Anal. Chem. **2005,** *77,* 3807−3838

Water Analysis: Emerging Contaminants and Current Issues

Susan D. Richardson*,† and Thomas A. Ternes‡

National Exposure Research Laboratory, U.S. Environmental Protection Agency, Athens, Georgia 30605, and Federal Institute of Hydrology, Koblenz, D-56068 Germany

Review Contents

This biennial review covers developments in water analysis over the period of 2003−2004. A few significant references that appeared between January and February 2005 are also included. *Analytical Chemistry*'s current policy is to limit reviews to include 100−200 significant references and to mainly focus on new trends. As a result, as was done in the previous 2003 water analysis review (*1*), this 2005 review will limit its focus to new, emerging contaminants and environmental issues that are driving most of the current research. Even with a more narrow focus, only a small fraction of the quality research publications could be discussed. Thus, this review will not be comprehensive, but will highlight new areas and discuss representative papers in the areas of focus. We would welcome any comments you have, in particular regarding this more narrow focus—whether you find it more (or less) useful than a broader approach (richardson.susan@epa.gov).

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

The overall trends in analytical methods for water analysis include an increased use of solid-phase microextraction (SPME), the use of newly developed solid-phase extraction (SPE) sorbents for improved extraction, and an increased use of other reduced solvent extraction methods, such as the recently developed single-drop microextraction (SDME) method and stir bar sorptive extraction method. SDME involves the suspension a small drop of extraction solvent directly from the tip of a microsyringe into the vial containing the water sample, where the target analyte is extracted into the drop, and the drop is retracted back into the needle and injected directly into the injection port of a gas chromatograph. Examples of this presented in this review include the analysis of methyl-*tert*-butyl ether (MTBE) and chemical warfare agents. Stir bar sorptive extraction involves the use of a sorbent-coated stir bar, which is stirred in the aqueous sample to extract the analyte of interest. The analyte is then thermally desorbed and analyzed by gas chromatography (GC)/mass spectrometry (MS). Examples of this presented in this review include the analysis of phenolic xenoestrogens and organotins. New derivatization methods continue to be developed, including the development of fluorinated chloroformate derivatizing agents to enable the GC/MS identification of highly polar polyalcohol, amine, and carboxylic acid disinfection byproducts in drinking water. There also seems to be an increase in the use of in situ derivatization for the GC/MS analysis of aqueous samples. The fluorinated chloroformate derivatization is an example of this, along with the use of in situ acetylation, which is also presented in this review.

For detection methods, the use of liquid chromatography (LC)/MS has now become common place for analyzing many emerging contaminants, including pharmaceuticals, hormones, and endocrine disrupting compounds (EDCs), in aqueous environmental samples. The use of LC/MS allows the identification of highly polar organic pollutants without derivatization, down to nanogram per liter levels in aqueous samples, including surface water, wastewater, groundwater, and drinking water. To gain enhanced selectivity and sensitivity, tandem-MS is increasingly being used with LC/MS for the measurement of environmental contaminants in water. Drawbacks of LC/MS include matrix effects (e.g., ion suppression, which can vary with varying environmental matrix composition) and difficulty in separating highly polar analytes in the aqueous LC eluent. Increasingly, researchers are developing techniques to overcome these drawbacks—for example, through the use of deuterated or ^{13}C-labeled internal standards to overcome matrix effects, and the use of ion-pair reagents or hydrophilic interaction chromatography (HILIC) to allow highly polar analytes to elute away from the LC solvent front.

† U.S. Environmental Protection Agency.
‡ Federal Institute of Hydrology.

10.1021/ac058022x CCC: $30.25
Published on Web 05/11/2005

Table 1. List of Acronyms

AAS	atomic absorption spectrometry
APCI	atmospheric pressure chemical ionization
APEOs	alkylphenolethoxylates
APPI	atmospheric pressure photoionization
BMX	brominated forms of MX
BP-3	benzophenone-3
CCL	Contaminant Candidate List
CDC	Centers for Disease Control and Prevention
CE	capillary electrophoresis
CI	chemical ionization
DAD	diode array detection
DBPs	disinfection byproducts
DIPE	di-isopropyl ether
DNPH	2,4-dinitrophenylhydrazine
E1	estrone
E2	17β-estradiol
E3	estriol
EE2	17α-ethinylestradiol
ECNI	electron capture negative ionization
EDCs	endocrine disrupting compounds
EHMC	ethylhexyl methoxycinnamate
ELISA	enzyme-linked immunosorbent assay
EPA	Environmental Protection Agency
ESA	ethane sulfonic acid
ESI	electrospray ionization
ETBE	ethyl-*tert*-butyl ether
FAIMS	high-field asymmetric waveform ion mobility spectrometry
FID	flame ionization detection
FOSA	perfluorooctanesulfonylamide
FT	Fourier transform
GAC	granular activated carbon
GC	gas chromatography
HAAs	haloacetic acids
HILIC	hydrophilic interaction chromatography
IC	ion chromatography
ICP	inductively coupled plasma
ICR	ion cyclotron resonance
LC	liquid chromatography
LOD	limit of detection
LPME	liquid-phase microextraction
LT2ESWTR	Long Term 2 Enhanced Surface Water Treatment Rule
MALDI	matrix-assisted laser desorption ionization
4-MBC	4-methylbenzylidene camphor
MCL	maximum contaminant level
MDL	method detection limit
MRM	multiple reaction monitoring
MS	mass spectrometry
MSTFA	*N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide
MTBE	methyl *tert*-butyl ether
MTBSTFA	*N*-(*tert*-butyldimethylsilyl)-*N*-methyltrifluoroacetamide
MX	3-chloro-(4-dichloromethyl)−5-hydroxy-2(5*H*)-furanone
NDMA	nitrosodimethylamine
NMR	nuclear magnetic resonance
NOM	natural organic matter
OA	oxanilic acid
OC	octocrylene
ODPABA	octyl-dimethyl-*p*-aminobenzoic acid
PCBs	polychlorinated biphenyls
PBDEs	polybrominated diphenyl ethers
PFC	perfluorinated chemical
PFBS	perfluorobutanesulfonate
PFHS	perfluorohexanesulfonate
PFNA	perfluorononanoic acid
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonate
PFOSA	perfluorooctane sulfonamide
SDME	single drop microextraction
SPE	solid-phase extraction
SPMDs	semipermeable membrane devices
SPME	solid-phase microextraction
SSI	sonic spray ionization
TAME	*tert*-amyl methyl ether
TBA	*tert*-butyl alcohol
THMs	trihalomethanes
TOF	time-of-flight
TOX	total organic halide
UCMR	Unregulated Contaminants Monitoring Rule
VOCs	volatile organic compounds

Table 2. Useful Websites

website	comments
www.epa.gov	U.S. EPA's Web site; provides a searchable link to U.S. EPA regulations and methods
www.epa.gov/safewater/methods/methods.html	link to U.S. EPA and non-EPA drinking water methods
www.epa.gov/safewater/methods/sourcalt.html	methods developed by U.S. EPA's Office of Ground Water and Drinking Water
www.epa.gov/safewater/data/ncod.html	U.S. National Contaminant Occurrence Database
www.epa.gov/safewater/dwinfo/index.html	local drinking water quality reports (U. S.)
www.gpoaccess.gov/fr/index.html	direct link to the Federal Register
www.chbr.noaa.gov/CoastalResearch/algaeInfo.htm	NOAA's Web site for algal toxin information
www.dhs.ca.gov/ps/ddwem/chemicals/NDMA/NDMAindex.htm	California Department of Health Services site for NDMA information
www.epa.gov/safewater/mtbe.html	U.S. EPA webpage for MTBE information
http://wwwsd.cr.usgs.gov/nawqa/vocns/nat_survey.html	U.S. MTBE occurrence study
www.epa.gov/ncerqa/grants	U.S. EPA's STAR Grants solicitations

The use of LC/electrospray ionization (ESI)-MS, LC/inductively coupled plasma (ICP)-MS, and ion chromatography (IC)/ICPMS has also increased for the analysis of inorganic contaminants, including arsenic species. In addition, new enzyme-linked immunosorbent assays (ELISAs) continue to be developed for aqueous contaminants, which allow a rapid and inexpensive method for many analytes. There continues to be an increase in chiral separations (usually with chiral GC columns). As new methods are developed, detection limits are being pushed lower and lower—several examples included in this review give detection limits of subnanogram per liter, and some even at picogram per liter levels. The use of matrix-assisted laser desorption/ionization (MALDI)-MS and ESI-MS has also increased for the analysis of microorganisms. MALDI- and ESI-MS are also increasingly being used to probe the structures of high molecular weight natural organic matter (i.e., humic materials), and the use of high-resolution Fourier transform (FT)-ion cyclotron resonance (ICR)-MS and MS/MS is providing empirical formula information for natural organic matter, which is leading to early structural information.

Six new categories of emerging contaminants are added to the water analysis review this year: perfluorooctanoic acid (PFOA)/

perfluorooctanesulfonate (PFOS), polybrominated diphenyl ether (PBDE) flame retardants, sunscreens/UV filters, contaminant disinfection byproducts, pesticide degradation products, and chemical warfare agents. PFOA and PFOS are widely used to make products, such as soil, stain, grease, and water-resistant coatings, and concern stems from their widespread global distribution in the blood of the general population and in wildlife, including remote locations in the Arctic and North Pacific Oceans. PBDEs are widely used as flame retardants in products, such as furniture, textiles (including children's clothing), plastics, paints, and electronic appliances, and they have been found to be environmentally persistent, having been found in human milk, human blood, and wildlife. Most previous PBDE studies have focused on the measurement of PBDEs in biological samples; however, because there are increasing measurements in environmental waters, PBDEs are included in this water analysis review for the first time. UV filters are widely used in products, such as sunscreens, cosmetics, beauty creams, skin lotions, hair sprays, hair dyes, and shampoos, and their analysis in environmental waters has increased substantially the last two years, so this new category of emerging contaminant is included in this review for the first time. While drinking water disinfection byproducts (DBPs) have been an issue for several years (and new emerging DBPs have recently become important), reaction products of contaminants (such as pesticides, antibacterial agents, estrogens, alkylphenol ethoxylates, cyanobacterial toxins, and bisphenol A) with disinfectants such as chlorine or ozone are now being investigated. Pesticide degradation products have also seen an increase in interest, since these degradation products (often hydrolysis products) can be present at greater levels in the environment than the parent pesticide itself. Finally, investigations on chemical warfare agents have increased over the last two years. This is likely due to a combination of the September 11, 2001 events and the 1997 Chemical Weapons Convention, which requires verification for the reduction of chemical weapons. While there has been a steady interest in this area for many years due to military and environmental issues, interest in this area has seen new growth.

Other areas covered in this review again include pharmaceuticals, hormones, EDCs, DBPs, algal toxins, perchlorate, MTBE, organotins, arsenic, chiral contaminants, natural organic matter, and microorganisms. These continue to be intense areas of research. Finally, new regulations and regulatory methods are again included in this review. Several new U.S. regulations are being promulgated for drinking water, and several new regulatory methods have been published in the last two years, covering contaminants, such as nitrosodimethylamine (NDMA) and other nitrosamines, perchlorate, organotins, bromate, chlorite, haloacetic acids, pesticides and their degradation products, and brominated flame retardants. The second drinking water Contaminant Candidate List (CCL) has also recently been adopted, and it will be discussed.

GENERAL REVIEWS

This section includes general reviews relating to water analysis. Reviews that relate to specific areas (e.g., pharmaceuticals, chiral compounds, or microorganisms) can be found in those specific sections. Many reviews have been published over the last two years that relate to water analysis, and several of these focus specifically on emerging contaminants. The previous water analysis review published in 2003 contained 193 references and discussed advances in research for new regulations and regulatory methods for water and emerging contaminants, including, drinking water DBPs, pharmaceuticals, hormones, endocrine disruptors, chiral contaminants, MTBE, algal toxins, organotins, perchlorate, arsenic, natural organic matter, and microorganisms (*1*).

A special issue of *Trends in Analytical Chemistry* published in 2003 focused specifically on emerging pollutants in water Analysis and included such topics as emerging DBPs in drinking water, analysis and removal of emerging contaminants in wastewater and drinking water, determination of endocrine disruptors, contaminants in paper mill effluents and industrial waste landfills and effluents, MTBE, and LC/time-of-flight (TOF)/MS methods for emerging contaminants (*2*). Emerging contaminants were also the focus of two recent books. The first, *Emerging Organic Pollutants in Wastewaters and Sludge*, includes discussions about pharmaceuticals, surfactants, estrogenic compounds, and methods for emerging industrial pollutants (*3*). The second, *Liquid Chromatography/Mass Spectrometry, MS/MS, and Time-of-Flight Mass Spectrometry: Analysis of Emerging Contaminants*, focuses mostly on the use of LC/MS and LC/MS/MS for emerging contaminants and resulted from an American Chemical Society symposium held in 2002 (*4*). The book details how the advent of LC/MS has had a major impact on the identification of new environmental contaminants, including pharmaceuticals, pesticide degradates, and surfactants. A chapter in this book written by Thurman and Ferrer discusses the type of structural information that can be obtained for emerging contaminants using quadrupole-TOF, triple quadrupole, and ion trap MS/MS (*5*).

Several review articles also focus on the use of LC/MS and LC/MS/MS for measuring and identifying emerging contaminants. A review by Lopez de Alda et al. reviewed LC/MS and LC/MS/MS methods for determining alkylphenol ethoxylate surfactants, steroid sex hormones, and pharmaceuticals in environmental waters (*6*). Zwiener and Frimmel published a two-part review on LC/MS analysis in the aquatic environment and in water treatment. The first part covered instrumentation and general aspects of analysis and detection (*7*). This review discussed the current status and future perspectives of mass analyzers, ionization techniques to interface LC with MS, and methods for preconcentration and separation for water analysis (which includes a discussion of SPE with different sorbents, reversed-phase (RP)-LC, and on-line and miniaturized sample extraction and introduction approaches). Issues of compound identification, matrix effects, development of MS libraries, and linking analysis with toxicity bioassays are also addressed. The second part covered applications of LC/MS for emerging contaminants and related pollutants, microorganisms, and humic acids (*8*). Reemtsma reviewed LC/MS strategies for trace-level analysis of polar organic pollutants (*9*). This review discusses the selection of appropriate LC conditions and the most sensitive ionization mode for various polar analytes.

Petrovic et al. published an overview of toxicity identification and evaluation procedures used for effect-based analysis of EDCs. This review also includes a discussion of trends in chemical analysis and an overview of concentrations of EDCs and other

Table 3. New U.S. Regulations

rule/regulation	website
Stage 2 D/DBP Rule	www.epa.gov/safewater/stage2/index.html
LT2ESWTR	www.epa.gov/safewater/lt2/redirect.html
Groundwater Rule	www.epa.gov/safewater/gwr.html
Arsenic Rule	www.epa.gov/safewater/arsenic.html
Radon Rule	www.epa.gov/safewater/radon/proposal.html
Contaminant Candidate List (CCL)	www.epa.gov/safewater/ccl/cclfs.html

Table 4. New Regulatory Methods

method	analytes	website
EPA Method 552.3	haloacetic acids (9 chloro/bromoacetic acids) and dalapon	www.epa.gov/safewater/methods/sourcalt.html
EPA Method 300.1	bromate, chlorite, chlorate, bromide, chloride, fluoride, nitrite, nitrate, ortho-phosphate-P, sulfate	www.epa.gov/safewater/methods/sourcalt.html
EPA Method 521	NDMA and 6 other nitrosamines	www.epa.gov/nerlcwww/m_521.pdf
EPA Method 330.0	perchlorate (LC/ESI-MS)	www.epa.gov/nerlcwww/ordmeth.htm
EPA Method 331.0	perchlorate (LC/ESI-MS/MS)	www.epa.gov/safewater/methods/sourcalt.html
EPA Method 314.1	perchlorate (IC)	www.epa.gov/safewater/methods/sourcalt.html
EPA Method 8323	organotins	http://www.epa.gov/epaoswer/hazwaste/test/new-meth.htm#8323
EPA Method 327.0	chlorite and chlorine dioxide	www.epa.gov/safewater/methods/sourcalt.html
EPA Method 535	chloroacetanilide, other acetamide herbicide degradates	www.epa.gov/nerlcwww/ordmeth.htm
EPA Method 527	brominated flame retardants, pesticides	www.epa.gov/safewater/methods/sourcalt.html
EPA Method 5030C	>100 VOCs (including fuel oxygenates)	www.epa.gov/epaoswer/hazwaste/test/pdfs/5030c.pdf
EPA Method 9015	metal cyanide complexes	www.epa.gov/epaoswer/hazwaste/test/pdfs/9015.pdf

emerging contaminants in environmental samples (*10*). New analysis techniques and elimination of emerging contaminants in wastewater and drinking water was the focus of another review, which included discussions of acidic pharmaceuticals, antibacterial agents, acidic pesticides, and surfactant metabolites (*11*).

Mass spectrometry techniques for emerging contaminants was the focus of another biennial review published in *Analytical Chemistry* in 2004 (*12*). This review (covering the period of 2002−2003) included many of the same emerging contaminants discussed in the present review, but with a focus on mass spectrometry techniques and including environmental matrixes in addition to water (e.g., biological, air, sediment, and water samples). Koester et al. published the biennial *Analytical Chemistry* review on environmental analysis (covering the period of 2001−2002), which included a review of sample collection and extraction methods, separation and detection techniques (including LC/MS and ICPMS), emerging detection techniques (nuclear magnetic resonance spectroscopy (NMR) and MS), and analytes of emerging interest (*13*). This article not only reviews key papers published in those areas, but also gives detailed discussions on the advantages and disadvantages of the analytical techniques, making this article a must-read for analytical chemists desiring the latest developments in environmental analysis. Finally, Rosenberg reviewed the potential of LC/MS for speciation analysis (*14*). In this article, a brief review on the fundamentals of atmospheric pressure ionization techniques is given, followed by a discussion of recent applications, use of ESI-MS for structural elucidation of metal complexes, and characterization and quantitation of small organometallic species.

NEW REGULATIONS/REGULATORY METHODS

New U.S. Regulations. Several developments in new regulations and regulatory methods have taken place in the last two years that impact water analysis. Table 2 includes websites that can be used to obtain additional details on the regulations and regulatory methods. Table 3 lists the new regulations, and Table 4 summarizes the new regulatory methods. An excellent review of new and proposed drinking water regulations was published in 2004 by Pontius (*15*). Included in this review are the scope and status of new regulations, as well as schedules for key regulations that are currently under development by the U.S. EPA. Pontius also edited a book (published in 2003) entitled *Drinking Water Regulation and Health*, which provides a history and summary of drinking water regulations (*16*). This book does an excellent job in explaining these regulations and providing background on why they were developed and how the process works in bringing about a new regulation. Included in this book are sections on the history of drinking water and public health protection, waterborne disease and the history of outbreaks, an explanation of epidemiology and case studies, the toxicological basis for risk assessment, control of drinking water pathogens and DBPs, treatment technologies for regulatory compliance, achieving sustainable water systems, protecting sensitive subpopulations, and water system security. *Drinking Water Regulation and Health* should be considered a must-read for water utilities, consultants, and regulators.

The U.S. EPA also has an excellent website that can be used to obtain details on regulations and regulatory methods: www.epa.gov. This website has a search function to allow easy access to this information, and it has links to the *Federal Register*, where the complete published rules can be obtained. A direct link to the *Federal Register* can also be made with the following address: www.gpoaccess.gov/fr/index.html. Currently, there are primary drinking water regulations for 92 contaminants, including 11 DBPs, 53 organic contaminants, 16 inorganic contaminants, 4

Table 5. DBPs Regulated under the Stage 1 and Stage 2 D/DBP Rules

DBP	MCL (mg/L)
total THMs[a]	0.080
HAAs[b]	0.060
bromate	0.010
chlorite	1.0

[a] Total THMs are the sum of the concentrations of chloroform, bromoform, bromodichloromethane, and dibromochloromethane. [b] The HAAs are the sum of monochloro-, dichloro-, trichloro-, monobromo-, and dibromoacetic acids.

radionuclides, 7 microorganisms, and turbidity. The U.S. EPA has a website where local drinking water quality reports can be obtained (www.epa.gov/safewater/dwinfo/index.html). There is also a National Contaminant Occurrence Database that contains occurrence data for both regulated and unregulated contaminants in public water systems (www.epa.gov/safewater/data/ncod.html), as well as a National Water Quality Assessment Database that contains water quality information at the state and local level (www.epa.gov/305b/2002report).

Three major drinking water rules are to be issued in 2005: the Stage 2 Disinfectants (D)/DBP Rule (in the summer), the Long Term 2 Enhanced Surface Water Treatment Rule (LT2ESWTR) (in the summer), and the Ground Water Rule (expected by the end of the year).

Stage 2 D/DBP Rule. The Stage 2 D/DBP Rule is an extension of the Stage 1 Rule, which took effect on January 1, 2002, for large surface water treatment systems, and lowered permissible levels of trihalomethanes (THMs) to 80 μg/L and regulates five of the haloacetic acids (HAAs), bromate, and chlorite for the first time (www.epa.gov/safewater/stage2/index.html). The Stage 2 D/DBP Rule will maintain the Stage 1 Rule maximum contaminant levels (MCLs) for THMs and HAAs (Table 5) but will require that MCLs be based on locational running annual averages (i.e., *each location* in the distribution system will need to comply on a running annual average basis). The reason for this change is that the running annual averages (used with the Stage 1 D/DBP Rule) permitted some locations within a water distribution system to exceed MCLs, as long as the average of all sampling points did not exceed the MCLs. As a result, consumers served by a particular section of the distribution system could receive water that regularly exceeded the MCLs. The Stage 2 D/DBP Rule is intended to target those higher DBP levels and reduce the variability of exposure for people served by different points in the distribution system. The Stage 2 D/DBP Rule will maintain the MCLs for bromate and chlorite; however, the U.S. EPA plans to review the bromate MCL as part of their 6-year review process (additional details area available at www.epa.gov/safewater/stage2/index.html).

LT2ESWTR Rule. The final LT2ESWTR is an extension of the former Long Term 1 Rule, which was published in January 2002 and strengthened microbial controls for water systems by extending the previous interim ESWTR (which applied only to large water systems) to small systems serving fewer than 10,000 people. The LT2ESWTR will further improve control of microbial pathogens (including specifically *Cryptosporidium*) in drinking water and address risk tradeoffs with disinfection byproducts (additional details are available at www.epa.gov/safewater/lt2/redirect.html).

Ground Water Rule. This rule was initially proposed in 2000 and is expected to be finalized by the end of 2005. This rule will establish a targeted risk-based regulatory strategy for all groundwater systems through a multiple-barrier approach, which includes periodic sanitary surveys of groundwater systems, hydrogeologic assessments to identify wells sensitive to fecal contamination, source water monitoring for systems drawing from sensitive wells without treatment, correction of significant deficiencies and fecal contamination, and compliance monitoring to ensure disinfection treatment is reliably operated when it is used. Additional details can be found at www.epa.gov/safewater/gwr.html.

Arsenic Rule. The Arsenic Rule was issued in 2001, which lowered the arsenic MCL from 50 to 10 μg/L (www.epa.gov/safewater/arsenic.html). This rule became effective February 22, 2002, and drinking water systems must comply with this new standard by January 23, 2006.

Radon Rule. The proposed rule (which was published in 1999 and is expected to be finalized in December 2005) would establish an MCL of 300 pCi/L for radon in water. An alternative MCL (at a higher level of 4000 pCi/L) could also be used if a multimedia mitigation program is put in place to also reduce radon in indoor air. The proposed standards will apply only to community water systems that regularly serve 25 or more people and that use groundwater or mixed ground and surface water. They will not apply to systems that rely on surface water where radon levels are typically very low, and they will not apply to private wells. Radon exposures from drinking water are much less (1−2%) than radon exposures from air; however, radon can be released into the air from tap water, and there is an increased risk of lung cancer associated with this exposure route. Additional information can be found at www.epa.gov/safewater/radon/proposal.html.

Contaminant Candidate List. In 1996, the Safe Drinking Water Act Amendments required the U.S. EPA to publish a CCL every five years to identify potential substances for future regulation. Monitoring data are collected from drinking water utilities to determine whether a contaminant occurs at a frequency and in concentrations to warrant further analysis and research on potential health effects and possible regulation. From the CCL, a minimum of five candidates must be selected to be considered for regulation within a five-year period. The first CCL (CCL1) was published in March 1998 and contained 50 chemical and 10 microbial contaminants. Chemical contaminants included many pesticides (such as triazine and its degradation products), volatile contaminants (such as tetrachloroethane), metals (such as aluminum, boron, manganese, and vanadium), an explosive (RDX), and other chemical contaminants, such as organotins, perchlorate, methyl bromide, MTBE, and algal toxins (the complete CCL1 list can be found in the previous 2003 water analysis review (*1*)). In July 2003, determinations regarding whether to regulate were made for eight chemical contaminants (aldrin, dieldrin, hexachlorobutadiene, manganese, metribuzin, naphthalene, sodium, and sulfate) and one microbial contaminant (*Acanthanmoeba*). The U.S. EPA decided against regulation for these contaminants (www.epa.gov/safewater/ccl/pdfs/reg_determine1/fs_ccl1_regdetermine_july03.pdf); details regard-

Table 6. Second Drinking Water Contaminant Candidate List (CCL2)

chemical contaminants[a]
1,1,2,2-tetrachloroethane
1,2,4-trimethylbenzene
1,1-dichloroethane
1,1-dichloropropene
1,2-diphenylhydrazine
1,3-dichloropropane
1,3-dichloropropene
2,4,6-trichlorophenol
2,2-dichloropropane
2,4-dichlorophenol
2,4-dinitrophenol
2,4-dinitrotoluene
2,6-dinitrotoluene
2-methylphenol (*o*-cresol)
acetochlor
alachlor ESA and other acetanilide pesticide degradation products
aluminum
boron
bromobenzene
DCPA monoacid degradate
DCPA diacid degradate
DDE
diazinon
disulfoton
diuron
EPTC (*s*-ethyl-dipropylthiocarbamate)
fonofos
p-isopropyltoluene (*p*-cymene)
linuron
methyl bromide
methyl *tert*-butyl ether
metolachlor
molinate
nitrobenzene
organotins
perchlorate
prometon
RDX
terbacil
terbufos
triazines and their degradation products (including, but not limited to cyanazine and atrazine-desethyl)
vanadium
microbiological contaminants
adenoviruses
Aeromonas hydrophila
caliciviruses
coxsackieviruses
cyanobacteria (blue-green algae), other freshwater algae, and their toxins
echoviruses
Helicobacter pylori
microsporidia (Enterocytozoon and Septata)
mycobacterium avium intracellulare (MAC)

[a] Note that algal and cyanobacterial (blue-green algae) toxins are listed with microbial contaminants

ing potential health effects and reasons not to regulate them can be found in the review by Pontius (*15*).

The second Contaminant Candidate List (CCL2) was published on February 23, 2005, and preliminary regulatory determinations for this list are expected in August 2005, with final determinations in August 2006. Table 6 lists the CCL2 contaminants, which are the same as the original CCL1 list, except that the contaminants mentioned above (for which regulatory determinations were made) have been removed. A preliminary notice for the third CCL is expected in February 2007. There is particular interest in the timing of future regulatory determinations for other contaminants on the CCL, especially perchlorate and MTBE (*15*). Further details on the CCL can be found at www.epa.gov/safewater/ccl/cclfs.html.

New Regulatory Methods. Several new regulatory methods have been developed over the last two years by the U.S. EPA. Some of these are directed toward the measurement of CCL chemicals in drinking water, some are directed toward the measurement of Unregulated Contaminant Monitoring Rule (UCMR) analytes, and others are directed toward the upcoming Stage 2 D/DBP Rule.

Haloacetic Acids. EPA Method 552 was improved to enable the analysis of all nine chloro/bromo-haloacetic acids (HAA9) (www.epa.gov/safewater/methods/sourcalt.html). The new method, EPA Method 552.3 (Determination of Haloacetic Acids and Dalapon in Drinking Water by Liquid−Liquid Microextraction, Derivatization, and Gas Chromatography with Electron Capture Detection), improves the detection of the trihalogenated brominated DBPs by increasing the amount of methanol to improve methylation efficiency, incorporating *tert*-amyl methyl ether (TAME) as an optional extraction solvent to allow higher methylating temperatures (and better methylation efficiencies), and discontinuing the use of copper sulfate to prevent degradation of some HAAs (*17*). In support of this new method, the use of ammonium chloride was investigated as a chlorine quenching agent (*18*). Quenching is an important component of tap water methods because it halts the continued formation of chlorination DBPs, ensuring that the analytical results reflect HAA concentrations at the time and point of sample collection. However, there were issues with the use of ammonium chloride, since it reacts with chlorine to form chloramines, which produce HAAs on their own. When this was investigated using chlorine-treated waters with moderate total organic carbon and high levels of chlorine, it was found that ammonium chloride-quenched drinking water did form a small amount of HAAs, but the total formation was minimal over the 14-day sample holding time (<2 μg/L as compared to 41 μg/L for the unquenched drinking water). Therefore, it was decided that ammonium chloride could still be used as a quenching agent for Method 552.3 under the current preservation and sample storage times promulgated under the Stage 1 D/DBP Rule.

Bromate. EPA Method 300.1, Determination of Inorganic Anions in Drinking Water by Ion Chromatography (www.epa.gov/safewater/methods/sourcalt.html), is the only method approved for compliance monitoring of bromate until the Stage 2 D/DBP Rule is promulgated and has also been the subject of new research for method improvements. On occasion, there have been problems with low-level ($\leq$5.0 μg/L) bromate measurements in high ionic strength water using this method. In addition, the U.S. Food and Drug Administration (FDA) regulated bromate in bottled water (which can contain higher ionic levels than tap water) for the first time (at 10 μg/L) and recommended EPA Method 300.1 as the compliance monitoring method. As a result, U.S. EPA researchers investigated different suppressor technologies to improve the trace determination of bromate in high ionic matrixes (*19*). Of the three suppressors tested, the Anion Micro Membrane Suppressor (AMMS III) (Dionex, Sunnyvale, CA) was found to be the most effective for reducing baseline noise, which gave the best resolu-

tion and lowest bromate detection limits (≤5.0 μg/L) in high ionic strength waters.

NDMA and Other Nitrosamines. A new EPA method has also been created for measuring NDMA and six additional nitrosamines in drinking water (EPA Method 521, Determination of Nitrosamines in Drinking Water by Solid-Phase Extraction and Capillary Column Gas Chromatography with Large Volume Injection and Chemical Ionization Tandem Mass Spectrometry (MS/MS)) (www.epa.gov/nerlcwww/m_521.pdf). This method, created in September 2004, was developed for inclusion in the U.S. EPA's UCMR to enable the collection of nationwide occurrence data on nitrosamines in drinking water for regulatory determination. If NDMA or other nitrosamines become regulated drinking water contaminants in the future, the method could also be used for compliance monitoring (www.epa.gov/nerl/research/2004/g2-6.html). This method enables the measurement of NDMA and six other nitrosamines (*N*-nitrosomethylethylamine, *N*-nitrosodiethylamine, *N*-nitroso-di-*n*-propylamine, *N*-nitroso-di-*n*-butylamine, *N*-nitrosopyrrolidine, and *N*-nitrosopiperidine) in drinking water at detection limits ranging from 1.2 to 2.1 ng/L. This method is an improvement over previously published methods for nitrosamines, in that the sample preparation steps are simple, efficient, and inexpensive; the use of tandem-MS provides positive identification of all analytes without the use of additional confirmatory methods; and quality control steps ensure precision and accuracy.

Chlorite and Chlorine Dioxide. Another new method, EPA Method 327.0 (Determination of Chlorine Dioxide and Chlorite in Drinking Water using Lissamine Green B and Horseradish Peroxidase with Detection by Visible Spectrophotometry) was completed in July 2003 and was proposed as part of the Stage 2 D/DBP Rule (www.epa.gov/safewater/methods/sourcalt.html). Performance of this method is demonstrated for combined concentration ranges for chlorine dioxide and chlorite of 0.2−2.2 mg/L. Chlorite is a DBP from chlorine dioxide disinfection and was regulated for the first time (at 1.0 mg/L) by the Stage 1 D/DBP Rule.

Perchlorate. Several other methods have been created in support of the CCL. For example, there are three new methods created for perchlorate. These methods utilize LC/ESI-MS, LC/ESI-MS-MS, and IC, respectively, and were created to overcome matrix interferences in high ionic strength waters and also to lower detection limits to levels that are of human health concern. The only previously approved EPA method for measuring perchlorate (EPA Method 314.0) has a minimum reporting level of 4 μg/L and is vulnerable to sensitivity loss and false positive identifications in high ionic strength waters. The new ESI-MS method (Method 330.0), Determination of Perchlorate in Drinking Water by Ion Chromatography with Suppressed Conductivity and Electrospray Ionization Mass Spectrometry (www.epa.gov/nerlcwww/ordmeth.htm), uses an O-18 labeled perchlorate internal standard, an IC suppressor column, and ESI-MS for detection (*20*). The O-18 labeled perchlorate enabled a higher degree of accuracy in recovery from both low and high ionic strength waters. Also, by monitoring selective ions specific to perchlorate, potential false positives that can occur with an IC-conductivity method (due to coelution of other contaminants) were minimized. Low detection limits ranging from 0.02 (deionized water) to 0.05 μg/L (1000 ppm chloride, carbonate, sulfate) were obtained with this method.

The LC/ESI-MS/MS method, Method 331.0, Determination of Perchlorate in Drinking Water by Liquid Chromatography Electrospray Ionization Mass Spectrometry (www.epa.gov/safewater/methods/sourcalt.html), is an extension of the new 330.0 method. It also uses O-18 labeled perchlorate, but it utilizes multiple reaction monitoring (MRM) with a triple quadrupole mass spectrometer, giving further selectivity to the measurement of perchlorate. This method allows 0.02 μg/L detection limits.

The new IC method, Method 314.1, Determination of Perchlorate in Drinking Water Using Online Column Concentration/Matrix Elimination Ion Chromatography with Suppressed Conductivity Detection (www.epa.gov/safewater/methods/sourcalt.html), utilizes a concentrator column to retain perchlorate, while potentially interfering anionic contaminants (chloride, carbonate, sulfate) are washed from the column to waste. The concentrator column is then switched in-line with the IC system, which also utilizes a guard column, an analytical column, a suppressor device, and conductivity detection. This new IC method allows 0.2 μg/L detection limits of perchlorate in water. Challenges encountered during the development of this new method are published in a journal article by Wagner et al. (*21*).

Organotins. A micro-LC/ESI-ion trap-MS method, Method 8323, Determination of Organotins by Micro-Liquid Chromatography-Electrospray Ion Trap Mass Spectrometry (http://www.epa.gov/epaoswer/hazwaste/test/new-meth.htm#8323), was developed to avoid the use of hydrolysis and derivatization and to lower background interferences that are common with traditional methods. This method permits the measurement of mono-, di-, and tributyltin and mono-, di-, and triphenyltin at subnanogram per liter detection limits.

Pesticides and Brominated Flame Retardants. Two new methods were published for the measurement of pesticide degradates and pesticides/flame retardants, respectively. First, EPA Method 535, Measurement of Chloroacetanilide and Other Acetamide Herbicide Degradates in Drinking Water by Solid Phase Extraction and Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS), addresses ethanesulfonic acid (ESA) and oxanilic acid (OA) degradation products of acetanilide/acetamide herbicides that have been found in U.S. groundwaters and surface waters (www.epa.gov/nerlcwww/ordmeth.htm). The substitution of the sulfonic acid or the carbonic acid for the chlorine atom in these degradates greatly increases their water solubility relative to the parent compound and contributes to increased potential for leaching into groundwater (www.epa.gov/nerl/research/2004/g2−5.html). As a result, alachlor ESA and other acetanilide degradation products are listed on the CCL. Because existing methods for these degradates did not address issues specific to analyzing these compounds in drinking water (e.g., dechlorination, matrix effects), and because methods were not available for all 12 ESA and OA degradates of the six acetanilide/acetamide herbicides registered in the United States, the U.S. EPA developed this new method. For this method, graphitized carbon was the only solid-phase sorbent that was capable of extracting all 12 degradates from water, and LC/negative ion-ESI-MS/MS detection was used for detection. Tandem mass spectrometry was necessary to eliminate interfering humic and fulvic acid material present in the drinking water samples, which caused significant background interferences with

LC/MS. Method detection limits ranged from 0.016 to 0.11 μg/L.

EPA Method 527, Determination of Selected Pesticides and Flame Retardants in Drinking Water by Solid-Phase Extraction and Capillary Column Gas Chromatography/Mass Spectrometry (www.epa.gov/safewater/methods/sourcalt.html), allows sub- to low-ppb level detection for five flame retardants: hexabromobiphenyl (PBB-157); 2,2′,4,4′,5,5′-hexabromodiphenyl ether (BDE−153); 2,2′,4,4′,5-pentabromodiphenyl ether (BDE-99), 2,2′,4,4′,6-pentabromodiphenyl ether (BDE-100), and 2,2′,4,4′-tetrabromodiphenyl ether (BDE-47); and the following 21 pesticides, atrazine, bifenthrin, bromacil, chloropyrifos, dimethoate, esbiol, esfenvalerate, fenvalerate, hexazinone, kepone, malathion, mirex, norflurazon, nitrofen, oxychlordane, parathion, prometryne, propazine, terbufos-sulfone, thiobencarb, and vinclozolin. This method uses solid-phase extraction of a 1-L water sample, followed by GC/MS analysis using internal standards.

Volatile Organic Compounds (VOCs). EPA Method 5030C, Purge-and-Trap for Aqueous Samples (www.epa.gov/epaoswer/hazwaste/test/pdfs/5030c.pdf) added updated holding times and utilizes high-temperature purge-and-trap for the measurement of fuel oxygenates in water. This method is applicable to >100 VOC analytes, which includes fuel oxygenates—MTBE, ethyl-*tert*-butyl ether (ETBE), TAME, *tert*-butyl alcohol (TBA), and diisopropyl ether (DIPE)—one nitrosamine (*N*-nitroso-di-*n*-butylamine), and several common contaminants (e.g., trichloroethene). This extraction method can be linked with existing GC/flame ionization detection (FID) methods (e.g., EPA Method 8015) or GC/MS methods (e.g., EPA Method 8260).

Metal Cyanide Complexes. EPA Method 9015, Metal Cyanide Complexes by Anion Exchange Chromatography and UV Detection (www.epa.gov/epaoswer/hazwaste/test/pdfs/9015.pdf) was created to differentiate and quantify metal cyanide complexes of iron, cobalt, silver, gold, copper, and nickel in water and solid waste extracts. This IC−UV method can detect down to 0.5 μg/L, with minimal sample preparation and no derivatization.

PFOA/PFOS

Fluorinated surfactants (also referred to as fluorotelomer acids, alcohols, and sulfonates) have been manufactured for more than 50 years and have been used to make stain repellents (such as Teflon) that are widely applied to fabrics, carpets, and paper (*22*). They are also used in the manufacture of paints, adhesives, waxes, polishes, metals, electronics, and caulks (*23*). During 2000−2002, an estimated 5 million kg/year of these compounds was produced worldwide, with 40% of this in North America (*24*). Two of these fluorinated surfactants, PFOS and PFOA are currently receiving a great deal of attention as emerging contaminants in the United States. PFOS was once used to make the popular Scotchgard fabric and carpet protector, and since 2002, it is no longer manufactured due to concerns about widespread global distribution in the blood of the general population and in wildlife, including remote locations in the Arctic and North Pacific Oceans (*25*, *26*). However, other fluorinated surfactants such as PFOA are still manufactured and are used to make soil-, stain-, grease-, and water-resistant coatings used on textiles, carpet, cookware, and automobiles. Like PFOS, PFOA appears to be ubiquitous at low levels in humans, even in those living far from any obvious sources (*27*). Research questions include understanding the sources of PFOA and other fluorinated surfactants, their environmental fate and transport, pathways for human exposure and uptake, and potential health effects. Scientists in academia, industry, and the U.S EPA have launched investigations to tackle these questions. In addition, the Centers for Disease Control and Prevention (CDC) has recently nominated PFOS and PFOA to be included in their National Health and Nutrition Examination Survey (NHANES) to provide a better assessment of the distribution of these chemicals in the human population (*25*).

In January 2005, the U.S. EPA issued a draft risk assessment on PFOA, which included an analysis of how PFOA causes liver tumors in rats and the relevance of this mode of action for human health risk assessment (www.epa.gov/oppt/pfoa/pfoarisk.htm). While previous studies have shown PFOA can cause cancer in animals (liver, testicular, and pancreatic), there are questions regarding the relevance of these animal results to humans (*28*). A preliminary epidemiologic investigation of workers at a plant occupationally exposed to PFOA and residents living near this plant is indicating the possibility of elevated rates for prostate cancer in young men and uterine cancer in women, along with uncommon cancers, such as non-Hodgkin's lymphoma, leukemia, and multiple myeloma (*27*). This plant is also conducting its own survey of possible PFOA effects on 750 volunteer employees (*27*). There are also new studies into the possible developmental toxicity of PFOA and other fluorinated surfactants (*25*). Fluorinated surfactants are unusual chemically, in that they are both hydrophobic (repel water) and lipophobic (repel lipids/grease), and they contain one of the strongest chemical bonds (C−F) known. Because of these properties, they are highly stable in the environment (and in biological samples), and they are expected to have unique profiles of distribution in the body (*25*).

Three reviews have been published the last two years on PFOS, PFOA, and other fluorinated surfactants. Kennedy et al. wrote a review on the toxicology of PFOA, where they discuss the different mechanisms involved in the types of tumors observed in animal studies (*28*). Lau et al. reviewed the developmental toxicity of PFOA and PFOS (*25*). Issues involved in extrapolating animal data to humans are discussed, and future research and directions are outlined. Schultz et al. published a review that focused on the analysis and the environmental occurrence of fluorinated surfactants (*29*). Research needs, such as the elucidation of transport processes and the development of new methods for efficiently treating wastewaters, are also outlined.

While PFOS and PFOA were the first fluorinated surfactants to receive considerable attention, research is expanding beyond these two contaminants to other long-chain perfluorinated acids and alcohols (*23*). LC/MS and LC/MS/MS are the most common analytical techniques used for the measurement of these compounds; however, there can be difficulty in obtaining clean analytical blanks, due to inherent contamination in LC systems (fluoropolymer coatings on seals, etc.). As a result, GC/MS and GC/MS/MS are sometimes used. In a nice systematic study, Yamashita et al. isolated and determined sources of perfluorinated chemical (PFC) contamination for SPE-LC/MS measurements (*30*). Initially, solvent blanks (using a 10-μL injection of pesticide-grade methanol) were found to consistently contain significant PFOS and PFOA contamination when analyzed by LC/MS. PFOA

was the most abundant contaminant, at 30 pg/10 μL injected. The LC tubing [made of poly(tetrafluoroethylene)], internal LC instrument parts (coatings and seals in the degasser and solvent selection valves), and the autosampler vial septum were all found to be sources of the PFC contamination. As a result, the investigators replaced the LC tubing with PEEK (polyetheretherketone) and stainless steel tubing, replaced solvent inlet filters with stainless steel filters, and replaced Teflon or Viton autosampler vial caps with polyethylene, which decreased the instrumental blank contamination considerably. The authors also found that polypropylene sample bottles can contain up to 27 ng/L PFOA, and Sep-pak SPE cartridges can contain 46 and 12 pg/L PFOA and PFOS, respectively. By switching to an Oasis SPE cartridge (Waters, Milford, MA), levels of PFOA and PFOS were reduced by a factor of 10 and 5−10, respectively. Purified reagent water used for field blanks was also found to be contaminated with PFCs; however, Milli-Q and high-performance (HP)LC-grade water contained relatively lower background levels than distilled water. Finally, nylon syringe filters that are used to remove particles from extracts prior to LC/MS/MS injection were also found to contain PFOA (25−75 pg) in three different brands investigated, with PFOS also being detected in two of these brands. Washing the filters with methanol (2 mL) prior to filtration of the samples was found to eliminate the PFOA and PFOS residues. It is evident that in order to determine PFOA, PFOS, and other PFCs at low detection limits, considerable effort must be taken to ensure clean blanks.

Several studies have been gathering occurrence information and investigating the source of PFOA in the environment and in humans. In 2004, Mabury and colleagues discovered that fluorotelomer alcohols used to make fluorinated stain repellents undergo atmospheric transport and degrade to form perfluorinated carboxylates, including PFOA (*23, 31*). The overall mechanism of biodegradation was found to involve the oxidation of the hydroxyl group to a transient aldehyde, which further oxidized to form an unsaturated acid, and finally the highly stable PFOA (*23*). Biological transformation is suggested to be a major degradation pathway for fluorotelomer alcohols in aquatic systems. In this study, GC/MS was used to identify the volatile metabolites, and LC/MS/MS was used to identify and quantify the nonvolatile metabolites, including PFOA. A 2005 study by Wang et al. confirmed this biodegradation pathway for the formation of PFOA (*32*). In their study, ^{14}C-labeled perfluorodecanol was used to follow the biodegradation in diluted activated sludge from a wastewater treatment plant. On-line LC/accurate radioisotope counting was used to provide a complete mass balance. LC/MS/MS (with a quadrupole-TOF mass spectrometer) was used to identify three transformation products, which included PFOA [$CF_3(CF_2)_6{}^{14}COOH$], an 8−2 saturated decanoic acid [$CF_3(CF_2)_6{}^{14}CF_2CH_2COOH$], and an 8−2 unsaturated decanoic acid [$CF_3(CF_2)_6{}^{14}CF{=}CHCOOH$]. These three products represented 2.1, 27, and 6.0% of the initial ^{14}C mass. A new transformation product, not previously reported, was also tentatively identified as 2*H*,2*H*,3*H*,3*H*-perfluorodecanoic acid [$CF_3(CF_2)_6{}^{14}CH_2CH_2COOH$].

In one of the recently published occurrence studies, Yamashita et al. measured PFOA, PFOS, perfluorohexanesulfonate (PFHS), perfluorobutanesulfonate (PFBS), perfluorononanoic acid (PFNA), and perfluorooctane sulfonamide (PFOSA) in ocean waters using a newly developed LC/negative ion-ESI-MS/MS method (*30*). This method can detect low-picogram per liter (ppq) levels of these contaminants. Samples at different depths were collected from Tokyo Bay, the Mid-Atlantic Ocean, the Sulu Sea, the South China Sea, the Eastern Pacific Ocean, and the Central-to-Western Pacific Ocean. PFOA, PFOS, PFHS, and PFOSA were detected in all of the seawaters sampled, except for PFHS, which was not found in the Sulu Sea samples. PFOA was the major PFC detected, with a maximum level of 192 ng/L observed in Tokyo Bay. This study is important because it is one of the first to measure this group of fluorinated surfactants in ocean waters, which serve as a sink for a variety of environmental pollutants. Thus, it is an important component in the understanding of pathways and mechanisms of transport of these PFCs. In another study of ocean waters, So et al. used SPE-LC/high-resolution-ESI-MS to measure PFCs (PFOA, PFOS, PFBS, PFHS, PFNA, PFOSA, and 1*H*,1*H*,2*H*,2*H*-perfluorooctanesulfonate) in coastal waters around Hong Kong, South China, and Korea (*33*). PFOA was found up to 320 pg/mL (ng/L), and PFOS was found up to 730 pg/mL (ng/L). The spatial and seasonal variations in PFC concentrations in seawaters from the Pearl River Delta and South China Sea indicated a strong influence of the Pearl River discharge on the magnitude and extent of PFC contamination in southern China.

Groundwater was the focus of another study. Schultz et al. used a direct injection-LC/ESI-MS/MS method to measure fluorotelomer sulfonates in groundwater collected from U.S. military bases where PFCs had been used in fire-fighting foams during military exercises (*34*). This method allows detection down to 0.60 μg/L and was used to measure 11 PFCs, including PFOS, PFOA, PFBS, and PFHS. Total fluorotelomer sulfonate concentrations ranged from below quantitation to 14 600 μg/L. A separate analysis of this fire-fighting foam revealed only small amounts of fluoroteomer sulfonates, but substantial contribution from fluoroalkylthioamido sulfonates.

Surface water studies include those conducted in Japan and in the United States. Saito et al. measured PFOA and PFOS in Japanese surface waters using a SPE-LC/MS method, which could achieve 0.06 and 0.04 ng/L detection limits, respectively (*35*). The highest mean concentrations reached 21.5 and 5.73 ng/L for PFOA and PFOS, respectively, and systematic searches revealed a major point source contamination of PFOA from a public water disposal site. An airport was a major source of contamination of PFOS. Great Lakes waters were the focus of another study. Boulanger et al. used LC/MS and LC/MS/MS to measure eight perfluorooctane surfactants, including PFOA, PFOS, and six PFOS precursors in Lake Erie and Lake Ontario (*36*). This study represents the first measurement of PFOS precursors in any water body. PFOS and PFOA levels ranged from 21 to 70 and 27−50 ng/L, respectively. Three PFOS precursors—2-(*N*-ethylperfluorooctanesulfonamido)acetic acid, perfluorooctanesulfonylamide, and perfluorooctane sulfinate were found in several samplings at 4.2−11, 0.6−1.3, and <2.2−17 ng/L, respectively. Finally, Takino et al. developed a new LC/atmospheric pressure photoionization (APPI)-MS method for measuring PFOS in surface water (*37*). This method utilizes on-line extraction with turbulent flow chromatography and allows 5.35 pg/mL (ng/L) detection, with no off-line sample preparation. and a total analysis time of ∼19 min.

PHARMACEUTICALS, HORMONES, AND ENDOCRINE DISRUPTING COMPOUNDS

The focus of environmental research has recently been extended from the more classic" environmental pollutants, such as polychlorinated biphenyls (PCBs), DDT, and pesticides, to pharmaceuticals, personal care products, and EDCs that enter the environment primarily through regular domestic use. For example, ~3000 different substances are used as pharmaceutical ingredients today, including painkillers, antibiotics, antidiabetics, β-blockers, contraceptives, lipid regulators, antidepressants, and impotence drugs. A large number of these bioactive compounds are consequently entering wastewater and receiving water bodies (rivers, lakes, etc.) without being tested for special environmental effects. Although the number of effects studies is rather limited, estrogenic effects (*38*) and renal alterations (*39*) in the range of environmental concentrations were reported for 17α-ethinylestradiol and diclofenac, respectively. It is expected that future effects research will show similar effects for other pharmaceuticals at environmentally relevant concentrations. Within the last 10−15 years, the increasing use of LC/MS has led to a "revolution" in environmental analysis, providing a new analytical tool that enables the identification of highly polar organic pollutants without derivatization, down to nanogram per liter levels in all kinds of water bodies (wastewater, surface water, groundwater, drinking water) and in solid matrixes (sewage sludge, manure, soil, sediments). The major innovation that enabled this involved the development of appropriate ionization interfaces to couple LC with MS. Currently, ESI and atmospheric pressure chemical ionization (APCI) are the most commonly used LC interfaces. Recently, APPI and sonic spray ionization (SSI) have also been used. Rapid biochemical techniques, such as biosensors and immunoassays, have also been recently developed for selected pharmaceuticals and EDCs, allowing surprisingly low limits of detection (LODs) in the range of environmental concentrations. Further innovations have been made in rapid on-line extraction, microextraction, and on-line derivatization techniques in combination with GC/MS(/MS) detection.

Pharmaceuticals. Considering the large number of registered pharmaceutical ingredients (>3000) and the larger number of corresponding metabolites, analytical methods have only been developed for a very small subset of compounds (~150) in environmental matrixes. Antibiotics are currently a focus of environmental and veterinary research, due to the potential effects on human therapy by the formation of resistant strains. Hence, many analytical methods reported are for the detection of antibiotics in a variety of environmental and veterinary samples. For aqueous samples, the combination of SPE and LC/tandem-MS or LC/ion trap-MS is prevalent. A comprehensive summary on the use of LC/MS and appropriate SPE materials for the analysis of pharmaceuticals can be found in Zwiener and Frimmel (*8*). To date, in addition to RP materials, copolymer materials are becoming popular for the extraction of nonpolar to very polar analytes. For example, styrene−divinylbenzene copolymers (e.g., LiChrolut EN, Merck, or Isolute 101, International Sorbent Technology); OH-styrene−divinylbenzene copolymers (e.g., Isolute ENV+, International Sorbent Technology), and divinylbenzene-*N*-vinylpyrrolidone copolymers (Oasis HLB, Waters) are used for a broad range of antibiotics and other pharmaceuticals. The detection of most antibiotics is performed with LC/ion trap-MS, LC/quadrupole-tandem-MS, or LC/quadrupole-TOF-MS. SPE is typically used to extract the antibiotics from aqueous samples, such as wastewater or surface waters, often without the need for further cleanup. For example, Göbel et al. developed a method for the determination of five sulfonamides, the metabolite *N*4-sulfamethoxazole, four macrolide antibiotics, and trimethoprim in wastewater with SPE using Oasis HLB and LC/ESI-MS/MS detection (*40*). The authors used deuterated standards for quantitation, to compensate for ion suppression. The analysis of the aminoglycoside, gentamicin, in aqueous samples, such as groundwater and hospital wastewater, was described by Löffler and Ternes (*41*). This method used SPE with a weak cation exchange material, followed by an ion-pair LC (C18 with heptafluorobutyric acid) and ESI-MS/MS detection (*41*). Because gentamicin tends to sorb onto glass surfaces, Teflon and polypropylene materials were extensively used.

As an alternative to SPE, methods using hollow fiber liquid-phase microextraction (LPME) have recently been published. LPME involves the use of a hollow fiber membrane that is imprenated with small amounts of organic solvents. Using LPME, acidic pharmaceuticals (containing carboxylic acid groups) were detected in wastewater with LC (*42*). Another alternative for the future might be membranes modified by molecular imprinting. Suedee et al. were able to incorporate a tetracycline-imprinted polymer in a poly(vinyl chloride) membrane (*43*). These affinity membranes were able to extract tetracyclines with a high efficiency at pH 7.

The main disadvantage of LC/MS detection is the matrix effects associated with ionization interfaces such as ESI-MS, which frequently cause reduced ionization of the target analytes (ion suppression) or in a few cases even elevated ionization (ion enhancement). Either may result in incorrect quantitative results. Matrix influences cannot be compensated by "offline" calibrations over the whole method, since the matrix composition and matrix quantity differ from sample to sample. However, there are three common options for obtaining correct quantitative results for samples with difficult matrixes: (1) using appropriate surrogate standards (preferably deuterated or ^{13}C-labeled compounds); (2) including effective cleanup steps to remove matrix components; and (3) using an alternative interface (e.g., APCI), which causes frequently less matrix suppression. Restricted-access materials (RAMs) can be used for on-line cleanup or extraction. RAMs combine size exclusion of high molecular weight compounds and simultaneous enrichment of pharmaceuticals (on the inner pore surface that is coated with a sorbent, e.g., C4 material). Although RAMs have been used with biological samples since 1985, they have only recently become popular for environmental analysis (*44*).

In addition to antibiotics, many other pharmaceuticals have been detected in aqueous samples with LC/MS/MS, predominantly in the positive ion mode with ESI. A multicompound LC/ESI-MS/MS method was developed by Vanderford et al., which enabled the determination of 27 compounds, including various pharmaceuticals, pesticides, steroids, and personal care products. SPE (HLB material) was used for extraction, and limits of quantitation (LOQs) down to 1 ng/L were achieved (*45*). Miao and Metcalfe developed a method for the determination of carbamazepine and several metabolites, such as epoxycarbam-

azepine, dihydroxycarbamazepine (3 isomers), hydroxycarbamazepine, and dihydrocarbamazepine in wastewater and surface water with SPE (OASIS HLB, Waters) and positive ion-LC/ESI-MS/MS (*46*). Instrumental detection limits of 0.8−4.8 pg and LOQs below 1 ng/L were achieved. Ion suppression was a problem in treated and raw wastewater, and even in surface water; as a result, surrogate standards were crucial for reliable measurements. A sensitive determination of 11 acidic pharmaceuticals (e.g., salicylic acid, piroxicam, clofibric acid, diclofenac, naproxen, ketorolac) and triclosan in aqueous samples by ion pair-RP-LC/MS/MS was reported by Quintana and Reemtsma (*47*). The sensitivity was significantly increased by adding tri-*n*-butylamine, and the authors were able to directly inject wastewater without preconcentration, with LODs ranging between 0.006 and 0.2 μg/L. Another analytical method that does not require sample preconcentration was described by van der Ven (*48*). They directly injected 0.45-μm-filtered wastewater into a capillary-LC/MS/MS, and achieved an LOD of 0.1 μg/L for diazepam.

SPE and LC/ESI-MS/MS have been applied for many other pharmaceuticals, such as statin drugs (e.g., atorvastatin, lovastatin, pravastatin, simvastatin), which were present up to 117 ng/L in raw sewage, up to 59 ng/L in treated sewage, and at 1 ng/L in surface waters from Canada (*49*). Zühlke et al. developed a LC/ESI-MS/MS method for the detection of three phenazone-type pharmaceuticals, six metabolites, and carbamazepine in sewage, surface water, and drinking water after SPE (*50*). Cahill et al. detected 22 different pharmaceuticals from more than 15 different medicinal classes, such as analgesics, histamine H2 inhibitors, diuretics, antidepressants, antibiotics, antihistamines, antihypertensives, and central nervous system stimulants in surface water and groundwater by SPE and LC/MS at levels up to 5.2 μg/L (*51*). In a few papers, LC with fluorometric detection was used for measuring pharmaceuticals in environmental samples. For example, Prat et al. detected quinolones (e.g., ciprofloxacin, norfloxacin, difloxacin, danofloxacin) in aqueous samples after SPE and LC with fluorometric detection (*52*). For the fluoroquinolones, LOQs were in the low-nanogram per liter range and are, therefore, comparable with LC/MS/MS methods; however, for the selected acidic and neutral pharmaceuticals, further improvements are needed to compete with LC/MS/MS. Nevertheless, analytical methods using lower cost instruments are of importance for applications where higher concentrations are expected.

GC/MS applications have been rather limited, since analytes have to be transferred to the gas phase either directly or after an appropriate derivatization. β-Blockers were determined in U.S. wastewater effluents by Hugget et al. using Empore SDB-XC extraction disks and a two-step derivatization with *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA) and *N*-(*tert*-butyldimethylsilyl)-*N*-methyltrifluoroacetamide (MTBSTFA) prior to GC/MS detection (*53*). Propranolol, metoprolol, and nadolol were detected up to 1.9, 1.2, and 0.36 μg/L, respectively. Acidic pharmaceuticals have been measured by GC/MS using several derivatization procedures, including silylation and pentafluorobenzyl bromide derivatization. An innovative approach was reported by Lin et al. who detected six selected pharmaceuticals (clofibric acid, ibuprofen, carbamazepine, naproxen, ketoprofen, diclofenac) after SPE as butylated derivatives by GC/MS using large-volume injection and on-line derivatization with tetrabutylammonium salt achieving LOQ down to 1 ng/L (*54*).

Many methods use SPME in combination with GC/MS, e.g., for the analysis of selective serotonin reuptake inhibitors, such as venlafaxine, fluvoxamine, fluoxetine, citalopram, and sertraline (*55*), and with on-fiber silylation for the analysis of antiinflammatories (*56*) in aqueous samples.

A radioimmunoassay was developed by Yang and Carlson (57). The authors were able to determine tetracyclines and sulfonamides after SPE down to 0.05 μg/L. An ELISA was developed by Deng et al. for the analysis of diclofenac down to 0.020 μg/L without any sample enrichment (*58*). Due to the reduced sample pre-enrichment and the lack of sophisticated and expensive instruments, these techniques allow extremely rapid and inexpensive analyses and might, therefore, be a viable option for many applications in the future.

A rapid analysis was also introduced by Grant et al., who developed a method enabling the analysis of sulfamethazine and its metabolite, *N*4-acetylsulfamethazine, in water, aqueous soil solutions, and composted manure with a solid-phase immunoextraction (SPIE) system and detection by MALDI-TOF-MS (*59*). Capillary electrophoresis (CE)-ESI-MS following SPE was reported for the analysis of naproxen, clofibric acid, and bezafibrate, with detection limits down to 0.1 μg/L (*60*).

Endocrine Disrupting Compounds and Hormones. Certain synthetic and natural chemicals have the ability to mimic hormones and, thus, are able to interfere or disrupt normal hormonal functions. EDCs are of high concern due to their ecotoxicological and toxicological potencies. A variety of natural compounds and anthropogenic chemicals are known or predicted to influence the endocrine system, such as natural estrogens (e.g., 17β-sitosterol, estrone), natural androgens (e.g., testosterone), phytosteroids (e.g., 17β-sitosterol), isoflavenoids (e.g., daidzeine), synthetic estrogens (e.g., 17β-ethinylestradiol), pesticides (e.g., atrazine), phthalates, alkylphenol ethoxylate surfactants, dioxins, coplanar PCBs, parabenes (hydroxybenzoate derivatives), bisphenol A, and organotins. Due to the enormous number of chemicals with different modes of action and different affinities to hormonal receptors (e.g., estrogen, androgen, thyroid, AH receptor), their EDC potencies differ substantially. Many efforts have been undertaken for the accurate analysis of estrogens in aqueous and solid samples down to nanograms per liter and even subnanogram per liter concentrations. The first methods at the end of the 1990s used primarily GC/MS or GC/ion trap-MS/MS detection. Today, an increasing number of methods use LC/MS and LC/MS/MS. The main benefits of LC/MS/MS, in comparison to GC/MS, are lower statistical errors and no need for derivatization. The lower sensitivity of the first-generation LC/MS(/MS) methods is no longer a disadvantage, since new LC/MS(/MS) systems are competitive with GC/MS sensitivities. Only when resolution is mandatory to separate isomers or congeners (such as for PCBs, dioxins, or brominated flame retardants), GC/MS/MS systems are still the method of choice.

In the last two years, several reviews have summarized the current knowledge for the analysis of estrogens in aqueous matrixes (*6*, *61*, *62*). SPE at pH 2−7 was frequently applied for the extraction of aqueous samples and for cleanup of solid matrixes. SPE sorbents include divinylbenzene-*N*-vinylpyrrolidone

copolymers (Oasis HLB, Waters) styrene−divinylbenzene copolymers (e.g., LiChrolut EN, Merck, or Isolute 101, International Sorbent Technology), OH-styrene−divinylbenzene copolymers (e.g., Isolute ENV+, International Sorbent Technology) and RP-C_{18} or C_{18}-end-capped materials. Cleanup procedures include the use of silica gel columns, gel permeation chromatography, or semipreparative LC (RP−C_{18}) fractionation. Cleanup procedures applied are related to the matrixes measured.

The derivatization of estrogens prior to GC/MS analysis is performed mainly by silylation using MSTFA and MTBSTFA. For example, an analytical method using MSTFA derivatization and GC/ion trap-MS/MS was developed for the analysis of natural estrogens and 17α-ethinylestradiol in water down to a LOQ of 0.10 ng/L (*63*). Solid-phase extraction (RP-C_{18} disk, Varian) of a 10-L sample and silica gel cleanup were utilized in this method. Lerch et al. presented a method using fluorinated derivatization agents—heptafluorobutyric acid anhydride and trifluoroacetic acid anhydride—as optimum agents for measuring 21 EDCs (estrogens, bisphenol A, androgens, corticosteroids, octylphenol) by GC/ECNI-MS (*64*). For estrogens, GC/ion trap-MS/MS, GC/single quadrupole-MS, as well as LC/MS and LC/MS/MS, are used for detection. However, tandem-MS and the MS^n mode of ion trap-MS combine high sensitivity and a high level of confirmation. Therefore, they should be recommended for more complex matrixes, such as sludge and sediments. ESI is the most commonly used interface in LC/MS; however, three LC/MS interfaces that have been recently used—ESI, APCI, and SSI—have been shown to exhibit similar LOQs (*65*).

Rodrigues-Mozaz et al. used online SPE-LC/MS/MS for the determination of estrogens down to 0.02 ng/L (*66*). Additionally, two conjugates—estrone-3-sulfate and estradiol-17-glucuronide—were also determined. In river water from Spain, estrone-3-sulfate and estrone were present at 0.33 and 0.68 ng/L, respectively. However, neither the estrogens nor the conjugates were detected in finished drinking water. An interesting study with regard to the conjugates was reported by Komori et al. (*67*). They developed an analytical method that enabled the simultaneous analysis of estrogens and eight conjugates using SPE (Oasis HLB), two cleanups (Sep-pak Plus Florisil, Sep-pak Plus NH_2), deuterated standards, and detection with LC/ESI-MS/MS. The authors detected estrone (E1), 17β-estradiol (E2), estriol (E3), 17α-ethinylestradiol (EE2), and eight related conjugates (sulfates (S), E1-S, E2-S, E3-S; and glucuronides (G), E1-G, E2-G, E3-G; and disulfates, E2-diS, sulfate-glucuronide E2-S, G) in influents and effluents of 20 Japan sewage treatment plants. In addition to the nonconjugated estrogens (E1, E2, E3), higher concentrations of the conjugates were observed, with a maximum of 1.5 μg/L estradiol disulfate. Median values for all eight conjugates were determined above the LOQ in the wastewater influents and effluents. These results are important because these very polar conjugates were able to pass environmental barriers (such as soil), and thus, reformation of the active estrogens by conjugate cleavage must be considered. Furthermore, the reformation of estrogens from conjugates might be an explanation for the concentrations measured in many sewage treatment plant effluents, although it is possible that biodegradation could lead to major removal.

Finally, an optical biosensor for an estrone detection was developed by Tschmelak et al. (*68*). With this fully automated immunoassay system, a LOQ down to 1.4 ng/L was achieved.

In addition to estrogens, alkylphenols and alkylphenolethoxylates (APEOs) are EDCs that are ubiquitously present in the environment, close to concentrations that can cause adverse health effects. Lopez de Alder provides an interesting survey about the current analytical methods for aqueous and solid samples, as well as biota, using LC/MS for these compounds (*6*). It becomes obvious that LC/MS is a competitive alternative to GC/MS. For aqueous samples, SPE with RP-C18 is the most widely applied method for neutral and acidic alkylphenolic compounds, but graphitized black carbon and anion exchange material (SAX) are also used. A simultaneous determination of APEOs, including 4-*tert*-octylphenol monoethoxylate, 4-nonylphenol monoethoxylate, 4-*tert*-octylphenol diethoxylate, and 4-nonylphenol diethoxylate, was reported for water samples using SPE at pH 2 on RP-C_{18} cartridges, silica gel cleanup, and silylation with MSTFA, prior to GC/MS/MS detection (*63*). Furthermore, the same authors described an analytical method for the analysis of two alkylphenoxy acetic acids (4-*tert*-octylphenoxy acetic acid, 4-nonylphenoxy acetic acid) in aqueous samples with SPE (HLB Oasis) at pH of ∼2, and detection by LC/ESI-MS/MS (*63*). A surrogate standard, 1*H*,1*H*,2*H*,2*H*-perfluorooctanesulfonic acid, was used, and detection limits of ∼2 ng/L were achieved. A relatively new approach for the analysis of phenolic xenoestrogens (e.g., bisphenol A, alkylphenols) in water samples was reported by Kawaguchi et al. using stir bar sorptive extraction combined with in situ acetylation and thermal desorption GC/MS (*69*).

Pojano et al. developed a method that enables the analysis of alkylphenols, bisphenol A, benzophenone, and nonylphenol monocarboxylate simultaneously with estrogens in coastal lagoon waters, with LOQs ranging from 0.1 to 2.6 ng/L (*70*). This method consists of SPE at pH 2.5 with RP-C_{18} and detection with LC/ESI-ion trap-MS using four deuterated standards for quantitation. A method for 35 different EDCs was reported by Benijts et al., which achieved LOQs ranging from 0.1 to 20 ng/L (*71*). Estrogens, parabens, and several alkylphenols, as well as 19 herbicides, were measured with quality assurance, since matrix effects were compensated by using 16 different deuterated internal standards. Wenzel et al. used GC/MS to determine phytosteroids and Bisphenol A in surface water and drinking water after filtration, solid-phase extraction (RP-C_{18}), silica gel cleanup, and silylation by MSTFA. LOQs down to 10 ng/L were achieved (*63*).

Liu et al. rerported an ionic liquid-based, LPME for the determination of nonylphenol and octylphenol, achieving LODs of 0.3 and 0.7 mg/L, respectively (*72*). The LPME was coupled with LC, and 1-hexyl-3-methylimidazolium hexafluorophosphate was used as the extraction solvent in the hollow fibers. Badea et al. described the screening of APEOs and alkyl phenols in aqueous samples using a competitive enzyme flow injection immunoassy (*73*). The detection limits for octylphenol ethoxylates, nonylphenol ethoxylates, and nonylphenol were 0.5, 2−3, and 50 μg/L, respectively.

A solvent-free analytical method was developed by Alzaga et al. for the analysis of four phthalates in aqueous samples using diazomethane on-fiber derivatization with SPME-GC/MS. Under

optimum conditions, concentrations of 0.3−8.6 μg/L could be detected (*74*).

Fate in Drinking Water Treatment Plants. Source waters of drinking water treatment plants can be contaminated by EDCs. This is especially the case if surface water is used as the source water. Efficient drinking water treatment trains can be used to avoid drinking water contamination by EDCs (e.g., using ozonation, activated carbon, and bank filtration). Snyder et al. published a comprehensive review on the implications of pharmaceuticals, personal care products, and EDCs for water treatment, summarizing the literature until 2001 (and a few papers of 2002), with regard to analytical methods and removal during water treatment (*75*). The authors concluded that conventional drinking water and wastewater treatment plants do not completely remove pharmaceuticals and EDCs, while advanced treatment technologies, such as activated carbon and reverse osmosis appear viable for their removal. Furthermore, it was pointed out that oxidation with chlorine and ozone can result in transformations of selected compounds.

Huber et al. determined second-order rate constants for the reactions of selected pharmaceuticals with ozone (k_{O_3}) and OH radicals (k_{OH}) in bench-scale experiments (*76*). High reactivities with ozone (k_{O_3}) were found for carbamazepine ($\sim 3 \times 10^5$ M^{-1} s^{-1}), diclofenac ($\sim 1 \times 10^6$ M^{-1} s^{-1}), 17α-ethinylestradiol ($\sim 3 \times 10^6$ M^{-1} s^{-1}), sulfamethoxazole ($\sim 2.5 \times 10^6$ M^{-1} s^{-1}), and roxithromycin ($\sim 7 \times 10^4$ M^{-1} s^{-1}), indicating that these compounds are very rapidly transformed during ozonation. Lower reactivities were found for bezafibrate (590 ± 50 M^{-1} s^{-1}), diazepam (0.75 ± 0.15 M^{-1} s^{-1}), ibuprofen (9.6 ± 1 M^{-1} s^{-1}), and iopromide (<0.8 M^{-1} s^{-1}). Finally, the authors concluded that ozonation and advanced oxidation processes are promising for the efficient removal of pharmaceuticals in drinking waters. In another study, Huber et al. demonstrated that O_3 doses typically applied for the disinfection of drinking waters were sufficient to reduce estrogenicity by a factor of >200 (*77*). However, it proved impossible to completely remove estrogenic activity, due to the slow reappearance of 0.1−0.2% of the initial EE2 concentration after ozonation. Additionally, several oxidation products of EE2, as well as of the natural steroid hormones E2 and E1, were identified. The chemical structures of the oxidation products were significantly altered compared to the parent compounds, which explains the diminished estrogenic activity after ozonation.

The identification of chlorination products of EDCs and antibiotics was described by several authors. Dodd and Huang elucidated the kinetics of the antibiotic sulfamethoxazole (SMX) with chlorine, and identified three major chlorination products of SMX (*N*-chloro-*p*-benzoquinoneimine, 3-amino-5-methylisooxazole, and ring-chlorinated SMX) using LC/ESI-MS and GC/MS (*78*). They concluded that these reactions should at least partly contribute to a reduction or elimination of the original antibacterial activity. Hu et al. identified seven chlorination products (e.g., 2,4-dichloro-17β-estradiol, 2,4-dichloroestrone, and monochloroestrone) in chlorinated E2 solution with LC/ESI-MS (*79*). However, the authors found that the products formed still had a relatively high estrogenic activity.

Finally, Wenzel et al. (*63*) investigated the fate of a numerous of EDCs (estrogens, alkylphenols, tin organics, alkylethoxylates, alkylphenoxyacetic acids, and phytosteroids). Even if source waters of drinking water treatment plants are free of EDCs, drinking water/tap water might be contaminated by individual EDCs, such as dibutyltin or phytosteroids (e.g., β-sitosterol), due to leaching from materials used in water treatment and water pipes. Nevertheless, if the highest concentration of an individual EDC reported for drinking water is considered for the assessment of effects on humans, based on the current knowledge, endocrine effects via the consumption of drinking water are very unlikely.

SUNSCREENS/UV FILTERS

The analysis of sunscreens/organic UV filters in water has increased substantially the last two years, so this new category of emerging contaminant is included in this review for the first time. There are two types of UV filters—organic UV filters, which work by absorbing UV light, and inorganic UV filters (TiO_2, ZnO), which work by reflecting and scattering UV light. Organic UV filters are increasingly used in personal care products, such as sunscreens, and in cosmetics, beauty creams, skin lotions, lipsticks, hair sprays, hair dyes, and shampoos (*80*). Examples include benzophenone-3 (BP-3), octyldimethyl-*p*-aminobenzoic acid (ODPABA), 4-methylbenzylidene camphor (4-MBC), ethylhexyl methoxycinnamate (EHMC), octyl methoxycinnamate (OMC), octocrylene (OC), butylmethoxydibenzoylmethane, terephthalylidine dicamphorsulfonic acid, ethylhexyltriazone, phenylbenzimidazolesulfonic acid, ethylhexyl salicylate, and 1-(4-*tert*-butylphenyl)-3-(4-methoxyphenyl)-1,3-propanedione (BMMP). The majority of these are lipophilic compounds (low water solubility) with conjugated aromatic systems that absorb UV light in the wavelength range of 280−315 (UVB), 315−400 nm (UVA), or both (*81*). Most sunscreen products contain several UV filters, often in combination with inorganic micropigments (*81*).

Because of their use in a wide variety of personal care products, these compounds can enter the aquatic environment indirectly from showering, washing off, washing clothes, etc., via wastewater treatment plants and also directly from recreational activities, such as swimming and sunbathing in lakes and rivers. Recent studies have included measuring their occurrence in lakes, rivers, and the influents and effluents of wastewater treatment plants, as well as investigating aqueous photolysis reactions, and halogenation reactions in swimming pool water. GC/MS has been primarily used to track the organic UV filters and identify reaction products, since the majority of these UV filter compounds are lipophilic. Also, because they are lipophilic, extreme care must be taken during sampling and sample preparation, as these UV filter compounds are easily transferred to glassware and consumables, which can contribute to analytical blank problems (*81*).

Giokas et al. developed an analytical method using SPE with both LC-diode array detection (DAD) and GC/MS to quantify four UV filters in natural waters (*82*). LC-DAD was able to detect all four compounds (BP-3, 4-MBC, BPMP, OMC), but two compounds coeluted. This was not a problem when the DAD was used (since the two compounds had different UV spectra), but if a simple UV−visible detector was used (with a single wavelength measured), the use of sodium dodecyl sulfate as a phase modifier was necessary to allow chromatographic separations. Only three of the four UV filter compounds were detected by GC/MS; however, GC/MS offered much lower detection limits (low-ng/L levels). This method was used to measure these UV filters in

coastal waters from northwestern Greece and in shower wastewater. Sunscreen residues were found up to 10 ng/L.

Poiger et al. carried out an occurrence study of nine organic UV filter compounds from sunscreens in two Swiss lakes where recreational swimming is popular (*81*). SPE with GC/MS allowed low-nanogram per liter detection limits; semipermeable membrane devices (SPMDs) were also used for passive sample collection and to determine the potential for bioaccumulation. Concentrations measured (<2−125 ng/L) were lower than predicted based on surveys taken from swimmers and bathers at these lakes. This was proposed to be due to (1) an overestimation of these inputs (e.g., less than the 50% washoff of UV filters assumed to occur during swimming) and (2) some removal of these compounds from the lakes by degradation, sorption/sedimentation, or both. UV filters were detected in the SPMDs at concentrations of 80−950 ng per SPMD, which indicated a potential for bioaccumulation.

Another nice occurrence study by Balmer et al. measured four organic UV filters in the influent and effluent of wastewater treatment plants, in surface waters from four Swiss lakes and a river, and in fish collected from six Swiss lakes (*80*). The maximum concentration of UV filters in wastewater influents was 19 μg/L, and was much lower in the treated effluent water, indicating substantial elimination of these filters in the treatment plants. UV filters were detected in all surface waters sampled but were all at nanogram per liter levels, with a maximum of 125 ng/L observed for BP-3 in one of the lakes. 4-MBC was the most prevalent compound measured, followed by BP-3, EHMC, and OC. No UV filters were detected in the remote mountain lake sampled. All fish that were analyzed contained low concentrations of UV filters, with a maximum of 5 (whole fish) and 166 ng/g lipid.

Finally, Sakkas et al. studied the aqueous photolysis of the UV filter, ODPABA, and its reaction in chlorinated swimming pools to form halogenated byproducts (*83*). LC-DAD was used to follow the kinetics in the photolysis experiments, and SPE with GC/MS was used to identify swimming pool byproducts. Photolysis experiments were carried out both in controlled laboratory settings (using a xenon light source) and in natural sunlight conditions in seawater, swimming pool water, and distilled water. ODPABA was significantly photodegraded, with half-lives varying between 1.6 and 39 h in laboratory experiments and 27−39 h in natural sunlight conditions. Photodegradation mainly involved dealkylation and hydroxylation reactions; in swimming pool water, a number of additional halogenated byproducts were also found.

DRINKING WATER DISINFECTION BYPRODUCTS

In addition to new regulations involving DBPs (e.g., the Stage 2 D/DBP Rule), there are also new, emerging issues with DBPs (*84*). New human exposure research is revealing that ingestion is not the only important route of exposure—inhalation from showering (*85*) and dermal absorption (from bathing and other activities) can provide equivalent exposures or increased exposures to certain DBPs (*84*). Therefore, these exposure routes are now being recognized in new epidemiologic studies that are being conducted. And, epidemiology studies are beginning to focus more on reproductive and developmental effects—which recent studies have been shown to be important.

Toxicologically Important DBPs. Also, DBPs beyond those that are currently regulated are becoming important. For example, brominated DBPs are now being recognized as toxicologically important because brominated DBPs are proving to be much more carcinogenic than their chlorinated analogues (*84*), and preliminary studies are indicating that iodinated compounds may be more toxic than their brominated analogues (*84*). Brominated and iodinated DBPs form due to the reaction of the disinfectant (such as chlorine) with natural bromide or iodide present in source waters. Coastal cities, whose groundwaters and surface waters can be impacted by saltwater intrusion, and some inland locations, whose surface waters can be impacted by natural salt deposits from ancient seas or oil field brines, are examples of locations that can have high bromide and iodide levels. A significant proportion of the U.S. population and several other countries now live in coastal regions that are impacted by bromide and iodide; therefore, exposures to brominated and iodinated DBPs are important. Early evidence in epidemiologic studies also gives indication that brominated DBPs may be associated with the new reproductive and developmental effects, as well as cancer effects.

Specific DBPs that are of current interest include iodo acids, bromonitromethanes, iodo-THMs, brominated forms of 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone (MX), and NDMA (which is not brominated, but is classified as a probable carcinogen). Iodoacetic acid, one of five iodo acids identified for the first time in chloraminated drinking water, has recently been shown to be more genotoxic and cytotoxic to mammalian cells than all DBPs that have been studied, including the regulated HAAs and bromate (*86*). It is a factor of 2× more genotoxic than bromoacetic acid, which is the most genotoxic of the regulated HAAs. Other iodo acids identified—bromoiodoacetic acid, (*Z*)-3-bromo-3-iodopropenoic acid, (*E*)-3-bromo-3-iodopropenoic acid, and (*E*)-2-iodo-3-methylbutenedioic acid (*86*)—have been synthesized and are currently under investigation for possible genotoxic and cytotoxic effects. They were initially discovered in chloraminated drinking water extracts using methylation with GC/high-resolution-MS. In addition, analytical methods for the five iodo acids are currently under development for an occurrence study to determine their concentrations in chloraminated drinking water. These iodo acids are of concern not only for their potential health risks but also because early research indicates that they may be maximized (along with iodo-THMs) in waters treated with chloramines. Chloramination has become a popular alternative to chlorination for plants that have difficulty meeting the regulations with chlorine, and its use is expected to increase with the advent of the new Stage 2 D/DBP Rule. Chloramines are generated from the reaction of chlorine with ammonia, and it appears that the length of free chlorine contact time (before ammonia addition to form chloramines) is an important factor in the formation of iodo acids and iodo-THMs (*86*). Because of chlorine's competing reaction to form iodate as a sink for the natural iodide, it is likely that plants with significant free chlorine contact time before the addition of ammonia will not produce substantial levels of iodo acids or iodo-THMs (*86*).

The bromonitromethanes (including dibromonitromethane, tribromonitromethane, and bromonitromethane) have been recently shown to be extremely cytotoxic and genotoxic to mammalian cells (*87*). For example, dibromonitromethane is at least an order of magnitude more genotoxic to mammalian cells than MX and is more genotoxic than all of the regulated DBPs, except

for monobromoacetic acid. This study also involved the identification of new halonitromethanes using GC/high-resolution-MS. Following this investigation, nine chloro-/bromonitromethanes (equivalent to the nine chloro-/bromo-HAAs) were characterized as DBPs from chlorine and chloramines and have been shown to be increased in formation when preozonation is used before chlorine or chloramine treatment.

Bromonitromethanes, iodo-THMs, brominated forms of MX (so-called BMXs), and other "high-priority" DBPs were the focus of a U.S. Nationwide DBP Occurrence Study completed in 2002 (www.epa.gov/athens/publications/DBP.html). This Nationwide Occurrence Study focused on ~50 high-priority DBPs that were selected from an extensive prioritization effort (according to predicted cancer effects) of all DBPs that have been reported.

Many of the high-priority DBPs are also being measured as part of a large collaborative research effort involving scientists from the National Laboratories/Centers of the U.S. EPA's Office of Research and Development (ORD)— the National Health and Environmental Effects Research Laboratory, the National Exposure Research Laboratory, the National Risk Management Research Laboratory, and the National Center for Environmental Assessment (*88*). This effort involves the joint chemical and toxicological evaluation of mixtures of DBPs produced by different water treatment processes. A comprehensive chemical evaluation of the drinking waters is being made, including the quantitation of most of the high-priority DBPs included in the nationwide occurrence study. The toxicological evaluation focuses on reproductive and developmental end points, with assays for other important end points and target organs, such as mutagenicity, carcinogenicity, hepatotoxicity, nephrotoxicity, immunotoxicity, neurotoxicity, developmental neurotoxicity, and pharmacokinetics (*88*).

Other brominated DBPs have been the subject of new studies. First, Richardson et al. identified 2,3,5-tribromopyrrole and several brominated DBPs that have not been reported previously (*89*). This was the first report of a halogenated pyrrole as a DBP, and this was the first study of chlorine dioxide DBPs formed under high bromide/iodide conditions. GC with low- and high-resolution-MS was used for DBP identification. Most of the brominated DBPs were formed during prechlorination at an initial reservoir prior to the addition of chlorine dioxide−chloramines. Iodo-THMs were also identified and were found at higher levels in the water treated with chlorine dioxide−chloramines than in the prechlorinated water. In mammalian cell toxicity testing, tribromopyrrole was found to be 8× more cytotoxic than dibromoacetic acid (a regulated DBP) and to have about the same genotoxic potency as MX. When the formation of these DBPs was investigated using isolated humic and fulvic acid fractions collected from the source waters (as natural organic matter precursors), tribromopyrrole was found to be formed primarily from humic acid, whereas the THMs, HAAs, and aldehydes were mostly formed from fulvic acid.

Huang et al. investigated the effect of bromide and natural organic matter (NOM) on the formation of brominated DBPs, including bromo- and dibromoacetic acid, dibromoacetonitrile, and bromate, from ozonated groundwaters (*90*). 2,4-Dibromophenol was a new DBP identified. In addition, Lumbard et al. published a simple method for synthesizing brominated analogues of MX (BMXs) (*91*). Three BMXs could be made by a halogen exchange reaction of MX.

DBP Reviews. Four reviews have been published on DBPs in the last two years. Richardson published a review on DBPs and other emerging contaminants in drinking water for a special issue of *Trends in Analytical Chemistry* that focused on emerging contaminants (*84*). Several of the emerging, unregulated DBPs discussed earlier are included in this review. Von Gunten published two reviews on the ozonation of drinking water (*92, 93*). The first focused on the oxidation kinetics and byproduct formation (*92*), and the second focused on DBP formation in the presence of bromide, iodide, or chlorine (*93*). In the second article, the formation of iodate and bromate is discussed. Paull and Barron published a review on the use of IC to monitor HAAs in drinking water (*94*). Included in this review are discussions of ion interaction chromatography, ion exchange chromatography, and ion exclusion chromatography, as well as the coupling of IC with ESI-MS and ICPMS. Preconcentration methods and issues involving SPE extraction (e.g., poor recovery, nonreproducible recovery for different sample matrixes, etc.) are presented in detail.

Discovery Research for New Highly Polar and High Molecular Weight DBPs. More than 50% of the total organic halide (TOX) formed in chlorinated drinking water remains unidentified, and much lower percentages for ozone, chloramine, and chlorine dioxide DBPs have been accounted for. Because DBPs are typically present at nanogram to microgram per liter levels, they are usually extracted into an organic solvent (with solid-phase extraction or liquid−liquid extraction) and concentrated prior to measurement by GC or GC/MS. This means that most previous DBP research has focused on low molecular weight, volatile, and semi volatile DBPs that are easy to extract from water. As a result, high molecular weight DBPs and highly polar DBPs are likely to be found in the "missing" DBP fraction. In fact, earlier ultrafiltration studies indicate that >50% of the TOX in chlorinated drinking water is >500 Da in molecular mass (*84*), and new research is revealing that highly polar DBPs are also part of this missing fraction.

New Derivatizing Agents for Identifying Highly Polar DBPs. New derivatizing agents are being explored for the identification of highly polar DBPs that are believed to be present in treated drinking water but are missed with current methods. Zwiener et al. refined a previously published 2,4-dinitrophenylhydrazine (DNPH) derivatization-LC/MS method through the use of tandem mass spectrometry and also explored the use of *O*-(carboxymethylhydroxylamine) (CMHA) derivatization for as an alternative to DNPH (*95*). It was discovered that halogenated carbonyl DBPs can undergo side reactions with DNPH, where the chlorine atoms are substituted by DNPH. As a result, halogentated DBPs would be misidentified as nonhalogenated, oxygenated DBPs. CMHA was found to be a suitable alternative because it does not participate in any side reactions, and it also produced more structurally diagnostic ions that DNPH. Using the DNPH and CMHA as derivatizing agents, highly polar aldehydes, ketones, hydroxybenzaldehyde, and dicarbonyl DBPs were identified in chlorinated drinking water.

Vincenti et al. also explored the use of new derivatizing agents to identify highly polar DBPs with multiple hydroxyl, carboxy, and amino substituents (*96*). In this research, four highly

fluorinated chloroformate derivatizing agents were synthesized and reacted directly in water with several test compounds, including malic acid, resorcinol, 2,4-dihydroxylbenzoic acid, hydroxylamine, 3-aminopropanol, 3-aminophenol, and valine—some of these have been suspected to be potential drinking water DBPs. GC with chemical ionization (CI)-MS was used to measure the derivatization products. Direct aqueous sample derivatization is often tricky because most derivatizing agents undergo hydrolysis as soon as they come in contact with water. Vincenti et al. developed a clever solution to this problem by creating hydrophobic derivatizing reagents (alkyl and aryl chloroformates) that do not mix well enough with water to induce hydrolysis, but are put in contact with the DBP analytes through the use of ultrasonic emission. In addition, the use of fluorine atoms imparts volatility to the derivatives, allowing them to be measured by GC/MS. The fluorines also allow sensitive detection with ECNI-MS. These derivatizing reagents were successful in derivatizing the analytes, with octafluoropentyl chloroformate and pentafluorobenzyl chloroformate being the best candidates. The derivatizing reagents could be easily synthesized in 4 h, and the entire procedure from raw aqueous sample to ready-to-inject solutions of the derivatives requires less than 10 min.

High Molecular Weight DBPs. A new area of DBP research involves probing high molecular weight halogenated material that is formed upon disinfection. ESI-MS and MALDI-MS are allowing researchers to study this more in depth. Most of this work is very preliminary, due to the complexity of the mass spectra obtained ("a peak at every mass" situation). As a result, Minear's research group at the University of Illinois has been trying to find diagnostic ions that can be used to select halogenated DBPs from the complex mixture of high molecular weight DBPs (*97*). Chlorine-containing DBPs were found to form chloride ion fragments by MS/MS, which was suggested to be used as a "fingerprint" for chlorinated DBPs. Fractions of chlorinated Suwannee River fulvic acid were collected using size exclusion chromatography (SEC) and were analyzed by ESI-MS/MS. Hundreds of peaks were observed in the different SEC fractions, and preliminary MS/MS information was obtained for them. In a 2005 study, Minear and collaborators investigated high molecular weight DBP material from chlorinated Suwannee River fulvic acid with and without coagulation pretreatment (*98*). Fractions were collected using SEC, and the high molecular weight fractions were analyzed by negative ion-ESI-MS and ESI-MS/MS. Each fraction showed a distribution of ions from m/z 10 to 4000, with most ions present in the m/z 100−500 region. For the high molecular weight fractions, the ion intensities in fractions with coagulation pretreatment were much weaker than those in the corresponding fraction without coagulation pretreatment, indicating that coagulation may be significantly reducing the formation of high molecular weight DBPs. Precursor (parent) ion scans of m/z 35 (chlorine) were found to be useful for uncovering chlorine-containing DBPs, and product (daughter) ion scans were performed to confirm the presence of chlorine. However, full scan product ion spectra were too complex to allow definitive structural information. It was suggested that it is unlikely that any particular MS peak in the ESI-MS spectrum is due solely to a single structural or compositional isomer. However, this work does demonstrate that high molecular weight chlorine-containing DBPs are formed during chlorination, and it is an advance in the area of high molecular weight DBPs.

New Methods for Known DBPs. New analytical methods for known DBPs have also been developed. Jia et al. created a GC/electron capture negative ionization (ECNI, also called negative ion chemical ionization)-MS/MS method for determining nine HAAs in water, plasma, and urine at 25−1000 pg/mL (ng/L) detection limits (*99*). Rather than using methylation derivatization, as most HAA methods do, this method utilizes derivatization with pentafluorobenzyl bromide, which allows increased sensitivity for ECNI-MS. This is one of the first analytical methods developed that can measure the nine HAAs in biological samples at environmentally relevant concentrations.

Dixon et al. created a new HILIC-LC/MS/MS method that can quantify dichloroacetic acid in drinking water without derivatization (*100*). Common methods used to measure HAAs in drinking water generally involve the use of methylating agents (e.g., diazomethane, H_2SO_4/methanol, BF_3/methanol), two of these involving the use of strong acids. This HILIC-LC/MS/MS method was developed because of a recent finding that trichloroacetic acid can convert to dichloroacetic acid with acid methylation, which would result in artificially high levels of dichloroacetic acid being reported. HILIC is a method by which the aqueous solvent, rather than the organic, determines how quickly the compound elutes (*100*). HILIC columns contain a polar end group (such as an amino group), and retention is based on the affinity of the polar analyte for the charged end group of the column stationary phase. The use of HILIC-ion chromatography allowed dichloroacetic acid to elute away from the solvent front. Other methods have used ion-pairing agents to separate HAAs by LC, but the use of ion pairing reagents can suppress ionization in the mass spectrometer. With this HILIC-LC/MS/MS method, detection limits of 5 ng/mL (μg/L) were achieved using only a 500-μL water sample. This method is the only method for dichloroacetic acid analysis that has been validated using the criteria recommended by the U.S. FDA.

Gabryelski et al. developed a new ESI-high-field asymmetric waveform ion mobility spectrometry (FAIMS)-MS method for measuring HAAs in drinking water (*101*). FAIMS has been shown to significantly reduce the chemical background from ESI, allowing much lower detection limits with ESI-MS. This method can detect submicrogram per liter detection of the nine HAAs, with no sample preparation, derivatization, or chromatographic separation required. In addition, quantitation results using the FAIMS-MS method compared favorably to those from existing GC and GC/MS methods.

One of the more unusual methods developed involved the creation of a molecularly imprinted sensor for screening HAAs in drinking water (*102*). This sensor was based on a trichloroacetic acid-imprinted polymer membrane, which could bind selectively to HAAs. The sensors showed good cross reactivity with a wide range of HAAs, which would be useful for screening the HAAs together as a group. The sensor calibrations were linear over a range of 25−1000 μg/L, with the detection limit of each HAA in the range of 0.2−5.0 μg/L. This simple method appears to be promising for the rapid and sensitive detection of HAAs in drinking water.

Membrane introduction mass spectrometry (MIMS) was used by other researchers to investigate the stability of cyanogen chloride in chlorinated and chloraminated drinking water (*103*). In previous research, cyanogen chloride has been found as a DBP primarily in chloraminated drinking water. In this study, cyanogen chloride was found to decompose rapidly in the presence of free chlorine (half-life of 1 h with 0.5 mg/L free chlorine) but was stable in the presence of monochloramine. This may partly explain why cyanogen chloride is typically associated with chloraminated drinking water.

New methods have also been created for the measurement of iodophenols in water. A SPME-GC/ICPMS method reported the measurement of iodophenols (2-iodophenol, 4-iodophenol, 2,4,6-triiodophenol) down to low-nanogram per liter levels (*104*). A new commercially available interface between the GC and the ICPMS instrument helped to improve the sharpness of the peaks. A corresponding CE-ICPMS method created by the same research group allowed the detection of these iodophenols at submicrogram per liter detection limits (*105*). SPME was also used in this method to extract the analytes from water.

Choi and Reckhow developed a LC-fluorometric method for determining dichloroacetamide in water (*106*). Dichloroacetamide has been previously found as a DBP in chlorinated and chloraminated drinking water. After eluting from the LC column, dichloroacetamide was reacted with postcolumn reagents (*o*-phthaldialdehyde and sulfite ion at pH 11.5) to produce a highly fluorescent isoindole fluorophore, which was measured with fluorescence detection down to 23 μg/L. Diaz et al. evaluated the odor threshold of chlorobrominated anisoles in drinking water using a GC equipped with olfactometry and electron capture detectors (*107*). Trihalophenols have been found to be DBPs from chlorination or chloramination and can be biomethylated into trihalogenated anisoles that are suspected in odor episodes in drinking water around the world.

Human Exposure Studies. Interesting human exposure studies continue to be conducted for DBPs. These human exposure studies are not only useful to demonstrate exposure/uptake of DBPs in the human body, but they can also ultimately provide more accurate information about an individual's exposure, as compared to using water consumption questionnaires and quarterly water treatment plant data, which have been traditionally used in epidemiologic studies. Previous research has revealed that showering and bathing can result in higher blood levels of THMs than ingesting 1 L of water, and other recent research has demonstrated the permeability of certain DBPs across the skin. In a new study published in 2005, Xu and Weisel conducted a controlled human study on six subjects to determine the respiratory uptake of haloketones and chloroform (as a reference compound) during showering (*85*). Breath and air concentrations of the DBPs were measured using GC-electron capture detection during and following the inhalation exposures. A lower percentage of the haloketones (10%) was released from shower water to air than was chloroform (56%), which is more volatile. Breath concentrations were elevated during the inhalation exposure but declined rapidly afterward. Approximately 85−90% of the inhaled haloketones were absorbed, as compared to only 70% of the chloroform.

Other DBP Studies. Krasner and Wright investigated the effect of boiling water on DBP exposure (*108*). Hot water-based beverages can contribute substantially to overall water consumption levels and may have higher levels of certain DBPs compared to cold water (due to continued reactions of organic matter with residual chlorine in the hot water). Yet, few studies have measured DBPs formed from boiling water. This study investigated the effects of boiling on a wide range of regulated and emerging DBPs in chlorinated and chloraminated drinking water (*108*). In the chloraminated water, no significant change was observed for dihalogenated HAAs, but trihalogenated HAAs decreased in concentration upon boiling. In the chlorinated water, increased dihalogenated HAA levels were observed, and some of the trihalogenated HAAs decreased. THM levels were reduced in both the chloraminated and chlorinated waters, with chloroform being reduced by 75% after a 1-min boil in chloraminated water, but only by 34% in chlorinated water after a 1-min boil. Most of the remaining DBPs (haloketones, chloral hydrate, haloacetonitriles) were removed by at least 90% after 1-min boiling in both samples.

In another interesting occurrence study, an IC method was used to determine bromate and chlorinated HAAs in bottled water down to submicrogram per liter levels (*109*). In bottled natural water, levels of bromate, chlorate, and dichloroacetic acid were detected at 0.1, 0.9, and 0.6 μg/L. The total concentration of DBPs in the natural water sample was the highest among all of the bottled drinking waters, and the order from highest DBPs to lowest was, natural water > mineral water > spring water > purified water. Bromate and chlorate were stable over time in the bottled waters (when found), but dichloroacetic acid did decrease in concentration over time.

Finally, Monarca et al. developed a combined toxicity−chemical identification approach to investigate the formation and toxicity of DBPs and used it to investigate a new disinfectant, peracetic acid (PAA) in a drinking water pilot plant (*110*). Waters treated with chlorine dioxide and hypochlorite were also studied for comparison. A battery of short-term in vivo and in vitro tests were used to evaluate the toxicity and genotoxicity in treated drinking waters. These tests included plant, fish, and mollusk bioassays and in vitro tests with bacteria, yeast, fish, and human cells. GC with low- and high-resolution-MS was used to comprehensively identify all of the DBPs detected. Among the disinfectants studied, hypochlorite produced the highest levels of DBPs, with PAA always producing the lowest DBP levels observed. However, the bactericidal activity of PAA was lower than for hypochlorite and chlorine dioxide. Results from the in vivo and in vitro toxicity/genotoxicity tests were used to adjust the amounts of disinfectants added to avoid toxicity in the bioindicators (fish, mollusks, plants).

NDMA and Other Nitrosamines. Until recently, concerns about NDMA primarily stemmed from its presence in food, beverages, consumer products, contaminated groundwater (from the use of rocket fuel), and polluted air (e.g., tobacco smoke) (*111*). However, it has recently become evident that NDMA is also a drinking water DBP, which could make human exposure more widespread. It has primarily been found in chloraminated drinking water, where the nitrogen in monochloramine (NH_2Cl) is incorporated into the structure of the NDMA byproduct formed. Chlorination can also form NDMA to some extent, when there

are nitrogen precursors present (e.g., natural ammonia in the source water or nitrogen-containing coagulants used in the water treatment process). NDMA was initially discovered in chlorinated drinking waters from Ontario, Canada, and has recently been found in other locations and in laboratory studies. The observation of NDMA in U.S. waters is largely due to improved analytical techniques that have allowed its determination at low-nanogram per liter concentrations. Recent measurements have shown it is generally present at low-nanogram per liter concentrations in chloraminated/chlorinated drinking water, but it can be formed at much higher levels in wastewater treated with chlorine. Following its discovery in California well water, the State of California issued an action level of 0.002 μg/L (2 parts per trillion) for NDMA, which was subsequently revised to 0.01 μg/L, due to the analytical difficulty in measuring it at the original proposed level. The California Department of Health Services has a website that provides further background and details about NDMA (www.dhs.ca.gov/ps/ddwem/chemicals/NDMA/NDMAindex.htm). This site also provides a link to the 2002 U.S. National Toxicology Program report on NDMA. NDMA is not currently regulated in the United States for drinking water. It has been considered for the CCL but is currently not listed. Canada (as a country) does not regulate NDMA, but Ontario has issued an interim maximum acceptable concentration for NDMA at 9 ng/L (www.ene.gov.on.ca/envision/gp/4449e.pdf).

Mitch et al. published a review in late 2003 that discusses issues with NDMA as a drinking water contaminant, including potential approaches for removing organic nitrogen precursors and the use of UV treatment to minimize/eliminate NDMA in drinking water (*111*). This review article also discusses analytical methods used for the analysis of NDMA and the sources and occurrence of NDMA.

New research is expanding beyond NDMA, the first nitrosamine discovered as a DBP, to other nitrosamines. As mentioned earlier in the Regulatory Methods section, a new EPA method has been created for measuring NDMA and six additional nitrosamines in drinking water (EPA Method 521, Determination of Nitrosamines in Drinking Water by Solid-Phase Extraction and Capillary Column Gas Chromatography with Large Volume Injection and Chemical Ionization Tandem Mass Spectrometry (MS/MS) (www.epa.gov/nerlcwww/m_521.pdf). This method enables the measurement of NDMA and six other nitrosamines (*N*-nitrosomethylethylamine, *N*-nitrosodiethylamine, *N*-nitroso-di-*n*-propylamine, *N*-nitroso-di-*n*-butylamine, *N*-nitrosopyrrolidine, *N*-nitrosopiperidine) in drinking water at detection limits ranging from 1.2 to 2.1 ng/L.

Probably the most significant study of NDMA and nitrosamines in the last two years was the discovery of nitrosamines beyond NDMA in finished drinking water. Charrois et al. discovered two new nitrosamines—*N*-nitrosopyrrolidine and *N*-nitrosomorpholine—in finished drinking water (both at the plant and in the distribution system) from two cities in Canada that use chloramination for treatment (*112*). This represents the first report of other nitrosamines besides NDMA in drinking water. Levels of *N*-nitrosopyrrolidine ranged from 2 to 4 ng/L, and *N*-nitrosomorpholine was found in drinking water from one city at 1 ng/L. NDMA was also found in drinking water from these cities and ranged from 2 to 180 ng/L. This 180 ng/L level, which was found in the distribution system of one city, is one of the highest to-date concentrations that has been observed for NDMA in drinking water. The data in this study indicate that NDMA (and other nitrosamines) can continue to form in the distribution system and show dramatically increased levels in the distribution system as compared to the drinking water treatment plant (e.g., from an initial 67 ng/L NDMA at the plant to 180 ng/L in the distribution system). This suggests that previous measurements of NDMA at the treatment plant may substantially underestimate the public's exposure to this probable carcinogen. A SPE-GC/positive ion-CI-MS method (with 0.4−1.6 ng/L detection limits), which used both isotope dilution/surrogate standards and internal standards, was used to measure these nitrosamines.

In another important study, Wilczak et al. investigated the effect of a popular nitrogen-containing coagulant on the formation of NDMA in drinking water (*113*). For this research, controlled laboratory studies were carried out by reacting the diallyldimethylammonium chloride (DADMAC) polymer with chlorine and chloramines in pure water; pilot plant studies were carried out by using the DADMAC polymer in a pilot plant that utilized chlorine, chloramines, ozone, and their combinations; and full-scale drinking water treatment plants using DADMAC and chlorine/chloramine disinfection were investigated. Results showed that chloramine was necessary to form significant levels of NDMA with DADMAC; much lower levels were observed with free chlorine. The levels of NDMA observed strongly depended on the amount of DADMAC used; NDMA concentrations in the distribution system decreased with decreasing DADMAC doses. The length of free chlorine contact time before ammonia addition (to form chloramines) was also an important component—a free chlorine contact time of 1−4 h before ammonia addition resulted in much lower NDMA levels. Further, it appeared that recycled filter backwash water was a significant source of NDMA precursors, likely due to recycling of residual DADMAC polymer. For this study, a GC/CI-MS/MS method was used, which involved liquid−liquid extraction into methylene chloride and the use of an NDMA-d_6 internal standard. Method detection limits ranged from 0.2 to 0.7 ng/L.

GC/CI-MS/MS was also used by Garecke and Sedlak in another study to investigate the precursors of NDMA in natural waters (*114*). For this study, samples from lakes, reservoirs, groundwaters, and isolated natural organic matter were reacted with monochloramine. A compound that had been previously suggested to be an important precursor of NDMA—dimethylamine—turned out to be responsible for only a small fraction of the NDMA produced. Results showed that NOM accounts for a significant fraction of the precursors. However, NOM could not account completely for the amount of NDMA formed in drinking water treatment. As a result, it is suggested that nitrogen-containing coagulants (like DADMAC mentioned above) are probably also significant precursors. Unplanned wastewater reuse was also suggested as a source of NDMA, as wastewater typically contains 50−500 nM dimethylamine, which would be enough to contribute to increased NDMA formation. In an investigation of NDMA precursors in wastewater treatment plants, Mitch and Sedlak measured NDMA after extended chloramination in advanced wastewater treatment plants and in reactions of model precursors (*115*). Of the model precursors investigated, only

dimethylamine, tertiary amines with dimethylamine functional groups, and dimethylamides formed significant NDMA levels upon chloramination. In samples from municipal wastewater treatment plants, dissolved NDMA precursors were always present in primary and secondary effluents. Biological treatment was found to remove dimethylamine, but it was not effective for removing the other NDMA precursors.

Choi and Valentine investigated the mechanism of formation of NDMA in chlorinated drinking water (*116*). The formation of NDMA by the nitrosation of dimethylamine was found to be greatly enhanced by the presence of free chlorine, which suggested the formation of a highly reactive nitrosating intermediate. However, the general importance of this mechanism in drinking water is limited by the amount of dimethylamine generally present, which suggests the potential involvement of other nitrogen redox reactions.

Formation of DBPs from Contaminants in Source Waters. All of the DBP studies discussed above primarily involve the traditional formation of DBPs from natural organic matter. However, there have been a number of recent investigations that have shown that water contaminants can also react with disinfectants used in drinking water treatment to form their own byproducts. For example, there are recent reports of DBPs formed by chlorine or ozone treatment of bisphenol A, estrogens (ethinylestradiol, estradiol), alkylphenol ethoxylates and their metabolites, pesticides, an antibacterial agent, and cyanobacterial toxins. It is actually not surprising that DBPs can form from these contaminants, as many of them have activated aromatic rings that can readily react with oxidants such as chlorine and ozone. However, until recently, these types of DBPs have not been investigated. Due to the growth in this area and the potential toxicological significance of these new types of byproducts (by increasing or decreasing the toxicity/biological effect relative to the parent compound), this research area is included in this review for the first time.

Moriyama et al. investigated the formation of reaction products formed by the chlorination of ethinylestradiol (EE2), which is a widely used synthetic estrogenic steroid in birth control pills and in postmenopausal hormonal supplements (*117*). In reactions with chlorine, six products were identified, with 4-chloroethinylestradiol (4-ClEE2) and 2,4-dichloroethinylestradiol (2,4-diClEE2) being the major products. LC/APCI-MS, preparative LC, high-resolution fast atom bombardment (FAB)-MS, and NMR spectroscopy were used to identify the reaction products. The estrogenic activity of 4-ClEE2 was found to be similar to the parent EE2, whereas the estrogenic activity of 2,4-diClEE2 was 10 times lower. In another study, Huber et al. identified ozonation products of EE2 and the natural steroid hormones, 17β-estradiol (E2) and estrone (E1), using LC/ESI-MS/MS and GC/MS (*77*). Reactions involving model compounds also helped in determining precise structures of the byproducts. EE2 formed 11 ozonation reaction products, including adipic acid, cyclohexanone, 1-hydroxycyclohexane-1-carboxylic acid, 1-hydroxycyclopentane-1-carboxylic acid, and other carboxylic acids containing cyclohexane or cyclopentane rings. Surprisingly, E1 and E2 formed the same two major byproducts (keto acids containing cyclohexane and cyclopentane rings), which were also formed in the ozonation of EE2. Significantly diminished estrogenic activity was observed in the water following ozonation, which indicates that ozonation may be promising for controlling estrogens in drinking water and wastewater.

Reaction products of the antibacterial agent sulfamethoxazole with chlorine were also recently investigated using LC/MS. Sulfamethoxazole is an important member of the class of sulfa drugs that has been used for many years in human and veterinary medicines, and it has been found as a contaminant in drinking waters, surface waters, and wastewaters. In this study by Dodd and Huang, chlorine was found to react with the aniline nitrogen, resulting in halogenation to form a ring-chlorinated product, or rupture of the sulfonamide group to form 3-amino-5-methylisoxazole, sulfate, and *N*-chloro-*p*-benzoquinoneimine (*78*). Reactions investigated in real drinking water and wastewater matrixes revealed that substantial conversion of the sulfamethoxazole would be achieved for typical residence times (1−24 h for drinking water and 3−30 min for wastewater). However, it was noted that the parent compound can be re-formed from an intermediate under wastewater treatment conditions that are typical in North America (dechlorination using reduced sulfur compounds), and this may partly explain the presence of sulfamethoxazole in surface waters.

Alkylphenol ethoxylates, which are widely used surfactants in detergents and other cleaning agents, have also been found to react during drinking water disinfection with chlorine. In a study by Petrovic et al., source waters for the drinking water treatment plant investigated contained significant inputs of nonylphenol ethoxylates and their nonylphenol and nonylphenoxy carboxylate metabolites from several wastewater plant effluents (*118*). Significant natural bromide levels were also present in the source waters, due to salt mine runoff upstream of the drinking water treatment plant. Halogenated nonylphenolic compounds represented 13% of the total reaction products observed, and 97% of these were brominated. Brominated nonylphenol ethoxylates, nonylphenol carboxylates, and nonylphenols were formed after prechlorination at the plant, with a maximum of ~2.5 μg/L for a bromononylphenolcarboxylate. However, levels decreased substantially during subsequent treatment in the plant (flocculation, sand filtration, ozonation, and granular activated carbon (GAC) filtration), such that levels in the finished water rarely exceeded 20 ng/L. A highly sensitive LC/MS/MS method was developed to quantify these byproducts.

Pesticides have been the focus of other studies. For example, the reaction of the herbicide isoxaflutole in chlorinated tap water was investigated using LC−UV and LC/MS/MS (*119*). Rather than producing halogenated products, the major byproduct was a benzoic acid metabolite (an oxidation product), which is the same nonbiologically active degradation product that isoxaflutole forms under natural, environmental conditions. One milligram per liter hypochlorite residual in tap water was found to completely oxidize up to 1600 μg/L of this herbicide, with no biological activity observed after 48 h of storage.

Another study investigated the oxidation of the cyanobacterial toxin, microcystin-LR by chlorine dioxide (*120*). LC/MS/MS was used to identify the reaction products formed, which were dihydroxy isomers of microcystin-LR and were nontoxic in a protein phosphatase inhibition assay. MS/MS helped to determine that the main point of attack of chlorine dioxide was directed at the two conjugated double bonds in the Adda residue of the microcystin.

BROMINATED FLAME RETARDANTS (POLYBROMINATED DIPHENYL ETHERS)

PBDEs have been used for many years as flame retardants in a variety of commercial products including foam cushions in chairs and other furniture, plastics, textile coatings, electronic appliances, and printed circuit boards. Of the 175 different types of flame retardants, the brominated ones dominate the market due to their low cost and high performance (*121*). The use of these flame retardants is believed to have successfully reduced fire-related deaths, injuries, and property damage. However, there is recent concern regarding these emerging contaminants because of their widespread presence in the environment and in human and wildlife samples and their presence in locations far from where they were produced or used. There is also strong evidence of increasing contamination (*121*). Worldwide, more than 200 000 metric tons of brominated flame retardants are produced each year, with PBDEs accounting for 67 400 metric tons per year, and more than 50% of that being used in the United States and Canada (*121*). The greatest health concern for potential health effects comes from recent reports of developmental neurotoxicity in mice (*121*), but there are also concerns regarding the potential for hormonal disruption and, in some cases, cancer. Due to concerns about potential adverse development effects and the widespread presence of these compounds, there has been a directive established to control emissions of these compounds in Europe. In the United States, however, it has taken more time for these contaminants to be noticed. Only very recently were studies from the United States beginning to be published. As evidence of increased interest in this area, there are several reviews on the subject published within the last two years and many more studies that have been completed. In 2003, California voted to ban the use of octa- and pentylbromodiphenyl ether beginning in 2008; however, PBDEs are not regulated on a national scale in the United States (*121*).

Although the most frequently used PBDE is deca-BDE, lower brominated PBDEs are more often found in environmental samples (*122*). In contrast to the deca-BDE, which is poorly absorbed biologically, rapidly eliminated, and not bioaccumulated, the lower molecular weight congeners (tri- to hexa-BDEs) are almost completely absorbed, slowly eliminated, and highly bioaccumulated (*122*).

Most previous PBDE studies have focused on the measurement of PBDEs in biological samples, including human blood, milk, and tissues, as well as marine mammals and other wildlife. However, over the last two years, there are increasing measurements in environmental waters. As a result, PBDEs are included in this water analysis review for the first time. Because PBDEs are hydrophobic, GC with EI-MS and ECNI-MS can be used for their measurement. Some methods also use high-resolution EI-MS with isotope dilution, and a new method uses GC/tandem-MS.

One of the PBDE reviews, published by U.S. EPA authors, Birnbaum and Staskal, was entitled, "Brominated Flame Retardants: Cause for Concern?" (*121*). In this article, the authors discuss scientific issues associated with the use of PBDEs, tetrabromobisphenol A, and hexabromocyclododecane, including occurrence, chemical properties, bioaccumulation, health effects, and environmental fate. These authors cite the need for more systematic environmental and human monitoring to understand how and where these chemicals are being released into the environment, how they get into people, their environmental fate, and more health effects research. Alaee also wrote an excellent review article entitled, "Recommendations for Monitoring of Polybrominated Diphenyl Ethers in the Canadian Environment" (*123*). Reports of PBDE occurrence in air, surface waters, suspended sediments, soil, sediment, fish, marine mammals, and bird eggs throughout Canada are cited, including in the most northernmost reaches of the Canadian Arctic. PBDEs have also been found in human breast milk in every Canadian province (*123*). This review discusses several different analytical methods that have been used to measure PBDEs in environmental and biological samples. GC/high-resolution-based isotope dilution methods are cited as representing the best tools for future environmental monitoring programs. Hale et al. published a similar review covering PBDE flame retardants in the North American environment (*124*). Occurrence of PBDEs in air, surface waters, sewage treatment plant effluents, sewage sludge, sediments, soil, and aquatic organisms was reviewed. D'Silva et al. published another review that discusses the ecological and environmental impact of the use of PBDEs and other brominated flame retardants (*125*).

Covaci et al. reviewed analytical methods for determining brominated flame retardants, with a special emphasis on PBDEs (*126*). In this review, sample pretreatment, extraction, cleanup and fractionation, injection techniques, chromatographic separation, detection methods, quality control, and method validation are discussed. Scrimshaw et al. reviewed analytical methods for determining PBDEs in wastewaters and sewage sludge (*127*). Extraction, cleanup, and quantitation by GC/MS are included.

In another review article, Hites summarizes PBDE concentrations measured in several environmental media and analyzes these data in terms of relative concentrations, concentration trends, and congener profiles (*128*). The data show increasing levels of PBDEs in human blood, milk, and tissues, as well as in marine mammals and bird eggs. A case was made that the environment and people from North America are much more contaminated with PBDEs as compared to Europe and that these levels have doubled every 4−6 years. However, analyses did not show patterns that could be used to attribute specific sources of contamination.

Polo et al. developed a new SPME-GC/MS/MS method for measuring PBDEs and polybrominated biphenyls in water (*122*). This is the first published method to use SPME for determining PBDEs in water and also the first tandem-MS method. The lower brominated PBDEs that are highly absorbed and bioaccumulated were the target of this method: 2,2′,4,4′-tetrabromodiphenyl ether (BDE-47), 2,2′4,4′,5-pentabromodiphenyl ether (BDE-99), 2,2′4,4′,6-pentabromodiphenyl ether (BDE-100), 2,2′3,4,4′-pentabromodiphenyl ether (BDE-85), 2,2′,4′,5,5′-hexabromodiphenyl ether (BDE-153), and 2,2′4,4′,5,6′-hexabromodiphenyl ether (BDE-154). Headspace-SPME allowed effective recoveries for these compounds, and detection limits were extremely low, ranging from 7.5 to 190 pg/L. This method was tested using tap water, influent wastewater, and effluent wastewater.

In one of the occurrence studies, Oros et al. measured PBDEs in water, surface sediments, and bivalves from the San Francisco estuary using GC/EI-MS (*129*). PBDE levels ranged from 3 to 513 pg/L, with the highest concentrations found in the Lower

South Bay region, which receives ~26% of the estuary's wastewater treatment plant effluents.

ALGAL TOXINS

The increase in frequency and intensity of harmful algal blooms has led to increased incidence of shellfish poisoning, large fish kills, and deaths of livestock and wildlife, as well as illness and death in humans. Toxins produced by these algae have been implicated in these adverse effects. Algal toxins that impact human health are generally categorized as neurotoxins or hepatotoxins that are produced from dinoflagellates, diatoms, or cyanobacteria (blue-green algae). Dinoflagellate and diatom toxins impact humans primarily through the consumption of seafood, and cyanobacterial toxins can impact humans through drinking water contamination. For example, saxitoxins, which have heterocyclic guanidine structures, are produced by dinoflagellates and cyanobacteria and cause paralytic shellfish poisoning. Anatoxins, which have heterocyclic structures, are produced by cyanobacteria and are neurotoxic. Microcystins, nodularins, and cylindrospermopsin, which have cyclic peptide structures, are produced by cyanobacteria and are hepatotoxic. "Red tide" toxins, which have heterocyclic polyether structures, are produced by red tide dinoflagellates (mostly from *Gymnodinium breve*) and are neurotoxic. The National Oceanic and Atmospheric Administration (NOAA) has a nice website that provides the structures of these algal toxins and further details (www.chbr.noaa.gov/CoastalResearch/algaeInfo.htm). Algal toxins are currently on the U.S. EPA's CCL list. Australia also has a guideline limit for microcystin-LR of 1.3 μg/L in drinking water. Many of these toxins are peptide-related, have relatively high molecular weights, and are highly polar, which hindered their environmental measurement until the recent application of ESI- and APCI-MS techniques.

Methods that have been developed for algal toxins include ELISAs, protein phosphatase inhibition assays, LC-photodiode array/UV, LC/ELISA, LC/MS, LC/MS/MS, MALDI-MS, and ESI-FAIMS-MS. Using these methods, detection limits ranging from low-nanogram to low-microgram per liter can be achieved.

Although there has been some epidemiologic evidence linking symptoms of human poisoning to cyanobacterial toxins, the presence of specific algal toxins in finished drinking water had not been proven analytically until a recent discovery of cyanobacterial toxins in finished drinking waters in Florida (*1*) and in a survey of U.S. and Canadian drinking waters sponsored by the American Water Works Association Research Foundation (*1*). To that end, Svrcek and Smith published a review on cyanobacterial toxins and the current state of knowledge on water treatment options (*130*). Included in this review is a discussion of cyanobacteria and their ability to produce a variety of toxins, proposed or accepted regulatory guidelines, common detection techniques, recommendations for future research to advance the abilities of utilities to deal with these toxins, and immediate steps that can be taken for utilities to minimize human exposure to these toxins.

Hoeger et al. used ELISA, a colorimetric protein phosphatase assay, LD-DAD, and LC/MS/MS to measure the occurrence of three cyanobacterial toxins—microcystins, saxitoxins, and cylindrospermopsin—in Australian drinking water plants (*131*). Depending on the predominant cyanobacterial species in bloom, concentrations in the raw source waters reached 8.0, 17.0, and 1.3 μg/L for microcystins, saxitoxins, and cylindrospermopsin, respectively. One-third of the source water samples contained significant concentrations of cyanobacterial toxins. However, much lower levels (<1.0 μg/L) of these toxins were detected in the finished tap water. Issues were raised with regard to water treatment including the potential for chlorine to destroy intact cells and release the intracellular toxins, the potential for mechanical pumping to cause cell lysis and release toxins, and the inability of chlorine to destroy microcysins and saxitoxins. Because the risk of breakthrough of toxin concentrations exceeding the Australian guidelines (1.3 μg/L) was recognized to be possible, it was suggested that treatment plants closely monitor phytoplankton and toxin concentrations during the treatment steps to ensure the production of safe drinking water.

Several new LC/MS methods have been developed over the last two years for measuring algal toxins in water. First, Maizels and Budde created a new LC/ESI-TOF-MS method (*132*). A resolution of 5000 allowed exact mass information to be obtained, with most single measurement errors of <10 ppm. Because the TOF-mass spectrometer allows sensitive full scan acquisition and real-time exact m/z measurements, this method precludes the need to specify target m/z ions for selected ion monitoring or MRM. Method detection limits (MDLs) were generally <1 μg/L for anatoxin-a, microcystin-LR, microcystin-RR, microcystin-YR, and nodularin. Zhang et al. created a LC/ESI-MS/MS method for determining microcystin-LR in surface water, which permitted extremely low detection limits of 2.6 ng/L (*133*). Meriluoto et al. created a high-throughput LC/ESI-MS method for analyzing 10 microcystins and nodularins (*134*). This method enabled very fast analysis times of 2.8 min/sample, which allowed the measurement of 514 samples/day. Detection limits were 50−100 pg/injection but could be lowered further to 5−10 pg through the use of newer instrumentation. Dahlmann et al. developed a LC/ESI-MS/MS method for measuring saxitoxin, anatoxin-A, domoic acid, nodularin, microcystins, okadaic acid, and dinophysistoxin-1 with a single chromatographic run (*135*). In addition, the chromatographic conditions allowed the isolation and identification of substances suspected to be new microcystins (cyclic peptides) by fraction collection, hydrolysis, derivatization of free amino acids, and enantioselective analysis of the amino acid derivatives by LC/ESI-MS.

LC/MS/MS has also been used by several researchers to identify new algal toxins. For example, Furey et al. used LC/ESI-MS and LC/MS/MS to identify a rare cyanobacterial toxin—homoanatoxin-a—in waters from four lakes in Ireland (*136*). This toxin was originally detected using SPE, derivatization, and LC−UV detection. Confirmation of the toxin identity was made using LC/MS and LC/MS/MS. In another study, MALDI-TOF-MS was used to measure microcystins in lake water in Algeria. Microcystin levels ranged from 3 to 29 163 μg/L (*137*).

Yuan and Carmichael used an unusual technique, surface-enhanced laser desorption/ionization-TOF-MS, to develop a method for microcysins and nodularins in water (*138*). This technique involves the capture, purification, analysis, and processing of complex biological mixtures directly onto a hydrophobic chip. With this method, 2.5 pg of microcystin-LR could be detected in 2 μL of water (equivalent to 1.2 μg/L). Finally, Moutfort et al. used a combination of a protein phosphatase inhibition assay and

ELISA to measure microcystins in water (*139*). This new method allowed the stoichiometric determination of microcysins, along with the indicative toxicity, and helps to overcome the overestimation of toxicity using a single ELISA.

PERCHLORATE

Perchlorate has recently become an important environmental issue since its discovery in 1997 in a number of water supplies in the western United States. It has also recently been found in water supplies across the United States at microgram per liter levels. High quantities of perchlorate have been disposed of since the 1950s in Nevada, California, and Utah, which is believed to have contributed to much of the contamination in the western United States. However, new analyses have revealed that perchlorate contamination is not limited to the western United States; even areas such as Washington, D.C. have reported perchlorate contamination, possibly caused by buried munitions. Ammonium perchlorate has been used as an oxygenate in solid propellants used for rockets, missiles, and fireworks, and there is also possible contamination that can occur through the use of fertilizers (that contain Chilean nitrate). Perchlorate is an anion that is very water soluble and environmentally stable. It has shown to accumulate in plants, which could be a potential source of perchlorate exposure to humans and animals. In addition, perchlorate is not removed by conventional water treatment processes, so human exposure could also come through drinking water. Health concerns arise from perchlorate's ability to disrupt the thyroid gland's use of iodine in metabolic hormones, which could affect normal metabolism, growth, and development. Due to these concerns, the U.S. EPA has placed perchlorate on the CCL for further study.

Most earlier methods have used IC for measuring perchlorate in water. As mentioned earlier in the Regulatory Methods section, there have been three new EPA methods created for perchlorate. One uses IC with suppressed conductivity detection, another uses IC-suppressed conductivity-ESI-MS with an O-18 labeled internal standard, and the third uses LC/ESI-MS/MS with an O-18 labeled internal standard. Other new methods developed over the last two years involve the use of LC/MS/MS, IC with suppressed conductivity, Raman spectroscopy, attenuated total reflectance-FT-infrared (IR) spectroscopy, and a new perchlorate sensor.

The new LC/MS/MS method allows a MDL of 0.05 μg/L in water and did not show significant suppression effects at high salt levels tested (*140*). An IC-suppressed conductivity method developed by Smith et al. allowed an MDL of 1.0 μg/L and was used to measure perchlorate in water, soil, vegetation, and rodents collected from the Las Vegas Wash, NV (*141*). Despite recent remedial efforts, which have reduced the total input of perchlorate, an estimated 500 lbs of perchlorate still enters the Las Vegas Wash each day (*141*). Liu and Mou developed an IC method to simultaneously measure perchlorate and nine HAAs in drinking water (*142*). With a hydrophilic column and a gradient elution of sodium hydroxide, methanol, and deionized water, the nine HAAs, perchlorate, fluoride, chloride, nitrite, and nitrate could be simultaneously determined in one run within 34 min. MDLs ranged from 1.11 to 9.32 μg/L for the HAAs and 0.60 μg/L for perchlorate.

Alternative techniques to IC and MS methods have been recently developed, although they are generally not as sensitive and cannot reach sub-ppb detection limits. However, they still could be useful for highly contaminated groundwaters and are potentially simpler methods. Gu et al. developed a surface-enhanced Raman spectroscopy method for perchlorate, which permitted MDLs of 10−100 μg/L (*143*). Raman spectroscopy has the potential for in situ measurements of perchlorate (since it is "invisible" to water), and in situ probes can be developed for real-time monitoring. Hebert et al. developed an attenuated total reflectance-FT-IR method, which permitted ~3 μg/L detection limits for perchlorate and also allowed the detection of chlorate and sulfonate and phosphonate contaminants in a 10-min analysis (*144*). Finally, Ganjali et al. developed a highly selective and sensitive perchlorate sensor that could detect perchlorate at 20−50 μg/L levels (*145*). These sensors were based on Ni(II)−hexaazacyclotetradecane complexes and showed good selectivity for perchlorate in comparison with most common organic and inorganic ions.

METHYL *TERT*-BUTYL ETHER

MTBE contamination is a relatively recent concern, due to its introduction to groundwater and surface waters through leaking underground gasoline storage tanks and discharges of fuel from boats and other watercraft. MTBE has been used as a gasoline additive since its introduction in 1979 as an octane enhancer during the organolead phaseout. It is also used to improve combustion and to reduce emissions of ground-level ozone and other toxic pollutants; by 1998, MTBE was added to ~30% of all gasoline sold in the United States. In the United States, the 1990 Amendments to the Clean Air Act require a minimum oxygen content of 2.7 (w/w) and 2.0% (w/w) for gasolines sold in areas of the country where carbon monoxide and ozone air standards are exceeded, respectively. In Europe, there are no minimum oxygen content requirements for gasoline, but the addition of up to 15% (v/v) is allowed, and it is estimated that ~2 million tons of MTBE is added to gasoline in Europe each year. MTBE is the most common oxygenate added to gasoline because of its low cost, availability, and high octane rating. Ethanol, ETBE, TAME, DIPE, and TBA are also sometimes used as gasoline oxygenates, but are not as popular as MTBE.

MTBE has been responsible for taste and odor problems in drinking water, and there are also concerns about possible adverse health effects. The U.S. EPA recommends monitoring of oxygenate compounds in groundwater at leaking underground storage tank sites, and MTBE has been included in the final Unregulated Contaminant Monitoring Rule that will require all large public water systems and a statistical sampling of small and medium public water systems to monitor and report the presence of MTBE in their water supplies (www.epa.gov/safewater/mtbe.html). The U.S. EPA is continuing to study both the potential health effects and the occurrence of MTBE, and it is currently on the CCL for which EPA is considering setting health standards. While there are not U.S. federal bans or MCLs yet, several states have developed their own standards for MTBE in drinking water, and several states have banned the use of MTBE in gasolines. These include Arizona, California, Colorado, Connecticut, Delaware (effective 2006), Illinois, Indiana, Iowa, Kansas, Kentucky (effective

2006), Maine (effective 2007), Massachusetts (effective December 2005), Michigan, Minnesota, Missouri (effective July 2005), Nebraska, Nevada (Washoe County), New Hampshire (effective 2007), New Jersey, New York, Ohio (effective July 2005), Pennsylvania, Rhode Island (effective July 2005), South Dakota, Vermont (effective July 2005), Washington, and Wisconsin. In addition, the State of California was a bit forward-thinking when they set limits on the use of other oxygenates that might be used as alternatives to MTBE—as of December 2003, California no longer permits the sale of gasolines containing ETBE, TAME, DIPE, methanol, 2-propanol, 1-propanol, 1-butanol, isobutanol, *sec*-butanol, *tert*-butyl alcohol, or *tert*-pentanol (*tert*-amyl alcohol) that total more than 0.10% (w/w). There are strategies to remove MTBE from source waters or drinking water, including air stripping, GAC, advanced oxidation, and home treatment units (www.epa.gov/safewater/mtbe.html).

GC/MS is probably the most common analytical technique used to measure MTBE. SPE, headspace-SPME, and purge-and-trap are popular extraction techniques. Direct aqueous injection and direct headspace analysis have also been used. Methods can generally detect MTBE in the low-microgram per liter range. In water, MTBE can degrade to TBA and *tert*-butyl formate (TBF), so these degradates are sometimes analyzed along with MTBE. A review of analytical techniques for measuring MTBE and its degradate, TBA, was published in 2003 by Schmidt (*146*). Advantages and disadvantages of each technique are discussed. Deeb et al. also published a review on environmental sources, analysis, occurrence, and treatment strategies for MTBE and other oxygenates (*147*).

The occurrence of MTBE has been the focus of studies both in the United States and in Europe. A national U.S. survey on the frequency of detection, concentration, and distribution of MTBE in source waters was published in 2003 (http://wwwsd.cr.usgs.gov/nawqa/vocns/nat_survey.html). This study was conducted by the U.S. Geological Survey and the Metropolitan Water District of Southern California and was sponsored by the American Water Works Association Research Foundation. This study includes samples from ~1000 untreated groundwater and surface water sources for drinking water used by community water systems in the United States. In another occurrence study, Williams et al. compared MTBE levels in groundwater versus surface waters collected from 1995 to 2002 in California (*148*). Results showed that MTBE was found more often in surface waters than in groundwater, although levels appear to have declined since 1996. Rosell et al. conducted an occurrence study of MTBE and its degradation products, TBA and TBF in groundwaters from Catalonia in Spain (*149*). Purge-and-trap-GC/MS measurements revealed the presence of MTBE in all samples analyzed at levels between 0.3 and 70 μg/L. Seven highly contaminated waters contained up to 670 μg/L. Samples with high levels of MTBE were also found to contain 0.1−60 μg/L TBA, which suggested in situ degradation of MTBE. Morgenstern et al. conducted an occurrence study of MTBE in drinking water and source waters from The Netherlands (*150*). Purge-and-trap-GC/MS measurements (with an MDL of 2 ng/L) revealed concentrations ranging from <10 ng/L and 3.2 μg/L (median concentration <29 ng/L) for surface waters, <10−300 ng/L (median concentration of 10 ng/L) for groundwater, and <10 ng/L and 3.2 μg/L (median concentration of 20 ng/L) for drinking water. The highest concentration of MTBE in surface water (3.2 μg/L) was collected at a river intake location that was near a boat landing, and the highest groundwater concentration of MTBE was found in a well impacted by a nearby gasoline station.

The impact of boats and other watercraft containing two-stroke engines was evident in a recent study published by Lico in 2004 (*151*). In this study, MTBE levels in Lake Tahoe were compared before and after the 1999 ban of carbureted two-stroke engines on boats and watercraft. Following this ban, MTBE levels were found to be 90% lower than pre-ban levels, which supports the idea that two-stroke engines are a major source of MTBE in surface waters and is encouraging for states considering similar bans. In another occurrence study, Ayotte et al. measured the occurrence of MTBE in public and private wells in southeast New Hampshire (*152*). In this study, 40% of the public wells and 21% of the private wells had MTBE levels of >0.2 μg/L. Four of the public wells sampled exceeded the 13 μg/L New Hampshire standard. A surprising result was that MTBE was correlated positively with well depth for public supply wells, which is significant because deep bedrock wells are often considered to be less vulnerable to contamination than shallow wells. This finding is probably not typical, but it suggests that deep well water cannot always be assumed to be free of MTBE contamination.

While there are several analytical methods that are commonly used to measure MTBE in water, new methods continue to be developed. Yazdi and Assadi developed a headspace-SDME-GC method for measuring MTBE down to 7 μg/L (*153*). This method involves the extraction of MTBE by suspending a 1.8-μL drop of benzyl alcohol directly from the tip of a microsyringe into the vial containing the water sample. The syringe needle is first inserted through the septum of the sample vial, and then the drop is suspended from the needle tip for a few minutes, where the target analyte is extracted into the drop; then, the drop is retracted back into the needle and injected directly into the injection port of the GC. This seems to be a particularly clever and easy way to measure MTBE in water samples, provided the MDL of 10 μg/L is adequate for sampling purposes. Schuhmacher et al. carried out an interlaboratory comparison for the determination of MTBE in water using various analytical methods, including static headspace, purge-and-trap, SPME, or direct aqueous injection with GC/MS or GC/FID (*154*). Twenty-eight laboratories from 7 European countries participated in this study, and 20 of those submitted their results. The coefficient of variation between the laboratories was 32%. Accuracy of the results varied with different sample preparation and quantitation techniques used at the different laboratories. Better accuracies were obtained using purge-and-trap or SPME preconcentration, and the use of internal standards also gave better accuracies.

McLoughlin et al. found a problem with an existing heated headspace method that can be used to measure MTBE (*155*). The authors found that temperatures used to improve the volatilization of MTBE for headspace-GC analysis (80 °C) can hydrolyze MTBE to form TBA. The acid used as a preservative was found to catalyze this reaction. In groundwater samples measured by this method, hydrolysis of MTBE to TBA ranged from 19 to 87%, with an average of 59%. The authors suggest substituting 1% (w/w) trisodium phosphate dodecahydrate for HCl

or neutralizing the acid before analysis to overcome this problem.

Environmental fate studies have also recently been conducted for MTBE. Schmidt et al. investigated the occurrence and fate of MTBE in Lake Zurich, which supplies source water for drinking water (*156*). MTBE was found mostly in the upper layer (epilimnion) of the lake, and stratification of the lake during boating season, along with very limited exchange across the thermocline, favored the volatization of MTBE and lack of introduction into drinking water when the water was taken below the thermocline.

PESTICIDE DEGRADATION PRODUCTS

Herbicides and pesticides continue to be studied more than any other environmental contaminant. Lately, however, there is more of an emphasis on their degradation products, with the recognition that the degradation products (often hydrolysis products) can be present at greater levels in the environment than the parent pesticide itself. Results from a large occurrence study by Battaglin et al. is evidence of this (*157*). In this study, conducted in the midwestern United States, water samples were collected from 71 streams and 5 reservoirs and were analyzed for 13 herbicides and 10 herbicide transformation products. The transformation products were found to occur as frequently or more frequently than the parent herbicides and at concentrations that were often larger. In other papers, these transformation products are also referred to as "metabolites", so those terms will be used interchangeably in the remainder of this review.

Two sets of pesticide degradation products are currently on the CCL: alachlor ESA and other acetanilide pesticide degradation products, and triazines and their degradation products (including, but not limited to cyanazine and atrazine-desethyl). LC/MS and LC/MS/MS are now becoming common place techniques for measuring these pesticide degradates, which are generally more polar than the parent pesticides, making LC/MS ideal for their detection.

Vargo published a SPE-LC/MS/MS method for determining chloroacetanilide herbicides (acetochlor, alachlor, metolachlor) and chloroacetamide herbicides (dimethenamide) and their ESA and OA degradation products in water (*158*). Detection limits of 0.025 μg/L were possible with this method. Spalding et al. used LC/ESI-MS, LC/ESI-MS/MS, GC/high-resolution-EI-MS, and FAB-high-resolution-MS to measure pesticides and their transformation products in a 6-year study of pesticides in groundwater beneath the Nebraska Management System's Evaluation Area (*159*). During this study conducted from 1991 to 1996, 14 pesticides and their transformation products were detected in 7848 groundwater samples from the aquifer. Triazine and acetamide herbicides and their transformation products were detected the most often. The major degradation route for atrazine appeared to be hydrolysis to hydroxyatrazine. Metolachlor oxanilic acid was also frequently detected, and in groundwater profiles, concentrations of metolachlor ethanesulfonic acid exceeded those of deethylatrazine. Alachlor ethanesulfonic acid was also present in most samples and was an indicator of past alachlor use.

LC/MS and LC/MS/MS have also been used in the discovery of new pesticide degradation products. For example, Thurman et al. used LC with TOF-MS and ion trap-MS/MS to identify two new amide degradates of acetochlor, alachlor, and metolachlor in groundwater (*160*). The strategy to identify these new degradates involved the following: (1) the hypothesis that the secondary amide ESAs of the acetanilide herbicides were present; (2) quadrupole ion trap (QIT)-MS/MS analysis of several samples for the molecular ion and characteristic fragment and diagnostic ions; (3) synthesis of standards and verification of retention times and MS/MS spectra, followed by exact mass analysis and molecular formula determination with TOF-MS; and (4) the discovery of the secondary amide ESA degrades in groundwater with LC and QIT-MS/MS. Using QIT-MS/MS, two degradates with the same exact mass could be differentiated by differences in MS/MS fragmentation. Subsequent analysis of 82 shallow groundwater samples in the midwestern United States showed that the secondary amide ESA degradates of acetochlor, alachlor, and metolachlor occur at detection frequencies of 21−26%.

Examples of non-MS methods developed for pesticide degradates include CE and IC methods. Chicharro et al. developed a CE method to measure amitrole (3-amino-1,2,4-triazole) and its principal degradation product, atrazin-2-hydroxy (*161*). MDLs were <100 μg/L initially (which is high compared to LC/MS methods) but could be lowered through the use of preconcentration to 4 μg/L. You and Koropchak developed an IC-condensation nucleation light scattering detection method for analyzing glyphosate and its major metabolite, aminomethylphosaphonic acid, without pretreatment or derivatization (*162*). MDLs of 53 and 41 μg/L were achieved. While the MDL for glyphosate is high compared to typical LC/MS methods, it is well below the U.S. regulatory limit of 700 μg/L in drinking water.

CHIRAL CONTAMINANTS

A major development, particularly in pesticides research, is the use of chiral chromatography to analyze individual chiral isomers. Chemically, chiral isomers are very similar, having the same boiling points, melting points, and typically the same solubility, reactivity, and other chemical properties. Microbially and biologically, however, they can behave very differently. Typically, one form is active against the insects, weeds, or other pests that the pesticide is designed to attack, and the other form is inactive. Likewise, in the environment, one form can be actively degraded by microbes, and the other form can accumulate. It was not until recent developments allowed the separation and low-level detection of these isomers that their environmental behavior could be studied. However, early research is showing that the environmental behavior of chiral compounds is not straightforward—it is not always possible to predict the enantiospecific transformation. Microbial populations in environmental matrixes can change, and even reverse, the enantiomeric ratios (so microbial processes may not always show selective degradation of the same enantiomer). Some environmental processes are not enantioselective toward a particular chemical, even if microorganisms are involved. Sometimes microbial degradation rates are sufficiently rapid for both enantiomers, so that enantioselective degradation is not important. Some compounds are degraded much faster chemically (abiotically) than microbially, so that enantioselective degradation is not important, and sometimes enantiomerization can occur, where one enantiomer is microbially converted to the other.

The ability to separate enantiomers and produce a single enantiomeric isomer has not been lost on pesticide manufacturers.

This ability has allowed manufacturers to sell a new, patented enantiomeric form of a pesticide, creating new markets for their products. The development of enantiomerically enriched pesticides may actually be a benefit for the environment, as less material could potentially be applied to crops, less may be accumulated in the environment, and there may be fewer unintended side effects on nontarget species. However, more research is needed to make this determination.

Most research to-date has investigated chiral profiles in surface waters, soil, and vegetation. The most commonly used analytical techniques to separate and measure chiral isomers include the use of chiral columns with GC and LC (often including the use of mass spectrometry). CE is also often used. Chiral selectors now include cyclodextrins, proteins, crown ethers, polysaccharides, polyacrylamides, polymeric chiral surfactants, macrocyclic antibiotics, and ergot alkaloids. Cyclodextrins still remain the most popular chiral selectors for environmental applications.

Ward published a 2004 *Analytical Chemistry* review on chiral separations, which covered recent developments from 2002 to 2004 (*163*). This review provided details on the types of chiral phases used for separations, various separation techniques (including LC, GC, CE, microchip-CE, supercritical fluid chromatography, and thin-layer chromatography), and applications to the measurement of a number of different chiral compounds.

Poiger et al. used enantioselelective-GC/MS to investigate the occurrence and sources of two chiral pollutants—the chiral herbicide mecoprop and the chiral pharmaceutical ibuprofen—in Swiss lakes (*164*). In Switzerland, the active, pure (*R*)-enantiomer of mecoprop has replaced the racemic mixture for agricultural use. When waters from Swiss lakes were investigated, those lakes (Baldeggersee and Sempachersee) that receive mainly agricultural inputs contained mostly the pure (*R*)-enantiomer, consistent with its use. On the other hand, waters from lakes that receive more water from residential areas (and wastewater treatment plant effluents) (e.g., Greifensee) contained mostly the racemic mixture and sometimes a slight excess of the (*S*)-enantiomer. This source of mecoprop was attributed to the use of racemic mecoprop as an additive to membranes used for sealing flat roofs (to prevent perforation of the membranes by plant roots). While laboratory studies show that mecoprop can undergo enantiomerization to the (*S*)-enantiomer, field studies in lakes indicate that enantiomerization in natural waters may be negligible. For the measurements of ibuprofen, it was consistently detected in lake water samples receiving wastewater treatment plant effluents, at concentrations up to 8 ng/L. The (*S*)-enantiomer is the pharmacologically active form. The enantiopure form of ibuprofen has recently become available, but the racemic form is still the predominant form used. In humans and other mammals, the inactive (*R*)-enantiomer in the racemic mixture undergoes chiral inversion to yield the active (*S*)-enantiomer. Because measurements in lakes showed a predominant (*S*)-enantiomer, which is similar to human urine, inputs from human therapeutic use of the drug was indicated as the source in the Swiss lakes.

Liu and Gan developed a SPME-enantioselective-GC method for determining enantiomers of pyrethroid pesticides (*165*). Enantiomers of (2)-*cis*-bifenthrin and *cis*-permethrin were separated using a β-cyclodextrin-based GC column, and this method was used to analyze surface runoff samples. Results showed preferential degradation of the 1*S*-3*S* enantiomer over the 1*R*-3*R* enantiomer for both (2)-*cis*-bifenthrin and *cis*-permethrin. Jantunen et al. used enantioselective-GC/ECNI-MS to investigate the behavior of α-hexachlorocyclohexane (α-HCH, a chiral pesticide) enantiomers in the South Atlantic Ocean and Antarctica (*166*). α-HCH was found to enantioselectively metabolize, with resulting enantiomer fractions that differed from the racemic value of the technical product. The enantiomeric ratios decreased at lower latitudes, indicating a preferential loss in different ocean regions. Padma et al. used enantioselective-GC to investigate the effect of microbial activity in a temperate estuary on α-HCH enantiomers (*167*). Enantiomeric ratios were essentially equivalent in the freshwater region of the estuary with the highest bacterial activity (and lowest levels of α-HCH), and enantiomeric ratios were nonracemic in the higher salinity region of the estuary, where bacterial activity was lower (and α-HCH levels were higher). Therefore, the enantiomeric ratios are not necessarily reflective of a lack of biodegradation or recent input into the environment, and nonenantioselective biodegradation may be important in certain areas.

CHEMICAL WARFARE AGENTS

Following the events of September 11, 2001, a new Department of Homeland Security was created in the United States, and increased funding was made available for research involving rapid detection of chemical and biological warfare agents. The analysis of chemical warfare agents is also an important component of verification in support of the Chemical Weapons Convention, which as of 1997, prohibits the development, production, stockpiling, and use of chemical weapons (*168*). While there has been a steady interest in this area for many years due to military and environmental issues, interest in this area has seen new growth. Interest in this area is evidenced by new sessions on the topic at scientific meetings (such as the American Society for Mass Spectrometry Conference) and a number of new publications, including review articles and a new book. A book, edited by Mesilaakso, *Chemical Weapons Convention Chemicals Analysis: Sample Collection, Preparation, and Analytical Methods*, describes methods that can be used for on- and off-site analysis of chemical weapons (*169*). In a 2003 review article, Black and Muir summarized derivatization reactions used in the analysis of chemical warfare agents and their degradation products (*168*). As for other chemicals, derivatization is used for chemical warfare agents to allow the analysis of polar compounds by GC, improve the chromatography, or enhance the selectivity or sensitivity of detection, as in the creation of fluorinated derivatives to allow very sensitive detection by ECNI-MS. Recent advances discussed in this review include the increased use of fluorinated derivatives, derivatization on a solid support, and in situ derivatization in water.

Of the new analytical methods recently published, Palit et al. developed a SDME method to extract chemical warfare agents and detect them using GC/MS (*170*). Three toxic chemical warfare agents were included, *O*-isopropyl methylphosphonofluoridate (Sarin), *O*-cyclohexylethylphosphonofluoridate (cyclosarin), and bis(2-chloroethyl)sulfide; and six nontoxic markers for chemical warfare agents (byproducts, precursors, starting materials, or degradation products) were included, *O,O*-dibutyl *n*-propylphosphonate, *O*-ethyl-*O*-cyclohexyl *n*-propylphosphonate, *O,O*-dimethyl

methylphosphonate, *O,O*-dimethyl ethylphosphonate, *O,O*-diethyl-*N,N*-diethylphosphoramidate, and *O,O*-dicyclohexyl methylphosphonate. This method is similar to the SDME method described earlier for the analysis of MTBE and involves the extraction of the analytes by suspending a 1.0-μL drop of methylene chloride/carbon tetrachloride (3:1, v/v) directly from the tip of a microsyringe into the vial containing the water sample (which was stirred during the 30-min extraction time). After extraction, the drop was retracted back into the needle and injected directly onto a GC column. Detection limits of 10−75 μg/L were obtained with this simple method.

Another new method published by Chen et al. used ion/molecule reactions with 1,4-dioxane in the mass spectrometer to aid in the detection of the chemical warfare agent simulant dimethyl methylphosphonate (*171*). The authors discovered that phosphonium ions react selectively with 1,4-dioxane to form unique cyclic ketalization products, and this reaction can be used to detect phosphonium ions in aqueous solutions using ESI-MS with low-ppb detection limits. Finally, Hanaoka et al. developed an analytical method using GC and LC to analyze diphenylarsine chloride and diphenylarsine cyanide in contaminated water and soil (*172*). Derivatization with *n*-propanethiol allowed higher analytical reproducibility. Detection limits were 0.5 ng with GC-FID and 1 mg/L with LC−UV.

ORGANOTINS

Organotins are used in antifouling paints for ships and have been measured widely in coastal waters and sediment. Their toxicity generally follows the order, trialkyl > dialkyl > monoalkyl, but the dialkyl form is much more neurotoxic, with an effect in brain cells as low as 30 ppb. The discovery that dibutyltin leaches from poly(vinyl chloride) (PVC) pipe at 1 μg/L levels created a new concern for drinking water. There have also been reports of organotins in Canadian drinking water that was supplied by PVC pipe. European countries have proposed banning the use of PVC, due to the leaching of organotin from PVC plastic products, and organotins are included on the U.S. EPA's Contaminant Candidate List (www.epa.gov/safewater/ccl/cclfs.html).

Dibutyltin is used as a heat stabilizer in PVC pipe and is highly toxic. Because PVC pipe is widely used as a domestic water supply carrier from main water lines into homes, the potential for widespread exposure to dibutyltin is enormous. A variety of analytical methods have been developed to measure organotins in environmental samples, including GC with mass spectrometry, atomic absorption spectrometry (AAS), flame photometry, ICPMS, or microwave-induced plasma atomic emission spectrometry, as well as LC coupled to mass spectrometry, AAS, ICPMS, and fluorescence detection. Headspace-SPME sampling is also becoming more popular, as this allows for easy and rapid extractions that avoid the use of solvents. Several methods can detect low-nanogram per liter levels of organotins in water. A poly(dimethylsiloxane)-coated stir bar has also been used for extracting organotins from water, with subsequent analysis by thermal desorption-GC/ICPMS (*1*).

As mentioned earlier in the Regulatory Methods section, a micro-LC/ESI-ion trap-MS method developed by Jones-Lepp has recently become an official EPA method (Method 8323, http://www.epa.gov/epaoswer/hazwaste/test/new-meth.htm#8323). This method permits the measurement of mono-, di-, and tributyl tin and mono-, di-, and triphenyltin at subnanogram per liter detection limits. This micro-LC/ESI-MS/MS method was used in a recent study to measure dibutyltin and triphenyltin in freshwaters and in fish from the United States (*173*). Concentrations ranged from nondetect to 2 ppb, and nondetect to 6 ppb, respectively, in water.

New GC/MS methods also continue to be developed for organotins. A new low-pressure-GC/MS/MS method was developed for simultaneously measuring monobutyltin, dibutyltin, tributyltin, tetrabutyltin, monophenyltin, diphenyltin, triphenyltin, and tetraphenyltin in water, sediments, and mussels (*174*). This method was based on sodium diethyldithiocarbamate complexation of the ionic organotins, followed by extraction and derivatization with a Grignard reagent. Low-pressure-GC/MS involves the use of a wide-bore capillary column (0.53-mm i.d.) coupled to a narrow and short restriction capillary at the GC injector, which is interfaced to a mass spectrometer. The mass spectrometer provides the vacuum that permits much shorter analysis times (reduced by a factor of 2), and large-volume injection can be used to obtain lower detection limits. This method gave detection limits of 0.1−9.6 ng/L for the alkyltins in water. Jitaru et al. created a SPME-multicapillary-GC/ICP-TOF-MS method to allow the simultaneous analysis of several organometallic compounds, including monomethyl-, dimethyl-, and trimethyltin; monobutyl-, dibutyl-, and tributyltin; dimethyl- and trimethyllead; and inorganic mercury and methyl mercury (*175*). Detection limits of <1 pg/L were obtained for the organotins. Also, the use of TOF-MS enabled the method to be very rapid, allowing the analysis of all of these analytes in <200 s. Parkinson et al. created an automated SPME-GC/MS method for determining alkyltin, -lead, and -mercury compounds (*176*). The use of a Twin PAL dual-arm robotic system (LEAP Technologies, Carrboro, NC) allowed complete automation of extraction and analysis.

Finally, Cukrowska et al. developed a new supported liquid membrane extraction probe for extracting and preconcentrating organotins from water (*177*). Extraction efficiencies were 63−94% for deionized water and 52−89% for seawater. Detection limits ranged from 0.5 μg for triphenyltin to 1.5 μg for monobutyltin.

ARSENIC

Unlike many other contaminants that are anthropogenic, arsenic contamination of waters generally comes from natural sources, through the erosion of rocks, minerals, and soils. For several years, the U.S. EPA has conducted research on arsenic (occurrence, health effects, bioavailability) and, in 2002, lowered the MCL from 50 to 10 μg/L, which is believed to be a level that would better protect human health (www.epa.gov/safewater/arsenic.html). Drinking water systems must comply with this new standard by January 23, 2006. The World Health Organization (WHO) also has this same standard of 10 μg/L in drinking water. The general toxicity of arsenic is well known, but studies have also linked long-term exposure of arsenic (at lower, nontoxic levels) to a variety of cancers in humans. In addition, there are recent reports of excess risk of spontaneous abortion, stillbirth, and neonatal death.

Probably the most publicized sites of natural arsenic contamination are in Bangladesh and West Bengal, India, where the creation of wells to supply these impoverished areas with micro-

bially safe drinking water unintentionally led to extensive human exposure to arsenic. Levels up to 2500 μg/L in groundwater have been reported. However, there is also natural arsenic contamination in other areas of the world, including the United States, Taiwan, Chile, Argentina, China, Nepal, and Turkey.

Arsenic research issues that have become important are determining individual species of arsenic (rather than total arsenic) and their occurrence in water, foods, and biological samples. Different arsenic species have different toxicities and chemical behavior in aquatic systems, so it is important to be able to identify and quantify them. In aquatic systems, arsenic has four oxidation states: −III, 0, +III, and +V; arsenite(III) and arsenate(IV) are the two main species found in water. Karthikeyan and Hirata review recent progress in extraction and identification of different arsenic species in environmental samples, including sediments, soils, foods, fruits, vegetables, and marine samples (*178*). Extraction, separation, and detection techniques are discussed.

In the 2003 biennial review on water analysis (*1*), several new analytical methods for measuring different arsenic species were discussed. These methods included SPME and SPE used with GC/MS, LC/ESI-MS, LC/ICPMS, and IC/ICPMS. The number of papers involving the development or use of LC/ICPMS techniques had grown significantly from 2001 to 2002, and over the last two years, this trend continues. For example, Shibata et al. developed a LC/ICPMS technique for measuring diphenylarsinic acid in human and environmental samples, including groundwater (*179*). A combination of hydrophilic polymer-based gel permeation-LC and ICPMS was used to measure diphenylarsinic acid in groundwater, hair, fingernail samples, and urine at submicrogram per liter detection limits. This method was also very rapid, requiring only 7 min per sample, and it was applied to arsenic-contaminated groundwater in Japan.

As with the above-mentioned method, there appears to be an increase in the number of high-throughput methods created for arsenic analysis. For example, Leal et al. developed a multisyringe flow injection-hydride generation-atomic fluorescence spectrometry method that allows 30 ng/L detection limits for inorganic arsenic and a high sample throughput of 10 samples/h (*180*). Ease of use is also an important feature in new methods, particularly for carrying out analyses in the field. To this end, Dhar et al. created a rapid colorimetric method for measuring arsenic concentrations in groundwater (*181*). This method allows arsenic measurements over the range of <2−400 μg/L, it has good linearity, and the accuracy compares favorably with existing high-resolution ICPMS methods. Antimonyl tartrate was used for sample pretreatment and color development.

Finally, arsenic removal papers have increased over the last two years. This is likely due to both the drinking water contamination problems in Bangladesh and West Bengal, India and also the lowered arsenic standard in the United States, which will force many U.S. treatment plants to implement new treatment technologies for removing arsenic. Technologies that have been identified by the U.S. EPA as best available technologies for arsenic removal include ion exchange, activated alumina, reverse osmosis, electrodialysis reversal, and coagulation/filtration (*182*). The coagulation/microfiltration process was once thought to be too expensive and complex for small systems, so that it was believed that only a few large systems would consider this technology. Recently, however, coagulation/microfiltration has been evaluated in pilot plants, and it appears to be within reach of both large plants and smaller plants. Chwirka et al. summarize the results of pilot testing for the removal of arsenic from drinking water (*182*). This process consists of the addition of an iron-based coagulant, such as ferric chloride, followed by filtration through microfiltration membranes. In water, ferric chloride forms ferric hydroxide, which has a net positive charge on the surface of the particles formed, and negatively charged arsenate is sorbed onto these particles for removal.

NATURAL ORGANIC MATTER

NOM is a complex mixture of substances, such as amino acids, carbohydrates, lipids, lignins, waxes, organic acids, humic acids, and fulvic acids. Humic substances, which are the major component of aquatic, dissolved organic matter, are complex macromolecular structures. The understanding of NOM is important because it impacts such processes as the sorption or transformation/degradation of environmental pollutants, provides sources and sinks for carbon, serves as a carbon and energy source for biota, and controls levels of dissolved oxygen, nitrogen, phosphorus, sulfur, trace metals, and acidity. Also importantly, NOM serves as the precursor material for the formation of drinking water DBPs. Understanding the structure of NOM could aid in the design of new treatment processes for removing it from drinking water and lessening or preventing the formation of DBPs. Previous research using gel permeation chromatography indicated that, of these humic substances, fulvic acids generally have molecular weights of 200−2000, and humic acids have much higher molecular weights (1000−100 000). However, new information provided by ESI- and APCI-MS is showing much lower molecular weight distributions (e.g., 300−1200 for humic acid). These new data have caused scientists to rethink "truths" about NOM that have been accepted for many years. As such, this area is a fascinating, emerging one. The questions to answer are as follows: (1) Did the earlier measurements using gel permeation chromatography measure individual NOM molecules, or were these colloidal aggregates? (2) Are the earlier data correct, but the new mass spectrometry data instrumentally biased toward low molecular weight—either due to the difficulty in obtaining stable molecules with multiple charges or ionization suppression of larger molecules? New work is probing these questions, and the use of FT-MS is enabling ultrahigh resolution data that indicate many molecules are singly charged, but it has not yet unequivocally resolved the two major questions above. New mass spectrometry developments are enabling a wealth of new information that has not been available for many years. This area should be an exciting one to follow as the old "truths" about humic matter are questioned and new humic models may arise.

Abbt-Braun et al. published an overview of different analytical methods that have been used to characterize aquatic NOM (*183*). Methods discussed include the following: spectroscopic methods, mass spectrometry, NMR, UV/visible, and fluorescence, spectroscopy; physical/chemical analysis methods, elemental analysis, acid/base titration; fractionation methods, gel chromatography, flow-field-flow fractionation; and degradation methods, oxidation, pyrolysis, and hydrolysis. The influence of different isolation procedures on the character of the fractions is also discussed.

Several research groups have been engaged in new mass spectrometry work to probe the structure of NOM. Stenson et al. used FT-ICR-MS to obtain exact masses and chemical formulas for Suwannee River fulvic acids (*184*). Molecular formulas were assigned for 4626 individual fulvic acids, based on exact mass measurements, and were structurally consistent with degraded lignin as a source for the fulvic acids. A Kendrick mass analysis revealed the presence of 266 odd-mass homologous series between 316 and 1098 Da. The numbers of carbon atoms ranged from 14 to 58, the number of oxygens from 5 to 29, and the number of rings plus double bonds from 6 to 33. These data also show that Suwannee River fulvic acid is a complex but highly ordered system with an almost polymeric character. Each ion within this continuous series seems to be related to other ions by the patterns observed.

Kim et al. published a paper describing a graphical method—the van Krevelen diagram—that can be used to visualize complicated ESI-MS spectra, identify possible reaction pathways, and find major classes of compounds (*185*). In addition, the van Krevelen diagram can be expanded to a 3-D plot by using peak intensities or relative intensities as the *z*-axis, and this can allow an evaluation of the relative significance of structurally related compounds. It can also be used to differentiate compositional differences among samples.

Reemtsma and These combined size exclusion chromatography with ESI-MS/MS for analyzing aquatic fulvic and humic acids (*186*). Results seemed to indicate that there might be a molecular weight bias with ESI-MS in the measurement of fulvic and humic acids because ESI-MS sensitivities dropped off with increasing mass, while parallel UV recording did not. In this study, SEC was used to separate the fulvic and humic acids into three fractions, which had different mass ranges and differences in the fine structure of their mass spectra. The average molecular mass of the low molecular weight fraction was lower than reported from infusion ESI-MS measurements, and the average molecular mass of the high molecular weight fractions was higher than previous infusion experiments. A striking feature of the high molecular weight ESI mass spectra of both the fulvic and humic acids was a "wavy" pattern of signal intensity, with maximums in the range of m/z 200, 550, and 950. Humic acids exhibited a fourth maximum around m/z 1500. The ions in the lower m/z range were postulated to be fragment ions of the higher molecular weight material, generated by in-source fragmentation. The wavy spectra were probably not seen in previous infusion studies because the fragment ions in the lower m/z range were superimposed by the more prominent molecular ions of the lower molecular weight compounds and also because the parallel introduction of the high molecular weight and low molecular weight compounds likely suppressed the ionization of the high molecular weight compounds. In the full-scan mass spectra, homologous series (+2 Da, +14 Da) were evident in the low molecular weight fractions. Also, neutral loss analyses showed fragmentation of the CO_2 group, which is consistent with the acid structure in fulvic and humic acid molecules and consistent with previous studies.

Rostad and Leenheer investigated factors that affect molecular weight distribution of aquatic fulvic acids when analyzing them by ESI-MS (*187*). The effects of methylation, molar response, multiple charging, solvents, and positive/negative ionization were all considered. Positive ion ESI-MS was found to be less effective and produced more complex spectra than negative ion-MS. Ionization in methanol/water produced a greater response than in acetonitrile/water. Molar response varied widely for the selected free acid standards when analyzed individually and as a mixture, but after methylation of carboxylic acid groups, this variation decreased. The use of methylation was explored as an option to eliminate multiply charged species and possible aggregate formation. A lower weight averaged molecular weight after methylation indicated that methylation was causing large aggregated ions to disaggregate.

Kujawinski et al. used ESI-FT-ICR-MS to probe molecular-level transformations in dissolved organic matter (DOM) associated with photochemical degradation and to probe DOM extracted from biological organisms (bacteria and protozoa) (*188*). Striking molecular differences were found in ESI mass spectra following photoirradiation of DOM at long wavelengths; for example, at m/z 413, every other peak is missing from the irradiated sample (the nonirradiated sample contains ions at approximately m/z 413.02, 413.04, 413.05, 413.07, 413.09, 413.11, 413.12, 413.14, and 413.16, whereas the irradiated sample contains the ions at m/z 413.04, 413.07, 413.11, and 413.14, but every other peak is missing). Further, the peaks that have been removed differ from each other by multiples of 0.036 Da, which is the difference between CH_4 and O, likely from the replacement of a methyl group by an aldehyde or ketone. Mass spectra for the biologically derived DOM was significantly less complex than for the fulvic acids, and Kendrick mass analysis indicated that it was very different structurally. The biological cultures had higher H:C and lower O/C ratios than the fulvic acid, suggesting that biological DOM is significantly more aliphatic than fulvic acids. This result is not surprising, but it does indicate that ESI-MS is capable of providing information on a subfraction that is representative of the bulk DOM. In this preliminary work, empirical formula information was obtained, but additional work will be needed to gain structural information. For this, the authors plan to carry out MS/MS experiments, a comparison of GC/MS and ESI-FT-ICR-MS experiments to get information on lipids, and preconcentration of fractions to enhance detection of specific chemical groups.

CE has also been used recently with ESI-MS to characterize NOM. In a study by Schmitt-Kopplin and Kettrup, Suwannee River NOM showed possible fragmentation, formation of adducts, and multiple charging prior to MS detection (*189*).

An LC-NMR method has also recently been developed to study the structure of NOM. Simpson et al. used LC NMR and LC-SPE-NMR in a preliminary investigation of NOM collected from water and soil (*190*). The use of LC-SPE-NMR allowed chromatographic separations to be carried out with less expensive nondeuterated solvents and additives (e.g., ion pair reagents) that are not compatible with NMR spectroscopy. SPE also allowed preconcentration to enhance NMR signals, and multiple solid-phase extractions could be used to concentrate trace components that might not be detected otherwise. Sharp NMR peaks were obtained, which suggested three scenarios: (1) SPE helped to separate paramagnetic species that lead to degradation of NMR signals; (2) after LC separation, species are no longer able to aggregate (aggregation has been shown to cause line broadening); and (3) species are eluted as sharp chromatographic peaks and

are more likely to be relatively "pure" components within the mixture.

MICROORGANISMS

Outbreaks of waterborne illness in the United States and other parts of the world (including *Escherichia coli*-induced gastroenteritis in Walkerton, Ontario in 2000, cryptosporidiosis in Milwaukee in 1993, and cholera in Peru beginning in 1991) have necessitated improved analytical methods for detecting and identifying microorganisms in water and other environmental samples. Mass spectrometry had played a minor role in the past through the use of pyrolysis-GC/MS, but is beginning to play a more important role, with increased research using MALDI-MS and ESI-MS techniques, which can be used on whole or treated cells. These MS methods offer a very rapid analysis time (~10 min) and specific information that can be used to distinguish different strains of the same organism. In the last two years, further advances have been made, including a new data analysis method and the use of ^{13}C- and ^{15}N-depleted culture media to enable additional structural information. In addition, mass spectrometry is enabling the characterization of the virulent form of *E. coli*, O157:H7 and the severe acute respiratory syndrome (SARS) virus, and there has been an increase in combining traditional biochemical methods with mass spectrometry (such as LC-protein expression mapping with ESI or MALDI-MS).

Reviews. Increased interest in mass spectrometry techniques for analyzing microorganisms is evidenced by the number of reviews that have been published in this area. Examples of reviews published in the last two years include one from Trauger et al. on the investigation of viral proteins and intact viruses with mass spectrometry (*191*) and another by Vater et al. on the state of research for whole-cell MALDI-TOF-MS analysis (*192*).

Mass Spectrometry Methods. Several authors have published papers on the development of new mass spectrometry methods or information on microorganisms obtained by mass spectrometry. This area continues to explode, and space permits the inclusion of only a few representative papers here. Pineda et al. published a new database-generation method that automatically generates a microorganism database from biomarker masses derived from ribosomal protein sequences and a model of N-terminal Met loss (with MALDI-TOF-MS data) (*193*). This method was validated with a blind study involving the identification of microorganisms with known ribosomal protein sequences. It was found that microorganisms with 20 or more biomarkers were correctly identified from their MALDI-TOF mass spectra 100% of the time, with no incorrect identifications. Microorganisms with seven or less biomarkers (incompletely sequenced genomes) were either not identified or misidentified. Stump et al. used an innovative approach of growing bacteria on double-isotopically depleted ^{13}C and ^{15}N media followed by analysis with MALDI-FT-ICR-MS, which significantly reduced chemical interferences and made it possible to detect subtle details, such as the posttranslationally modified and unmodified versions of the same protein (*194*). In another paper, Warscheid et al. applied a novel quadrupole ion trap-TOF-mass spectrometer for peptide sequencing in proteolytic digests generated from bacilli spores (*195*).

Zheng et al. used two-dimensional LC-protein expression mapping, ESI-TOF-MS, and MALDI-TOF-MS to differentially analyze proteins from normal *E. coli* and virulent O157:H7 *E. coli* (*196*). Proteins were separated in the first dimension using chromatofocusing and further separated by nonporous reversed-phase LC in the second dimension. A 2-D expression map of bacterial protein content was created for the normal *E. coli* and the virulent O157:H7 *E. coli*. Differentially expressed proteins were further characterized using ESI-TOF-MS for intact protein molecular weight and MALDI-TOF-MS peptide mass fingerprinting for protein identification. With this method, normal *E. coli* could be distinguished from the virulent O157:H7 strain, and several proteins were identified as potential biomarkers for detection. Lee et al. used thin-layer chromatography (TLC), MALDI-TOF-MS, and ESI-MS/MS to identify a lipid from the virulent *E. coli* O157:H7 (*197*). TLC was used to isolate the lipid from the organism, after which it was reextracted with chloroform-methanol and analyzed.

Finally, Krokhin et al. used MALDI-TOF-MS to identify a prominent protein in the SARS virus (*198*). It was found to be a novel nucleocapsid protein that matched one predicted by an open reading frame of the recently published nucleotide sequence of the SARS virus. Also, a second viral protein was analyzed and was found to contain 12 glycosylation sites. These results suggested that the nucleocapsid protein is a major immunogen that might be useful for early diagnostics.

Non-Mass Spectrometry Methods. Lee et al. created an improvement in the fluorophore that can be used in the detection of *Cryptosporidium parvum* oocysts (*199*). *Cryptosporidium* is a highly resistant protozoan organism that has been implicated in several incidents of waterborne outbreaks of illness, including the well-documented outbreak in Milwaukee in 1993. A fluorophore is used in EPA Method 1622 to label *Cryptosporidium* oocysts by conjugation with a monoclonal antibody and allows detection by fluorescence spectroscopy. However, the organic fluorophore used (fluorescein isothiocyanate) is susceptible to photodegradation following periods of illumination. Therefore, Lee et al. developed an inorganic fluorophore (called a quantum dot) that could be used for *C. parvum* detection. It was highly photostable compared to the organic fluorophore, which decreased to 20% of its original intensity after only 5 min of continuous illumination. The new inorganic fluorophore also allowed the sensitive detection of *Cryptosporidium* oocysts. Finally, Aboytes et al. published a significant occurrence study of *Cryptosporidium* in finished drinking waters (*200*). Eighty-two surface water treatment plants were monitored using a slight modification of EPA Method 1622, and results revealed that 1.4% of the 1690 finished drinking water samples tested positive for infectious *Cryptosporidium*. Infectious oocysts were detected in finished water from 22 treatment plants (26.8%). Further, more than 70% of the positive samples occurred in filtered water samples with <0.1 ntu, and 20% of the positive samples were in water with <0.05 ntu. This is disturbing because turbidity is generally used as an indicator for the presence of harmful pathogens, including *Cryptosporidium*, and these turbidity values above are extremely low. The authors conclude that nearly all conventional treatment plants would be at the risk for passing infectious oocysts, and the risk of *Cryptosporidium* infection for conventionally treated drinking water was 52 infections per 10 000 people per year. The authors recommend that an additional treatment barrier, such as UV light disinfection, be added to conventional treatment to reduce this risk.

ACKNOWLEDGMENT

We thank Dave Munch, Pat Fair, Jim Weaver, Stacy Pfaller, and Barry Lesnik of the U.S. EPA, Sergio Ghittori of the Salvatore Maugeri Foundation, and Dirk Löffler of the BfG for valuable input. This paper has been reviewed in accordance with the U.S. EPA's peer and administrative review policies and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use by the U.S. EPA.

NOTE ADDED AFTER ASAP PUBLICATION

This paper was posted ASAP on May 11, 2005 with the incorrect abbreviation for octyl methoxycinnamate. The correct version was posted on May 20, 2005.

Susan D. Richardson *is a research chemist at the U. S. Environmental Protection Agency's National Exposure Research Laboratory in Athens, GA. She received her B.S. degree in chemistry and mathematics from Georgia College in 1984 and her Ph.D. degree in chemistry from Emory University in 1989. At the U.S. EPA, Dr. Richardson has led a team of chemists in developing and applying multispectral analysis techniques (GC/MS, LC/MS, CE/MS, and GC/IR) to environmental problems. Her recent research has focused on the identification/characterization of new disinfection byproducts (DBPs), with special emphasis on alternative disinfectants and polar byproducts. She led a recent Nationwide DBP Occurrence Study mentioned in this paper and is particularly interested in promoting new health effects research so that the risks of DBPs can be determined and minimized.*

Thomas A. Ternes *graduated with an undergraduate degree in Chemistry from the University of Mainz (Germany) in 1989. In 1993, he completed his Ph.D. at the University of Mainz in analytical chemistry. In January 2001, he completed his habilitation and became an official lecturer at the University of Mainz. Since 1995, his research has focused on the analysis and fate of organic pollutants, such as pharmaceuticals and personal care products (PPCPs), in various kinds of environmental matrixes. Dr. Ternes is the coordinator of the Pharma-cluster project POSEIDON (http//www.eu-poseidon.com) dealing with the removal of PPCPs in wastewater and drinking water treatment, and soil aquifer treatment and with environmental risk assessment. Since May 2003, he has been at the Federal Institute of Hydrology (BfG) in Koblenz, Germany, and is responsible for the coordination and management of research projects in the field of organic trace analysis and fate studies.*

LITERATURE CITED

(1) Richardson, S. D. *Anal. Chem.* **2003**, *75* (12), 2831−2857.
(2) *Emerging Pollutants in Water Analysis*; Barceló, D., Ed.; *TrAC, Trends Anal. Chem.* **2003**, *22* (1).
(3) *Emerging Organic Pollutants in Wastewaters and Sludge*; Barceló, D., Ed.; Springer-Verlag: Berlin, 2005.
(4) Ferrer, I.; Thurman, E. M. In *Liquid Chromatography/Mass Spectrometry, MS/MS and Time of Flight MS: Analysis of Emerging Contaminants*; Ferrer, I., Thurman, E. M., Eds.; ACS Symposium Series 850; American Chemical Society: Washington, DC, 2003; pp 2−13.
(5) Thurman, E. M.; Ferrer, I. In *Liquid Chromatography/Mass Spectrometry, MS/MS and Time of Flight MS: Analysis of Emerging Contaminants*; Ferrer, I., Thurman, E. M., Eds.; ACS Symposium Series 850; American Chemical Society: Washington, DC, 2003; pp 14−31.
(6) Lopez de Alda, M. J.; Diaz-Cruz, S.; Petrovic, M.; Barceló, D. *J. Chromatogr., A* **2003**, *1000* (1−2), 503−526.
(7) Zwiener, C.; Frimmel, F. H. *Anal. Bioanal. Chem.* **2004**, *378* (4), 851−861.
(8) Zwiener, C.; Frimmel, F. H. *Anal. Bioanal. Chem.* **2004**, *378* (4), 862−874.
(9) Reemtsma, T. *J. Chromatogr., A* **2003**, *1000* (1−2), 477−501.
(10) Petrovic, M.; Eljarrat, E.; Lopez de Alda, M. J.; Barceló, D. *Anal. Bioanal. Chem.* **2004**, *378* (3), 549−562.
(11) Petrovic, M.; Gonzalez, S.; Barceló, D. *TrAC, Trends Anal. Chem.* **2003**, *22* (10), 685−696.
(12) Richardson, S. D. *Anal. Chem.* **2004**, *76* (12), 3337−3363.
(13) Koester, C. J.; Simonich, S. L.; Esser, B. K. *Anal. Chem.* **2003**, *75* (12), 2813−2829.
(14) Rosenberg, E. *J. Chromatogr., A* **2003**, *1000* (1−2), 841−889.
(15) Pontius, F. W. *J. Am. Water Works Assoc.* **2004**, *96* (3), 56−69.
(16) *Drinking Water Regulation and Health*; Pontius, F. W., Ed.; John Wiley & Sons: New York, 2003.
(17) Domino, M. M.; Pepich, B. V.; Munch, D. J.; Fair, P. S. *J. Chromatogr., A* **2004**, *1035*, 9−16.
(18) Pepich, B. V.; Domino, M. M.; Dattilio, T. A.; Fair, P. S.; Munch, D. J. *Water Res.* **2004**, *38* (4), 895−902.
(19) Wagner, H. P.; Pepich, B. V.; Hautman, D. P.; Munch, D. J. *J. Chromatogr., A* **2003**, *1011* (1−2), 89−97.
(20) Hedrick, E.; Munch, D. *J. Chromatogr., A* **2004**, *1039* (1−2), 83−88.
(21) Wagner, H. P.; Suarez, F. X.; Pepich, B. V.; Hautman, D. P.; Munch, D. J. *J. Chromatogr., A* **2004**, *1039* (1−2), 97−104.
(22) Renner, R. *Environ. Sci. Technol.* **2005**, *39* (2), 35A.
(23) Dinglasan, M. J. A.; Ye, Y.; Edwards, E. A.; Mabury, S. A. *Environ. Sci. Technol.* **2004**, *38*, 2857−2864.
(24) Ellis, D. A.; Martin, J. W.; Mabury, S. A.; Hurley, M. D.; Andersen, M. P. S.; Wallington, T. J. *Environ. Sci. Technol.* **2003**, *17*, 3816−3820.
(25) Lau, C.; Butenhoff, J. L.; Rogers, J. M. *Toxicol. Appl. Pharmacol.* **2004**, *198* (2), 231−241.
(26) Olsen, G. W.; Hansen, K. J.; Stevenson, L. A.; Burris, J. M.; Mandel, J. H. *Environ. Sci. Technol.* **2003**, *37* (5), 888−891.
(27) Renner. R. *Environ. Sci. Technol.* **2004**, *38* (14), 264A−265A.
(28) Kennedy, G. L.; Butenhoff, J. L.; Olsen, G. W.; O'Connor, J. C.; Seacat, A. M.; Perkins, R. G.; Biegel, L. B.; Murphy, S. R.; Farrar, D. G. *Crit. Rev. Toxicol.* **2004**, *34* (4), 351−384.
(29) Schultz, M. M.; Barofsky, D. F.; Field, J. A. *Environ. Eng. Sci.* **2003**, *20* (5), 487−501.
(30) Yamishita, N.; Kannan, K.; Taniyasu, S.; Horii, Y.; Okazawa, T.; Petrick, G.; Gamo, T. *Environ. Sci. Technol.* **2004**, *38* (21), 5522−5528.
(31) Ellis, D. A.; Martin, J. W.; De Silva, A. O.; Mabury, S. A.; Hurley, M. D.; Andersen, M. P. S.; Wallington, T. J. *Environ. Sci. Technol.* **2004**, *38* (12), 3316−3321.
(32) Wang, N.; Szostek, B.; Folsom, P. W.; Sulecki, L. M.; Capka, V.; Buck, R. C.; Berti, W. R.; Gannon, J. T. *Environ. Sci. Technol.* **2005**, *39* (2), 531−538.
(33) So, M. K.; Taniyasu, S.; Yamashita, N.; Giesy, J. P.; Zheng, J.; Fang, Z.; Im, S. H.; Lam, P. K. S. *Environ. Sci. Technol.* **2004**, *38* (15), 4056−4063.
(34) Schultz, M. M.; Barofsky, D. F.; Field, J. A. *Environ. Sci. Technol.* **2004**, *38* (6), 1828−1835.
(35) Saito, N.; Harada, K.; Inoue, K.; Sasaki, K.; Yoshinaga, T.; Koizumi, A. *J. Occup. Health* **2004**, *46* (1), 49−59.
(36) Boulanger, B.; Vargo, J.; Schnoor, J. L.; Hornbuckle, K. C. *Environ. Sci. Technol.* **2004**, *38* (15), 4064−4070.
(37) Takino, M.; Daishima, S.; Nakahara, T. *Rapid Commun. Mass Spectrom.* **2003**, *17* (5), 383−390.
(38) Routledge, E. J.; Sheahan, D.; Desbrow, C.; Brighty, G. C.; Waldock, M.; Sumpter, J. P. *Environ. Sci. Technol.* **1998**, *32* (11), 1559−1565.
(39) Triebskorn, R.; Casper, H.; Heyd, A.; Eilemper, R.; Köhler, H.-R.; Schwaiger, J. *Aquat. Toxicol.* **2004**, *68* (2), 151−166.
(40) Göbel, A.; McArdell, C. S.; Suter, M. J. F.; Giger, W. *Anal. Chem.* **2004**, *76*, 4756−4764.
(41) Löffler, D.; Ternes, T. A. *J. Chromatogr., A* **2003**, *1000*, 583.
(42) Wen, X.; Tu, C.; Lee, H. K. *Anal. Chem.* **2004**, *76*, 228−232.
(43) Suedee, R.; Srichana, T.; Chuchome, T., Kongmark, U. *J. Chromatogr., B* **2004**, *811*, 191−200.
(44) Kuster, M.; Lopez de Alda, M.; Barceló, D. *TrAC, Trends Anal. Chem.* **2004**, *23* (10−11), 790−798.
(45) Vanderford, B. J.; Pearson, R. A.; Rexing, D. J.; Snyder, S. A. *Anal. Chem.* **2003**, *75*, 6265−6274.
(46) Miao, X. S.; Metcalfe, C. D. *Anal. Chem.* **2003**, *75*, 3731−3738.
(47) Quintana, J. B.; Reemtsma, T. *Rapid Commun. Mass Spectrom.* **2004**, *18*, 765−774.
(48) van der Ven, K.; Dongen, W. V.; Maes, B. U. W.; Esmans, E. L.; Blust, R.; De Coen, W. M. *Chemosphere* **2004**, *57*, 967−973.
(49) Miao, X. S.; Metcalfe, C. D. *J. Chromatogr., A* **2003**, *998*, 133−141.
(50) Zühlke, S.; Dünnbier, U.; Heberer, T. *J. Chromatogr., A* **2004**, *1050*, 201−209.
(51) Cahill, F. D.; Furlong, E. T.; Burkhard, M. R.; Kolpin, D.; Andersen, L. G. *J. Chromatogr., A* **2004**, *1041*, 171−180.
(52) Prat, M. D.; Benito, J.; Compano, R.; Hernandez-Artesero, J. A.; Granados, M. *J. Chromatogr., A* **2004**, 1041, 27−33.
(53) Huggett, D. B.; Khan, I. A.; Foran, C. M.; Schlenk, D. *Environ. Pollut.* **2003**, *121*, 199−205.
(54) Lin, W.-C.; Chen, H.-C.; Ding, W.-H. *J. Chromatogr., A* **2005**, *1065*, 279−285.
(55) Lamas, J. P.; Salgado-Petinal C.; Garcia-Jares, C.; Llompart, M. Cela, R.; Gomez, M. *J. Chromatogr., A* **2004**, *1046*, 241−247.
(56) Rodriguez, I.; Quintana, J. B.; Carpinteiro, J.; Carro, A. M.; Lorenzo, R. A., Cela, R. *J. Chromatogr., A* **2003**, 265−274.
(57) Yang, S.; Carlson, K. H. *J. Chromatogr., A* **2004**, *1038*, 141−155.
(58) Deng, A.; Himmelbach, M.; Zhu, Q.-Z.; Frey, S.; Sengl, M.; Buchberger, W.; Niessner, R.; Knopp, D. *Environ. Sci. Technol.* **2003**, *37*, 3422−3429.
(59) Grant, G. A.; Frison, S. L.; Sporns, P. *J. Agric. Food Chem.* **2003**, *51*, 5367−5375.
(60) Macia, A.; Borrull, F.; Calull, M.; Agulier, C. *Electrophoresis* **2004**, *25*, 3441−3449.
(61) Gomes R. L.; Scrimshaw, M. D., Lester, J. N. *TrAC, Trends Anal. Chem.* **2003**, *22* (10), 697−707.
(62) Hanselmann, T. A.; Graetz, D. A.; Wilke, A. C. *Environ. Sci. Technol.* **2003**, *37 (24)*, 5471−5478.
(63) Wenzel, A.; Müller, J.; Ternes, T. A. Study on endocrine disrupters in drinking water, European report, ENV.D.1/ETU/2000/0083, 2003.
(64) Lerch, O.; Zinn, P. *J. Chromatogr., A* **2003**, *991*, 77−97.

(65) Benijts, T.; Günther, W.; Lambert, W.; Leenheer, A. D. *Rapid Commun. Mass Spectrom.* **2003**, *17*, 1866−1872.
(66) Rodrigues-Mozaz, S.; Lopez de Alda, M.; Barceló, D. *Anal. Chem.* **2004**, *76*, 6998−7006.
(67) Komori, K.; Tanaka, H.; Okayasu, Y.; Yasojima, M.; Sato, C. *Water Sci. Technol.* **2004**, *50* (5), 93−100.
(68) Tschmelak, Proll, G.; Gauglitz, G. *Talanta* **2005**, *65*, 313−323.
(69) Kawaguchi, M.; Inoue, K.; Yoshimura, M.; Sakuri, N., Okanouchi, N.; Ito, R.; Yoshimura Y.; Nakazawa, H. *J. Chromatogr., A* **2004**, *1041*, 19−26.
(70) Pojano, G.; Bonfa, A.; Busetti, F.; Collarin, A.; Marcomini, A. *Int. J. Environ. Anal. Chem.* **2004**, *84* (10), 717−727.
(71) Benijts, T.; Lambert, W.; Leenheer, A. D. *Anal. Chem.* **2004**, *76*, 704−711.
(72) Liu, R.; Zhou, J. L.; Wilding A. *J. Chromatogr., A* **2004**, *1038*, 19−26.
(73) Badea, M.; Nistor, C. Goda, Y., Fujimoto, S., Dosho, S.; Danet, A.; Barceló, D.; Francesc Ventura, F.; Emnéus, F. *Analyst* **2003**, *128* (7), 849−856.
(74) Alzaga, R.; Pena, A.; Bayona, J. M. *J. Sep. Sci.* **2003**, *26*(1−2), 87−96.
(75) Snyder, S. A.; Weterhoff, P.; Yoon, Y, Sedlak, D. *Environ. Eng. Sci.* **2003**, *20* (5) 449- 469.
(76) Huber, M. M.; Canonica, S.; Park, G.-Y.; von Gunten, U. *Environ. Sci. Technol.* **2003**, *37*, 1016- 1024.
(77) Huber, M. M.; Ternes, T. A. von Gunten, U. *Environ. Sci. Technol.* **2004**, *38*, 5177−5186.
(78) Dodd, M. C.; Huang, C.-H. *Environ. Sci. Technol.* **2004**, *38* (21), 5607−5615.
(79) Hu, J.; Cheng, S.; Aitawa, T.; Terao, Y.; Kunikane, S. *Environ. Sci. Technol.* **2003**, *37*, 5665−5670.
(80) Balmer, M. E.; Buser, H.-R.; Müller, M. D.; Poiger, T. *Environ. Sci. Technol.* **2005**, *39* (4), 953−962.
(81) Poiger, T.; Buser, H. R.; Balmer, M. E.; Bergqvist, P. A., Müller, M. D. *Chemosphere* **2004**, *55* (7), 951−963.
(82) Giokas, D. L.; Sakkas, V. A.; Albanis, T. A. *J. Chromatogr., A* **2004**, *1026* (1−2), 289−293.
(83) Sakkas, V. A.; Giokas, D. L.; Lambropoulou, D. A.; Albanis, T. A. *J. Chromatogr., A* **2003**, *1016* (2), 211−222.
(84) Richardson, S. D. *TrAC, Trends Anal. Chem.* **2003**, *22* (10), 666−684.
(85) Xu, X.; Weisel, C. P. *J. Exp. Anal. Environ. Epidemiol.* **2005**, *15* (1), 6−16.
(86) Plewa, M. J.; Wagner, E. D.; Richardson, S. D.; Thruston, A. D., Jr.; Woo, Y.-T.; McKague, A. B. *Environ. Sci. Technol.* **2004**, *38* (18), 4713−4722.
(87) Plewa, M. J.; Wagner, E. D.; Jazwierska, P.; Richardson, S. D.; Chen. P. H.; McKague, A. B. *Environ. Sci. Technol.* **2004**, *38* (1), 62−68.
(88) Simmons, J. E.; Teuschler, L. K.; Gennings, C.; Speth, T. F.; Richardson, S. D.; Miltner, R. J.; Narotsky, M. G.; Schenck, K. D.; Hunter, E. S.; Hertzberg, R. C.; Rice, G. *J. Toxicol. Environ. Health, Part A* **2004**, *67* (8−10), 741−754.
(89) Richardson, S. D.; Thruston, A. D., Jr.; Rav-Acha, C.; Groisman, L.; Popilevsky, I.; Juraev, O.; Glezer, V.; McKague, A. B.; Plewa, M. J.; Wagner, E. D. *Environ. Sci. Technol.* **2003**, *37* (17), 3782−3793.
(90) Huang, W. J.; Tsai, Y. Y.; Chu, C. W. *J. Environ. Sci. Health, Part A* **2003**, *38* (12), 2919−2931.
(91) Lumbard, K. W.; Nixon, N. S.; Scheinmann, F. *Synth. Commun.* **2003**, *33* (19), 3411−3417.
(92) von Gunten, U. *Water Res.* **2003**, *37* (7), 1443−1467.
(93) von Gunten, U. *Water Res.* **2003**, *37* (7), 1469−1487.
(94) Paull, B.; Barron, L. *J. Chromatogr., A* **2004**, *1046* (1−2), 1−9.
(95) Zwiener, C.; Glauner, T.; Frimmel, F. H. In *Liquid Chromatography/Mass Spectrometry, MS/MS and Time of Flight MS: Analysis of Emerging Contaminants*; Ferrer, I., Thurman, E. M., Eds.; ACS Symposium Series 850; American Chemical Society: Washington, DC, 2003; pp 356−375.
(96) Vincenti, M.; Ghiglione, N.; Valsania, M. C.; Davit, P.; Richardson, S. D. *Helv. Chim. Acta* **2004**, *87* (2), 370−375.
(97) Zhang, X.; Minear, R. A.; Guo, Y.; Hwang, C. J.; Barrett, S. E.; Ikeda, K.; Shimizu, Y.; Matsui, S. *Water Res.* **2004**, *38*, 3920−3930.
(98) Zhang, X.; Minear, R. A.; Barrett, S. E. *Environ. Sci. Technol.* **2005**, *39* (4), 963−972.
(99) Jia, M. H.; Wu, W. W.; Yost, R. A.; Chadik, P. A.; Stacpoole, P. W.; Henderson, G. N. *Anal. Chem.* **2003**, *75* (16), 4065−4080.
(100) Dixon, A. M.; Delinsky, D. C.; Bruckner, J. V.; Fisher, J. W.; Bartlett, M. G. *J. Liq. Chromatogr. Relat. Technol.* **2004**, *27* (15), 2343−2355.
(101) Gabryelski, W.; Wu, F. W.; Froese, K. L. *Anal. Chem.* **2003**, *75* (10), 2478−2486.
(102) Suedee, R.; Srichana, T.; Sangpagai, C.; Tunthana, C.; Vanichapichat, P. *Anal. Chim. Acta* **2004**, *504* (1), 89−100.
(103) Na, C. Z.; Olson, T. M. *Environ. Sci. Technol.* **2004**, *38* (22), 6037−6043.
(104) Wuilloud, R. G.; de Wuilloud, J. C. A.; von der Heide, A. P.; Caruso, J. A. *J. Anal. At. Spectrom.* **2003**, *18* (9), 1119−1124.
(105) Kannamkumarath, S. S.; Wuilloud, R. G.; Jayasinghe, S.; Caruso, J. A. *Electrophoresis* **2004**, *25* (12), 1843−1851.
(106) Choi, Y. W.; Reckhow, D. A. *Bull. Korean Chem. Soc.* **2004**, *25* (6), 900−906.
(107) Diaz, A.; Fabrellas, C.; Ventura, F. *J. Agric. Food Chem.* **2005**, *53* (2), 383−387.
(108) Krasner, S. W.; Wright, J. M. *Water Res.* **2005**, *39*, 855−864.
(109) Liu, Y.; Mou, S. *Chemosphere* **2004**, *55* (9), 1253−1258.
(110) Monarca, S.; Zani, C.; Richardson, S. D.; Thruston, A. D., Jr.; Moretti, M.; Feretti, D.; Villarini, M. *Water Res.* **2004**, *38* (17), 3809−3819.
(111) Mitch, W. A.; Sharp, J. O.; Trussell, R. R.; Valentine, R. L.; Alvarez-Cohen, L.; Sedlak, D. L. *Environ. Eng. Sci.* **2003**, *20* (5), 389−404.
(112) Charrois, J. W. A.; Arend, M. W.; Froese, K. L.; Hrudey, S. E. *Environ. Sci. Technol.* **2004**, *38* (18), 4835−4841.
(113) Wilczak, A.; Assadi-Rad, A.; Lai, H. H.; Hoover, L. L.; Smith, J. F.; Berger, R.; Rodigari, F.; Beland, J. W.; Lazzelle, L. J.; Kinicannon, E. G.; Baker, H.; Heaney, C. T. *J. Am. Water Works Assoc.* **2003**, *95* (9), 94−106.
(114) Gerecke, A. C.; Sedlak, D. L. *Environ. Sci. Technol.* **2003**, *37* (7), 1331−1336.
(115) Mitch, W. A.; Sedlak, D. L. *Environ. Sci. Technol.* **2004**, *38* (5), 1445−1454.
(116) Choi, J. H.; Valentine, R. L. *Environ. Sci. Technol.* **2003**, *37* (21), 4871−4876.
(117) Moriyama, K.; Matsufuji, H.; Chino, M.; Takeda, M. *Chemosphere* **2004**, *55*, 839−847.
(118) Petrovic, M.; Diaz, A.; Ventura, F.; Barceló, D. *Environ. Sci. Technol.* **2003**, *37* (19), 4442−4448.
(119) Lin, C. H.; Lerch, R. N.; Garrett, H. E.; George, M. F. *J. Agric. Food Chem.* **2003**, *51* (27), 8011−8014.
(120) Kull, T. P. J.; Backlund, P. H.; Karlsson, K. M.; Meriluoto, J. A. O. *Environ. Sci. Technol.* **2004**, *38* (22), 6025−6031.
(121) Birnbaum, L. S.; Staskal, D. F. *Environ. Health Perspect.* **2004**, *112* (1), 9−17.
(122) Polo, M.; Gomez-Noya, G.; Quintana, J. B.; Llompart, M.; Garcia-Jares, C.; Cela, R. *Anal. Chem.* **2004**, *76* (4), 1054−1062.
(123) Alaee, M. *Environ. Monit. Assess.* **2003**, *88* (1−3), 327−341.
(124) Hale, R. C.; Alaee, M.; Manchester-Neesvig, J. B.; Stapleton, H. M.; Ikonomou, M. G. *Environ. Int.* **2003**, *29* (6), 771−779.
(125) D'Silva, K.; Fernandes, A.; Rose, M. *Crit. Rev. Environ. Sci. Technol.* **2004**, *34* (2), 141−207.
(126) Covaci, A.; Voorspoels, S.; de Boer, J. *Environ. Int.* **2003**, *29* (6), 735−756.
(127) Scrimshaw, M. D.; Langford, K. H.; Lester, J. N. *Environ. Technol.* **2004**, *25* (8), 967−974.
(128) Hites, R. A. *Environ. Sci. Technol.* **2004**, *38* (4), 945−956.
(129) Oros, D. R.; Hoover, D.; Rodigari, F.; Crane, D.; Sericano, J. *Environ. Sci. Technol.* **2005**, *39* (1), 33−41.
(130) Svrcek, C.; Smith, D. W. J. *Environ. Eng. Sci.* **2004**, *3* (3), 155−185.
(131) Hoeger, S. J.; Shaw, G.; Hitzfeld, B. C.; Dietrich, D. R. *Toxicon* **2004**, *43* (6), 639−649.
(132) Maizels, M.; Budde, W. L. *Anal. Chem.* **2004**, *76* (5), 1342−1351.
(133) Zhang, L. F.; Ping, X. F.; Yang, Z. G. *Talanta* **2004**, *62* (1), 193−200.
(134) Meriluoto, J.; Karlsson, K.; Spoof, L. *Chromatographia* **2004**, *59* (5−6), 291−298.
(135) Dahlmann, J.; Budakowski, W. R.; Luckas, B. *J. Chromatogr., A* **2003**, *994* (1−2), 45−57.
(136) Furey, A.; Crowley, J.; Shuilleabhain, A. N.; Skulberg, A. M.; James, K. J. *Toxicon* **2003**, *41* (3), 297−303.
(137) Nasri, A. B.; Bouaicha, N.; Fastner, J. *Arch. Environ. Contam. Toxicol.* **2004**, *46* (2), 197−202.
(138) Yuan, M.; Carmichael, W. W. *Toxicon* **2004**, *44* (5), 561−570.
(139) Mountfort, D. O.; Holland, P.; Sprosen, J. *Toxicon* **2005**, *45* (2), 199−206.
(140) Winkler, P.; Minteer, M.; Willey, J. *Anal. Chem.* **2004**, *76* (2), 469−473.
(141) Smith, P. N.; Yu, L.; McMurry, S. T.; Anderson, T. A. *Environ. Pollut.* **2004**, *132* (1), 121−127.
(142) Liu, Y. J.; Mou, S. F. *J. Chromatogr., A* **2003**, *997* (1−2), 225−235.
(143) Gu, B. H.; Tio, J.; Wang, W.; Ku, Y. K.; Dai, S. *Appl. Spectrosc.* **2004**, *58* (6), 741−744.
(144) Hebert, G. N.; Odom, M. A.; Bowman, S. C.; Strauss, S. H. *Anal. Chem.* **2004**, *76* (3), 781−787.
(145) Ganjali, M. R.; Yousefi, M.; Poursaberi, T.; Naji, L.; Salavati-Niasari, M.; Shamsipur, M. *Electroanalysis* **2003**, *15* (18), 1476−1480.
(146) Schmidt., T. C. *TrAC, Trends Anal. Chem.* **2003**, *22* (10), 776−784.
(147) Deeb, R. A.; Chu, K. H.; Shih, T.; Linder, S.; Suffet, I.; Kavanaugh, M. C.; Alvarez-Cohen, L. *Environ. Eng. Sci.* **2003**, *20* (5), 433−447.
(148) Williams, P. R. D.; Benton, L. Sheehan, P. J. *Environ. Forensics* **2003**, *4* (3), 175−189.
(149) Rosell, M.; Lacorte, S.; Ginebreda, A.; Barceló, D. *J. Chromatogr., A* **2003**, *995* (1−2), 171−184.
(150) Morgenstern, P.; Versteegh, A. F. M.; de Korte, G. A. L.; Hoogerbrugge, R.; Mooibroek, D.; Bannink, A.; Hogendoorn, E. A. *J. Environ. Monit.* **2003**, *5* (6), 885−890.
(151) Lico, M. S. *Lake Reservoir Manage.* **2004**, *20* (2), 164−174.
(152) Ayotte, J. D.; Argue, D. M.; McGarry, F. J. *Environ. Sci. Technol.* **2005**, *39* (1), 9−16.

(153) Yazdi, A. S.; Assadi, H. *Chromatographia* **2004**, *60* (11−12), 699−702.
(154) Schuhmacher, R.; Fuhrer, M.; Kandler, W.; Stadlmann, C.; Krska, R. *Anal. Bioanal. Chem*. **2003**, *377* (7−8), 1140−1147.
(155) McLoughlin, P. W.; Pirkle, R. J.; Fine, D.; Wilson, J. T. *Ground Water Monit. Rem*. **2004**, *24* (4), 57−66.
(156) Schmidt, T. C.; Haderlein, S. B.; Pfister, R.; Forster, R. *Water Res*. **2004**, *38* (6), 1520−1529.
(157) Battaglin, W. A.; Thurman, E. M.; Kalkhoff, S. J.; Porter, S. D. *J. Am. Water Works Assoc*. **2003**, *39* (4), 743−756.
(158) Vargo, J. D. In *Liquid Chromatography/Mass Spectrometry, MS/MS and Time of Flight MS: Analysis of Emerging Contaminants*; Ferrer, I., Thurman, E. M., Eds.; ACS Symposium Series 850; American Chemical Society: Washington, DC, pp 238−255, 2003.
(159) Spalding, R. F.; Exner, M. E.; Snow, D. D.; Cassada, D. A.; Burbach, M. E.; Monson, S. J. *J. Environ. Qual*. **2003**, *32* (1), 92−99.
(160) Thurman, E. M.; Ferrer, I.; Furlong, E. T. In *Liquid Chromatography/Mass Spectrometry, MS/MS and Time of Flight MS: Analysis of Emerging Contaminants*; Ferrer, I., Thurman, E. M., Eds.; ACS Symposium Series 850; American Chemical Society: Washington, DC, pp 128−144, 2003.
(161) Chicharro, M.; Zapardiel, A.; Bermejo, E.; Moreno, M. *Talanta* **2003**, *59* (1), 37−45.
(162) You, J.; Koropchak, J. A.; *J. Chromatogr., A* **2003**, *989* (2), 231−238.
(163) Ward, T. J.; Hamburg, D. M. *Anal. Chem.* **2004**, *76* (16), 4635−4644.
(164) Poiger, T.; Buser, H. R.; Muller, M. D.; Balmer, M. E.; Buerge, I J. *Chimia* **2003**, *57* (9), 492−498.
(165) Liu, W. P.; Gan, J. J. *J. Agric. Food Chem*. **2004**, *52* (4), 736−741.
(166) Jantunen, L. M.; Kylin, H.; Bidleman, T. F. *Deep-Sea Research Part II* **2004**, *51* (22−24), 2661−2672.
(167) Padma, T. V.; Dickhut, R. M.; Ducklow, H. *Environ. Toxicol. Chem*. **2003**, *22* (7), 1421−1427.
(168) Black, R. M.; Muir, B. *J. Chromatogr., A* **2003**, 1000 (1−2), 253−281.
(169) *Chemical Weapons Convention Chemicals Analysis: Sample Collection, Preparation, and Analytical Methods*; Mesilaakso, M., Ed.; John Wiley & Sons: New York, 2005.
(170) Palit, M.; Pardasani, D.; Gupta, A. K.; Dubey, D. K. *Anal. Chem*. **2005**, *77* (2), 711−717.
(171) Chen, H.; Zheng, X. B.; Cooks, R. G. *J. Am. Soc. Mass Spectrom*. **2003**, *14* (3), 182−188.
(172) Hanaoka, S.; Nagasawa, E.; Nomura, K.; Yamazawa, M. *Appl. Organomet. Chem*. **2005**, *19* (2), 265−275.
(173) Jones-Lepp, T. L.; Varner, K. E.; Heggem, D. *Arch. Environ. Contam. Toxicol.* **2004**, *46* (1), 90−95.
(174) Vidal, J. L. M.; Vega, A. B.; Arrebola, F. J.; Gonzalez-Rodriguez, M. J.; Sanchez, M. C. M.; Frenich, A. G. *Rapid Commun. Mass Spectrom*. **2003**, *17* (18), 2099−2106.
(175) Jitaru, P.; Infante, H. G.; Adams, F. C. *J. Anal. At. Spectrom*. **2004**, *19* (7), 867−875.
(176) Parkinson, D. R.; Bruheim, I.; Christ, I.; Pawliszyn, J. *J. Chromatogr., A* **2004**, *1025* (1), 77−84.
(177) Cukrowska, E.; Chimuka, L.; Nsengimana, H.; Kwaramba, V. *Anal. Chim. Acta* **2004**, *523* (1), 141−147.
(178) Karthikeyan, S.; Hirata, S. *Anal. Lett*. **2003**, *36* (11), 2355−2366.
(179) Shibata, Y.; Tsuzuku, K.; Komori, S.; Umedzu, C.; Imai, H.; Morita, M. *Appl. Organomet. Chem*. **2005**, *19* (2), 276−281.
(180) Leal, L. O.; Semenova, N. V.; Forteza, R.; Cerda, V. *Talanta* **2004**, *64* (5), 1335−1342.
(181) Dhar, R. K.; Zheng, Y.; Rubenstone, J.; van Geen, A. *Anal. Chim. Acta* **2004**, *526* (2), 203−209.
(182) Chwirka, J. D.; Colvin, C.; Gomez, J. D.; Mueller, P. A. *J. Am. Water Works Assoc*. **2004**, *96* (3), 106−114).
(183) Abbt-Braun, G.; Lankes, U.; Frimmel, F. H. *Aquat. Sci.* **2004**, *66* (2), 151−170.
(184) Stenson, A. C.; Marshall, A. G.; Cooper, W. T. *Anal. Chem*. **2003**, *75* (6), 1275−1284.
(185) Kim, S.; Kramer, R. W.; Hatcher, P. G. *Anal. Chem*. **2003**, *75* (20), 5336−5344.
(186) Reemtsma, T.; These, A. *Anal. Chem*. **2003**, *75* (6), 1500−1507.
(187) Rostad, C. E.; Leenheer, J. A. *Anal. Chim. Acta* **2004**, *523* (2), 269−278.
(188) Kujawinski, E. B.; Del Vecchio, R.; Blough, N. V.; Klein, G. C. *Mar. Chem*. **2004**, *92* (1−4), 23−37.
(189) Schmitt-Kopplin, P.; Kettrup, A. *Electrophoresis* **2003**, *24* (17), 3057−3066.
(190) Simpson, A. J.; Tseng, L. H.; Simpson, M. J.; Spraul, M.; Braumann, U.; Kingery, W. L.; Kelleher, B. P.; Hayes, M. H. B. *Analyst* **2004**, *129* (12), 1216−1222.
(191) Trauger, S. A.; Junker, T.; Siuzdak, G. *Mod. Mass Spectrom. Top. Curr. Chem*. **2003**, *225*, 265−282.
(192) Vater, J.; Gao, X. W.; Hitzeroth, G.; Wilde, C.; Franke, P. *Comb. Chem. High Throughput Screening* **2003**, *6* (6), 557−567.
(193) Pineda, F. J.; Antoine, M. D.; Demirev, P. A.; Feldman, A. B.; Jackman, J.; Longenecker, M.; Lin, J. S. *Anal. Chem*. **2003**, *75* (15), 3817−3822.
(194) Stump, M. J.; Jones, J. J.; Fleming, R. C.; Lay, J. O.; Wilkins, C. L. *J. Am. Soc. Mass Spectrom*. **2003**, *14* (11), 1306−1314.
(195) Warscheid, B.; Jackson, K.; Sutton, C.; Fenselau, C. *Anal. Chem*. **2003**, *75* (20), 5608−5617.
(196) Zheng, S. P.; Schneider, K. A.; Barder, T. J.; Lubman, D. M. *Biotechniques* **2003**, *35* (6), 1202−1212.
(197) Lee, C. S.; Kim, Y. G.; Joo, H. S.; Kim, B. G. *J. Mass Spectrom*. **2004**, *39* (5), 514−525.
(198) Krokhin, O.; Li, Y.; Andonov, A.; Feldmann, H.; Flick, R.; Jones, S.; Stroeher, U.; Bastien, N.; Dasuri, K. V. N.; Cheng, K. D.; Simonsen, J. N.; Perreault, H.; Wilkins, J.; Ens, W.; Plummer, F.; Standing, K. G. *Mol. Cell. Proteomics* **2003**, *2* (5), 345−356.
(199) Lee, L. Y.; Ong, S. L.; Hu, J. Y.; Ng, W. J.; Feng, Y. Y.; Tan, X. L.; Wong, S. W. *Appl. Environ. Microbiol*. **2004**, *70* (10), 5732−5736.
(200) Aboytes, R.; Di Giovanni, G. D.; Abrams, F. A.; Rheinecker, C.; McElroy, W.; Shaw, N.; LeChevallier, M. W. *J. Am. Water Works Assoc*. **2004**, *96* (9), 88−98.

AC058022X