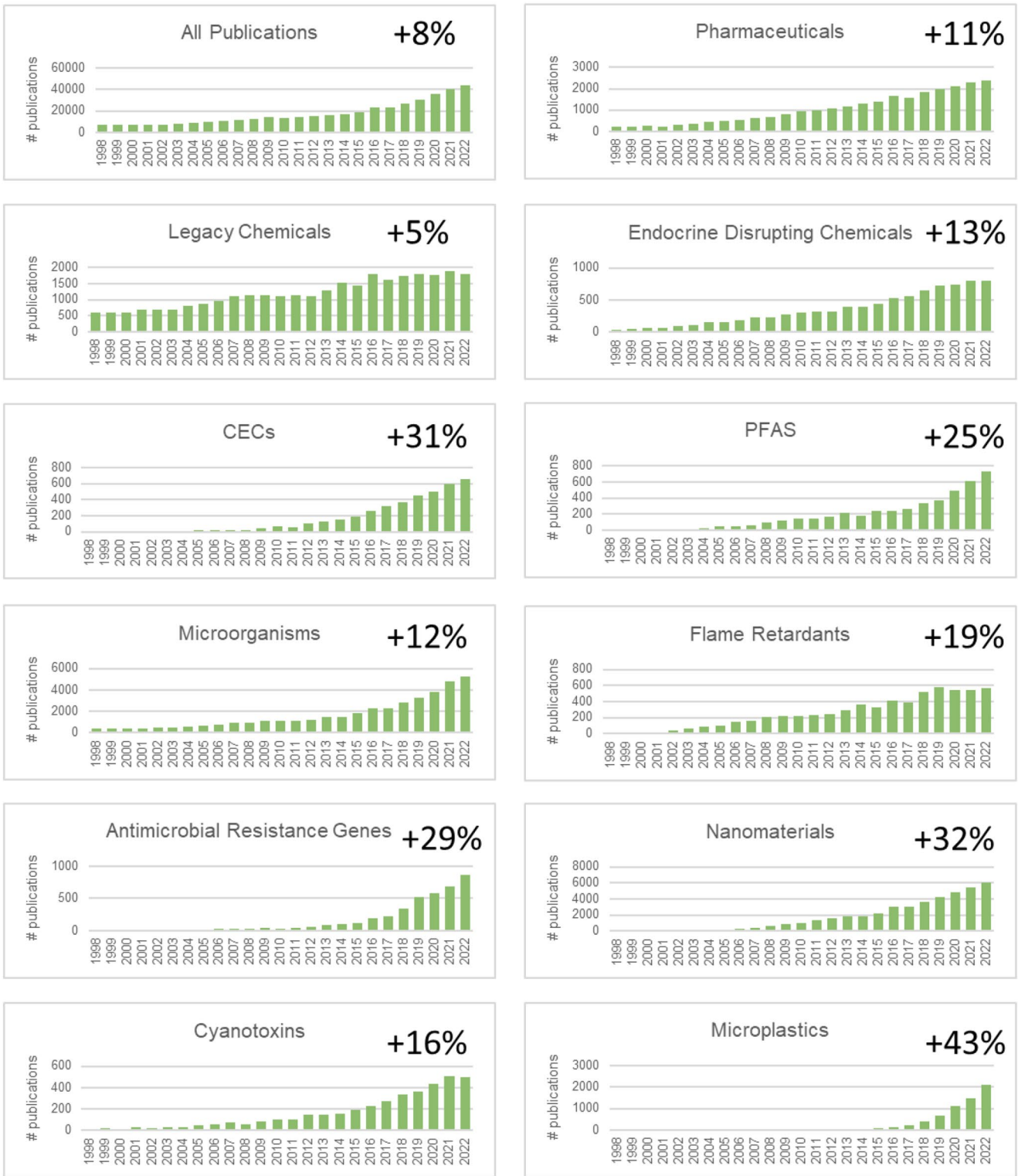

Figure 3. Publication rates for various classes of contaminants of emerging concern (CECs). Bar charts list the number of papers in 20 of the leading CEC journals. Number in top right-hand corner of each panel is the annual percent increase.

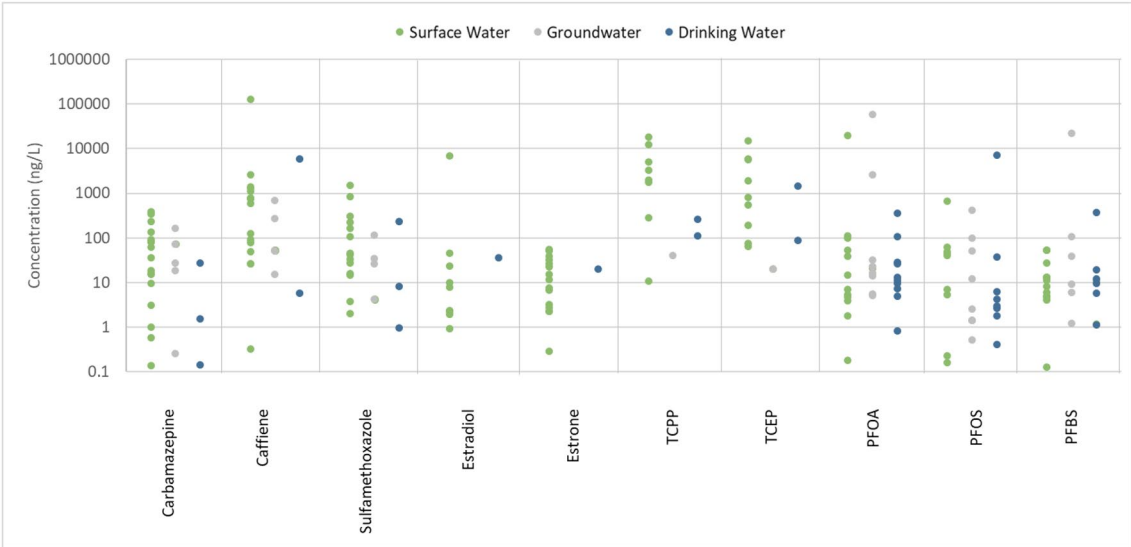

Figure 4. Comparison of maximum measured concentrations in surface water, groundwater, and drinking water for select pharmaceuticals, hormones, flame retardants and per- and polyfluoroalkyl substances (PFAS). For all compounds and all matrices, measured concentrations varied by several orders of magnitude, but surface water (green symbols) tended to be higher than groundwater (gray) and drinking water (blue).

in the chemicals waned over the next 14.1 years until a baseline number of annual publications was achieved, a 28.6-year period of increased research interest. These analyses demonstrate the relative importance of CECs in the field of environmental science, which is not only expanding but continually evolving to include new analytical targets of environmental interest.

The concentrations of CECs vary based on the hydrologic compartment type of water. For a given chemical, surface water generally tends to be more susceptible to contamination than groundwater. Figure 4 plots the literature concentrations (see Tables S2–S5 in Supporting Information S1) for representative pharmaceuticals (carbamazepine, caffeine, and sulfamethoxazole), hormones (estradiol and estrone), chlorinated organophosphate flame retardants (tris (1-chloro-2-propyl) phosphate [TCPP] and tris (2-chloroethyl) phosphate [TCEP]), and PFAS (perfluorooctanoic acid [PFOA], perfluoroctane sulfonate [PFOS], and perfluorobutane sulfonate [PFBS]). Some outliers are notable in the trend of surface water having the highest concentration, for example, the high measured concentration of caffeine in drinking water. Additionally, the fewer measurements in groundwater and drinking water relative to surface water make the trends more difficult to visualize. Nevertheless, the general concentration trend of relatively higher surface water concentrations holds true for many of the CEC classes. The notable exceptions are the PFAS chemicals. The groundwater concentrations are generally higher than the other CECs. The environmental stability of these chemicals may be a cause of this trend (Crone et al., 2019).

1.5. Limitations of Current Environmental Monitoring Data

We observed a bimodal distribution of frequency of research on the individual chemicals within a CEC class: that is, within a chemical class, an individual chemical tended to be either present in a plurality of the studies or to be only measured in a single study (Figure 5). The compounds listed on each panel are the ones that were frequently measured (i.e., analytes in at least of a third of the papers surveyed for a given CEC class). Chemicals that only appeared in a single report (the far-left bar of each graph) had the highest frequency for each CEC class, ranging from 22% to 57% of the surveyed analytes. PFAS analytical methods all tend to include the same core list of chemicals (mostly 4–12 carbon chain perfluorinated carboxylic acids), which is why those analytes have a high frequency in the literature. Conversely, the papers on flame retardants tended to focus either on the brominated or on the organophosphate flame retardants, thus no one chemical was in more than half of the surveyed papers. The EDC papers tended to be focused either on the endogenous hormones or on industrial chemicals, thus lowering

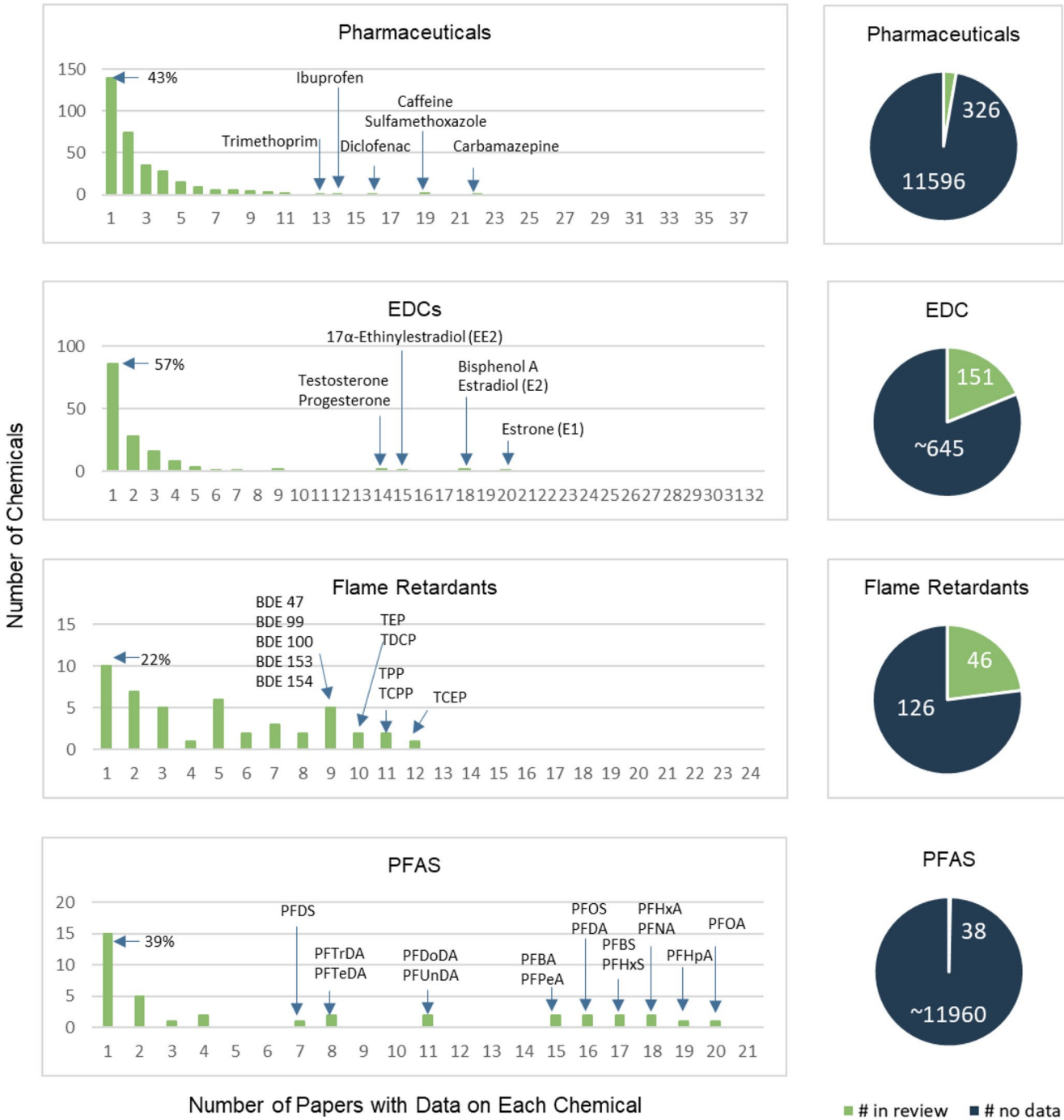

Figure 5. Frequency of individual contaminants of emerging concern (CECs) in literature review, by CEC class. A plurality of the CECs in this limited review appeared in a single paper (22%–57% of the analytes, depending on class). Chemicals in at least one-third of the papers included in the review are identified on each bar chart. The number of CECs that appeared in reviewed publications (light green wedge) is dwarfed by the estimated number of CECs in each class (dark blue wedge), indicating how few of the CECs have been investigated in environmental studies.

the possibility for an analyte to appear in all EDC papers surveyed. For the pharmaceuticals, most papers are focused on both over-the-counter and prescription human pharmaceuticals, but a minority of the papers focused on veterinary or illicit drugs. In total, this literature review captured data on 326 pharmaceuticals, 151 EDCs, 46 flame retardants, and 38 PFAS chemicals (Tables S2–S5 in Supporting Information S1). As shown in Figure 5 for each of the CEC classes, the number of chemicals reported in the environmental literature is a fraction of the

total estimated number of chemicals in each class. A growing array of tools is available to assist in closing this data gap.

2. What Else Is Out There? Current and Next Generation Tools

Excluding specific spills or other discrete contamination events, the biggest challenge in linking observed toxic effects and the contaminant or contaminant mixtures initiating the toxic effect is the identification of the toxicants within an environmental water sample. This is particularly problematic when the water sample contains a complex mixture of organic and inorganic components whose absolute, often low, concentrations and relative compositions change with hydrologic and biologic conditions within the watershed or aquifer. As a result, considerable effort has been made in developing tools that more specifically tie toxicity to the initiating contaminant, and in light of anticipated sample complexity, to make the connections comprehensively for as many contaminants and toxicologic responses as possible.

In this section, we assess state-of-the-art techniques for two complementary aspects of toxicity to accurately and comprehensively identify: (a) the full range of contaminants present, and (b) the corresponding observed responses or effects. These two components are necessary and fundamental to fully characterizing the entirety of water (source-water systems and treated-water systems) toxicity and subsequently developing an objective assessment of the potential risk to human and ecosystem health. Following this assessment, we identify potential tandem combinations of the best of these approaches for future water quality and risk assessments in light of the future challenges of maintaining safe water supplies for potable water and ecosystem needs.

2.1. Nontarget Analysis: A New Tool for CEC Identification and Quantitation

Mass spectrometry has been an important means of identifying and quantifying organic contaminants in environmental samples since the late 1960s (Budde, 2015). Over the ensuing decades many regulatory and research methods using coupled chromatography/mass spectrometry have been developed, primarily using gas or liquid chromatography (GC or LC), permitting unambiguous identification of organic contaminants in environmental samples at parts-per-billion and lower reporting levels (Abian, 1999; Lebedev, 2012). The availability of pure, verifiable authenticated standard materials of the contaminants of interest has been, and continues to be, key to the accuracy of these methods.

Over the last 20 years, however, advances in mass spectrometer design, computerized automation of instrument operation, data collection, and data analysis have resulted in the mass spectrometers that routinely measure the mass of an ionized molecule or its fragments to a mass resolution of 0.001 Da or lower. With this accuracy, the likely elemental compositions of ions and, subsequently, identification of organic contaminants can be determined (Zedda & Zwiener, 2012). Identification quality from these high-resolution mass spectrometers (HRMSs) has been improved by incorporating additional information from chemical information databases and in silico computational predictive tools (Aalizadeh et al., 2016, 2019; McEachran et al., 2017, 2018; Samanipour et al., 2018). Thus, the researcher using HRMS can prioritize the synthesis and/or acquisition of new standards for presumably identified unknown contaminants and contaminant classes whose presence, concentration, and behavior indicate environmental significance.

The two most common HRMS techniques in current use, the quadrupole-time of flight mass spectrometer and the hybrid linear ion trap (Orbitrap) mass spectrometer (Orbitrap-MS) have been available since 1996 and 2005, respectively (Makarov et al., 2006; Morris et al., 1996). Both have revolutionized the identification of organic contaminants in environmental samples, especially the challenging polar, hydrophilic compounds that comprise many CECs. These HRMS systems typically collect all ions produced and, when coupled to high-performance LC or GC separations, high resolution full-scan spectra (each containing thousands of potentially pertinent ions) can be continuously collected in 50 millisecond intervals over a 20- to 30-min chromatographic separation; recent developments coupling ion mobility spectroscopy to chromatographic separation (Celma et al., 2020) adds an additional potential identifying feature, further increasing file size. The resulting gigabyte-sized data files would be difficult to productively evaluate without the concomitant development of high-speed data acquisition and analysis software, which permits deconvoluting and interrogating the highly complex, data-rich results from environmental samples. As all ions are captured and available for analysis, targeted contaminants (with associated

analysis of standards), contaminants that are suspected to be present, and truly unknown but present contaminants can be evaluated, at least qualitatively, from a single file processed iteratively.

Environmental analytical chemists have recognized the utility of such an all-encompassing analytical tool and have expanded its use in environmental analysis. Since the defining publication by Krauss et al. (2010), nontarget analysis (NTA), sometimes referred to as nontarget screening (NTS) has become a rapidly expanding research area. Sufficient numbers of authors, approaches, and publications have resulted in an ongoing dialogue regarding the rapid proliferation of this approach, potential pitfalls, and needs for clear, exact definitions and metrics of the qualitative and quantitative scientific content that results from NTA (Angeles, et al., 2021; Black et al., 2023; Hites & Jobst, 2018, 2019; Knolhoff et al., 2019; Samanipour et al., 2019).

To identify the full range of CECs and other contaminants present in a sample, the most relevant aspect of NTA is post-analysis data processing. Timewise, this step is the largest fraction of the work, accomplishing several functions including (a) normalization of multiple analysis results files into a single set to account for run-to-run analysis variations, (b) automatic identification of "molecular features" (chromatographic retention time-molecular/fragment ion-ion intensity combinations) that are presumed to be characteristic of individual compounds (known, suspected, or unknown), and (c) additional data filtering to remove redundancies that arise from the presence of salts and other ionic complexes of each compound or element isotope compositions (isobaric interferences).

Ideally, an NTA workflow first sequentially identifies compounds that are either (a) verified against authentic standards (known compounds) analyzed at the same time as the environmental samples, and thus quantifiable, or (b) suspected to be present because they are related to knowns, or have common environmental sources and input histories, with comparison against external publicly available mass spectra databases of known and suspect contaminants (e.g., MassBank of North America,; https://mona.fiehnlab.ucdavis.edu/) and in-house and vendor-supplied databases. Public and vendor-supplied databases are particularly helpful because the database entries are curated, containing low energy and high energy, controlled fragmentation full HRMS spectra of defined quality, and typically have standardized chromatographic separation conditions. These systematic comparisons, against documented consensus-acceptance standards (Hollender et al., 2019) provide support for identification in the absence of a standard. Finally, after the prior evaluation for known or suspect compounds, and in-depth searching of extant databases and literature, what remain are the set of molecular features containing HRMS spectra and chromatographic characteristics for identifying unknown compounds (i.e., previously unreported, unsuspected environmentally relevant compounds).

The NTA strategy described above can be applied to samples regardless of source or relationship between samples. An experimental design where samples are collected so that a "before/after" condition or state can be distinguished may provide NTA results that can be used to determine if the distributions of features between samples reflect an environmental change of state. For example, comparing samples from contaminant-exposed and unexposed fish, or river water samples collected upstream and downstream from a wastewater discharge, may provide a more directed means of using NTA to identify known, suspected, and unknown compounds of environmental relevance specific to those scenarios. In this approach, the filtered, optimized HRMS results from these samples are compared using nonparametric statistical techniques such as principal component and multivariate data analysis. These nonparametric statistical techniques are used to identify distributions of molecular features that are distinctly characteristic of either the "before/upstream" or "after/downstream" samples, as well as those common to both samples. Molecular features common to both samples may reflect common sample components or experimental artifacts.

The approaches and standards of practice used by NTA practitioners are still evolving, and often incorporate and build upon approaches pioneered by researchers identifying and quantifying the metabolome, that is, all metabolites generated in each biological process (Cajka & Fiehn, 2016; Kind & Fiehn, 2006, 2010). As of 2023, however, sufficient research has been published to assess NTA in an environmental context, particularly as a tool to address short- and long-term water-quality challenges for human exposure and ecosystem health.

2.1.1. NTA Applications to Water Quality and Chemical Exposure

To date (2023), many studies have been published describing the application of NTA to identify agricultural, urban, and industrial contaminants and their potential sources in freshwater systems, many of which may also be drinking-water sources. In the following sections, we address recent NTA applications by the water types most

commonly addressed in studies. A number of studies reviewed herein address multiple water types; however, characterization by water type can be useful when considering routes of exposure and potential effects of CECs on human and ecosystem health.

2.1.1.1. Wastewater

Wastewater discharge is an important environmental contributor to complex contaminant mixtures with demonstrated potential for the presence of known, suspect, and unknown contaminants (Alygizakis et al., 2019; Baz-Lomba et al., 2016; Gago-Ferrero et al., 2015; Lara-Martín, et al., 2020), and has been the water type most studied using NTA approaches. Wastewater is a highly complex mixture in terms of the numbers and classes of CECs and other organic compounds derived from household, commercial, and industrial anthropogenic uses and those compounds normally excreted via human consumption and metabolism. This complexity, coupled with the inherently large contaminant concentrations relative to other typical environmental water types, imposes severe analytical challenges. The presence of ionizable "normal" biogenic organic compounds can interfere in the identification and quantitation of anthropogenic contaminants. Wastewater is recognized as an important source of CECs to water resources (Glassmeyer et al., 2005), and thus wastewater samples were generally the first water types tested to demonstrate the capability of any given NTA approach. Wastewater is an ideal medium to demonstrate capabilities in identifying target, suspect, and unknown compounds in the presence of a challenging, interference-rich sample matrix, while providing the widest array of potentially detectable, identifiable, and quantifiable contaminants. Although collecting samples from wastewater treatment plants can be challenging (Ort et al., 2010), it is relatively straightforward to collect representative samples from wastewater treatment compared to natural water systems. The likelihood of readily detectable compounds in the presence of potential interferences has made this water matrix an ideal choice for testing the robustness of NTA for rapidly identifying and quantifying the widest array of CECs and legacy contaminants (Alygizakis, et al., 2019; Blum et al., 2017; Choi et al., 2021; Gago-Ferrero et al., 2015; Helbling et al., 2010; Ouyang et al., 2015; Schollée et al., 2015; Schymanski et al., 2014b).

Typically, in these papers large numbers of contaminants are identified, and through iterative filtering and evaluation, substantially smaller sets of suspect or unknown compounds then become the focus of intensive assessment. In many cases, these suspect/unknown compounds are TPs of parent compounds (e.g., pharmaceuticals, pesticides). These results illustrate the need for further development of openly available databases that integrate known information about the disposition of a potential chemical contaminant (i.e., drug or pesticide registration requirements) with in silico predictive tools that can be used to better assess how HRMS results for an NTA unknown compare to known active ingredients or their likely TPs.

Synthesizing results from multiple wastewater influents and effluents yields insights from NTA analysis regarding the composition and concentrations of organic contaminants in wastewater, tying their presence to source inputs to the wastewater streams or degradative processes that occur during wastewater treatment. Although there can be considerable variation between wastewater treatment plants (WWTPs) from different locations, regionally and globally, a common group of compounds generally is present in many influents and effluents, likely reflecting the global use and presence of many chemicals (e.g., pesticides, pharmaceuticals and personal-care products) that have common active ingredients. Variation is introduced by differences in use and regulation between countries. However, pharmaceuticals and their corresponding TPs are commonly observed as either suspect or known compounds. This reflects their presence in wastewater influent (as a consequence of human metabolism) or from subsequent wastewater treatment processing.

2.1.1.2. Surface Water

In our literature review, surface waters (e.g., rivers, streams, lakes, and reservoirs) have been the second most commonly studied water body types where an NTA approach has been applied. These water types have been focused upon because the anticipated CEC sources, namely wastewater discharge and agricultural runoff, are likely to have myriad contaminants that are relevant to environmental health. In many studies, wastewater effluent, receiving surface waters, and in some cases groundwater, are discussed together because of the inherent connections between discharged wastewater and receiving waters (Hernández et al., 2015). Several papers have shown how a suspect or unknown contaminant may be present for substantial distances along surface water flow paths (Köppe, et al., 2020; Quadra et al., 2021), in a manner similar to compounds detected using targeted methods (Ruff et al., 2015). In previous research, NTA was a valuable complement to a comprehensive monitoring

program that used targeted chemical analysis and in vivo and in vitro bioassays to prioritize contaminants based on a combined presence and effects risk assessment (Tousova et al., 2017). This research was successfully coordinated over large spatial scales, using multiple laboratories, and applied to multiple European rivers, capturing crucial information at or near the points of introduction of wastewater to and then through the river systems, and assessing risk to aquatic life within and between river basins.

Surface-water derived drinking water sources likely contain a fractional discharged wastewater component, referred to as de facto reuse (Rice & Westerhoff, 2015; Rice et al., 2013), which likely include CECs (Nguyen et al., 2018). Some drinking water treatment systems situated on alluvial aquifers use riverbank filtration to reduce the load of natural organic matter and anthropogenic contaminants to produce drinking water. NTA has been used to assess CEC reduction by riverbank filtration at three drinking-water treatment plants in Switzerland (Albergamo, et al., 2020; Hollender et al., 2018) proceeding from source along the flow path of riverbank filtration through final reverse osmosis treatment. In these reports, the authors used a combined targeted/nontargeted screening approach to quantify removal of 526 targeted CECs, while the NTA characterization provided complementary qualitative information about persistence, reduction, or production of the 7,500 nontarget profile components that were identified.

The development of a comprehensive target and suspect contaminant database, and its application to seasonal samples collected in an urban surface-water system in the northeast United States, demonstrated how NTA can be used to characterize changes in presence/absence of suspect contaminants in: (a) a surface drinking water source, (b) the treatment of such a drinking water source, (c) the municipal wastewater influent and effluent using this drinking water source, and (d) the lake receiving treated effluent (Pochodylo & Helbling, 2017). The results demonstrate that confirmed suspect compounds (confirmation based on a detailed set of HRMS criteria) were as numerous as target compounds, and patterns of persistence and removal occur in the detection of suspect contaminants in consistently collected samples from each water type.

A different design used LC-HRMS to focus on a specific contaminant class, iodinated X-ray contrast compounds, using a target/suspect approach to estimate distributions of these contaminants within river systems while identifying new potential TPs and formation pathways (Zonja et al., 2015). Other research has addressed the substantial concentration differences, and thus compound detectability, between wastewater influent/effluent and surface water samples by using alternative means of sample pre-concentration than the typical solid-phase extraction of an ∼1-L water sample. For example, Guibal et al. (2015) combined target compound identification and quantitation embedded within the NTA workflow, with subsequent nontarget identification using polar organic chemical integrative sampler (POCIS), a passive sampler that integrates the collection of contaminants at variable concentrations and compositions from a large (hundreds of liters) water sample, detecting target and nontarget compounds that might otherwise have been undetectable. Other researchers collected ∼300-L samples, which were processed streamside to achieve similar levels of sample pre-concentration (Deyerling & Schramm, 2015). These studies demonstrate that large-volume sampling technologies, in combination with NTA workflows, can provide exceptionally high sensitivity for detecting known, suspect, or unknown CECs. This sensitivity is achieved by substantially increasing effective sample size, integrating sample collection over an extended period, which permits capture of episodically present contaminants, doing so in a cost- and time-effective sampling design.

2.1.1.3. Groundwater and Drinking Water

Analytically, groundwater and drinking water have similar characteristics. CEC contaminants measured using standard methods have shown that the anticipated numbers and concentrations of organic contaminants in these water types are typically an order of magnitude lower than in surface water and more than two orders of magnitude lower than in wastewater effluent (Glassmeyer et al., 2017). Thus, fewer studies have applied NTA approaches to these environmental compartments, particularly post-treatment drinking water. Soulier et al. (2016) used POCIS passive samplers and solid phase extraction of water samples, coupled with an iterative target/suspect/unknowns NTA workflow, to characterize groundwater contamination in two aquifers using multiple samples collected over a period of several months. They demonstrated improved detection of targeted compounds by POCIS versus discrete water samples, again likely due to the increase in contaminant concentration achieved by exposing the samplers for extended time periods versus instantaneously collecting discrete samples. The workflow design in this study allowed the identification of 342 target compounds and 279 suspect compounds. Using nonparametric

statistical tools applied to about 12,000 nontarget molecular markers (exact ion mass, retention time, and signal intensity), 41 markers unique to one aquifer and 36 to another were characterized (Soulier et al., 2016). Although these markers were not further identified by mass spectrometry, the authors point to the fact that these markers can be used forensically, even in the absence of full identification, to tie unique contamination sources to the observed contamination in these aquifers. Kolkman et al. (2021) used NTA to identify highly polar organic compounds in Dutch and Flemish drinking water and water sources and identified concentrations exceeding at least one provisional guideline; the lack of toxicity data for most of thes highly polar compounds indicated further research needs. Other authors have used NTA in laboratory scale experiments to identify TPs formed during the sand filtration and ozonation steps of drinking water treatment (Brunner et al., 2019b). The library of suspect TPs was then used as a tool for assessing the occurrence and distribution of likely TPs present in water supplies that are subjected to ozonation treatment.

2.1.2. Class-Specific NTA Applications

Most published research using NTA use inclusive, comprehensive approaches to the determination of organic contaminants, which is appropriate given the mixed urban, industrial, and agricultural sources of organic contaminants common to many water resources. In at least two cases, however, a chemical class-specific focus has yielded useful information and understanding for a global contamination problem that is receiving increasing attention.

Some of the most intensively studied drinking-water derived TPs are commonly referred to as DBPs and are commonly formed by reactions of chlorinating agents such as hypochlorite and chloramine with dissolved organic matter in drinking water during treatment. The occurrence and distribution of DBPs in treated drinking water has been actively studied using HRMS approaches as some DBPs are known carcinogens and produced during the chlorination processes used to treat source water, with complex and varying dissolved organic matter concentrations, can result in complex mixtures of DBPs (Richardson, 2003; Richardson & Kimura, 2017; Richardson et al., 2002; Weinberg, 2009) that can have deleterious effects through long term DBP exposures. Kimura et al. (2019) published an NTA workflow to characterize the DBP exposome, that is, the full complement of potential DBPs that an organism could be exposed to. Because many DBPs are volatile, a gas chromatography time-of-flight mass spectrometer (GC/ToF-MS) approach was used to separate, identify, and quantify a set of 39 priority unregulated DBPs, and subsequently identify 12 nontarget DBPs using the NTA identification confidence criteria approach proposed by Schymanski et al. (2014a).

PFAS are ubiquitously present in many aquatic environments (Field & Seow, 2017; Wang et al., 2017), particularly in groundwater aquifers subject to contamination from fire training activities (X. Xiao et al., 2017), and their presence in drinking water has been a high-profile research topic (Bradley et al., 2018; Hu et al., 2016; Kaboré et al., 2018). Several studies have used HRMS and NTA approaches to confirm or identify previously unreported or unidentified PFAS components and classes in many environmental media (Barzen-Hanson et al., 2017; Munoz et al., 2021; Strynar et al., 2015; Tousova et al., 2017). Because more than 3,000 PFAS have been introduced to the global market (Wang et al., 2017), additional applications of NTA would further characterize the presence of PFAS in the hydrosphere.

2.1.3. Challenges

The importance of contaminant identification to the understanding of human exposure and potential deleterious effects was highlighted in a recent National Science and Technology Council commissioned report on addressing critical research gaps related to CECs in drinking water (National Science & Technology Council, 2018). NTA is at a point in its development where the emphasis in published reports is quickly transitioning from method development and demonstration of applicability to field and laboratory applications such as drinking- and wastewater-treatment trains, stream reaches, watersheds, and organisms (Hollender et al., 2017). Yet major challenges remain as this transition occurs. Although important gains have been made in improving the efficiency of NTA workflows (Hollender et al., 2017; Moschet et al., 2013), the process of winnowing down thousands of molecular features of substantial signal to dozens of potential unknown candidates with structural information and metadata indicative of likely presence is both labor- and time-intensive. Often the proposed identities of these potential contaminant candidates could have been equally well inferred from a combination of a priori knowledge of the products and chemicals likely present in contaminant sources, of extant results of targeted analyses, and

of an understanding of abiotic and biotic mechanisms of chemical transformation in the environment (Brunner et al., 2019b). A potentially legitimate criticism would then be that it could be more cost effective to predict potential unknowns from targeted analysis and source data rather than to enter into the expense and effort of an NTA approach. One advantage of the NTA approach, however, is that any assumptions made about the importance or priority of a molecular feature are independent of prior knowledge and are initially based on the quality of the analysis results themselves (signal intensity, presence in blanks, quality of structural information, removal of adducts or other experimental artifacts). This unstructured approach allows the data to speak, in a sense, such that the presence of tentative unknowns of importance, a presence that might have been predicted by other means, acts to confirm the utility of the approach. At the same time, this unstructured approach keeps the analytical window open for unknown contaminants that would be missed by a prioritization scheme based on previous knowledge of sources and targeted analysis results.

In addition, discussion has been ongoing regarding the importance of authentic standards to confirm the putative unknowns from an NTA analysis (Hites & Jobst, 2018, 2019; Samanipour et al., 2019). In the midst of such debates, it is important to note that as the number of chemicals being introduced to the environment continues to expand, disparity—between (a) the number of available authentic standards available, and (b) the potential number of unknowns that can be identified to a high level of confidence using HRMS but that lack authentic standards—will only continue to grow. Nevertheless, having authentic standards for subsequent determination of concentration, and therefore toxicity due to a putative unknown, is of critical importance.

The primary value NTA offers is the ability to assay the widest possible range of putative unknowns, prioritize them based on relative abundance within and between samples, and relate those prioritized features to biological effects data where available. These features then drive development of authentic standards toward those unconfirmed compounds that have demonstrated correlative relationships to toxic responses of human or environmental health relevance. This is especially pertinent for TP identification, a common theme for many NTA workflows. This emphasis on identifying TPs is expected given that data and authentic standards are more likely available for targeted precursor compounds than for their TPs. It has been repeatedly documented that TPs may have similar or greater equivalent potency and effect relative to their parent compounds (Zindler et al., 2020). Nevertheless, because toxicity tests are typically conducted on only parent compounds during the chemical registration process, TPs are still not generally as well recognized as potentially affecting environmental health (Mahler et al., 2021).

2.2. Bio-Analytical Tools for Human and Ecological Health

In the field of non-targeted water quality monitoring, biological assays (bioassays) are emerging as an effective tool. Similar to NTA, bioassays can be used to assess environmental samples for potential contamination; however, bioassays do not detect distinct compounds. Rather, they provide insight into potential adverse physiological effects (relevant to human and/or ecological health) from the environmental sample through quantitative measurements of cumulative biological activity (B. Escher et al., 2021; Snyder & Leusch, 2018). Bioassays typically involve short-term in vitro, or low complexity in vivo, laboratory methods that exploit defined biochemical molecular initiating events (MIEs) (described below). The past decade has seen pronounced growth in the number and type of novel bioassays used in water quality screening efforts, especially in vitro bioassays. These tools have become commonplace in water quality screening of wastewater, drinking water, source, and recycled waters (Blackwell et al., 2018; Cavallin et al., 2014; Conley et al., 2017b; Daniels et al., 2018; B. I. Escher et al., 2014; Jia et al., 2015; König et al., 2017; Leusch et al., 2018; Neale et al., 2017). Future regulatory applications, however, would benefit from refined water sample extraction methods, confirmation of interlaboratory precision, and identification of accurate effects-based trigger values (Snyder & Leusch, 2018).

2.2.1. The Adverse Outcome Pathway Framework

Fundamental to the utility of in vitro bioassays is the adverse outcome (AO) pathway framework in which they function. Every unique AO pathway consists of sequential causally linked biological processes, beginning with a MIE, such as receptor and receptor ligand binding, and ending in an AO at the organismal or population level. While the AO pathway MIE typically is the biological step exploited by in vitro bioassays, the AOs are relevant to human health or ecological risk assessment (Ankley et al., 2010). Further, each AO pathway contains defined

key events, or successive and quantifiable biological events, that span increasing levels of biological organization (cellular, tissue, organ, organ system) and provide causal linkages between the MIE and ultimate AO. Ideally, xenobiotic activation of the MIE can be quantified using a bioassay and the results are quantitatively predictive of the expected AO. Bioassays indicative of reproductive and developmental toxicity have provided accurate predictions of in vivo test results (Sonneveld et al., 2005), although specific chemical classes may not extrapolate from in vitro to in vivo as well (Conley et al., 2016; Gray et al., 2019).

A diverse array of AOs is represented by existing bioassays including reproductive and developmental toxicity, growth inhibition, and neurotoxicity (Table 2). Types of bioassays include, but are not limited to, enzyme activation, whole cell reporter-gene transcriptional activation, and whole organism assays (B. I. Escher et al., 2014; Jia et al., 2015; Neale et al., 2017). More complex in vitro "-omics" tools have been developed for water quality assessment (Skelton et al., 2014; Zhen et al., 2018) and whole effluent test methods (Table 2) require whole organisms and quantify survival, growth, and reproduction endpoints (USEPA, 2000).

Table 2 illustrates current trends in bioassay development and application in water quality monitoring. For example, although bioassays are available for numerous biological endpoints, a few endpoints have many available bioassays for testing (e.g., estrogen and androgen receptor transcriptional activation bioassays). Disproportionate representation in bioassay MIEs is likely due to the specificity of the MIEs, interpretability of bioassay data output (direct impacts on human/ecological health), and whether key events linked to the in vitro MIE have been established in the respective AO pathway. Although numerous bioassays have been developed, only a few have Organization for Economic Co-operation and Development (OECD) test guidelines (internationally accepted standardized methods for chemical safety testing; Table 2, highlighted in red; OECD, 2019).

2.2.2. Chemical Toxicity Screening

Many bioassay methods were originally developed to assess effects of individual environmental chemicals, or mixtures of environmental chemicals on a single molecular mechanism of action (Altenburger et al., 1990; Hartig et al., 2002; McCann et al., 1975; Medlock Kakaley et al., 2017; Sonneveld et al., 2006; Wilson et al., 2002). One of the earliest examples of an in vitro bioassay is the bacterial Ames bioassay (McCann et al., 1975). The Ames bioassay utilizes mutagenicity as an indicator of carcinogenicity, as the MIE for many carcinogens is DNA mutation. More recently, bioassays have been used to characterize potency of CECs at a single MIE (Conley et al., 2016) and categorize compound classes according to the gene regulatory networks they affect (Martin et al., 2010). Such research used a multi-endpoint bioassay, Attagene's Cis- and Trans-FACTORIAL high-content bioassay, to assess 320 compounds for their effects on cellular gene regulatory networks involved in genotoxicity, hypoxia, immune function, and endocrine disruption.

In response to the National Research Council's hallmark publication, *Toxicity Testing in the* 21st *Century: A Vision and A Strategy* (NRC, 2007), both the United States and the European Union established initiatives to screen thousands of compounds for various types of toxicity using a wide array of in vitro bioassays (Table 2). United States' agencies including the USEPA and the National Institutes of Health designed Toxicity Forecaster (ToxCast; Dix et al., 2007) and Tox21 (NTP, 2004) programs, respectively, while the European Union developed ChemScreen (van der Burg et al., 2011), which focused solely on identifying reproductive toxicants. Each program is distinct, but similar with the common goal to develop efficient methods, often involving robotics, to screen toxicity of chemicals, although ToxCast does integrate predictive models for new chemicals based on acquired chemical toxicity data. Together, these efforts created a paradigm shift in chemical toxicity testing by allowing the prioritization of toxicants to reduce costly and time-intensive in vivo chemical toxicity testing. More recently, the USEPA described a strategic plan to reduce, refine, and replace in vivo vertebrate toxicity testing by incorporating new approach methodologies including some of the OECD standardized bioassays (Table 2 highlighted in red; USEPA, 2018). Additionally, The European Union Directive 86/609/ECC and 2010/63/EU restricted use of vertebrates in toxicity testing, initiating the application of equitable in vitro toxicological methods (European Union, 2010).

2.2.3. Water Quality Screening

Many of the bioassays originally developed for chemical toxicity testing have been adapted to environmental sample assessment. These methodologies have been discussed in detail previously (B. Escher et al., 2021; Snyder

Table 2
In Vitro and Low Complexity In Vivo Bioassays That Have Been Applied Previously to Water Quality Monitoring

	Bioassay endpoint	Available bioassays
Xenobiotic Metabolism	Pregnane X Receptor	HG5LN-hPXR, PXR-cisFACTORIAL, PXR-transFACTORIAL
	Constitutive Androstane Receptor	CAR-transFACTORIAL, CAR-yeast
	Peroxisome Proliferator-Activated Receptor gamma	PPARλ-bla, PPARλ-transFACTORIAL, PPARλ-CALUX, PPARλ-GeneBlazer, Anta-PPARλ-GeneBlazer
	Peroxisome Proliferator-Activated Receptor alpha	PPARa-transFACTORIAL, PPARa-CALUX
	Aryl Hydrocarbon Receptor	AhR-yeast, AhR CAFLUX, H4IIEluc, MCF7DRE, Ahr-cisFACTORIAL, AhR CALUX
	CYP19a1b Expression	CYP19a1b-GFP
	CYP1a	DART cyp1a induction
Specific Mode of Action	Estrogen Receptor	T47D-KBluc, (Anta) ER-CALUX, MELN, ZELH-zfERalpha, ZELH-zfERbeta2, ChgH-GFP, E-SCREEN, YES, hER yeast, medER yeast, HELN-Era, HELN-ERB, ERE-cisFACTORIAL, hERa-HeLa-9903, MCF-ERE, Era-trasFACTORIAL, DART cyp19a1b, ERa-GeneBLAzer
	Androgen Receptor	(Anta) MDA-KB2, CV1-chAR, (Anta) AR-CALUX, HELN-AR, MCF-ARE, AR-EcoScreen, YAS, AR-GEneBLAzer, AR-transFACTORIAL
	Glucocorticoid Receptor	CV1-hGR, (Anta) GR-CALUX, GR Switchgear, GR-transFACTORIAL, GR-MDA-KB2, (Anta) GR-GeneBLAzer
	Progesterone Receptor	PR-GeneBLAzer, (Anta) PR-CALUX
	Thyroid Hormone Receptor	THbZIP-GFP (XETA), TRβ-CALUX, T-SCREEN, THRα1-transFACTORIAL, HELN-TR
	Photosynthesis	Algae photosynthesis inhibition
	Acetylcholinesterase	Acetylcholinesterase Inhibition
	Reproductive and Developmental Effects	MCF-RARE, P19/A15, hRAR-Yeast Assay, RORβ-transFACTORIAL
	Steroidogenesis	H295R
	Acetylcholinesterase Inhibition	Acetylcholinesterase Inhibition
Reactive Mode of Action	Genotoxicity	umuC TA1535/pSK1002 (+S9), umuC NM5004, SOS chromotest
	Mutagenicity	Ames TA98 (±S9), Ames TAmix (±S9), Ames TA100
Cytotoxicity and Indicators of System Response		Caco 2 NRU, Nrf2-MTS, RTG2MTT, SK-N-SH cytotoxicity, THP1 cytokine, *Photobacterium phosphoreum*
	Oxidative Stress	AREc32, ROS formation RTG2, Nrf2-MDA-MB
	Growth Inhibition	Algae Growth Inhibition
	Bacterial Cytotoxicity	Vibrio fischeri (Microtox)
	Neurotoxicity	SK-N-SH
	Immunotoxicity	THP1-cp
Mortality/morbidity	Immobilization	Daphnia Immobilization Test
	Acute Toxicity	DART 48 hr lethality
	Phototoxicity	I-PAM
	Whole Effluent Test Methods	Acute Toxicity, Chronic Toxicity (Freshwater, Marine, Estuarine)
Adaptive Stress Response	Heath Shock Proteins	HSE-cisFATORIAL, hspb11 induction DART
	Adaptive Stress	Hypoxia-Switchgear

Table 2
Continued

	Bioassay endpoint	Available bioassays
	Osmotic Stress	Jurkat E6-1 I-κB
	HIF-1α	HIF-1α-cisFACTORIAL
	NF-κB	NF-κB-cisFACTORIAL, NF-κB-Geneblazer, NF-κB-CALUX
	ARE	AREc32
	Nrf2	Nrf2-keap, Nrf2/ARE-cisFACTORIAL, Nrf2-CALUX
	p53	p53-cisFACTORIAL, p53-CALUX, p53-CALUX+59, p53-GeneBlazer

Note. Highlighted in red are bioassays with Organization for Economic Co-operation and Development standardized methods (adapted from B. I. Escher et al., 2014; Jia et al., 2015; Neale et al., 2017).

& Leusch, 2018). One of the first efforts to apply in vitro bioassays to environmental samples commenced after female fish in the Fenholloway River (Florida, USA) exhibited secondary sex characteristics of male counterparts. The masculinization (AO) was linked to activation of the androgen receptor (AR; MIE) after the AR was activated in multiple bioassays after in vitro river water exposure (Parks et al., 2001). More recently, bioassays have been applied to isolated, or short-term, water quality screening projects for wastewater (Könemann et al., 2018; Roberts et al., 2015; Sonavane et al., 2018; Suzuki et al., 2015; van der Linden et al., 2008) and surface or source water (Conley et al., 2017a; Zwart et al., 2018). Many of these studies focused on differences between pre- and post-treatment water quality to quantify water treatment efficacy (Jia et al., 2016; Roberts et al., 2015). Fewer studies exist assessing drinking water (Conley et al., 2017b; Leusch et al., 2018) due to relatively low expected contaminant concentrations and sample extraction (concentration) limitations. Nevertheless, application of a tiered statistical approach has proven useful for screening drinking water samples with anticipated low-levels of biological activity (Medlock Kakaley et al., 2021). Overuse of fresh water supplies globally (UNWAPP, 2017) has prompted recent interest in screening recycled water for residual or post-treatment added biological activity (E. G. Brown et al., 2018; Jia et al., 2015; Macova et al., 2011).

Water quality research has seen an upward trend toward applying multiple bioassays (Daniels et al., 2018; Leusch et al., 2018; Macova et al., 2011; Roberts et al., 2015; van der Linden et al., 2008), even tens of bioassays (B. I. Escher et al., 2014; Jia et al., 2015; Neale et al., 2017), to a single screening program. The benefits of applying multiple bioassays with similar or variable MIEs have been described previously (B. I. Escher et al., 2014; Medlock Kakaley et al., 2019; van der Oost et al., 2017). Although applying multiple bioassays with the same MIEs initially may seem redundant, it can increase confidence in positive biological activity detections because sensitivity varies among assays. Conversely, the application of bioassays with variable MIEs presents a more accurate representation of the chemical complexity often found in environmental samples. One such study screened a small set of water samples using over one hundred bioassays to define a superior battery of bioassays that would offer the most comprehensive assessment of water samples (B. I. Escher et al., 2014). Ultimately, the authors concluded that a reliable screening battery should include bioassays representing induction of xenobiotic metabolism, endocrine disruption, reactive modes of action, adaptive stress responses, and cytotoxicity endpoints.

As noted previously, bioanalytical tools cannot distinguish the presence of individual compounds like their targeted analytical chemistry methods counterparts, but they do permit cumulative detection of biological activity from chemical mixtures present in environmental samples. For this reason, many water quality assessors chose to apply the two approaches in tandem. For example, environmental concentrations of each known contaminant (detected using targeted chemical analysis) can be converted to proportional bioassay responses ($\leq$100% response) using bioassay-specific chemical potency factors. If the sum of the bioassay responses from individual chemicals totals <100% response, then contaminants that were not targeted by analytical methods (or fell below analytical method detection limits) may be present. Recent studies have been able to illustrate this phenomenon. For example, although none of the targeted known glucocorticoid receptor agonists were detected above method detection limits, cumulative glucocorticoid activity was detected in surface and wastewaters in the United States using the CV1-hGR bioassay (Table 2; Bradley et al., 2017; Conley et al., 2017a; Glassmeyer et al., 2018;

Medlock Kakaley et al., 2019). This type of mass-balance analysis has been conducted using glucocorticoids (Daniels et al., 2018; Jia et al., 2016), estrogens (Conley et al., 2017a; Könemann et al., 2018) and more complex mixtures (Neale et al., 2015). However, rigorous "fingerprinting" studies would need to be conducted prior to mass-balance analysis to obtain bioassay-specific potency and efficacy for each compound (Medlock Kakaley et al., 2020; Neale et al., 2015).

Discrepancies between bioassay and targeted analytical contaminant results (i.e., detected biological activity with no corresponding detections of chemicals with known such activity) have been mitigated using effect-directed analysis (EDA; see Section 2.3 for further description), an integrated tiered approach to water quality screening. Applying bioassays during an initial EDA screening tier provides sample bioactivity information and guides analytical approaches, overcoming the impossible task of monitoring for all CECs using traditional targeted analytical methods. EDA has been especially valuable for identifying the myriad of potential DBPs in drinking water. The formation of DBPs relies on variable organic matter present during the disinfection process (H. Dong et al., 2020); therefore, many DBPs have yet to be identified.

2.2.4. Challenges

Despite their apparent utility, bioassays have some inherent limitations including lack of standardized protocols (B. I. Escher et al., 2014). For several MIEs, options are numerous for screening water samples, which has prompted investigations into inter-laboratory reproducibility and assay precision using bioassays with transcriptional activation of nuclear receptors as endpoints using both known (Altenburger et al., 2018; Di Paolo et al., 2016) and unknown environmental mixtures (Mehinto et al., 2015). In a step toward bioassay application to recurring water quality monitoring, the State of California released standard operating procedures (SOP) that permit the use of any estrogen and aryl hydrocarbon receptor transcriptional activation bioassay provided that the water sample preparation, bioassay methods, and data analysis meet the SOP criteria for recycled water assessment (Denison et al., 2020). Some inter- and intra-laboratory reproducibility may be optimized using extensive quality assurance/quality control practices and documentation (B. Escher et al., 2021; Hirsch & Schildknecht, 2019).

Additional limitations include the method optimization typically required for detection of biological activity when contaminants are present at low concentrations (e.g., low effect-recovery post-extraction and confidence in accurate activity reporting). In most water quality studies, large-volume water samples (≥1 L) are concentrated through solid phase extraction prior to bioassay assessment. This process is intrinsically variably selective for each compound class potentially present in the sample and has been shown to reduce effect recovery by 30% (Neale et al., 2018). Further, biological activity in water samples is reported in biological equivalents (BioEqs) of a known compound that is highly potent at producing the measured effect outcome. When detected biological activity is low (does not reach the concentration to cause half the maximum effect or EC50 value), the confidence in reporting accurate biological equivalency values for sample extracts is reduced. Low effect detections, however, could be remedied using a linear concentration-response model (B. I. Escher et al., 2018b), and the generalized concentration addition model when partial agonists are present (Brinkmann et al., 2018).

2.2.4.1. Effects-Based Trigger Values

Moving forward, the biggest hurdle for bioassay application to routine water quality monitoring may be establishing safety reporting limits for humans and wildlife (i.e., effect-based trigger values, EBTs). The lack of standardized EBTs has generally deterred the application of these tools to real-world water quality monitoring. In line with the European Union Water Framework Directive, the EU SOLUTIONS project was initiated to adapt bioassays to water quality monitoring by characterizing priority mixtures and primary drivers of toxicity in those mixtures (Altenburger et al., 2015; Brack et al., 2018, 2019). Therefore, bioassay-specific EBTs for many assays have been generated using existing environmental quality values for individual chemicals (B. Escher & Neale, 2021; B. I. Escher et al., 2018a; Neale et al., 2023). In addition to standardizing EBT development, the recycled water monitoring protocols for the State of California also contain trigger level values for estrogenic and dioxin-like activity (Denison et al., 2020). As indicated in the corresponding policy document, these values were not designed to regulate continued facility operation, but only to guide any further screening actions (State Water Resources Control Board, California Environmental Protection Agency, 2018), such as targeted analytical chemistry monitoring, increased frequency of bioassay monitoring, monitoring at additional locations, or modification to facility operations.

Overall, bioassay methodologies would need optimization before their application as stand-alone tools for water quality monitoring. As part of integrated screening processes, however, water quality managers have much to gain through their implementation. These tools provide useful information on the potential presence of various contaminants affecting many different biological functions and may serve as effective guides for additional targeted chemical monitoring.

2.3. Harmonizing Chemical and Bioanalytical Analyses of CECs: A Proposed Approach

EDA is a tiered testing strategy that harmonizes bioassay and analytical approaches to mitigate discrepancies in contaminant detection results. In EDA, the initial identification of biological activity can be used to guide, or "direct," the selection of contaminants in subsequent rounds of water sample screening with specific, targeted analytical methods (Brack et al., 2016; Maruya et al., 2016). Notably, EDA works best with bioassays measuring highly specific modes of action (Brack et al., 2016) such as estrogen, androgen, glucocorticoid, progesterone, and aryl hydrocarbon receptor ligand-mediated transcriptional activation (Sonavane et al., 2018; Table 2). With subsequent screening rounds, samples are fractionated further and analyzed again with a combination of bioassays and analytical methods (targeted or non-targeted) to elucidate the biological activity and chemical composition of each water sample. EDA often leads to screening numerous rounds of reduced fractions, but "downscaling" bioassays to smaller well sizes may be one solution to retaining high sample throughput (Zwart et al., 2018).

Using EDA to prioritize the application of NTA is of increasing interest as it has the potential to link target, suspect, and unknown identifications to the samples with the most important assay-specific responses. Although this iterative approach to contaminant identification is time and cost intensive, combining contaminant-specific cellular and subcellular assay responses with chemical fractionation techniques that reduce the complexity of the sample extracts simplifies the identification of toxicants by NTA. In particular, applying automated in vivo and in vitro assays, such as assays included in ToxCast (Knudsen et al., 2011), to whole or chemically fractionated samples, evaluating the most potent responses, and using the information available about likely chemical classes that produce those responses provides toxicological insight that informs the evaluation of NTA results. Such an approach has been successfully demonstrated previously (Brunner et al., 2019a), where a ToxCast evaluation was applied to 1,000 suspect chemicals from an NTA analysis of wastewater effluent and used to develop a combined exposure hazard data prioritization to determine those contaminants that warrant identification first.

A tandem bioassay-NTA approach that integrates the strengths of EDA and bioassays as a means of focusing NTA application to complex environmental settings might start by using AO pathways to identify transcriptional activation of nuclear receptor bioassays that are potentially most responsive (e.g., in targeted sites important to the watershed such as contaminant discharges upstream from drinking water intakes). After identifying relevant receptor bioassays, a toxicity identification evaluation approach (Norberg-King et al., 1991) could be implemented to fractionate samples and test fractions in the most responsive bioassays. Subsequently, an NTA optimized for a suspects-to-unknowns workflow could be applied to maximize identification of potential response-initiating contaminants. After establishing the relationship between all contaminant groups (i.e., targeted, suspect, and unknown) and corresponding bioassay responses, a combination of optimized arrays and a focused NTA workflow could be applied upstream/downstream from a contaminant source, and for human exposure, from source water through treatment, distribution, and consumption. Such an integrated, prioritized toxicity/chemistry workflow would likely have a probabilistically higher chance of associating bioassay responses and the initiating contaminants or contaminant classes, at the different degrees of NTA confidence. In addition, by applying the power of the combined, optimized assay/NTA workflow, downstream production of adverse initiating contaminants such as DBPs could also be accounted for.

2.4. Enhancements in Microbial Analysis

Recent research indicates a diverse toolbox approach may be warranted for the next generation of water quality monitoring for pathogens. Although cultivation-based methods are valuable for indicating viable pathogens, only a small fraction of microorganisms can be cultured in a laboratory. Advancements in molecular methods and next-generation DNA sequencing technologies, which do not require the growth of a microorganism, have

greatly expanded our knowledge of microbial pathogens in the environment by detecting non-culturable organisms, detecting pathogens directly, and providing more rapid results than culture-based methods. The most important analytical advancements have come from quantitative polymerase chain reaction (qPCR) and next-generation sequencing (NGS) technologies.

2.4.1. Advances in qPCR

In qPCR, DNA primers and fluorescent probes are used to detect organisms by binding to unique and highly specific segments in the organism's DNA and emitting a fluorescent signal detected by the instrument (Botes et al., 2013). Fluorescent hybridization probes increase the analytical specificity of qPCR (i.e., ability to measure a specific target; Saah & Hoover, 1997) and can be designed for any taxonomic level: domain, class, phylum, genus, and species-specific, and any gene (e.g., ARG, virulence). Results are generally obtained for qPCR within hours and assays demonstrate high analytical sensitivity (i.e., accurate measurement of low concentrations; Saah & Hoover, 1997). Recent advances include high-throughput methods, wherein nanoliter-scale reactions allow simultaneous analysis of multiple gene targets across multiple samples, and digital PCR, wherein reactions are divided into many partitions to allow absolute target quantification using Poisson statistics (Hindson et al., 2011; Waseem et al., 2019).

The quality of sewage-affected surface waters is now better understood with qPCR-based molecular microbial source tracking methods, which allow the detection of a wide range of fecal indicator bacteria that identify host-specific sources of fecal contamination (e.g., human, cow, swine, fowl). The most common microbial source tracking markers, their method performance characteristics, and correlations with pathogens and health effects, have been described previously (Harwood et al., 2014). The most widely studied microbial source tracking method for indicating human fecal contamination in water targets is human-specific *Bacteroides* spp., an anaerobic fecal bacterium, and is commonly referred to as HF183. The qPCR assay, developed by Seurinck et al. (2005), and recently adapted as an EPA method (USEPA, 2019), targets a DNA marker that is widely distributed in human feces but rarely found in animals, and that is highly concentrated in human sewage. In addition to markers specific for human feces, many assays have been developed specifically for identifying animal feces (Shanks et al., 2008). This is important because some intestinal pathogens in animals can also infect humans, yet the risk presented by different fecal contamination sources varies (Soller et al., 2010).

The water quality of fresh and marine recreational waters in the United States can be monitored with molecular methods to provide timely notification to swimmers if elevated fecal indicator bacteria are detected. The first qPCR methods for evaluating sewage-affected recreational waters, EPA Methods 1609 and 1611, which target enterococci, have associated health-based water quality target levels (Haugland et al., 2014; USEPA, 2012a; USEPA, 2013). The methods, which can be performed in 3–4 hr, have epidemiological support for indicating increased human health risk and have been validated for use in fresh and marine waters (Wade et al., 2006, 2008).

Molecular methods developed to detect water-based pathogens have recently been used to understand the effects of treatment on CEC pathogens at drinking water treatment plants/public water systems in the United States (King et al., 2016). qPCR was used to detect the fungi *Aspergillus fumigatus*, *A. niger*, *A. terreus*, and the bacteria *Legionella pneumophila*, *Mycobacterium avium*, *M. avium subspecies paratuberculosis*, and *M. intracellulare*, in paired source and treated water obtained from 25 treatment plants of various sizes and using a variety of drinking water treatments. Treatment was effective at removing all three species of fungi at 14 of 25 plants where *Aspergillus* spp. were detected in source water; 5 of 6 treatment plants where *L. pneumophila* were detected; and 7 of 12 treatment plants where mycobacteria were detected. Additionally, there were four treatment plants where *M. avium* and *M. intracellulare* and three treatment plants where *M. avium* subspecies paratuberculosis were not detected in source water but were detected in treated water. This indicates that treatment is effective at removing most *L. pneumophila*, but that mycobacteria may be growing during drinking water treatment (assuming well-paired samples).

Reverse-transcription qPCR (RT-qPCR) has now made detection of unculturable norovirus and slow-growing hepatitis A virus possible in water samples. Using RT-qPCR, previous research has determined that norovirus RNA remained detectable in groundwater for 1,266 days (Seitz et al., 2011). Although unknown viability of norovirus detected by RT-qPCR has been debated, human volunteers ingested groundwater spiked with human norovirus stored at room temperature for 61 days to demonstrate that the virus was still infectious (Seitz et al., 2011). In addition, RT-qPCR has been used to detect hepatitis A, rotaviruses, and enteroviruses in the Buffalo River and

source water dams in Cape Province, South Africa (Chigor & Okoh, 2012). Hepatitis A was detected in 43% of samples, rotaviruses in 13.9% of samples, and enteroviruses in 9.7% of samples. Hepatitis A virus was detected at all six sites sampled over the course of the year, indicating persistence of hepatitis A in the water environment. A drinking water treatment plant survey conducted in the United States used Bayesian statistics combined with RT-qPCR to estimate enterovirus, adenovirus, norovirus (NoV G1 and NoV GII), and polyomavirus concentrations in source and treated water samples. This fully probabilistic approach accounted for PCR inhibition and method recovery and demonstrated treated water contained decisively less virus than source water (Varughese et al., 2018).

2.4.2. Next Generation Sequencing (NGS) Technologies

NGS technologies use pyrosequencing (Roche 454 sequencing), sequencing by synthesis (Illumina sequencing), sequencing by oligonucleotide ligation detection (SOLiD sequencing), ion semiconductor sequencing (Ion Torrent sequencing), nanopore sequencing (Oxford Nanopore Technologies), and single-molecule, real time sequencing (Pacific Biosciences) to identify and characterize the genetic content of the microbial community (Niedringhaus et al., 2011). This technology is more rapid, cost-effective, and accurate than traditional sequencing technology (e.g., Sanger sequencing). By using primers (e.g., 16S rRNA gene) that allow phylogenetic identification of microorganisms, NGS allows millions of sequences in a sample to be amplified in parallel, and, combined with bioinformatics tools, can identify different genera or species present (Aw & Rose, 2012). Beyond identification, metagenomic analysis uses shotgun sequencing and bioinformatics to characterize the entire genetic content of the microbial community in an environmental sample, including genes coding for virulence factors and AMR.

To better understand the microbial community and pathogen component of wastewater effluent released from a WWTP in Zhengzhou City, China, pyrosequencing and metagenomics were used to identify pathogens and virulence factors at different stages of treatment (Lu et al., 2015). This study found that *Arcobacter butzleri*, which causes gastroenteritis, was the most abundant pathogen in samples collected along the treatment train, followed by *Aeromonas hydrophila*, *E. coli*, and *Klebsiella pneumoniae*. qPCR assays specific for each pathogen confirmed the metagenomic results. This study also reported that 99% of pathogen sequences and genes coding for virulence factors were removed during treatment, with the most efficient step being aerobic secondary treatment and removal of suspended solids.

2.5. Beyond the Next Generation

NTA, bioassays, and advancements in molecular methods and sequencing techniques for microorganisms have all worked to increase the number/fraction of environmental contaminants examined or the sample throughput or both. These methods, however, still require the analysis of samples. An individual sample is a snapshot in time. The factors that influence those samples either through decision (e.g., instantaneous grab sample vs. 24-hr composite) or circumstance (e.g., proximal rain events, intermittent contaminant releases) can affect the results and the decisions based on those analyses. Nevertheless, better identification of the true sources of contaminant effect in long-term monitoring and assessment programs is possible. A purposeful design of integrated sampling programs—with appropriate arrays of chemical, bioassay, and microbiological methods—and subsequent iterative application of appropriate modeling approaches offers this possibility. Modeling is one way to identify the variances between chemical, bioassay, and microbiological results from real aquatic systems, and predictions made from theoretical understanding of pertinent chemistry, hydrology, and both macrobiology and microbiology. Modeling inherently requires simplifications that may not fully reflect the complexity of the aquatic system in question.

3. The Challenge of Numerous and Ubiquitous CECs: The Role of Modeling

Important developments in the field of CEC exposure modeling have occurred alongside major advances in the quantification and identification of CECs in the environment in the past 20 years (Di Guardo et al., 2018). Environmental exposure models have been used to address a variety of environmental research and policy questions, functioning mainly as decision-support and regulatory tools for environmental risk assessment (Di Guardo &

Hermens, 2013). Monitoring data are valuable but expensive to obtain, and it would be impossible to measure all CECs throughout space and time.

Exposure models can guide monitoring by identifying the CECs, locations, and environmental media of greatest concern based on the emission pathways and physicochemical properties, thereby intelligently prioritizing CECs for further study and risk assessment (Burns et al., 2018; Ginebreda et al., 2018; Zhi et al., 2022). Similarly, models to characterize exposure levels of microbial contaminants can inform quantitative microbial risk assessment (QMRA), a key application for characterizing their associated health effects (Haas et al., 1999).

Exposure models can also be used to investigate the fate, transport, distribution, and the drivers of environmental exposure. Inverse modeling where an unknown or difficult to characterize parameter can be solved by working backwards from measured environmental concentrations (Boxall et al., 2014; Pistocchi et al., 2012). Hypothesis testing or sensitivity analysis can identify which environmental processes dominate CEC environmental behavior, thereby directing further laboratory or field research to where it is most needed, is another common application (Åberg et al., 2015; Dale et al., 2015). Investigating the impact of future changes in emissions or environmental conditions is another useful application (Keller et al., 2015; van Wijnen et al., 2019; Wu et al., 2023). This could include using exposure models to evaluate exposure mitigation strategies, such as the effect of upgrading WWTP removal technology (Kehrein et al., 2015), evaluating the relative environmental effect of prescribing one pharmaceutical over another (Allijn et al., 2018), or identifying where environmental quality standards could be exceeded (Arnot et al., 2006; Johnson et al., 2013). Environmental exposure models can also be used proactively to investigate the environmental fate and transport of next generation chemicals designed to replace chemicals of concern such as polybrominated diphenyl ethers or PFAS (Gomis et al., 2015; Liagkouridis et al., 2015).

3.1. CEC Exposure Modeling Approaches

In general, two types of models exist to estimate the aquatic exposure of CECs, multimedia fate and exposure models and single media models (Grill et al., 2016). The choice of which approach is best suited to a particular CEC and scenario benefits from upfront consideration (Hollander et al., 2012). Building a conceptual model of sources, pathways, and receptors is a logical starting point. For many CECs, the dominant environmental source is through consumer use of CEC-containing products (e.g., cleaning products, pharmaceuticals, and personal care products) and their subsequent down-the-drain disposal to WWTPs where municipal effluents are treated and released to the freshwater environment. For other CECs, this pathway could be one of several, which includes entering the aquatic environment directly through in situ wash-off (e.g., sunscreens which contain ultraviolet [UV] filters), combined sewer overflows, or degradation (e.g., secondary microplastic, TPs) in addition to various diffuse sources including industrial (e.g., fire-fighting foams), agricultural (e.g., pesticides, veterinary medicines, biosolid applications), solid waste disposal (landfill leachate) or stormwater runoff. All potential sources are important to consider; however, it is not always feasible or necessary depending on the objective and CEC under investigation. Physicochemical properties can then indicate whether a compound is volatile or hydrophobic, in which case a multimedia approach that estimates the distribution between environmental media (e.g., surface water, soil, air) would be preferred over a single media approach that focuses in detail on a single compartment (e.g., surface water) (Hollander et al., 2012). Therefore, these approaches are complementary rather than competing (Mackay & MacLeod, 2002). Ashraf et al. (2022) reviewed model selection based on the scenario and category of under investigation. We review a selection of recent CEC modeling developments in Table 3, the interested reader is directed to Tong et al. (2022) for a comprehensive review of the geographical and CEC domains of current models, in addition to their limitations.

3.1.1. Multimedia Fate and Exposure Modeling

Multimedia fate and exposure modeling posits that chemical fate, transport, and transformation is driven by the interaction between inherent physicochemical properties of a chemical and environmental conditions (X. Z. Kong et al., 2016). Environmental characteristics are variable and complex through both space and time, thus the computing power required to account for even a small amount of environmental spatial and temporal variability is a limiting factor for these models. To overcome this, the environment can be simplified into generic fixed compartments (e.g., air, water, soil, and biota) where only their ability to retain a contaminant is consid-

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Table 3
Summary of Recent Modeling Developments Organized by General Contaminant of Emerging Concern (Contaminants of Emerging Concern (CEC)) Category

Model type	Target compartment(s)	Target CEC category	Key contributions	Study
Spatiotemporal multimedia fate model	Aquaculture ponds	Antibiotics	• Identified 25% of applied antibiotic reached environment • Risk of antibiotic resistance development in all studied ponds	Rico et al. (2013), Rico and Van den Brink (2014), Rico et al. (2017)
Dynamic multimedia fate model	Plant uptake from biosolid amended soil (agroecosystem)		• Soil system dosed at realistic time intervals • Reasonable agreement with measured values	Polesel et al. (2015)
Spatiotemporal multimedia fate model	Urban environment		• Evaluated water reuse scenarios • Identified important temporal trends associated with chemical fate and environmental variability	H. Chen et al. (2018)
Multimedia fate model coupled with spatial water quality model	Basin-scale (soil along with surface water-sediment compartments)		• Incorporated urban and agricultural sources • Successfully simulated spatial distribution and concentration in soil and water	J. Dong et al. (2019)
Spatially explicit single media	Surface water	Pharmaceuticals	• High spatial resolution (1 km) and good agreement with measured concentrations • Predicted river network is promising approach for data poor regions	Oldenkamp et al. (2018)
Dilution-based single media model	Surface water		• Simplified alternative to data intensive spatially explicit catchment models • China gridded and characterized by population and average WWTP connection rate. Paired with dilution from global WWTP dilution model (Keller et al., 2014)	Zhu et al. (2019b)
Spatially explicit catchment model	Surface water		• Parameterized the GREAT-ER model for Bolivia by focusing on localized area and parameterizing flow and WWTP removal with measured values	Archundia et al. (2018)
Spatially explicit catchment model	Surface water		• Parameterized the GREAT-ER model China by making local inquires to locate and describe WWTPs and characterizing flow using the Soil and Water Assessment Tool (Santhi et al., 2006)	L. Zhang et al. (2015)
Spatially explicit catchment model	Surface water		• Expanded the model to include a key Canada-USA catchment • Explored the feasibility of expanding to a tool for the entirety of North America	Ferrer and DeLeo (2017)
Regional multimedia fate model (China)	Surface water-sediment	Personal care and down-the drain consumer chemicals	• Included spatial variability of environmental pH • Demonstrated the influence of pH on ionizable chemicals	Zhu et al. (2016)
Dilution-based single media model	Surface water		• Generates spatial predicted environmental concentrations at courser resolution than spatially explicit catchment models • Permits adaptation for global coverage due to decreased data requirements	Kilgallon et al. (2017)

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Table 3
Continued

Model type	Target compartment(s)	Target CEC category	Key contributions	Study
Spatially explicit single media	Surface water	Engineered nanoparticles	• First engineered nanoparticle model	Praetorius et al. (2012)
			• Demonstrated that a model could not be adequately parameterized due to lack of relevant empirical data	
Multimedia fate model	Water-sediment-soil-air		• Altered SimpleBox to accommodate nanoparticle specific-processes (e.g., Heteroaggregation, sedimentation)	Meesters et al. (2016)
Multimedia fate model	Water-sediment		• Incorporation of point and diffuse emissions from an urban environment	Domercq et al. (2018)
Multimedia fate model	Water-sediment		• Added Advanced Toxicant Module to WASP8 that includes nanoparticle specific fate processes	Knightes et al. (2019)
			• Investigated stream dynamics of engineered nanoparticle fate within a watershed	
Multimedia fate model	Water-sediment	Microplastics	• Used both SimpleBox and SimpleBox4Nano to predict concentrations of micro- and nanoplastics, simple and adjustable but large uncertainties	Kooi et al. (2018)
Spatially explicit catchment model	Water-sediment		• Used NanoDuFlow to investigate role of particle size on riverine transport, but particle morphology not yet considered	Besseling et al. (2017)
Spatially explicit catchment model	Surface water		• Predicted microplastic transport from rivers to seas based on assumption that they do not degrade	Siegfried et al. (2017)
			• Used existing nutrient transport model, GlobalNEWs	
Spatially explicit catchment model	Surface water		• Further developed approach by Siegfried et al. (2017) into the GREMiS model	van Wijnen et al. (2019)
			• Incorporated land-based and wastewater treatment plant discharges of microplastic to rivers and subsequent transport to seas	
Spatially explicit catchment model	Surface water		• Down-the-drain exposure modeling of microplastics at national (USA) level	Holmes et al. (2020)
			• Web-based visualization tool for relative surface water concentrations of microplastics based on simplified fate assumptions	

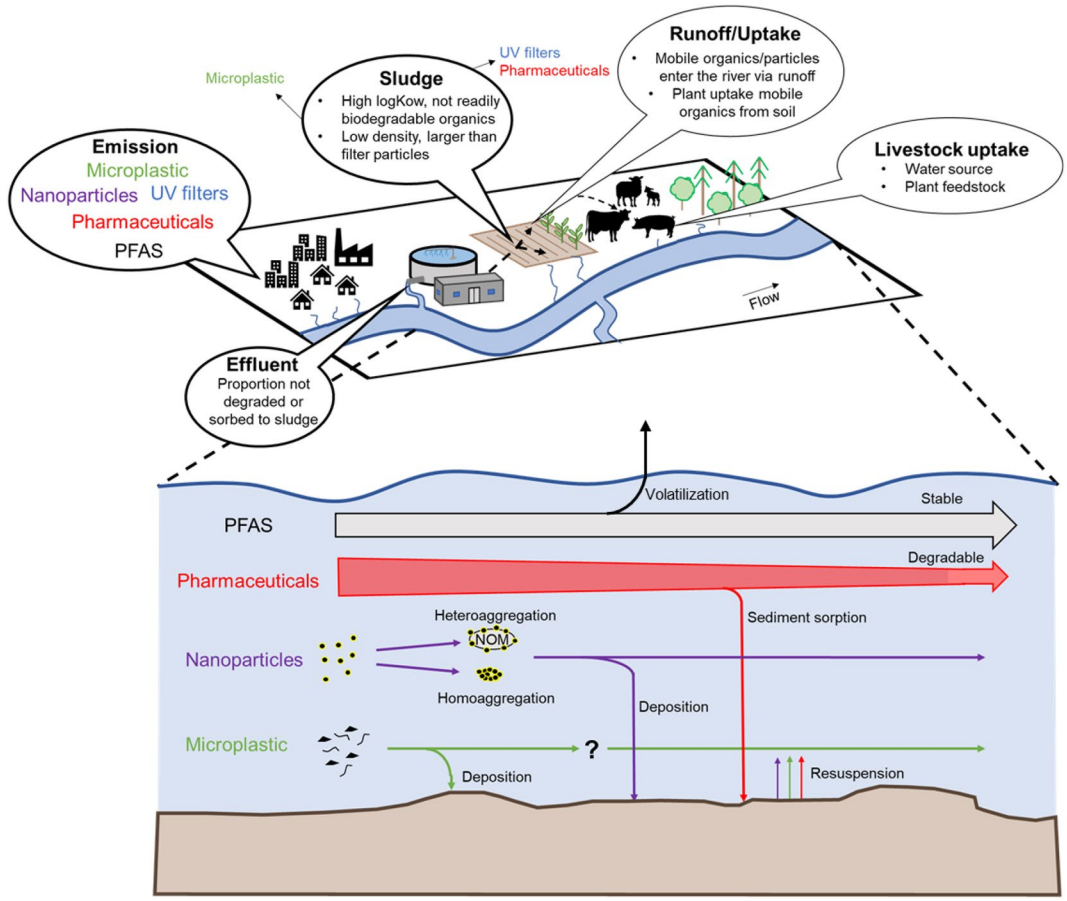

Figure 6. Hypothetical representation of the different environmental journeys various classes of contaminants of emerging concern (CECs) Take When Released to Wastewater. Certain CECs are highly mobile and/or persistent (e.g., per- and polyfluoroalkyl substances, microplastic) or can lead to more widespread environmental exposure (e.g., regional, global) in contrast to more localized exposure characterized by CECs that degrade (e.g., pharmaceuticals) or strongly sorb to solids (e.g., ultraviolet filters). Moreover, certain fate processes are relevant for some CECs, but not others (e.g., homoaggregation, volatilization), which is why numerous different modeling approaches of varying complexity have been developed to capture generalized fate processes important to each CEC class. For brevity, only select CECs are presented but note that many modeling approaches have been applied across the broad spectrum of CECs (e.g., pesticides, personal care products, veterinary medicines).

ered (MacLeod et al., 2010). A mass-balance approach, where an equation per compartment is parameterized by partition coefficients, mass transfer coefficients, and degradation rate constants, is commonly used (Csiszar et al., 2011). In this way, compartment-specific chemical transfer and degradation can be predicted using either experimental or predicted physicochemical properties (Figure 6).

Multimedia fate and exposure models are important tools for regulatory chemical risk assessment and decision-support because they provide a quantitative prediction of the transport of a chemical to relevant environmental compartments and the time to ultimate degradation, to sequestration, or to biotransformation (Su et al., 2019). The models favored for these national and regional applications utilize a generic spatial and temporal approach (e.g., SimpleBox) despite the availability of more complex spatial and dynamic models. There is debate as to whether increased complexity—in terms of the number of parameters, compartments, and processes considered—improves model performance and environmental relevance. For example, including variable environmental conditions and emissions through time is challenging to interpret and understand, which can affect external user utility and diminish confidence in results (MacLeod et al., 2010). Critically, the quality of model output is limited by the quality of data used to build and parameterize a model.

3.1.2. Spatially Explicit Catchment Modeling

Single-media models are focused on a specific environmental compartment and therefore can more easily incorporate an increased level of environmental detail over multimedia approaches, making them highly useful for compounds that are expected to predominately remain in the environmental compartment they were emitted to (Jagiello et al., 2015). Aquatic concentrations of CECs can vary over orders of magnitude at a local and regional scaleleading to notable differences in ecotoxicological risk within and across geographic regions (Oldenkamp et al., 2016). Therefore, spatially-explicit models that incorporate the spatial variability in flow, channel dimensions, river connectivity, chemical inputs, fate, and chemical transport have been developed to respond to the need for realistic localized exposure estimates within a watershed or region (Burns et al., 2021). These models can be thought of as a digitized river network that considers the spatial variability in key environmental parameters and chemical inputs within a watershed. These models such as GREAT-ER (Kehrein et al., 2015) LF200-WQX (A. P. Williams et al., 2009; R. J. Williams et al., 2009) and iSTREEM (Kapo et al., 2016) were developed for data-rich regions (e.g., USA and Europe). Efforts are on-going to expand their geographical application (e.g., McDonough et al., 2022) made possible through advances in large-scale hydrographic data sets, such as HydroSHEDS, generated from global elevation data (Lehner et al., 2008). On the other hand, Zhu et al. (2019) presented a simplified alternative for China to overcome river network and flow data limitations. The country was gridded and WWTP discharge to each grid was based on associated population and an average WWTP connection rate and previously derived dilution estimate (see Keller et al., 2014). The global dilution model (Keller et al., 2014) and a similar approach described by Kilgallon et al. (2017) are simpler models that do not have the computational or data demands of higher-tier models, but permit investigation of surface water concentrations at a coarser spatial resolution.

3.1.3. Spatially Resolved Environmental Fate Models

Recently models have been developed that bring together the advantages of detailed spatially explicit catchment models and multimedia models into a single modeling framework, as shown in Figure 7, and reviewed by Falakdin et al. (2022). This permits not only the prediction of realistic local concentrations but can also provide a starting point for the quantification of far-field aggregate human exposure (e.g., produce, surface water, fish, meat, milk) and incorporate the role of persistence for evaluating reservoir stocks of CEC in various environmental compartments (Wannaz, Franco, et al., 2018). The temporal component of these models permits investigation of seasonal changes on fate processes (Han et al., 2022), as well as over longer time scales (e.g., 10–100 years) (Han et al., 2019; Ross & Knightes, 2022).

Pangea, a multi-scale spatial multimedia fate, transport, and exposure model framework, recently introduced by Wannaz, Franco, et al. (2018), combines the advantages of the two modeling approaches to describe contaminant fate and transport globally using a novel multi-scale grid method. To demonstrate the usefulness of the approach, the authors examined the effect of just using local emissions versus including upstream emissions; they observed that concentrations exceeded a factor of 10 times higher for compounds with longer half-lives (Wannaz, Fantke, & Jolliet, 2018). Jolliet et al. (2020) increased the spatial resolution of Pangea and applied it to the prediction of personal care and household products in environmental media in Asia. It was determined that the uncertainty in predictions were far lower than the variability of exposure concentrations across the region.

The STREAM-EU model goes a step farther and is a temporally resolved multimedia model that generates spatially explicit concentrations at the sub-basin scale (e.g., 28 km^2) throughout Europe (Lindim et al., 2016). The model was created to incorporate both diffuse and point sources along with the interactions of surface water with groundwater, sediment, soil, air, snow, and suspended particulate material (Lindim et al., 2016). STREAM-EU also incorporates temporal changes in temperatures, transport velocity, and emissions, while also spatially distributing environmental parameters and emissions (Lindim et al., 2016).

STREAM-EU is a highly complex model; however, an alternative method is the openly available and site-specific spatiotemporal modeling framework WASP8 updated with advanced toxicant module that can predict the fate and exposure of solute chemicals, nanoparticles, and solids in surface water-sediment systems (Knightes et al., 2019). The model is limited to surface water-sediment interactions; however, it implements a detailed set of processes including settling, burial, resuspension, erosion, and bedload transport in addition to specific fate processes for nanoparticles, microparticles, and solute chemicals in these media.

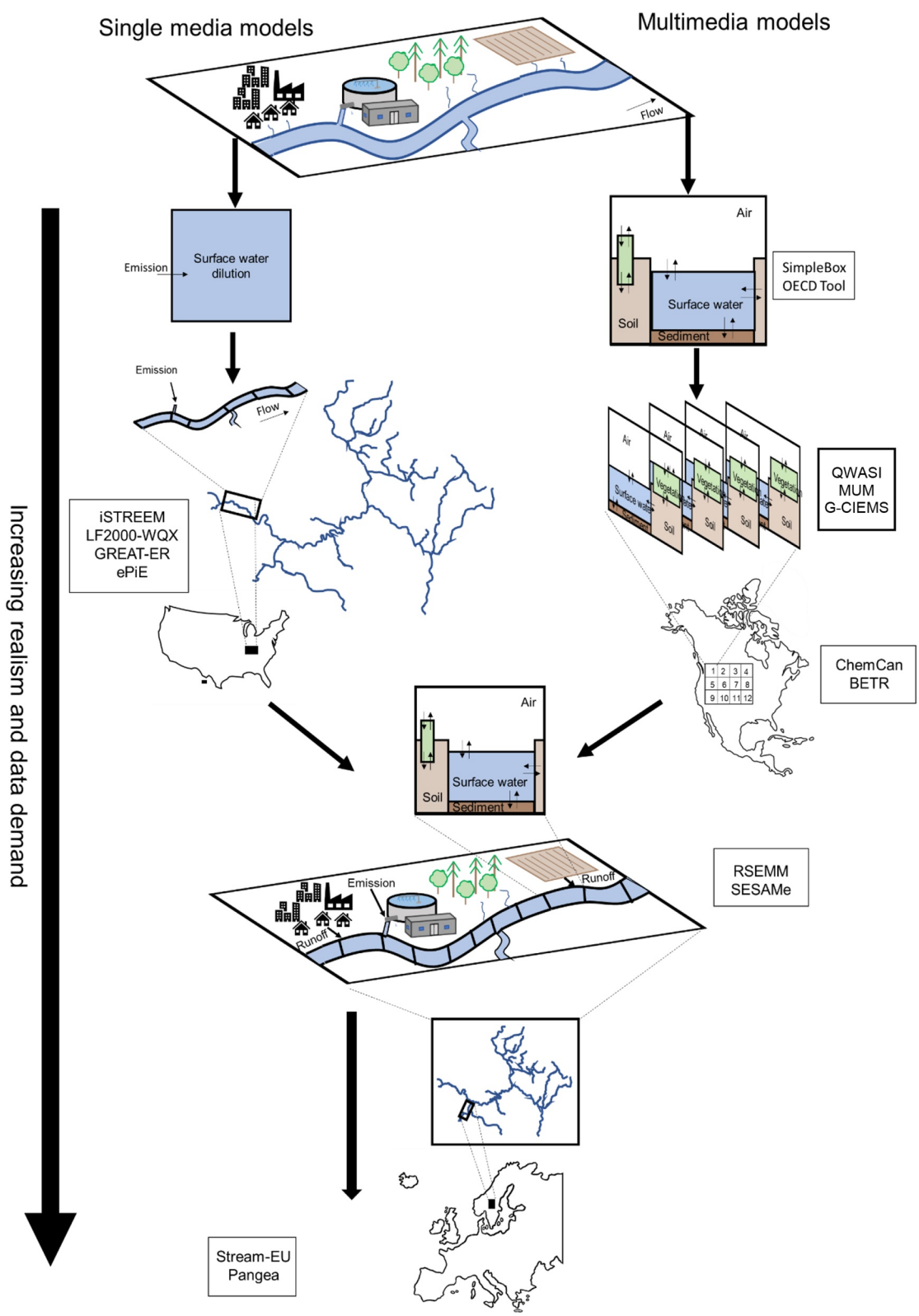

Figure 7. Simplified overview of the evolution of single media catchment models and multimedia fate models (MFM). A hypothetical scenario is given where with each step of increased spatial complexity is introduced. Once both types of models reach regional and global scale, small-scale combinations of MFMs and spatially explicit catchment models emerged. Most recently, the regional spatially explicit MFMs Stream-EU and Pangea have been developed, which combine the strengths of both approaches but are heavily data intensive.

3.1.4. Quantitative Microbial Risk Assessment (QMRA)

Microbial risk assessment is a process used to estimate the likelihood of adverse human health effects following exposure to microbial pathogens or microbiological products (Haas et al., 1999; Parkin, 2007; Schroeder et al., 2007). Although originally developed for food-borne illness, the methodology has since advanced to include other exposure routes, including drinking water and water reuse applications (Nappier et al., 2018; Owens et al., 2020; Petterson & Ashbolt, 2016; Zhiteneva et al., 2020). For quantitative assessments, uncertainty in measurements is further coupled with uncertainty about the human exposure pathway and specific health effects of microbial agents. QMRA methods therefore include a measure of uncertainty by expressing predictions as probability distributions rather than discreet point estimates. This is done by quantifying variability in input parameters and propagating this uncertainty through to model output, for example, with Monte Carlo simulation (Adgate & Ramachandran, 2007; Schroeder et al., 2007). This stochastic approach is advantageous because it recognizes that risk, by definition, is probabilistic, and provides decision makers with an objective range of outcomes from which to draw appropriate conclusions (Parkin, 2007). Furthermore, sensitivity analysis can then be used to determine which parameters contribute most to the overall uncertainty in risk estimates. This is useful for the identification of factors (e.g., environmental concentration, exposure rate, dose-response) on which calculated risk is most dependent, and thus where risk management activities are most effectively directed. Sensitivity analysis can also target data gaps by identifying parameters that drive risk estimates but for which little information is available (Parkin, 2007; Schroeder et al., 2007). Given the inherent uncertainty associated with emission, fate and transport, and health effects of emerging contaminants, these considerations are particularly critical for microbial CECs. Ongoing advances in QMRA include integration with molecular biology tools, such as microbial source tracking and whole genome sequencing (Haas, 2020; Rantsiou et al., 2018; Q. Zhang et al., 2019), incorporation of Bayesian network modeling approaches (Beaudequin et al., 2015; Greiner et al., 2013), and development of software applications for practical implementation (Chhipi-Shrestha et al., 2017; K. Kim et al., 2018; Schijven et al., 2015). Among microbial CECs, AMR presents unique challenges for QMRA (Ashbolt et al., 2013; Pires et al., 2018); see Section 1.3.2.

3.2. Modeling Considerations

3.2.1. Emissions

Chemical emission is the most critical model input and, frequently, the most challenging to characterize (Guillén et al., 2012). The starting point for any modeling exercise is an emission estimate, but these estimates can be difficult to obtain as either a chemical inventory does not exist, or chemical usage is proprietary information (Burns et al., 2018). When this information is publicly available, it may only represent a portion of the total environmental emission. Alternatively, national sales data collected by market research firms can be used (Hodges et al., 2014), but in certain cases can be prohibitively expensive. This leads the modeler to make a "best guess" emission estimate or base it on a proxy (Hodges et al., 2012). Spatial emission patterns are particularly challenging to account for because data are rarely available to account for them. In the absence of emission data, different approaches to estimating emissions have been taken. Hodges et al. (2012) spatially allocated consumer chemical emissions based on population density, product affordability, national sales data, and the spatial distribution of the gross domestic product across the country. Jolliet et al. (2020) identified through sensitivity analysis that emissions had the greatest impact on concentrations of CECs across Asia using the Pangea model. Aldekoa et al. (2015) determined that CEC emissions were the largest source of uncertainty in spatially explicit catchment models.

3.2.2. Parameters and Sensitivity Analysis

Models rely on CEC physicochemical data to predict transport and fate, which can be problematic because experimental data, particularly for CECs, are rare. The critical physicochemical parameters, and the environmental fate or degradation process they describe, are listed in Figure 6. The identification of the key physicochemical parameters that are needed is based on the type of exposure modeling being conducted. In a single media model, only parameters relevant to that media are generally necessary, while multimedia approaches incorporate a greater number of environmental processes and therefore require more parameters to describe them. Most chemical property estimation methods have been developed and validated for hydrophobic neutral chemicals (e.g., polybro-

minated diphenyl ethers), while CECs represent a much broader physicochemical diversity that falls outside the applicability of well-studied property estimation approaches (Jagiello et al., 2015; Wang et al., 2011).

The most common property estimation technique is quantitative structure-activity relationships (QSARs), where unknown properties can be predicted based on the likeness in molecular structure to a set of chemicals with known properties. The USEPA's EPISuite™ software or the OECD Toolbox are well-known collections of QSARs used to predict various physicochemical properties (e.g., log octanol/water partition coefficient [K_{ow}], log octanol/air partition coefficient [K_{oa}], log air/water partition coefficient [K_{aw}] and biodegradability) and have been used extensively to fill in data gaps for data-poor CECs (Burns et al., 2018). These QSARs have been validated externally and are robust within their applicability domain (Devillers et al., 2013; Posthumus et al., 2005); however, many CECs fall outside the applicability domain (e.g., polar and ionizable). Some work has been done to address this; for example, Franco and Trapp (2008) derived a soil-water QSAR for ionizable pharmaceuticals, and the WWTP removal prediction software SimpleTreat was updated to include ionizable compounds (Struijs, 2014). For a more in-depth review on the advantages and disadvantages of these predictive approaches, interested readers are directed elsewhere (Jagiello et al., 2015). Moving forward, Tratnyek et al. (2017) suggested that parameter estimation models will go beyond physicochemical properties to predicting TPs based on environmental factors.

Currently, analytical methods to detect engineered nanoparticles in environmental matrices are limited, which is further complicated by the inability to analytically differentiate between synthetic and naturally occurring nanoparticles (Baalousha et al., 2016). In the absence of monitoring data, models have taken on a particularly important role in expanding the knowledge surrounding engineered nanoparticle environmental exposure (Nowack, 2017). Partition coefficients, which dictate solute chemical equilibrium partitioning between environment media, were found to be unsuitable for describing engineered nanoparticles' behavior (R. J. Williams et al., 2019). Rather, the irreversible processes by which these nanoparticles attached to one other (homoaggregation) or to particulate matter (heteroaggregation) influenced their environmental fate (e.g., downstream transport, deposition to sediment, and resuspension). Dissolution was determined to be another important nano-specific process, where the agglomeration could also be affected by interactions with metals or organic matter present in the water column (Nowack, 2017). R. J. Williams et al. (2019) and Nowack (2017) provide detailed reviews on this growing field. The WASP8 model with the advanced toxicant module is a promising development for predicting the exposure, fate, transformation and environmental distribution of engineered nanoparticles (Han et al., 2022; Ross & Knightes, 2022).

Microplastics pose both similar (Hüffer et al., 2017) and divergent challenges (Kooi et al., 2018) to engineered nanoparticles for environmental exposure modeling. Kooi et al. (2018) summarized that their low-density (i.e., float in water), extreme persistency, large size range (nanometers to centimeters), variable morphology (e.g., fibers, films, foams, and fragments) and in-stream formation (degradation of larger plastic particles) make their modeling challenge unique. These properties indicate transport will be particle size/shape dependent, whereas larger particles could be affected by wind and flow (low-density), and nano-sized particles could mix within the water column (Besseling et al., 2017). Yu et al. (2020) proposed applying machine learning techniques to evaluate the exposure to microplastics. However, creation of a robust training regime is limited by a lack of standardized microplastic data and test protocols. This conclusion for the difficulty of microplastic modeling also reached by Uzun et al. (2022). Quik et al. (2023) adapted the SimpleBox4Nano framework to account for attachment, aggregation and fragmentation of microplastics, this development is a significant step forward in the predicting the relative distribution of microplastic between environmental media.

3.3. The Future of CEC Modeling

CECs are a large and evolving group of chemicals that possess a vast array of chemical properties that influence how they will behave in the environment. Generally, environmental occurrence and fate data are limited and a validated modeling framework for classes or specific CECs is rare (Geissen et al., 2015). Furthermore, CECs are present as a complex mixture, not only with other CECs, but other aquatic contaminants including nutrients, pathogens, or suspended solids that affect water quality. This leads to a situation where water quality could be affected simultaneously by multiple contaminants from similar sources where a holistic assessment is needed to comprehensively evaluate water quality (Kroeze et al., 2016). Strokal et al. (2019) presented a critical assessment of the potential challenges associated with developing a global multi-contaminant model that could simultaneously deal with numerous contaminants in rivers and their subsequent export from land to sea. An approach of this type could be important to meet the

challenge of integrating the effect of multiple water quality stressors (including CECs) on aquatic systems to holistically evaluate potential ecotoxicity (Nilsen et al., 2019) and drinking-water quality (van Vliet et al., 2017). Meanwhile, efforts to build models for data-poor regions by utilizing flow and emission proxies (e.g., Barbarossa et al., 2018; Hodges et al., 2014; Zhu et al., 2019) are valuable for increasing model coverage for currently underrepresented areas (e.g., tropical regions) and emission scenarios (e.g., direct wash-off; Ruiz-Gutiérrez et al., 2022).

Computing power and input parameters likely will continue to be a challenge for CEC exposure modeling. A potential solution is a tiered modeling framework (e.g., Figure 7) that begins with high-throughput screening and can incorporate a wide variety of compounds with limited environmental data, with the goal of prioritizing CECs for further investigation using more complex and data-intensive modeling (Di Guardo et al., 2018). To achieve this, the key would be expanding current parameter estimation applicability domains to handle a broader range of CECs alongside developing and refining the dominant CEC-specific processes, ensuring that increasing detail is included only up to the point where it is needed (Di Guardo et al., 2018; Ehret et al., 2014; Jagiello et al., 2015; MacLeod et al., 2010). Higher-tier models (e.g., spatially explicit single or multimedia models) can then be deployed for further investigation of CECs prioritized in the initial screening phase (Franco et al., 2017). A temporal and spatially explicit approach (e.g., STREAM-EU) could form the top tier, where investigations into the temporal dynamics could be evaluated if necessary. At the same time, as monitoring data are becoming increasingly available, these data can aid in the evaluation and improvement of the spatiotemporal processes described within these higher-tier modeling approaches and the role of these processes on chemical fluxes and exposure in the environment (Di Guardo et al., 2018).

Increased freshwater demand from growing populations, coupled with the regionally variable effects of climate change, can influence the occurrence of CECs in the water cycle. Models can help predict the effects of these changes on CEC exposure and fate through scenario-analysis (Di Guardo et al., 2018; Wu et al., 2023). Drinking water is a potentially important CEC human exposure route (Nguyen et al., 2018), particularly as the distance between wastewater and drinking water is reduced through the combination of regionally variable climactic and demographic factors. Furthermore, global food demand, paired with increasing water scarcity, may lead to increased wastewater effluent re-use for irrigation (Assouline et al., 2015). The necessity of this practice would be regionally variable, and CEC exposure would be strongly influenced by the local population and wastewater treatment connectivity. Taken together, changing demographics and climate will influence our water use and management practices. The scenario-analysis that environmental exposure models can provide would be a crucial proactive tool for predicting how these changes could influence CEC exposure, transport, fate, in. an increasingly urbanized water cycle

4. Water Treatment Technologies for CECs

Water is used by humans for countless purposes—direct consumption, food preparation, personal hygiene, recreation, irrigation, and in industrial processes—all of which require water of high quality. The continued development of new chemicals used in manufacturing and products can lead to the degradation of water quality, if not adequately controlled. Gogoi et al. (2018) stated that "there are as of now no laws or mandates illustrating the upper limits of concentrations of CECs in wastewater discharge, drinking water, or the environment," citing a lack of data on CEC fate and transport, concentrations, and their effects as the limiting factor for implementing policy. A lack of knowledge and understanding of the effects of individual CECs, mixtures of CECs, and mixtures of CECs with other contaminants likely will continue to be a hurdle in setting the necessary regulations for governing treatment requirements.

Water treatment processes are a primary barrier for both conventional contaminants and CECs. Conventional centralized wastewater treatment includes the following stages: preliminary treatment, primary treatment, secondary treatment, and tertiary treatment including disinfection (Amenu, 2013). Through such a treatment train, most microorganisms are removed in the tertiary treatment. Conventional drinking water treatment also includes several stages, with the source water type and quality determining the appropriate stages to include. In general, a conventional drinking water treatment train for surface water includes coagulation, flocculation, sedimentation, filtration, and disinfection. Under the right conditions, microorganisms are removed in filtration and inactivated via disinfection.

WWTPs are an important crux for CEC investigation. Effluent wastewaters affect surrounding environmental biomes and are often released into natural water systems that may serve as subsequent sources of drinking water; treated wastewater can also be directly reused for various purposes (Homem & Santos, 2011; S. Kim et al., 2018; Rivera-Utrilla et al., 2013; Teodosiu et al., 2018; Vidal-Dorsch et al., 2012; Y. Yang et al., 2017). Most CECs are

not fully removed or transformed by conventional wastewater treatment (M. B. Ahmed et al., 2017; Gu et al., 2018; Kasonga et al., 2021; S. Kim et al., 2018; Rizzo et al., 2019; Taheran et al., 2016; Vidal-Dorsch et al., 2012; Y. Yang et al., 2017), and there are knowledge gaps when it comes to CEC treatment efficacy (Gogoi et al., 2018; Y. Yang et al., 2017). WWTPs have been primarily designed to reduce microbes and biodegradable carbon, phosphorus, and nitrogenous substances—not more complex CECs (Gogoi et al., 2018). Processes typically used for drinking water treatment target a higher-quality water product and may provide insight for technologies that can specifically target CEC removal. Of concern is that some treatment technologies can transform CECs (e.g., through biological or chemical degradation) into new compounds that can have equal or higher toxicity (Gogoi et al., 2018).

Several critical reviews are available that examine the efficacy of water treatment technologies for CECs, including those identified in Table 4. Scientific inquires range from bench-scale testing of individual treatment technologies, some examining single-solute solutions and some of complex contaminant mixtures, to more holistic evaluations of an entire treatment train. For example, Y. Yang et al. (2017) provides percent removal data for various treatment studies on wastewaters from around the world, illustrating treatment efficacy for various stages (i.e., preliminary, primary, secondary, tertiary) of wastewater treatment processes, as well as more specific combination processes, such as sand filtration with chlorination, granular activated carbon adsorption, ultrafiltration, and reverse osmosis membrane rejection. M. B. Ahmed et al. (2017) presented a critical review of various chemical, biological, and combination wastewater treatment processes, summarizing advantages and challenges of each. Rodriguez-Narvaez et al. (2017) reviewed CEC removal by specific adsorption, membrane, biological, and advanced oxidation treatment processes. Rizzo et al. (2019) summarized advantages and challenges of various advanced wastewater treatment processes, including ozonation, advanced oxidation processes, activated carbon adsorption, nanofiltration, and reverse osmosis membrane processes. These authors also include a review of estimated operational costs and economic feasibility studies.

Contaminant response to a treatment technology is highly complex. Treatment efficacy can be influenced by variable process parameters, water matrix characteristics, and other environmental conditions. Selected studies and comprehensive reviews have been presented here to highlight some important influences on CEC water treatment.

Vidal-Dorsch et al. (2012) specifically looked at CECs in southern California. This study investigated 56 CECs in effluent wastewaters from four WWTPs on the coast, as well as seawater samples (near-seafloor) where these effluents were discharged into the ocean. Eighteen of the 56 CECs analyzed were present in all WWTP effluent samples (including the EDCs benzophenone, bisphenol A, and estrone), with 35 detected in at least one; 20 CECs were detected in at least one of the seawater samples. Fourteen of these 20 were among the CECs found in all WWTP effluent samples; the remaining six were found in at least one WWTP effluent sample. Generally, WWTPs that used more advanced secondary wastewater treatment processes resulted in lower CEC concentrations, both in the plants' effluents and in the receiving seawaters, indicating that advanced treatment processes hold a key toward more effective, but not complete, removal of these complex contaminants. Some CEC removal can be attributed to secondary treatment biological processes (via biodegradation and sorption). Assessing the full effects of an individual WWTP effluent discharge as a point-source is difficult because dilution (e.g., with ocean water), chemical transport and transformation, and additional discharge sources (e.g., other treatment facilities, storm water) will influence environmental concentrations.

A study of a South African WWTP (Archer et al., 2017) measured 90 CECs in the plant's influent and effluent waters over a 5-day period, as well as corresponding river surface water grab samples upstream and downstream from the discharge location. Archer et al. (2017) report that 55 CECs were detected in the WWTP influent and 41 in the effluent. Of the detected compounds, 28% had a percent removal efficacy (defined as change in the concentration from influent to effluent, normalized by influent concentration) of less than 50%, and 18% of the compounds had removal efficacies below 25%. Five compounds exhibited concentration increases after treatment (the pharmaceutical tramadol and two of its metabolites, azithromycin, and a pharmaceutical metabolite, desvenlafaxine), two of which were deemed statistically significant (azithromycin and desvenlafaxine). Archer et al. (2017) hypothesize possible sources, including the dissolution of CECs that have accumulated in aggregate material and/or the potential back-transformation of metabolites present in the influent waters into

Table 4
A Sampling of Reviews and Novel Publications Discussing Treatment Technologies for Contaminants of Emerging Concern (CECs)

	Adsorption		Membrane				Oxidation			Biodegradation			Holistic WWTP/ DWTP
Reference	Activated carbon	Other	UF	NF	RO	FO	Chlorination	Ozonation	Other AOPs	Activated sludge	Membrane bioreactors	Other	
M. B. Ahmed et al. (2017)	x	x	x	x	x			x	x	x	x		
Archer et al. (2017)													x
Bellona et al. (2010)				x									
Gogoi et al. (2018)	x			x			x	x	x	x	x	x	x
Gu et al. (2018)											x		
Homem and Santos (2011)	x		x	x	x		x	x	x				x
Jang et al. (2018)						x							
S. Kim et al. (2018)			x	x	x	x							
F. X. Kong et al. (2015)					x	x							
Kucharzyk et al. (2017)	x	x		x	x				x			x	
Noutsopoulos et al. (2015)							x						
Pan et al. (2016)													x
Rivera-Utrilla et al. (2013)							x	x	x				x
Rizzo et al. (2019)	x			x	x			x	x				
Rodriguez-Narvaez et al. (2017)	x	x	x	x	x	x		x	x	x			
Rout et al. (2021)	x	x						x		x	x		
Sichel et al. (2011)									x				
Sophia and Lima (2018)	x	x											
Taheran et al. (2016)			x	x	x	x							
Teodosiu et al. (2018)	x	x	x	x	x	x		x	x				
Trojanowicz et al. (2018)								x	x				
Vallejo-Rodríguez et al. (2014)								x					
Vidal-Dorsch et al. (2012)													x
Xie et al. (2012)					x	x							
K. Xiao et al. (2019)											x		
Y. Yang et al. (2017)	x							x	x				x
Zamri et al. (2021)	x	x	x	x	x		x	x	x		x	x	
S. Zhang et al. (2017)												x	

Note. UF = ultrafiltration, NF = nanofiltration, RO = reverse osmosis, FO = forward osmosis, AOP = advanced oxidation processes, WWTP = wastewater treatment processes, DWTP = drinking water treatment processes.

the original parent compounds, which subsequently show up in the effluent. The authors noted that the studied WWTP receives public, domestic, and industrial wastewater, with variable contribution from these sources that may not be captured during sampling. It is also worth noting that data used to track "removal" generally pertain to the parent compound, and thus, these data neglect tracking any TPs, which themselves may have negative effects on human and environmental health. Similarly, any CECs that have been transferred to a solid media (e.g., the aforementioned aggregate material) could be released into the environment through solids disposal or repurposing (e.g., biosolids used as soil amendments). Biosolids and wastewater effluent (used for irrigation) can be seen as beneficial in nutrient-deficient and arid environments, but they also have the potential to affect soil chemistry (e.g., salinity, pH, hydrophobicity) and to release bacterial pathogens (including fecal coliforms and antibiotic-resistant bacteria), heavy metals, organic contaminants (e.g., PAHs), and other CECs (Gatica & Cytryn, 2013).

When evaluating treatment technologies, it is most common for process efficacy to be quantified by comparing an initial (i.e., before treatment) compound concentration with a final (i.e., after treatment) concentration, which is often presented as a percentage (Rodriguez-Narvaez et al., 2017). Treatment process efficacy will be dependent on physicochemical and biological properties of the individual CEC, including hydrophobicity/hydrophilicity, solubility, volatility, and biodegradability (Y. Yang et al., 2017).

4.1. Adsorption Processes

Adsorption is a mass transfer process where a solute is removed from the aqueous phase and accumulates on a solid phase adsorbent. Table 5 highlights references that examine the effect of solute properties, adsorbent properties, and water conditions on the efficacy of adsorption for removal of CECs. Activated carbon is one of the most common types of adsorbents, especially in DWTP. Adsorbent "activation" allows alterations of the surface chemistry and can be done through chemical (e.g., acid activation) or physical (e.g., heat activation) processes. The raw material source for activated carbons (e.g., coal, wood, coconut shell), activation method, and the pore size distribution will greatly affect adsorption capacity. The adsorption phenomenon involves bulk solute transport, film diffusion, and pore diffusion (M. B. Ahmed et al., 2015). Adsorption mechanisms are complex and are influenced by the solubility and hydrophobicity of the adsorbate, the hydrophobicity of the adsorbent, and the strength of electrostatic interactions between the adsorbate and the adsorbent (including π-π interactions of aromatic rings; Rivera-Utrilla et al., 2013; Sophia & Lima, 2018; Zamri et al., 2021). The capacity of an adsorbent was shown to be related to the adsorbent-specific surface area and micropore volume

Table 5
Physicochemical Properties That Have Shown to Influence Adsorption of Contaminants of Emgering Concern (Contaminants of Emerging Concern (CECs))

	Supporting literature
Solute properties	
Size/molecular weight	Cuerda-Correa et al. (2010)
Charge/polarity	M. B. Ahmed et al. (2015), Gogoi et al. (2018), De Ridder et al. (2010), Sophia and Lima (2018)
Hydrophobicity	M. B. Ahmed et al. (2015), Diniz et al. (2022), Gogoi et al. (2018), Rivera-Utrilla et al. (2013), Rout et al. (2021), Sophia and Lima (2018), Y. Yang et al. (2017), Zamri et al. (2021)
Solubility	Rivera-Utrilla et al. (2013)
Functional groups	Rivera-Utrilla et al. (2013)
Adsorbent properties	
Hydrophobicity	M. B. Ahmed et al. (2015), Méndez-Díaz et al. (2010), Rivera-Utrilla et al. (2013), Rout et al. (2021), Sophia and Lima (2018), Zamri et al. (2021)
Surface functional groups	M. B. Ahmed et al. (2015), Cuerda-Correa et al. (2010), Diniz et al. (2022), Gogoi et al. (2018), Rivera-Utrilla et al. (2013), Rodriguez-Narvaez et al. (2017), Teodosiu et al. (2018), Zamri et al. (2021)
Surface area/porosity/pore size	Diniz et al. (2022), Gogoi et al. (2018), Homem and Santos (2011), Rodriguez-Narvaez et al. (2017), Rout et al. (2021), Sophia and Lima (2018), Teodosiu et al. (2018)
Source material	Diniz et al. (2022), Gogoi et al. (2018), Kucharzyk et al. (2017), Rodriguez-Narvaez et al. (2017), Rout et al. (2021), Sophia and Lima (2018)
Process/water conditions	
Contact time	Sophia and Lima (2018), Teodosiu et al. (2018), Y. Yang et al. (2017), Zamri et al. (2021)
pH	M. B. Ahmed et al. (2015), Cuerda-Correa et al. (2010), Diniz et al. (2022), Gogoi et al. (2018), Kucharzyk et al. (2017), Rivera-Utrilla et al. (2013), Rout et al. (2021), Sophia and Lima (2018), Teodosiu et al. (2018)
Presence of natural organic matter	Cuerda-Correa et al. (2010), Homem and Santos (2011), Rivera-Utrilla et al. (2013), Rout et al. (2021), Zamri et al. (2021)
Temperature	M. B. Ahmed et al. (2015), Cuerda-Correa et al. (2010), Gogoi et al. (2018)
Ionic strength	Cuerda-Correa et al. (2010), Sophia and Lima (2018)
Presence of other compounds (i.e., competition)	Diniz et al. (2022), Gogoi et al. (2018), Homem and Santos (2011)

(Cuerda-Correa et al., 2010). Adsorption capacity can also be increased by modifying chemical functional groups on the adsorbent surface (M. B. Ahmed et al., 2015). An advantage of activated carbons and other adsorbents is that they can be regenerated and reused through a reactivation process, which restores adsorbent surface chemistry. For carbon-based adsorbents, thermal decomposition processes are commonly used for regeneration (M. B. Ahmed et al., 2015). Regeneration techniques (e.g., thermal, solvent desorption) may result in air emissions or solvents that contain CECs and byproducts, which would then need to be appropriately disposed of M. B. Ahmed et al. (2015), Homem and Santos (2011).

Rizzo et al. (2019) reviewed activated carbon adsorption for removal of CECs, concluding that CEC adsorption is hindered in water matrices with high levels of organic matter because of competition for adsorbent surface sites. The level of competition is influenced by the physicochemical properties of both the target CEC and the organic matter. CEC size, charge and polarity, functional groups, and hydrophobicity will all affect adsorption (Rizzo et al., 2019). In wastewater treatment, activated carbon can be implemented at various stages in the water treatment process, such as within existing filter processes, within the existing biological treatment process, or as an independent post-biological treatment process (Rizzo et al., 2019). Generally, adsorption processes are controlled by contact time. Data were summarized by Rizzo et al. (2019) for studies examining activated carbon (both powdered and granular) as an advanced wastewater treatment; the authors targeted studies that examined real wastewater effluents to capture systems that consider the important effect of the background water matrix.

Adsorption studies compiled by Rodriguez-Narvaez et al. (2017) confirmed that the source material of activated carbon influenced removal capabilities. Four studies using biochar (created via pyrolysis of biomass) were summarized, showing some removal capabilities, but they were relatively low overall (Rodriguez-Narvaez et al., 2017). Although the activated carbon and carbon nanotubes seem to have higher performances for most CECs than biochar and clay mineral adsorbents, it is worth noting that overlap between data sets (which were themselves relatively small) was minimal and that additional factors (e.g., water matrix parameters, contact time) were not identified or compared (Rodriguez-Narvaez et al., 2017). Competition for adsorption sites, by other contaminants and/or natural organic matter present in the water matrix, may impact adsorption mechanism (Cuerda-Correa et al., 2010; Diniz et al., 2022; Gogoi et al., 2018; Homem & Santos, 2011; Rivera-Utrilla et al., 2013; Rout et al., 2021).

Unlike transformational treatment processes (e.g., oxidation, biodegradation), activated carbon has the advantage of not generating unknown (and potentially toxic) byproducts (Rivera-Utrilla et al., 2013). As previously mentioned, any adsorbed contaminants would need to be considered during carbon regeneration and disposal. Adsorption processes also have the advantage of being unaffected by CEC toxicity, whereas treatments relying on bioactivity (e.g., activated sludge) could be affected (M. B. Ahmed et al., 2015).

4.2. Membrane Processes

The most common membrane processes implemented for CEC removal are ultrafiltration, nanofiltration, forward osmosis, and reverse osmosis. Microfiltration is often not considered for CECs because of its limitation to contaminant sizes greater than 1 μm (Rodriguez-Narvaez et al., 2017). Ultrafiltration, nanofiltration, and reverse osmosis use a hydraulic pressure difference to transport water through the semipermeable membrane. Forward osmosis uses an osmotic pressure difference (S. Kim et al., 2018); such units are most commonly run in a cross-flow configuration (Rizzo et al., 2019). Table 6 highlights literature sources that provide more treatment details of membrane rejection efficacy, as influenced by solute properties, membrane properties, and water quality characteristics. Organic solute retention by membrane processes is controlled by size exclusions, electrostatic (i.e., charge) repulsion, and adsorption (Z. H. Liu et al., 2009; Rizzo et al., 2019; Taheran et al., 2016; Zamri et al., 2021). Membrane transport of CECs is substantially influenced by chemical properties of the individual CEC, membrane characteristics and operating parameters, and the quality of the water matrix (S. Kim et al., 2018; Taheran et al., 2016). Taheran et al. (2016) provide an extensive review of how membrane, compound, and process parameters influence membrane rejection of pharmaceutically active compounds. Bellona et al. (2010) highlight the importance of understanding membrane fouling (i.e., from background natural organic matter in the water matrix).

S. Kim et al. (2018) provide a critical review of numerous membrane transport studies for CECs. In general, membrane rejection of CECs increases from ultrafiltration, nanofiltration, forward osmosis, to reverse osmosis

Table 6
Physicochemical Properties That Have Shown to Influence Membrane Rejection of Contaminants of Emerging Concern (CECs)

	Supporting literature
Solute properties	
Size/molecular weight	Gogoi et al. (2018), Jang et al. (2018), S. Kim et al. (2018), Rizzo et al. (2019), Taheran et al. (2016), Xie et al. (2012), Zamri et al. (2021)
Charge/polarity	Gogoi et al. (2018), Homem and Santos (2011), Jang et al. (2018), S. Kim et al. (2018), Rizzo et al. (2019), Rodriguez-Narvaez et al. (2017), Taheran et al. (2016), Y. Yang et al. (2017), Zamri et al. (2021)
Hydrophobicity	Gogoi et al. (2018), Jang et al. (2018), S. Kim et al. (2018), Rizzo et al. (2019), Taheran et al. (2016), Xie et al. (2012), Zamri et al. (2021)
Solubility	Gogoi et al. (2018), Jang et al. (2018), K. Kim et al. (2018), Xie et al. (2012)
Membrane properties	
Molecular weight cut-off/pore size	Gogoi et al. (2018), S. Kim et al. (2018), Rodriguez-Narvaez et al. (2017), Taheran et al. (2016), Zamri et al. (2021)
Surface potential/charge	Gogoi et al. (2018), Homem and Santos (2011), Jang et al. (2018), S. Kim et al. (2018), Rodriguez-Narvaez et al. (2017), Taheran et al. (2016), Y. Yang et al. (2017), Zamri et al. (2021)
Hydrophobicity	Gogoi et al. (2018), S. Kim et al. (2018), Rodriguez-Narvaez et al. (2017)
Membrane material	S. Kim et al. (2018), Zamri et al. (2021)
Permeability	Jang et al. (2018), Zamri et al. (2021)
Process/water conditions	
pH	Jang et al. (2018), S. Kim et al. (2018), Rizzo et al. (2019), Taheran et al. (2016)
Fouling (presence of natural organic matter)	Gogoi et al. (2018), Homem and Santos (2011), S. Kim et al. (2018), Rivera-Utrilla et al. (2013), Rizzo et al. (2019)
Operating pressure	Gogoi et al. (2018), Jang et al. (2018), S. Kim et al. (2018)
Dead-end/cross-flow velocity	S. Kim et al. (2018)
Temperature	Homem and Santos (2011), Jang et al. (2018)
Recovery	Jang et al. (2018)
Draw solution (for forward osmosis)	Xie et al. (2012)

membranes. Compiled data indicate that compound size (i.e., molecular weight), charge, and hydrophobicity are influencing parameters for rejection. CECs that are relatively small can partition and diffuse through reverse osmosis and forward osmosis membrane material; size exclusion (including steric exclusion) contributes to rejection when compounds are above the molecular weight cut-off of the specific membrane. Electrostatic repulsion (due to compound charge) and hydrophobic interactions (potentially leading to adsorption) generally correlate to higher rejection values, especially for nanofiltration and ultrafiltration membranes. Because of the importance of compound charge, water pH also is an influencing characteristic, potentially on compound speciation. S. Kim et al. (2018) conclude that "more polar, less volatile, and less hydrophobic organic CECs have less retention than less polar, more volatile, and more hydrophobic organic CECs."

Rizzo et al. (2019) reviewed sources for primarily nanofiltration and reverse osmosis membrane processes. Membrane fouling can affect rejection through a process known as cake-enhanced concentration polarization. Some modeling approaches use process-based modeling for efficacy, such as the Spiegler-Kedem or the solution-diffusion models, while others attempt to correlate percent removal (i.e., rejection) data with solute properties. One problem with the latter is that with process performance being dependent on the solute, membrane, water matrix, and other system parameters, percent rejection values are rarely comparable between different studies and data sets. Rizzo et al. (2019) compiled experimental data, focusing on those that include four CECs (diclofenac, carbamazepine, estradiol, and n-nitrosodimethylamine [NDMA]), to portray the effect of contaminant and process variations. Scaling membrane processes from laboratory-scale to full-scale may prove challenging because of the difficulty in accurately scaling hydraulic conditions.

A study by Jang et al. (2018) of membrane rejection (presented as percent rejection) of 12 CECs by a forward osmosis membrane concluded that solute charge was an influencing parameter. In the context of membrane processes, the fraction of material (e.g., CECs) that remain on the feed-side of the membrane is said to be

"rejected" or "retained." CECs that were negatively charged had higher rejection than those positively charged, due to the electrostatic repulsion by the negatively charged membrane surface. The attraction between charged CECs and the membrane surface induces a concentration gradient, which increases the diffusion of absorbed particles through the membrane into the permeate solution (Jang et al., 2018). For neutral (i.e., non-charged) CECs, membrane rejection was positively correlated to molecular weight and hydrophobicity (Jang et al., 2018). Neutral hydrophobic compounds (indicated by high octanol-water partitioning coefficients) had strong affinity for the membrane surface, resulting in adsorption (Jang et al., 2018). Solution pH was important to consider in relation to compound pK_a (i.e., the negative log of the acid disassociation constant) because of its implication on compound charge; in water treatment schemes, pH would be an important operational parameter to monitor (Jang et al., 2018). Unlike other membrane processes, forward osmosis operates without an applied hydraulic pressure, which could potentially lower energy demand (therefore, operational costs) and allow for better control of membrane fouling (less severe and more reversible than nanofiltration and reverse osmosis; Xie et al., 2012).

While rejection of CECs by nanofiltration membranes may not be as high as reverse osmosis membranes, nanofiltration requires considerably lower hydraulic pressure, which can reduce operating costs (Taheran et al., 2016). A drawback to membrane processes is that CECs are not degraded, resulting in a concentrated waste stream that would still require additional treatment and/or disposal (Rizzo et al., 2019; Taheran et al., 2016; Y. Yang et al., 2017). Membrane characteristics, including material (e.g., polyamide, cellulose acetate), the structure of the active layer, pore size, surface charge and hydrophobicity, and the extent of membrane fouling will all affect membrane performance (S. Kim et al., 2018; Zamri et al., 2021). Increasing cross-flow velocity generally increases retention by decreasing concentration polarization effects (S. Kim et al., 2018). Although initial efforts provide some insight into CEC behavior in membrane treatment systems, investigations are often limited in the number of solute compounds, number/types of membranes, range of water quality parameters, and operating conditions. Because of the diverse molecular properties of CECs and countless permutations of membrane process parameters, future efforts would benefit from systematically coordinating such research to investigate influences on solute rejection (S. Kim et al., 2018; Rizzo et al., 2019).

4.3. Oxidation Processes

In water treatment, oxidation processes are implemented for the destruction of pathogens. Common oxidation processes use chlorine, UV, or ozone, each having varying effectiveness on pathogens. Chlorine can be applied as a solid, liquid, or gas, and important considerations include the concentration, mixing time, remaining residual, and concentration of interfering reactive substances (Naidoo & Olaniran, 2014). In wastewater treatment processes, excess chlorine is often removed to prevent contamination of receiving waters with residual chlorine or toxic DBPs like trihalomethanes. Chlorine is effective at killing most bacteria and inactivating viruses, but protozoan pathogens are relatively resistant. UV disinfection is becoming more routine due to its ease of use and lack of byproduct formation. UV inactivates microorganisms by damaging their DNA and preventing their replication. UV light is applied to wastewater through a mercury arc lamp, which uses electromagnetic energy to irradiate the effluent. In addition to inactivating bacteria and viruses, UV disinfection has also demonstrated effectiveness against the spore-forming protozoan pathogen *Cryptosporidium* spp., but must be used at the appropriate dose, optimal wavelength (250–270 nm), and exposure time for adequate inactivation (Morita et al., 2002). Ozone is preferred by some WWTPs for its on-site production, highly reactive nature, and lack of byproduct formation, but ozone can be expensive. The dose must be determined empirically and can range from a few milligrams per liter to 10 mg/L (Lazarova et al., 1999). Table 7, adapted from WHO (2011) describes the concentration of different disinfectants and contact time required to inactivate 99% of enteric bacteria, virus, and protozoa in drinking water, expressed in units of mg-min/L (milligram-minute per liter). Although DWTP are generally effective in reducing ARB and ARG, both ARB and ARG have nonetheless been detected in treated drinking water (Sanganyado & Gwenzi, 2019). In fact, disinfection processes may promote horizontal transfer of ARG, including to human pathogens (Sanganyado & Gwenzi, 2019).

In a series of chlorination batch reactor bench-scale experiments, Noutsopoulos et al. (2015) conclude that wastewater pH is one of the most influential parameters when evaluating chlorine degradation (via direct dosing of sodium hypochlorite solution) of the nine CECs included in the study. The chlorine dosing concentration and presence of humic acids (a common constituent of natural organic matter) minimally influenced degradation (Noutsopoulos et al., 2015). The authors also examined the influence of suspended solids, finding it primarily

Table 7
Concentration and Contact Time (Duration) for Different Disinfectants to Inactivate 99% of Enteric Bacteria, Virus, or Protozoa

Treatment	Enteric pathogen	Ct_{99} mg-min/L[a]	Temperature (°C)	pH
Chlorine	Bacteria	0.08	1–2	7
	Viruses	12	0–5	7–7.5
	Protozoa	230, *Cryptosporidium* not killed	0.5	7–7.5
Monochloramine	Bacteria	94	1–2	7
	Viruses	1,240	1	6–9
	Protozoa	2,550, *Cryptosporidium* not killed	1	6–9
Chlorine dioxide	Bacteria	0.13	1–2	7
	Viruses	8.4	1	6–9
	Protozoa	40	22	8
Ozone	Bacteria	0.2	5	6–7
	Viruses	0.9	1	Not specified
	Protozoa	40	1	Not specified
UV irradiation	Bacteria	7 mJ/cm^2[b]	Not specified	Not specified
	Viruses	59 mJ/cm^2	Not specified	Not specified
	Protozoa	10 mJ/cm^2	Not specified	Not specified

Note. Adapted from WHO (2011).

[a]Ct_{99} is defined as the concentration of disinfectant and contact time required to inactivate 99% of enteric bacteria, virus, or protozoa, and is expressed in units of milligram-minutes per liter (mg-min/L). [b]Ultraviolet (UV) irradiation dose is for 99% inactivation and is expressed in units of millijoule per square centimeter (mJ/cm^2).

dependent on individual compound physiochemical properties governing their likelihood to adsorb to the solids. Homem and Santos (2011) suggest chlorinating wastewaters containing pharmaceuticals, as a pretreatment for biological treatments, to oxidize them to less toxic (i.e., more biodegradable) compounds. However, this seems to assume that all pharmaceuticals will be effectively oxidized by chlorine, which is not necessarily the case (Rivera-Utrilla et al., 2013; X. Yang et al., 2016), and that the chlorination byproducts will be less toxic than the parent pharmaceuticals, which would also need to be verified (Rout et al., 2021; Zamri et al., 2021). For example, Huang et al. (2015) found that oxidation of ibuprofen created a transformation byproduct with an increased toxicity. The composition of the water matrix (e.g., the presence of bromide) will also influence DBP composition. Generally, brominated-DBPs have been found to have a higher toxicity than their parent compounds (Jeong et al., 2012). The rate of degradation of antibiotics via chlorination is affected by the water matrix pH and background natural organic matter (Homem & Santos, 2011). Chlorine dioxide has been suggested as a preferred chlorine species (e.g., instead of hypochlorous acid) because of its selectivity, making it unlikely to form trihalomethanes as DBPs (Homem & Santos, 2011). The complexity of oxidation processes, TP formation, and varying toxicity levels of those byproducts leave several areas open for future investigation.

Rizzo et al. (2019) reviewed the use of ozonation, typically a process used in drinking water treatment, for its application in wastewater treatment. When considering ozonation, the background water matrix would need to be taken into accounted. Organic matter, expressed as dissolved organic carbon and nitrite, are also reactive with ozone, competing with CECs. Chemical oxidation processes, such as ozonation, form TPs through the oxidation of CECs themselves and oxidation byproducts through the oxidation of the background water matrix. Rizzo et al. (2019) draw attention to a treatability test presented by Wildhaber et al. (2015), aimed to assess wastewaters as candidates for ozonation treatment, which indicates using NDMA and bromate as byproduct indicators and a series of bioassays to evaluate biological activity. Generally, water treatment by ozone oxidation will depend on the second-order oxidation reaction kinetics and liquid-gas transfer equilibrium, which are pertinent to process/reactor design (Vallejo-Rodríguez et al., 2014). For some CECs (i.e., steroids), kinetic rate constants were highly dependent on the system pH and the dosing concentration of ozone (Vallejo-Rodríguez et al., 2014). Vallejo-Rodríguez et al. (2014) conducted ozonation experiments of four CECs to determine kinetic constants based on stoichiometric coefficients. The authors cite stoichiometric coefficients as an important component of process design, particularly when scaling systems.

Advanced oxidation processes combine multiple oxidants to create hydroxyl radicals, resulting in rapid and complete oxidation of target compounds (Homem & Santos, 2011; Vallejo-Rodríguez et al., 2014). Advanced oxidation processes have been recently explored as treatment options for CECs, although they have not been implemented for full-scale application (Rizzo et al., 2019). Rizzo et al. (2019) provide a review of published studies for various advanced oxidation processes and their applications for removing CECs from wastewater effluent. Rivera-Utrilla et al. (2013) have also tabulated key findings of various studies of advanced oxidation treatment of CECs (specifically, pharmaceuticals) and include percent removal, summaries of experimental conditions, and notable observations from individual studies. A potential disadvantage of advanced oxidation processes that use UV photolysis to create hydroxyl radicals is the high cost associated with the high energy consumption for the process (M. B. Ahmed et al., 2017; Sichel et al., 2011). Advanced oxidation processes can also be limited to treating lower flow rates of wastewater (Homem & Santos, 2011).

In a study by Sichel et al. (2011), DBPs of UV/chlorine advanced oxidation processes (specifically trihalomethanes) were reduced by quenching with thiosulfate to remove excess chlorine. Sichel et al. (2011) also found that the UV/chlorine degradation of eight CECs was not hindered in modeled waters with higher dissolved organic carbon concentrations that were intended to simulate municipal WWTP waters.

4.4. Biological Processes

Activated sludge processes use aerobic biodegradation and are commonly used in wastewater treatment. Gogoi et al. (2018) compiled data for aerobic wastewater treatment processes, including activated sludge, membrane bioreactors, sequencing batch reactors, waste stabilization ponds, constructed wetlands, and for anaerobic activated sludge processes. Comparing reported percent removal data for selected CECs, aerobic processes seem to perform better than anaerobic processes, and activity of the sludge bacteria was temperature-dependent (Gogoi et al., 2018). WWTPs using microorganism-based treatments are often limited in their ability to remove CECs that cannot be biodegraded (e.g., many pharmaceuticals); they may even bioaccumulate and/or hinder biological activity (M. B. Ahmed et al., 2017; Homem & Santos, 2011; Rivera-Utrilla et al., 2013). Bioaccumulation in treatment microorganisms would need to be further addressed when considering disposal and/or repurposing of the biosolids to prevent reintroduction of CECs into environmental systems. Biological processes may also promote genetic exchange and increases in AMR, particularly under selective pressure from cocontaminants (antibiotics and metals) in the wastewater (Rizzo et al., 2013).

Membrane bioreactors provide a more advanced biodegradation wastewater treatment process by combining it with membrane filtration (Gu et al., 2018). Membrane bioreactors show promise for higher removal of CECs than traditional activated sludge systems, which may be attributed to the bioreactors' high sludge retention time; however, like other membrane processes, membrane bioreactors are subject to membrane fouling (Gu et al., 2018; K. Xiao et al., 2019). Gu et al. (2018) compiled data for the removal of pharmaceuticals from wastewater using membrane bioreactor processes; influences on process efficacy included hydraulic and sludge retention times, dissolved oxygen and pH of the water matrix, and physicochemical properties of the CECs themselves (e.g., molecular structure, hydrophobicity). K. Xiao et al. (2019) provide an overview of several existing membrane bioreactor systems and the breakdown of associated capital and operational costs and energy consumption. In general, membrane bioreactor processes have comparable costs to traditional activated sludge with tertiary treatment. K. Xiao et al. (2019) also highlight studies showing successful removal of microplastics by membrane bioreactor systems, proving vastly superior treatment compared to traditional wastewater treatment sedimentation. It is worth noting that this success can likely be attributed to the retention of microplastics by the membrane filter and that similar removal may be evident in traditional membrane processes. The key is the implementation of membranes into wastewater treatment, which could prevent the release of microplastics into natural environmental systems.

4.5. Data Gaps in the Understanding of Treatment Processes

While compounds classified as CECs have been the subject of scientific inquiry for decades, there are still many gaps in knowledge regarding their fate and transport in water treatment processes. Studies are often limited to small data sets (e.g., Xie et al., 2012) and results are often difficult to compare because of experimental variations. Varying and/or limited water matrices, operating conditions, and other factors, make a comparison of

percent rejection data difficult and often inconsistent (S. Kim et al., 2018). For membrane-based treatments, the effect of natural organic matter fouling on membrane rejection will vary for different membranes and the different compounds being targeted for removal (Bellona et al., 2010; Rout et al., 2021). The resulting adsorption and cake-enhanced concentration polarization effects would ideally be considered in future experimental design and analysis. Some studies (e.g., F. X. Kong et al., 2015) have started reporting membrane rejection using flux-based models, which provide more universal process parameters. An additional challenge of all bench-scale treatment technology research is appropriately scaling process parameters for full-scale treatment design (e.g., adsorption processes, membrane processes) (S. Kim et al., 2018; Rizzo et al., 2019; Rodriguez-Narvaez et al., 2017; Rout et al., 2021).

Risk assessments for aquatic life are still needed, as toxicity thresholds have only been determined for a few CECs and potential TPs (Gogoi et al., 2018; Rivera-Utrilla et al., 2013; Vidal-Dorsch et al., 2012). For example, little is known about the membrane bioreactor-generated TPs of pharmaceuticals and their potential for negative effects on environmental and human health (Gu et al., 2018). Additional challenges for membrane bioreactors include improving cost- and energy-effectiveness, improving control of membrane fouling, and optimizing operational parameters to maximize removal of target contaminants (K. Xiao et al., 2019). Chemical oxidation processes also introduce the risk of adverse effects from transformation byproducts.

As a collective, CECs cover a diverse range of physicochemical properties and are generally present as complex mixtures, which can greatly affect their fate and transport in environmental and treatment systems (Archer et al., 2017). The effects of competition, by other CECs and other water constituents (e.g., natural organic matter), need to be investigated further (M. B. Ahmed et al., 2015). CEC and water matrix diversity make evaluation and prediction of effective treatment technologies difficult (Rizzo et al., 2019). A single treatment technology cannot be used to remove all CECs, so combined processes would need to be implemented (M. B. Ahmed et al., 2015; Gogoi et al., 2018; S. Kim et al., 2018; Rivera-Utrilla et al., 2013; Rodriguez-Narvaez et al., 2017; Rout et al., 2021; Y. Yang et al., 2017). Strategic integration of advanced treatment processes (e.g., activated carbon adsorption) into current wastewater treatment trains can help improve the removal efficacy for CECs (M. B. Ahmed et al., 2015; Gu et al., 2018; S. Zhang et al., 2017).

5. Drinking Water Epidemiology

Epidemiology is an applied science that can provide insights into which exposures pose public health risks and thereby inform interventions to mitigate those risks (Galea, 2013; Susser, 1991). Observational epidemiology can complement experimental studies by looking at real-world situations faced by human populations, rather than idealized and simplified exposure scenarios, and can evaluate putatively toxic exposures in human populations when conducting experimental studies would be unethical (F. Ahmed et al., 2023; Vlaanderen et al., 2008). To assess whether specific contaminants pose health risks in observational epidemiology studies, it is necessary to describe exposures to contaminants in populations and to assess the correspondence between exposure levels and health outcomes in those populations. Contaminant exposure can occur through various media including drinking water, food, house dust, or air (Elert et al., 2011). Accurately apportioning the relative importance of different exposure pathways would be helped by detailed data collection on the multiple routes of exposure (Clayton et al., 2002; Georgopoulos et al., 2006, 2008; Sexton et al., 1995a, 1995b; K. W. Thomas et al., 1999), which can be challenging and impractical. All humans consume water, so chemical and microbial contaminants in water are often of interest. Various approaches exist to characterize exposure to drinking water contaminants in epidemiological studies, each with their advantages and disadvantages. These exposure assessments can be grouped broadly into studies using biomarkers, studies using environmental data, and hybrid approaches that leverage both kinds of data.

5.1. Biomarker Data

An "exposure biomarker" is a measurement taken from a biological matrix, such as urine, that reflects the amount of a chemical than enters the body (e.g., arsenic concentrations in urine) (Lam & Gray, 2003). A major strength of the biomarker-based approach to exposure assessment is that the measures are person-specific and integrate the multiple routes of exposure by which chemicals enter the body, thus allowing for clearer epidemiological

assessments of whether the chemical poses a health hazard than approaches only considering a single route of exposure (Navas-Acien & Guallar, 2008; Shin et al., 2011). This is useful for drinking water health effect studies because biomarkers measuring total intake of chemicals can reflect challenging-to-measure behavioral changes such as switching to bottled water when drinking water supplies are suspected to be contaminated (Zivin et al., 2011). However, biomarker-based exposure measures can sometimes be affected by the biology of the disease process under study in addition to the underlying exposure of interest (Weisskopf and Webster, 2017), leading to potential bias in health effect estimates (Bulka et al., 2017; Dhingra et al., 2017).

5.2. Individual Environmental Exposure Data

Measurements taken directly from point of consumption of drinking water (i.e., at the tap) can avoid some of the potential biases of biology-inflected exposure metrics, and account for contaminant transformation and introduction due to residence time, filtering, chemical additions, and premise plumbing (Figure 8). However, tap water data collection is limited by the large number of observations required to account for sampling variability in contaminant levels (Brunkard et al., 2011; Casteloes et al., 2015) and by high frequencies of left-censored data (i.e., contaminants occurring below the detection limit) (Bradley et al., 2018). In addition, people consume tap water at multiple locations (e.g., home, work, and other settings) (Zender et al., 2001) and sources (e.g., municipal drinking water, bottled water). Thus, assessment of water contamination at a single tap may misrepresent the total exposures encountered by individuals. Collection of water samples from each of the tap water sources encountered by each participant in a health effects study may be logistically prohibitive.

5.3. Aggregated Environmental Exposure Data

An expedient option sometimes used for modeling exposure in epidemiologic research is to assign a shared exposure measure for a study region, such as an "average" concentration of water contaminants in a source water or water supply, to all persons in that region (e.g., persons served by that water supply; Marie et al., 2018). Spatial assignment could possibly be used for multiple water supplies encountered by an individual, such as at work and at home (Avanasi et al., 2016a), to provide a more holistic picture of contaminant exposure. A common misperception is that health studies using an aggregated exposure metric are plagued by the potential for ecologic fallacy, wherein inaccurate conclusions may be drawn about individual-level health risks when analyzing aggregated group-level outcomes (Robinson, 2009; Subramanian et al., 2009). However, ecological bias does not arise when individual health outcomes are still the focus of the analysis rather than aggregated health outcomes, even when an aggregated exposure measure is used (Künzli & Tager, 1997). When the spatially aggregated measure represents an unbiased average of the true exposures for persons in the area, then for some kinds of epidemiological dose-response models, the measurement error of individuals' experienced drinking water contaminant exposures (i.e., the deviation of individuals' true exposures from the average) will not introduce bias into the health effect estimates, but instead only inflate the standard errors of the health effect estimates (Berkson, 1950). This is distinct from dose-response models based on individual-level exposures, whose measurement errors introduce some bias into dose-response estimates. Two important caveats are that (a) the lack of bias in dose-response models is only guaranteed under specific dose-response modeling conditions (e.g., normally distributed variables with linear relationships, as might be modeled in a linear regression, and errors that are unrelated to each other and unrelated to the true values of the variables; D. C. Thomas, 2009), and (b) real-world data are seldom so ideal. In real-world studies, using estimated average exposures based on imperfect environmental monitoring data leads to more complex measurement errors that likely introduce some bias into epidemiological dose-response estimates, because the aggregated exposure measures also include some error characteristics akin to individual-level exposure measures (Zeger et al., 2000). For example, CEC exposures assigned to epidemiological study participants based on water system average concentrations may have measurement errors due to differences across persons in daily water consumption rates, drinking water type (e.g., water as it comes from the tap, after filtration by a point-of-use device, or use of bottled water) and filtering efficiency (Wright et al., 2006). It is possible, by making assumptions about the nature of the measurement errors, to conduct sensitivity analyses to predict the likely direction of bias in the epidemiological dose-response estimates (VanderWeele and Hernán, 2012; Wright and Bateson, 2005), and sometimes under stronger assumptions about the magnitude and structure of measurement errors to account for at least some of the error in statistical analysis using "errors-in-variables" methods such as regression calibration (Bateson & Wright, 2010). However, higher quality exposure data (e.g., water

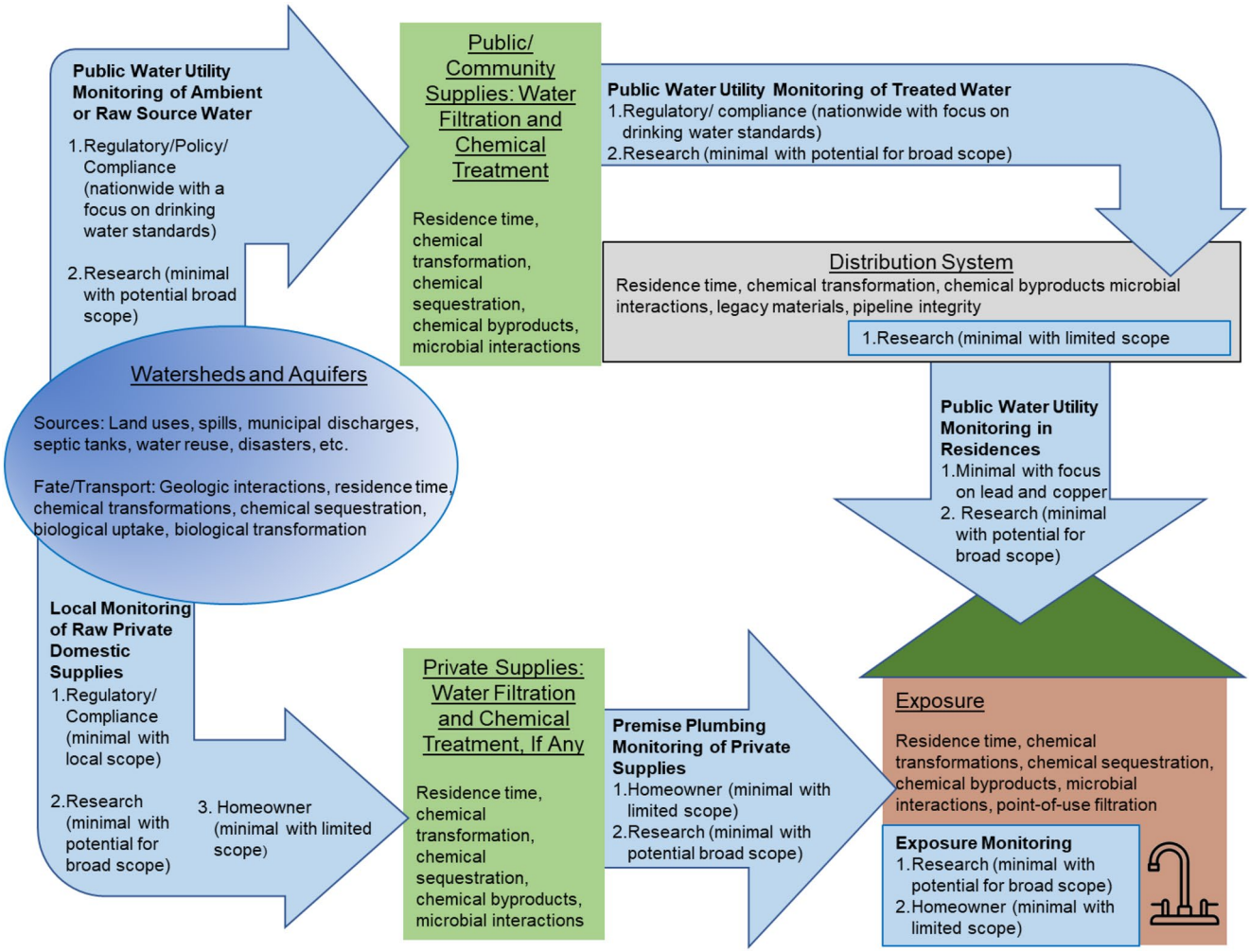

Figure 8. Natural and human-influences factors that control exposure to contaminant mixtures at the tap and monitoring considerations. Locations of sample collections within the drinking water distribution system (watersheds and aquifers, public and private supplies, the distribution system and point of exposure) and the targeted analytes/parameters are listed. Light blue arrows list current compliance and research monitoring by governments, utilities, academia, and homeowners.

quality data more proximate to the end-user tap) would allow firmer epidemiological conclusions than studies relying on limited-quality exposure data and modeling assumptions.

5.4. Instrumental Variables Analysis of Environmental Data

Spatially aggregated data on tap water contaminants can be regarded as measuring a key driver of the exposures experienced by persons, as opposed to the actual exposures encountered by individuals, and therefore analyzed using instrumental variable methods (Arellano & Bover, 1995; Baiocchi et al., 2014; Hernán & Robins, 2006; Imbens & Angrist, 1994). Treating the drinking water contaminant data as an instrumental variable predicting chemical exposure, rather than as a direct measure of chemical exposure, avoids some of the potential effect of disease-related biology on the exposure metric (Currie et al., 2013). However, to provide valid estimates, this approach requires that the drinking water supply contaminants only influence health through the actual encountered water contaminant exposures resulting from that water supply. This is often reasonable, but in contexts such as Flint, Michigan, where well-publicized contamination may have psychological implications distinct from the chemical exposures (Cuthbertson et al., 2016; Fortenberry et al., 2018), it is likely that mechanisms other than drinking water contaminant toxicity may connect the instrument of exposure (e.g., contaminant measures reported in the regional water supplies) to the health outcomes. For example, some effects might be driven by concerns about perceived water quality (Kruger et al., 2017). In contrast, a biomarker-based or household water

chemistry-based health effects study may be able to distinguish chemical toxicity from negative perceptions by modeling these jointly as predictors in a multivariable model.

5.5. Integrative Modeling of Biomarker and Environmental Data

It is possible to integrate biomarker measures and environmental measures, such as via explicit modeling of contaminant intake and flow of contaminants within the body (Bois et al., 1996; Johnson et al., 2005; Shin et al., 2011). These hybrid approaches leveraging multiple data streams can potentially increase precision in the estimated exposure experienced by a person at the time of toxicity in the organ of toxicity, but may be limited by uncertainties in the actual chemical intakes and in the parameters of the model used to describe how contaminants behave within the body (Avanasi et al., 2016b).

5.6. Opportunities for Collaborative Knowledge Generation

Federally funded monitoring and modeling programs can help contribute toward national-scale data sets of modeled and empirical chemical exposures that can be leveraged for future epidemiological studies and risk assessments. Figure 8 shows the types of research and investigators at each of the steps drinking water travels through from source to tap. U.S. Geological Survey (USGS) and USEPA scientists have begun nationally consistent characterization of the quality of United States streams and aquifers (Bexfield et al., 2019; Bradley et al., 2017; USEPA, 2020), drinking water sources (Glassmeyer et al., 2017), and tap water data sets (Bradley et al., 2017, 2020, 2021a, 2021b) collected using standardized protocols that can further contribute to epidemiological knowledge.

6. Natural and Human-Caused Events That Affect Water Quantity Can Also Degrade Water Quality: What Does the Future Hold for CEC Exposure?

It is unlikely that the current status quo for water resources will remain the same on a global or local scale in the decades ahead. Factors such as population growth and distribution and frequency of severe weather events (i.e., floods, droughts) likely will affect both the quantity and quality of available potable water. Somewhat paradoxically, these quantity and quality concerns may occur both in locations that experience an insufficient amount of water as well as those locations with an excess (Figure 1). Access to water has always been one of the main drivers of civilization (Cassardo & Jones, 2011). It is not a coincidence that many of the earliest communities were settled in locations along rivers as a means of transportation as well as sources of drinking water. As civilizations evolved and populations increased, however, so did our need for access to larger quantities of water that were potable. Consequently, access to water supplies is limited by the quality of the supply. As we have demonstrated above, our definition of the "quality" of a water supply has evolved with policy as well as our ability to detect ever lower levels of contaminants that might be present. Contaminant science therefore would need to be used carefully as these definitions alone could shrink access to water supplies. How that limitation is protective of public health while being economically and logistically feasible remains to be seen.

Regardless of definitions, other anthropogenic and natural events such as groundwater mining, droughts, and floods can have secondary effects on the quality of water as contaminants are mobilized, concentrated, or introduced into our watersheds and aquifers. For example, unsustainable water consumption (Duran-Llacer et al., 2020; Knappett et al., 2020; Rad et al., 2020; Salmoral et al., 2020; Yu et al., 2020) and droughts affect not only the quantity of water (Rodell et al., 2018), but also the quality, as nutrients and other contaminants become concentrated, thus increasing the potential for algal blooms (Khan et al., 2015; Whitehead et al., 2009), which in turn can deplete oxygen levels in water bodies, release algal toxins, and have other cascading effects on water chemistry. Such over-extraction of water creates "subsidence," causing the aquifers to compress like a gigantic empty water bottle. Once such subsidence occurs, the aquifer's ability to store water is permanently reduced. Even with mitigation practices to try to reverse the effects, the aquifers cannot be "re-inflated" due to the compaction/compression of the aquifer materials. The tandem increase in the global population and increase in frequency and intensity of droughts is translating to aquifer subsidence becoming a global concern. Within the next 20 years, an estimated 1.6 billion people could be affected by aquifer subsidence causing economic losses in the trillions of dollars (Herrera-García et al., 2021). In contrast to subsidence, an additional climate change issue for areas along

shorelines is rising groundwater levels. Such a rise in groundwater causes problems such as road deterioration, sewage backups, earthquake liquefaction zones, and remobilization of legacy toxic contaminants. These and other secondary effects can degrade water quality and thereby limit water supplies. This highlights the cornerstone role water contaminant science plays in helping manage and maintain access to drinking water supplies. Water scarcity has implications not only for the consumption of water for domestic purposes, but also for industrial and agricultural uses. Current global estimates find 70% of water used is for agricultural purposes, 19% is for industrial, and 11% is for domestic uses, including both consumption and hygiene (FAO, 2011). In agriculture, water not only is required to produce the crops, but also to protect the health of the soil (Cano et al., 2018). Poor soil health leads to erosion, which decreases the potential for crop productivity (Pimentel et al., 2010). It is important to note that the increased globalization in the sale of agricultural goods can result in the end user of the product being on the opposite side of the globe from the location the crop was produced (Konar et al., 2016). Thus, even locations with sufficient water supply for domestic, industrial, and local agricultural purposes may be severely affected by droughts in areas from which agricultural goods are produced, especially when the quality of that water is a factor.

Climate-driven temperature and rainfall changes can affect water quality even after treatment. The drinking water and wastewater distribution systems in most communities are installed underground. Depending on the composition and age of the pipes, these materials may fail more frequently in either hotter or colder than average temperatures (Laucelli et al., 2013; Wols & van Thienen, 2014), as well as to a lesser degree in drought conditions (Wols & van Thienen, 2014) due to contracting and shifting soils. When the wastewater lines are breached, untreated sewage can leak into the subsurface (Baah et al., 2015) and surface waters (Fork et al., 2021). When drinking water lines rupture, pathogens and chemicals can enter and surreptitiously contaminate the previously treated water (Gibson et al., 2019; LeChevallier et al., 2003).

Droughts can cause additional effects to water quantity and quality through wildfires (Hallema et al., 2018). Wildfires frequency and magnitude have been increasing in recent years (A. P. Williams et al., 2019). Forests can capture atmospheric contaminants (Simonich & Hites, 1995). Upon burning, these contaminants, as well as large stores of organic carbon, are released (Khan et al., 2015). Fighting these fires requires the use of flame retardants, which can further contaminate soil and water (Kalabokidis, 2000). The post-fire lack of vegetation can increase runoff and erosion (Robinne et al., 2018), decrease surface water quality, limit groundwater infiltration, and degrade water quantity (Hallema et al., 2018). Deforestation not due to wildfires has a similar negative effect on water quality and quantity (Emelko et al., 2011).

When water quality/quantity decreases, a community either needs to use less water or find additional, potentially non-optimal, sources of water. Both strategies have deleterious outcomes. For water restrictions, the risks can be both economic (Borgomeo et al., 2018) and health based. Decreased water usage increases the residence time of treated water in the distribution system. This increased time can lead to decreased chlorine residuals, potentially increasing the risk of pathogens (Khan et al., 2015). Recently, the COVID-19 pandemic and resulting shutdown of offices, businesses, and other places where multiple people normally assemble each day has caused drinking water supplies to remain stagnant in premise plumbing for weeks or months. As buildings reopen and as people return, these locations are being advised to flush their pipes (Proctor et al., 2020). This unanticipated event is causing precautionary measures to remove microbes or other contaminants that may now be present due to the increased residence time of water in such systems.

The alternative to restrictions is finding additional sources of water. Direct potable reuse uses highly treated wastewater as the source of drinking water (Lahnsteiner et al., 2017). Nevertheless, both chemical and microbial CECs in the reused wastewater have the potential to be in the finished drinking water (Khan et al., 2015). Most drinking water for direct potable reuse is produced by reverse osmosis as a means of limiting the contaminants present (see Section 4.2; Lahnsteiner et al., 2017). Reverse osmosis, however, creates a brine that is concentrated with contaminants that were removed from the corresponding source water. The disposal of this contaminated brine may then become a potential problem, especially for inland areas. In addition, the public perception of direct potable reuse, specifically the wastewater-derived water source, can limit implementation. Even with conventional water sources in the United States, there is a general distrust in drinking water quality among a small percentage of the population (Javidi & Pierce, 2018; Pierce & Gonzalez, 2016). Public perception of direct potable reuse is even less favorable (van Rensburg, 2016).

Desalination is another viable option available in coastal regions to provide additional potable water. Desalination has two substantial impediments that prevent widespread implementation: energy usage and brine production. Solar, wind, and geothermal sources can be used to either directly desalinate water or as the energy source for more conventionally designed plants (Manju & Sagar, 2017). As previously mentioned (Section 1.3.7), nanomaterials may also help improve desalination techniques (Teow & Mohammad, 2019). The brines generated during desalination (as well as those produced during direct potable reuse) can be disposed of in several ways, each have limiting costs or environmental disadvantages. Common disposal methods are discharge to surface water, land application, discharge to wastewater treatment plants, deep well injection, and evaporation ponds (Younos, 2005). Land application of brines can contaminate groundwater, further exacerbating water quantity difficulties (Mohamed et al., 2005).

When challenged by too much water, rather than too little, different problems can arise, both in the production of safe drinking water and the treatment of wastewater. Flooding, both inland due to excessive rainfall and/or snowmelt and on the coast during storm surges, can greatly affect both surface and subsurface water quality. Concentrations of both chemicals and microorganisms have been found to be higher in locations after floods (Arnade, 1999; Yard et al., 2014). Groundwater wells that are inundated during floods are equally susceptible to contamination as surface waters (Andrade et al., 2018), particularly those wells under the direct influence of surface water. While municipal drinking water treatment plants regularly monitor and implement additional treatment to reduce these flood-borne contaminants, private well owners have sole responsibility for disinfecting their systems (Stone, 2005). Storm events may not only result in flooding but also power outages. Municipal water production may be taken offline if the outages are long lived. Coastal locations have additional threats to groundwater wells due to saltwater intrusion from storms or rising sea levels. Desalination, with the associated brine and energy drawbacks, may be required to treat water that previously did not require treatment.

Wastewater treatment plants can also be affected by increased water levels. An estimated 60 existing WWTPs in the United States would be flooded during a 1-foot storm surges event (Hummel et al., 2018); many more inland cities may be affected by 100- or 500-year storm events (Kessler, 2011). As populations continue to grow, the number of people in coastal flooding zones is expected to double (Hauer et al., 2016). Combined sewer overflows may become a greater concern for WWTPs in the future due to spring snowmelt or summer storms because of their potential to release untreated sewage (Jalliffier-Verne et al., 2015). Updates and or upgrades to infrastructure to reduce these overflows is another economic cost to treatment.

Wastewater and drinking water treatment plant operators and local governments both may have challenges in the future due to too much or too little water, as shown in Figure 9 (Raseman et al., 2017). Balancing available (and variable) water volumes, infrastructure and energy costs, and potential health risks goes beyond the treatment plants themselves and often affects other local industries, such as agriculture and tourism (C. M. Brown et al., 2015; Jiricka-Pürrer & Wachter, 2019). Management priorities to accommodate such issues could include both increasing supplies and decreasing demands (Garnier & Holman, 2019).

Communication with stakeholders to determine the most effective science needed to develop strategies to solve these water surplus and deficit issues is vital (Harris-Lovett et al., 2018). For example, communities can perform hypothetical scenario exercises to explore potential regional issues (Deere et al., 2017), which in turn can lead to defining the underlying science gaps. When experts from a variety of fields are consulted, risks that are obvious and those that are less conspicuous can be planned for (Boholm & Prutzer, 2017). It should be noted that terrestrial and aquatic habitat threats can be simultaneously factored into such drinking water studies (Vörösmarty et al., 2010). Failure to adequately address the science can have both public health and political implications (Kreamer, 2012). Such issues can start as localized issues, such as the dispute between Tennessee and Georgia over the Tennessee River (Jett, 2019). Without the science to inform best management practices regarding the quantity/quality of water needed for consumption and food production, these conflicts may continue to escalate.

7. Concluding Thoughts

Humans realized long ago that the water can affect health. As civilizations progressed, scientists and engineers showed how drinking water could be treated to protect the public from acute diseases by chemical disinfection. Then science shined a light on the potential linkages between chronic diseases and contaminants in drinking water. In turn that led to an expanded scope of contaminants that could be deleterious to public health, requir-

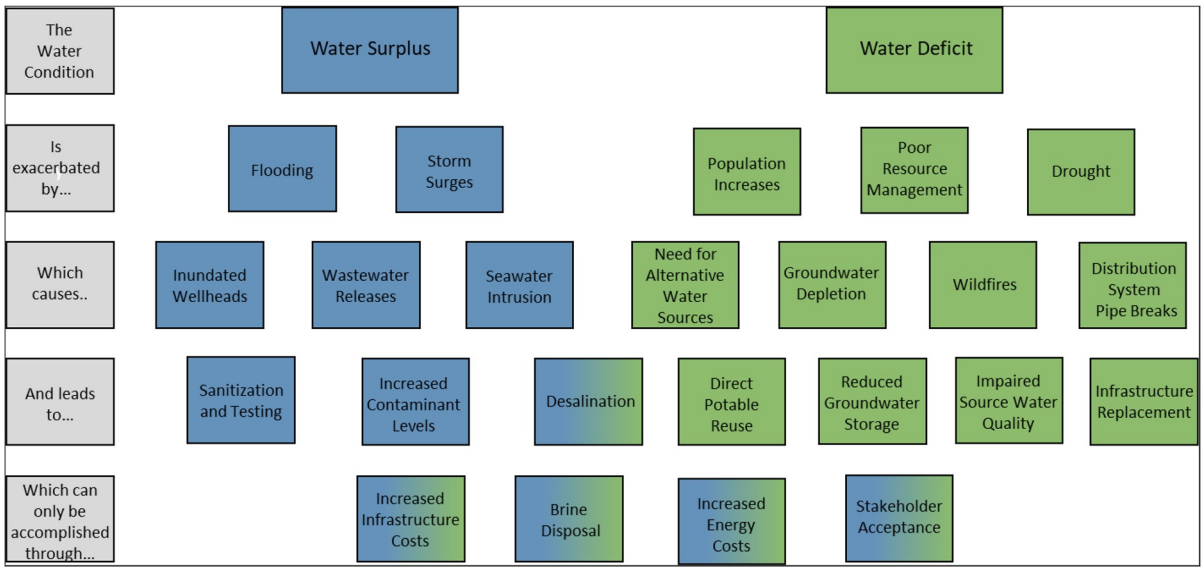

Figure 9. Predicted future key events and responses stemming from water surpluses or deficits.

ing an expansion in treatment technologies utilized and compliance monitoring. It was also demonstrated that contaminants can enter our watersheds and aquifers and how natural and human-caused events can degrade the quality of drinking water resources. Thus, protecting drinking water at the source or "source-water protection" became an integral part of water utility planning and management. Each of these milestones in water management began with increases in fundamental understandings. This knowledge helped focus cost effective water resource management on protecting public health.

Although we will soon be entering the fourth decade of research using the label CEC, it is important to remember that the use of the word "emerging" is a moving target. Concerns will continue to "emerge" when it comes to contaminants and there is no finite set of CECs today, tomorrow, or yesterday. And "concerns" will be subjective unless backed by scientific evidence that accurately depicts a hazard or a risk. Further, concerns would need to be contextualized in terms of whether they are institutional, policy-driven, regulatory, personal, or scientific. The science and tools used to put the term "CECs" in useful context warrants flexibility, innovations, integration of scientific and engineering disciplines, and the ability to prioritize scarce research dollars.

Improvements in instrumentation and analytical techniques have made it possible to detect the presence and persistence of these chemicals and microorganisms at low environmental concentrations. However, conventional analyte-by-analyte detection approaches are being augmented by non-targeted analyses and other screening methods. Thus, bioassays provide additional context and relevance to monitoring the broader range of chemical and biologically active components and mixtures found in our drinking water. Wastewater and drinking water treatment also continue to improve and although conventional treatment and advanced technologies can remove or inactivate most chemicals and pathogens, it remains elusive and challenging to do so for many reasons, including cost. Improvements in toxicology and epidemiology have helped us understand a range of health effects that can be caused by drinking water exposures to individual contaminants. It remains to be seen if high-throughput screening, tissues-on-a-chip, and other technologies currently being used and developed by the pharmaceutical and other industries can be adapted for drinking water uses. With increases in databases related to public health, there is an opportunity to contribute to multi-institutional data sources focused on drinking water exposures. Once established, these data sources could one day lead to models, pattern recognition, and other advanced software and artificial intelligence applications that could be used to find linkages, if they exist, between drinking water exposures and adverse health outcomes.

"Water, water everywhere but every drop unique" is poetic but can be interpreted literally as well. As used here, the phrase acknowledges each drop's unique characteristics that can lead to it being a potential source of contaminant exposure. Science will be relied on to unpack those unique characteristics in meaningful ways. Short-term successes can come through conventional and piecewise scientific channels. Longer-term, aspirational success

at reducing CEC exposure would depend on much. Natural sciences and engineering, that is, both investigative and the applied sciences, would need to be fully integrated. New and emerging transdisciplinary research would need to address gaps in our scientific knowledge. Emerging technologies would need to tackle advanced water monitoring and biomonitoring. And forward-thinking policies would need to be developed to protect source water and to enhance treatment infrastructure. With the right scientific evidence to determine if a contaminant is "of concern" or not, the future of watershed and aquifer management, how water is recycled, treated, and conveyed, as well as how it is handled at the point of use may bear little resemblance to today's practices.

Acronyms

AFFF	aqueous film-forming foam
AMR	antimicrobial resistance
AO	adverse outcome
AR	androgen receptor
ARB	antimicrobial resistance bacteria
ARG	antimicrobial resistance genes
BioEqs	biological equivalents
CCL	contaminant candidate list
CECs	contaminants of emerging concern
DBP	disinfection byproduct
EBTs	effect-based trigger values
EC	emerging contaminant
EC50	half maximal effective concentration
EDA	effect-directed analysis
EDCs	endocrine-disrupting chemicals
GC	gas chromatography
GC/ToF-MS	gas chromatography time-of-flight mass spectrometer
HABs	harmful algal blooms
HRMS	high-resolution mass spectrometer
K_{aw}	log air/water partition coefficient
K_{oa}	log octanol/air partition coefficient
K_{ow}	log octanol/water partition coefficient
L	liter
LC	liquid chromatography
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MFM	multimedia fate model
MIE	molecular initiating event
MONA	MassBank of North America
MS	mass spectrometer
NDMA	*n*-nitrosodimethylamine
NGS	next-generation sequencing
NTA	nontarget analysis
NTS	nontarget screening
OECD	Organization for Economic Co-operation and Development
OECD	Organization for Economic Co-operation and Development
OWC	organic wastewater contaminant
PA	polyamide
PAH	polycyclic aromatic hydrocarbon
PCB	polychlorinated biphenyl
PCR	polymerase chain reaction
PE	polyethylene
PEC	predicted environmental concentration
PET	polyethylene terephthalate

PFAS	per- and polyfluoroalkyl substances
PFBS	perfluorobutane sulfonate
PFOA	perfluorooctanoic acid
PFOS	perfluoroctane sulfonate
POCIS	polar organic chemical integrative sampler
PP	polypropylene
PS	polystyrene
PUR	polyurethane
PVC	polyvinyl chloride
qPCR	quantitative polymerase chain reaction
QMRA	quantitative microbial risk assessment
QSAR	quantitative structure-activity relationships
QToF-MS	quadrupole-time of flight mass spectrometer
RT-qPCR	Reverse-transcription qPCR
SDWA	Safe Drinking Water Act
SOP	standard operation procedure
TCEP	tris (2-chloroethyl) phosphate
TCPP	tris (1-chloro-2-propyl) phosphate
TPs	transformation products
TrOCs	trace organic chemicals
UCMR	unregulated contaminant monitoring rule
USEPA	U.S. Environmental Protection Agency
USGS	U.S. Geological Survey
UV	ultraviolet
WHO	World Health Organization
WWTP	wastewater treatment plant

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Conflict of Interest

The authors declare no conflicts of interest relevant to this study.

Data Availability Statement

This manuscript contains no primary environmental data. The secondary evaluations of literature used to construct Figures 2–5 can be found in Glassmeyer et al. (2023).

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