Review

Analysis of amphetamine and methamphetamine as emerging pollutants in wastewater and wastewater-impacted streams

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ABSTRACT

The identification and quantitation of the non-ecstasy amphetamine-type stimulants (ATSs) amphetamine and methamphetamine in lakes, rivers, wastewater treatment plant influents, effluents, and biosolids are reviewed. Neither monitoring nor reporting is required of these ATSs, which are considered emerging pollutants, but they have been identified in the environment. Amphetamine and methamphetamine enter our water supply by human excretion after legal or illegal consumption and via manufacturing in clandestine laboratories. Analytical methodology for sampling, sample preparation, separation, and detection of ATSs is discussed. Reported occurrences of ATSs in the environment and their use in municipal sewage epidemiology are noted. Future research needs that challenge applications of analytical techniques are discussed. The review focuses on research reported from 2004 to 2009.

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Contents

1. Introduction

The phrase "emerging pollutants" can be defined as substances that are not presently known to cause impairments in water systems but that have characteristics such as the ability to bioaccumulate, persistence in the environment, and toxicity and potentially impact the integrity of the water [1]. Neither monitoring nor reporting is required of these substances, but they may still be present in the urban water cycle. Much of the peer-reviewed literature has focused on pharmaceutical and personal care products (PPCPs) and endocrine disrupting chemicals (EDCs), but recent research has also included groups of illicit drugs such as cocaine, opioids, opioid pharmaceuticals, cannabis, and amphetamine-type stimulants (ATSs). Although drugs in all of these categories have been found in environmental samples, this review will focus on analytical determination of amphetamine and methamphetamine.

Amphetamine and methamphetamine enter our water supply by human excretion after legal or illegal consumption and

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via manufacturing in clandestine laboratories. Amphetamines and methamphetamines are sometimes legally prescribed for certain medical conditions such as attention deficit hyperactivity disorder and exogenous obesity; therefore, their presence in wastewater cannot be attributed solely to illegal consumption. However, according to the United Nations Office of Drug and Crime (UNODC), the global problem with clandestine ATS markets is worsening, with estimates showing that between 230 and 640 metric tons of amphetamine-group substances (excludes ecstasy-group substances) were manufactured in 2007 [2].

Approximately 62% of methamphetamine [3] and 30–40% of amphetamine [4] consumed is excreted in urine within 24 h of an oral dose, and both amphetamine and methamphetamine are primarily excreted as the intact drug [5]. Once these drugs enter the wastewater treatment plant (WWTP) as influent, they can potentially enter surface or groundwater from inadequately treated WWTP effluent, wet-weather run-off, landfill seepage, contaminated streams and lakes, drainage from fields irrigated with effluent, and even from effluent used to recharge aquifers [6]. Jones-Lepp et al. [6] also noted that unlike non-polar pollutants of historic concern, these polar compounds are not readily sorbed to the subsoil, increasing the potential to enter surface and groundwaters.

The purpose of this manuscript is to compile a review of state-of-the-art analytical methodology used for sampling, sample preparation, separation, and detection of ATSs in environmental samples. Reported occurrences of ATSs in the environment are noted, and future research needs that challenge applications of analytical techniques are discussed.

2. Analytical methodology

2.1. Sample types and collection

Samples from surface waters (rivers and lakes) and WWTP influent and effluent were collected in Europe and the United States. The types of water sampled, the geographic regions in which they were sampled, and the types of samples collected, for analysis of ATSs are summarized in Table 1.

Sampling methods varied and included (1) grab samples, (2) 24 h composite samples, and (3) passively collected samples. A grab sample is collected simultaneously and reflects a single data point in time. A 24 h composite sample involves collecting discrete samples taken at specific intervals of time and combining them at the end of 24 h into a single sample. The composite sample reflects an average concentration of the analyte in the water source over a 24 h time period. Passive water sampling is based on the free flow of water molecules across a sampling medium. Semipermeable membrane devices (SPMDs) and polar organic chemical integrative samplers (POCIS) are the most common passive sampling devices currently in use, but because of the polar nature of methamphetamine and amphetamine, only POCIS was used in the water sampling reviewed in this article.

2.2. Sample preparation

2.2.1. Solids removal and internal standards

After collection, Zuccato et al. [7] and Castiglioni et al. [11] filtered surface water and WWTP samples through Whatman GF/A

Table 1
Geographic regions and waters sampled for ATSs.

Reference	Region	Water type	Sample type
Zuccato et al. [7]	Rivers Po, Lambro and Olona and Lakes Maggiore, Varese, and Lugano in northern Italy; River Arno in central Italy; River Thames in Oxfordshire and London, UK.	River samples downstream from largely populated areas. Lake samples in order to study medium (Varese, Lugano) and large (Maggiore) water basins	2 h composite samples; pooled lake or river samples every 20 min
Kasprzyk-Hordern et al. [8]	Six sampling sites on the River Taff and four sample sites on the River Ely in South Wales, UK	River Taff samples from the source to where the river enters the Bristol Channel. WWTP[a] Cilfynydd is on the river. River Ely samples upstream and downstream of WWTP Coslech	Replicate grab samples
Kasprzyk-Hordern et al. [9]	River Taff samples collected upstream and downstream of WWTP Cilfynydd and WWTP influent and effluent. River Ely samples collected upstream and downstream of WWTP Coslech and WWTP influent and effluent.	River and WWTP influent and effluent	Replicate grab samples and 24 h composite samples were collected at WWTP Coslech
Bartelt-Hunt et al. [10]	Surface waters upstream and downstream of WWTP outfalls and in WWTP effluent in Nebraska, USA	Surface waters and Omaha, NE WWTP effluent	POCIS samplers were deployed for seven days. At one site, POCIS was recovered after four weeks due to vandalism
Jones-Lepp et al. [6]	Three WWTPs located in Nevada, Utah, and South Carolina, USA	WWTP effluent	POCIS samplers were deployed for 30 days
Castiglioni et al. [11]	WWTPs in Milan-Nosedo, Italy, and in Lugano, Switzerland	WWTP influent and effluent	Two 24 h composite samples; pooled every 20 min
Huerta-Fontela et al. [12]	WWTPs in Catalonia, Spain, and samples from the Llobregat River, Spain	WWTP influent and effluent and surface waters	24 h composite samples from WWTPs; grab samples from Llobregat River
Huerta-Fontela et al. [13]	WWTPs in Northeast Spain	WWTP influent and effluent	Grab samples initially, then 24 h composite samples; pooled every hour
van Nuijs et al. [14]	WWTPs in Belgium	WWTP influent	24 h composite samples
Bijlsma et al. [15]	WWTPs in Castellón, Spain	WWTP influent and effluent	24 h composite samples
Postigo et al. [16]	El Prat STP[b] in Barcelona, Spain; STPs in Valencia, Benicasim, and Gandia	WWTP influent and effluent	24 h composite samples
Chiaia et al. [17]	Seven WWTPs in the USA	WWTP influent	24 h composite samples
Loganathan et al. [18]	WWTP in Kentucky, USA	Various stages in WWTP; upstream and downstream	Grab samples

[a] WWTP – Wastewater treatment plant.
[b] STP – Sewage treatment plant.

Table 2
Extraction procedures.

Drugs detected	Sample type	Reference	Sorbent	Conditioning	Elution	Recovery %
AM[a], MA[b]	Surface waters, composite samples	Zuccato et al. [7]	Oasis MCX[c]	MeOH, Milli-Q H_2O, pH 2 H_2O	MeOH, 2% NH_3 in MeOH	AM – 101 ± 4.5 (sw [f]) MA – 108 ± 6.9 (sw)
AM	Surface waters, grab samples	Kasprzyk-Hordern et al. [8]	Oasis MCX	Not available	MeOH, 5% NH_4OH in MeOH	AM – 91 (sw)
AM	Surface waters and wastewater influent and effluent, composite and grab samples	Kasprzyk-Hordern et al. [9]	Gilson ASPEC XL4 and Oasis MCX	Not available	MeOH, 5% NH_4OH in MeOH	Not available
AM, MA	Surface waters and wastewater effluent, passively collected samples	Bartelt-Hunt et al. [10]	POCIS, Oasis HLB[d] sorbent	Not applicable	MeOH	Not available
MA	Wastewater influent and effluent, passively collected samples	Jones-Lepp et al. [6]	POCIS, Oasis HLB sorbent	Not applicable	MeOH	Not available
AM, MA	Wastewater influent and effluent, composite samples	Castiglioni et al. [11]	Oasis MCX	MeOH, Milli-Q H_2O, pH 2 H_2O	MeOH, 2% NH_3 in MeOH	AM – 110 ± 4.5 (inf [g]) MA – 112 ± 6.5 (inf) AM – 103 ± 4.2 (eff [h]) MA – 97 ± 3.4 (eff)
AM, MA	Surface waters, wastewater influent and effluent, composite and grab samples	Huerta-Fontela et al. [12]	Zymark Rapid Trace SPE Workstation using Oasis HLB	MeOH, Milli-Q H_2O, 5% MeOH in H_2O	MeOH	AM – 75 ± 3.9 (sw) MA – 83 ± 2.1 (sw) AM – 70 ± 6.8 (ww)[i] MA – 80 ± 4.3 (ww)
AM, MA	Wastewater influent and effluent, grab samples	Huerta-Fontela et al. [13]	Zymark Rapid Trace SPE Workstation using Oasis HLB	MeOH, Milli-Q H_2O, 5% MeOH in H_2O	MeOH	Not available
AM, MA	Wastewater influent and effluent, composite samples	Bijlsma et al. [15]	Oasis MCX	MeOH, Milli-Q H_2O, pH 2 H_2O	2% NH_3 in MeOH	AM – 113 (inf) MA – 116 (inf) AM – 102 (eff) MA – 94 (eff)
AM, MA	Wastewater influent and effluent, composite samples	Postigo et al. [16]	Online SPE, PLRP-s[e]	ACN, H_2O	ACN, H_2O	AM – 94 (inf) MA – 114 (inf)
AM, MA	Wastewater influent, composite samples	Chiaia et al. [17]	Not applicable	Not applicable	Not applicable	Not applicable
MA	Various stages in WWTP; upstream and downstream	Loganathan et al. [18]	Oasis HLB	MeOH, DI water	MeOH/1% CH_3COOH	Not available
AM	Sewage sludge (biosolids)	Kaleta et al. [19]	Oasis HLB	Acetone, H_2O, borate buffer (pH 10)	MeOH: HCOOH (20:80, v/v)	Not available
MA	Sewage sludge (biosolids)	Jones-Lepp et al. [20]	Not applicable	Not applicable	Not applicable	Not available

[a] AM – amphetamine.
[b] MA – methamphetamine.
[c] MCX – poly(divinylbenzene-co-N-vinylpyrrolidone) with a surface bonded sulfonic acid group.
[d] HLB – poly(divinylbenzene-co-N-vinylpyrrolidone).
[e] PLRP-s – cross-linked styrene-divinylbenzene polymer.
[f] sw – surface water.
[g] inf – influent.
[h] eff – effluent.
[i] ww – wastewater, influent/effluent not specified.

T.H. Boles, M.J.M. Wells / J. Chromatogr. A 1217 (2010) 2561–2568

2563

1.6 μm glass filters. Prior to solid-phase extraction (SPE), 50 mL of sample was spiked with 20 ng of either amphetamine-D_6 or methamphetamine-D_9 as an internal standard, and the pH was adjusted to 2.0 with 37% HCl. Alternatively, samples were acidified before filtration by Kasprzyk-Hordern et al. [8,9]. Surface water and WWTP samples were acidified to pH 2.0 with 37% HCl and vacuum-filtered through Whatman GF/F 0.7 μm glass fiber filters. A 1 L sample was spiked with 200 ng phenacetin-ethoxy-1-^{13}C as the internal standard/surrogate standard in preparation for SPE [8,9]. Huerta-Fontela et al. [12,13] filtered samples through Whatman GF/A 1.6 μm glass microfiber filters and added amphetamine-D_8 and methamphetamine-D_9 as the internal standards. A 100 mL sample was used for SPE. Influent and effluent 24 h composite samples collected by Postigo et al. [16] were vacuum-filtered through Whatman 1 μm glass fiber filters followed by 0.45 μm nylon membrane filters. The samples were spiked with amphetamine-D_5 and methamphetamine-D_{14}. Instead of using vacuum filtration, Chiaia et al. [17] centrifuged a 7 mL aliquot of the WWTP influent samples for 30 min at 7100 rpm. The supernatant was transferred to a 6 mL vial and spiked with amphetamine-D_6 and methamphetamine-D_5. Loganathan et al. [18] filtered wastewater and stream samples through 10 μm glass fiber filters. The samples (250 mL or less) were adjusted to pH < 3 prior to SPE.

2.2.2. Extraction procedures

In the 13 articles cited for this review, SPE was used to extract amphetamine and/or methamphetamine from environmentally contaminated samples. The sorbents used and conditioning and elution procedures for all articles reviewed are summarized in Table 2. SPE was not used in two articles: Jones-Lepp and Stevens [20] used accelerated solvent extraction (ASE) for the extraction of methamphetamine from biosolids, whereas Chiaia et al. [17] used large-volume injection followed by LC–MS/MS to eliminate SPE entirely. Postigo et al. [16] described a fully online SPE method in which the sorbent Polymer Laboratories Reversed-Phase-Styrene (PLRP-s), a cross-linked styrene-divinylbenzene polymer, was used for extraction of ATSs.

Six studies used Oasis hydrophilic–lipophilic balance (HLB) sorbents [6,10,12,13,18,19] and five used Oasis MCX sorbents [7–9,11,15] for SPE. Oasis HLB is a reversed-phase sorbent that can be used for all compounds, and Oasis MCX is a mixed-mode cation-exchange reversed-phase sorbent for bases with pK_a of 2–10. Oasis HLB sorbents are made by polymerizing divinylbenzene (lipophilic) and *N*-vinylpyrrolidine (hydrophilic) monomers. They are capable of extracting acidic, basic, and neutral analytes, which may be polar or non-polar. Oasis MCX sorbents are formed by introducing a sulfate functional group into the Oasis HLB sorbent to generate a benzenesulfonic acid moiety with a pK_a < 1.

van Nuijs et al. [14] compared the use of Oasis HLB and MCX sorbents for analysis of abused drugs in wastewater, and the results for amphetamine and methamphetamine are presented in Table 3. For Oasis HLB, 500 mg and 60 mg sorbent masses were tested at pH 7 and pH 3. The washing step was evaluated using Milli-Q water, Milli-Q water at pH 2, hexane, or no washing step. Oasis MCX 500 mg and 60 mg sorbent masses were evaluated only at pH 2, but as with the HLB cartridges, the washing steps tested were the same. Recoveries using the Oasis HLB sorbent at pH 7 were low (13–63%) regardless of the sorbent size. However, at pH 3, both the 500 mg and 60 mg HLB sorbents gave recoveries of 91–106%. Recoveries were also excellent (98–105%) for the Oasis MCX 60 mg sorbent. Because the Oasis HLB sorbent at pH 3 and the MCX sorbent at pH 2 yielded similar recoveries for amphetamine and methamphetamine in the van Nuijs et al. [14] study, the deciding factor influencing the choice of sorbent may be (a) the selection of additional illicit drugs or pharmaceuticals to be analyzed from the same sample and (b) removal of background co-extracted interferences.

2.2.3. Recovery from passive samplers

POCIS devices can contain a variety of sorbents for monitoring different types of pollutants. Jones-Lepp et al. [6] and Bartelt-Hunt et al. [10] both used the POCIS passive sampling system to collect surface water and WWTP samples. Three pharmaceutical POCIS devices, each with a 41 cm^2 surface area of hydrophilic polyethersulfone membranes (0.1 μm pore size) enclosing 200 mg of Oasis HLB sorbent were deployed in stainless-steel canisters. After 7-d and 28-d sampling periods, respectively, the POCIS apparatuses were rinsed with water to remove debris and then opened. The sorbents were washed with MeOH into silane-treated vials, and the analytes were eluted by passing MeOH through glass gravity-flow chromatography columns (1 cm inside diameter) fitted with silanized glass wool plugs and stopcocks. Extracts were filtered and concentrated before separation and detection.

2.3. Separation and detection

Of the manuscripts reviewed, HPLC or UPLC was used for separation followed by mass spectrometry, with C18 being used as the column sorbent in 14 of 15 studies (Table 4). A Phenomenex Luna hydrophilic interactive liquid chromatography (HILIC) column, rather than the ubiquitous C18 column, was used by van Nuijs et al. [14], who reported better ionization in MS detection and higher sensitivity as rationale for using the HILIC column. Multiple reaction monitoring (MRM) and selected reaction monitoring (SRM) were commonly utilized modes of spectrometry. Jones-Lepp et al. [6] used collision induced dissociation (CID) to detect and quantify analytes. Although atmospheric pressure ionization (API) was sometimes used, electrospray ionization (ESI) was most commonly reported, and the MS analyses were always performed in positive mode.

3. Occurrence

Occurrence reports of emerging pollutants including ATS-type stimulants were reviewed [21]. Wastewater treatment did not

Table 3
Extraction recoveries (in %) for Oasis HLB and Oasis MCX cartridges with different sample pH, sorbent mass and washing step.

Sample	Oasis HLB						Oasis MCX				
	pH 7				pH 3		pH 2				
Sorbent	500 mg/6 cm³			60 mg/3 cm³	500 mg/6 cm³	60 mg/3 cm³	500 mg/6 cm³	60 mg/3 cm³			
Washing step	No wash	Milli-Q	Hexane	Milli-Q	Milli-Q	Milli-Q	Milli-Q	No wash	Milli-Q	Water pH 2	Hexane
AM	20	16	13	53	106	91	68	103	102	105	100
MA	32	18	23	63	99	93	84	101	99	98	103

Table 4
Separation and detection.

Sample type	Reference	Column	Mobile phase	Detection	Mode
Surface waters, composite samples	Zuccato et al. [7]	Waters XTerra MS C18, 100 × 2.1 mm, 3.5 μm	Not available	Applied Biosystems-Sciex API 3000 triple quad with turbo ion spray source; Perkin-Elmer LC Series 200	SRM
Surface waters, grab samples	Kasprzyk-Hordern et al. [8]	ACQUITY UPLC BEH C18, 1 × 100 mm, 1.7 μm	H_2O, MeOH, CH_3COOH	Waters ACQUITY UPLC, ESI	MRM
Surface waters and wastewater influent and effluent, composite and grab samples	Kasprzyk-Hordern et al. [9]	ACQUITY UPLC BEH C18, 1 × 100 mm, 1.7 μm	H_2O, MeOH, CH_3COOH	Waters ACQUITY UPLC, ESI	MRM
Surface waters and wastewater effluent, passively collected samples	Bartelt-Hunt et al. [10]	Thermo Betabasic-18, 250 × 2.1 mm, 5 μm	MeOH, 0.1% HCOOH (in H_2O)	Quattro Micro triple quadrupole; Waters 2695 HPLC, ESI	MRM
Wastewater influent and effluent, passively collected samples	Jones-Lepp et al. [6]	Restek Allure C18, 150 × 3.2 mm, 5 μm	H_2O, NH_3CH_3COOH, CH_3COOH, MeOH	ThermoQuest Finnigan LCQ, ESI	CID
Wastewater influent and effluent, composite samples	Castiglioni et al. [11]	Waters XTerra MS C18, 100 × 2.1 mm, 3.5 μm	Not available	Applied Biosystems-Sciex API 3000 triple quad with turbo ion spray source; Perkin-Elmer LC Series 200	MRM
Surface waters, wastewater influent and effluent, composite and grab samples	Huerta-Fontela et al. [12]	ACQUITY UPLC BEH C18, 2.1 × 100 mm, 1.7 μm	ACN: 0.1% HCOOH, 30 mM HCOOH: NH_3COOH	Waters ACQUITY UPLC, ESI	SRM
Wastewater influent and effluent, grab samples	Huerta-Fontela et al. [13]	ACQUITY UPLC BEH C18, 2.1 × 100 mm, 1.7 μm	ACN: 0.1% HCOOH, 30 mM HCOOH: NH_3COOH	Waters ACQUITY UPLC, ESI	SRM
Wastewater influent, composite samples	van Nuijs et al. [14]	Phenomenex Luna HILIC, 150 × 3 mm, 3 μm	5 mM NH_3COOH, ACN	Agilent 6410 triple quad, ESI	MRM
Wastewater influent and effluent, composite samples	Bijlsma et al. [15]	ACQUITY UPLC BEH C18, 2.1 × 50 mm, 1.7 μm	MeOH, 5 mM NH_3COOH: 0.1% HCOOH	TQD triple quad, ESI	SRM
Wastewater influent and effluent, composite samples	Postigo et al. [16]	Merck Purospher Star RP-18e, 125 × 2.0 mm, 5 μm with guard column 4 × 4 mm, 5 μm	ACN: H_2O	Applied Biosystems-Sciex 4000QTRAP hybrid triple quad with turbo ion spray source	SRM
Wastewater influent, composite samples	Chiaia et al. [17]	Waters Atlantis T3 C18, 4.6 × 150 mm, 5 μm with Phenomenex C18, 2.0 × 4.0 mm guard column	5% MeOH: 0.1% CH_3COOH, ACN	Waters Quattro Micro tandem MS, ESI	MRM
Various stages in WWTP; upstream and downstream	Loganathan et al. [18]	Varian Pursuit XRs C18 100 × 2 mm, 3 μm with Varian C18 2.0 mm, 3 μm guard column	MeOH; ACN; 0.5% HCOOH	Varian μ-HPLC–ESI-ITMS	CID
Sewage sludge (biosolids)	Kaleta et al. [19]	Schermbeck YMC-Pack Pro C18, 12 nm bore, 3 μm with YMC ProC18 10 × 4.0 mm guard column	50 mM HCOOH; MeOH	Agilent UV–vis diode array detector and Thermo Finnigan LCQ Deca XP plus IT, API	SRM
Sewage sludge (biosolids)	Jones-Lepp et al. [20]	Agilent Zorbax RX-C18, 2.1 × 100 mm, 3.5 μm	82% MeOH: 18% ACN: 0.1% HCOOH, 99% H_2O: 0.1% HCOOH	Thermo Finnigan LCQ, ESI	SRM

ESI – Electrospray ionization; API – Atmospheric pressure ionization; SRM – Selected reaction monitoring; MRM – Multiple reaction monitoring; CID – Collision induced dissociation; ITMS – Ion trap mass spectrometry.

T.H. Boles, M.J.M. Wells / J. Chromatogr. A 1217 (2010) 2561–2568

2565

Table 5
Environmental occurrence of ATSs.

Reference	Amphetamine	Methamphetamine
Zuccato et al. [7]	River Olona <0.65 ng/L River Lambro <0.65 ng/L River Po <0.65 ng/L River Arno <0.65 ng/L River Thames <0.65 ng/L	River Olona 1.7 ng/L River Lambro 2.1 ng/L River Po <0.41 ng/L River Arno <0.41 ng/L River Thames <0.41 ng/L
Kasprzyk-Hordern et al. [8]	River Taff varied from below detection to 1–14 ng/L River Ely varied from below detection to 1–21 ng/L	Not tested
Kasprzyk-Hordern et al. [9]	River Taff found in very high frequency. Concentrations were 1–11 ng/L, with a mean of 3 ng/L. Samples downstream of the WWTP Cilfynydd showed in 100% of samples ranging 2–13 ng/L with a mean of 7 ng/L. Also found 100% of the time in the influent and 14% of the time in effluent samples. Influent 255–3225 ng/L and effluent 3–11 ng/L	Not tested
Bartelt-Hunt et al. [10]	Not tested	Grand Island, NE: upstream 1.4 ng/L, downstream 6.6 ng/L Columbus, NE: upstream 1.3 ng/L, downstream 2.3 ng/L Lincoln, NE: upstream ND, downstream 25.2 ng/L Hastings, NE: downstream 62.6 ng/L Omaha, NE: effluent 350.1 ng/L
Jones-Lepp et al. [6]	Not tested	Site 1: 1.3 ng/L; Site 1-II: 0.8 ng/L; Site 2: ND; Site 3: ND
Castiglioni et al. [11]	Nosedo: influent 14.7 ± 10.6 ng/L, effluent <LOQ Lugano: influent <LOQ, effluent <LOQ	Nosedo: influent 16.2 ± 7.1 ng/L, effluent 3.5 ± 2 ng/L Lugano: influent <LOQ, effluent <LOQ
Huerta-Fontela et al. [12]	WWTP influent 15 ng/L, effluent <LOQ	Not tested
Huerta-Fontela et al. [13]	42 WWTPs in NE Spain: 22 samples influent 3–688 ng/L, 10 samples effluent 4–210 ng/L	42 WWTPS in NE Spain: 17 samples influent 3–277 ng/L, 12 samples effluent 3–90 ng/L
van Nuijs et al. [14]	11 WWTPs in Belgium: 12 samples influent 3–681 ng/L	11 WWTPs in Belgium: 12 samples influent <1–16 ng/L
Bijlsma et al. [15]	WWTP in Spain: 28 samples influent <0.5–1.40 μg/L, effluent <0.5–0.21 μg/L	WWTP in Spain: 28 samples influent below detection limit
Postigo et al. [16]	El Prat: influent 41.1 ± 9.1 ng/L, effluent 0.5 ± 0.1 ng/L Valencia: influent 20.4 ng/L, effluent 2.2 ng/L Benicassim: influent 35.5 ng/L, effluent 1.0 ng/L Gandia: influent 6.5 ng/L, effluent 3.3 ng/L	El Prat: influent 18.2 ± 5.8 ng/L, effluent 6.3 ± 0.6 ng/L Valencia: influent 7.8 ng/L, effluent 2.7 ng/L Benicassim: influent 3.7 ng/L, effluent 2.0 ng/L Gandia: influent 3.0 ng/L, effluent 1.5 ng/L
Chiaia et al. [17]	Plant 1: 220 ± 30 ng/L, Plant 2: 550 ± 80 ng/L, Plant 3: 80 ± 10 ng/L, Plant 4: 120 ± 20 ng/L, Plant 5: 250 ± 40 ng/L, Plant 6: 90 ± 10 ng/L, Plant 7: 130 ± 20 ng/L	Plant 1: 920 ± 70 ng/L, Plant 2: 2000 ± 200 ng/L, Plant 3: ND, Plant 4: 10 ± 1 ng/L, Plant 5: 920 ± 70 ng/L, Plant 6: 150 ± 10 ng/L, Plant 7: <LLOQ
Loganathan et al. [18]	Not tested	Various sampling points within WWTP ranged from 35 ng/L to ND; ND upstream or downstream

remove amphetamine or methamphetamine completely from the effluent in most cases (Table 5); however, in instances in which ATSs were found in the influent, they were greatly reduced in the effluent.

The efficiency in removing ATSs strongly depended on the wastewater technologies used in the WWTPs [9], with two different types of treatment technology studied at two treatment plants in South Wales in the United Kingdom. At WWTP Cilfynydd, technology relied on trickling filter beds and resulted, on average, in less than 70% removal of the PPCPs studied. In contrast, WWTP Coslech reported a greater removal efficiency of more than 85%, which was attributed to the use of a more efficient activated sludge treatment as opposed to the trickling filter beds. Overall, activated sludge technology was found to be more effective in the removal of ATSs [9]. Huerta-Fontela et al. [13] reported 52–99% removal efficiency of amphetamine and 44–99% removal efficiency of methamphetamine. Bijlsma et al. [15] observed 85% removal efficiency for amphetamine and 99% removal efficiency for methamphetamine.

Loganathan et al. [18] reported a 54.5% WWTP removal efficiency for methamphetamine. They calculated mass loading to determine the amount of methamphetamine entering the receiving waters from the WWTP effluent. The total daily mass of methamphetamine released by the WWTP effluent in their study was estimated to range from 0 to 100 mg/day.

4. Municipal sewage epidemiology

Although the UNODC has reported an increase in the production of illegal amphetamine and methamphetamine from clandestine laboratories in different countries based on crime statistics, drug monitoring, and seizure rates, some consumption data are based on information supplied by drug consumers themselves. These estimation techniques create a high level of uncertainty [2]. Additionally, because data collection and analysis are time consuming, it is not always possible to detect changing patterns and to compare test results among local communities. In 2001, Daughton [22] first proposed the use of non-intrusive drug monitoring at sewage treatment facilities to determine drug usage at the community level. Several research groups have now implemented this approach.

Table 6
Amounts (mg/day/1000 People) of major drug target residues (DTR) from ATSs conveyed daily in urban wastewater to STPs in Milan, Lugano, and London.

DTR	Milan	Lugano	London
Amphetamine	2.7 ± 2.8	ND	24 ± 5
Methamphetamine	4.5 ± 1.6	ND	2.4 ± 0.3

Excerpted from Ref. [23] – Reproduced with permission from *Environmental Health Perspectives*.
ND – not detected.

Table 7
Drug concentrations (ng/L) in influent samples from WWTP in NE Spain sampled over seven consecutive days.

Drug	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Amphetamine	63 ± 4	35 ± 3	45 ± 7	24 ± 3	40 ± 5	72 ± 6	101 ± 10
Methamphetamine	<LOD	<LOD	<LOD	<LOD	1 ± 0.3	3 ± 1	12 ± 3

Excerpted from Ref. [13] with permission from Elsevier.
LOD: 0.4 ng/L.

To provide more realistic data, Zuccato et al. [23] reported a sewage epidemiology approach to monitoring collective community use of abused drugs. They conducted studies to provide objective, quantitative, near-real-time profiles of illicit drug consumption by monitoring the drugs entering the sewage system in Milan (Italy), Lugano (Switzerland), and London (England) (Table 6). The results shown are back-calculated rates of consumption determined by multiplying the concentration of the drug by the influent wastewater flow rate, normalizing the data for the local population size, and taking into account metabolic excretion.

A similar study was performed at 42 WWTPs in Northeast Spain by Huerta-Fontela et al. [13]. Load per capita (mg/(day 1000 inhabitants)) ranged from nondetectable to 427 (mg/(day 1000 inhabitants)) for amphetamine and nondetectable to 78 (mg/(day 1000 inhabitants)) for methamphetamine. Huerta-Fontela et al. [13] also examined daily variations in ATS concentrations at a WWTP during a one-week period (Table 7). ATS concentrations varied widely during the week but showed a sharp increase over the weekend [13].

Analyses of abused drugs and their human metabolites were also used by Postigo et al. [24] to estimate community levels of drug abuse. These compounds were determined to occur in the μg/L to ng/L range in surface water and sewage water. Banta-Green et al. [25] reported a population measure of community drug load based on analyses of municipal wastewater influent in single-day samples representing 65% of the population of the State of Oregon, USA. Index loads (mg/person/day) were estimated by multiplying drug concentration determined in wastewater effluent by the total flow divided by the population served. Methamphetamine was determined to be present in samples from all municipalities without distinction between urban and rural areas.

5. Drinking water impacts

Because contaminated surface waters can be used as source waters for drinking water production, the presence and removal of ATSs in conventional drinking water treatment processes is of concern, and has been reviewed elsewhere [26]. Huerta-Fontela et al. [27] determined that non-ecstasy ATSs were completely eliminated by pre-chlorination, flocculation, and sand filtration during drinking water treatment.

6. Future research needs

Further work must be done in the area of WWTPs to determine which method(s) of treatment best removes the ATSs from wastewater. The question unanswered to date is even if a substance is found, is it a threat to human or aquatic life? Zuccato et al. [7] stated that even if environmental concentrations are low, risks for human health and the environment cannot be excluded. ATSs and other illicit drugs have potent pharmacological activities, and their presence as complex mixtures in surface waters – together with residues of many therapeutic drugs – may lead to unforeseen pharmacological interactions causing toxic effects to aquatic organisms [7].

Although ATSs have been found in WWTPs, their presence in the sanitary sewer collection system has not been studied. As reported, some studies have been performed to determine the daily load of ATSs based on back-calculation of ATS concentrations in WWTP influent. However, the data from WWTPs does not provide information as to where the ATSs enter the system. Sampling of sanitary sewer lines in areas of suspected ATS abuse or manufacture could help pinpoint the location at which the ATSs enter the wastewater system and help locate hot spots of drug abuse.

Passive sampling has been used to determine time-weighted averages for concentrations of compounds in the water and to overcome the problem of capturing information just at the time of sampling that results from grab and composite samples. However, research is still needed to fully characterize how different environmental variables influence contaminant uptake rates for POCIS sorbents to fully assess whether calculated uptake rates can be used to quantify POCIS results [10].

Two groups of scientists reported finding amphetamine [19] and methamphetamine [20] in sludge or biosolids obtained from WWTPs. Both groups acknowledge that further research should be conducted in relation to overcoming inherent problems in extracting target compounds from the sludge, due to its negative surface charges and interstitial spaces [20], and in lessening matrix effects that cause ionization source fouling and result in ion suppression [19]. Because farmland application is one disposal mechanism for biosolids, ATSs can leach into groundwater through seepage or agricultural run-off or be dispersed via plant uptake and should be investigated.

Finally, although methamphetamine and amphetamine are excreted largely unchanged, metabolites of both drugs are also excreted, and additional metabolites may be formed during sewage collection and treatment. The primary metabolites of methamphetamine, p-hydroxymethamphetamine sulfate, and p-hydroxymethamphetamineglucuronide have been measured directly in the urine of rats and humans. However, no studies have been conducted to detect and quantify the metabolites in wastewater. Further research in this area is required.

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