Chapter 5

Occurrence, effects and methods for antibiotics and illicit drugs in the environment

Tammy Jones-Lepp
Research Chemist
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory – Environmental Sciences Division
Las Vegas, NV 89119 USA
702-798-2144
Fax 702-798-2142
Email: jones-lepp.tammy@epa.gov

Table of Contents

5.1 Introduction …… 3

5.2 Environmental occurrence – routes of exposure …… 4

5.3 Ecotoxicological effects ……... 6

5.3.1 Antibiotics ……..……... 6

5.3.2 Illicit drugs …...……... 8

5.4 Analytical methodologies ……... 9

5.4.1 Extraction ……..……... 9

5.4.2 Detection ……..……... 10

5.4.2.1 Gas Chromatography/mass spectrometry …….. 10

5.4.2.2 Liquid Chromatography/mass spectrometry …… 11

5.5 Conclusions ……..……... 11

5.6 Table 1. Classes of antibiotics and illicit drugs: Analytical methods, environmental matrix, country, reference ……..……... 15

5.7 References ……..……..…... 20

5.1 Introduction

From around the globe, a variety of emerging contaminants (ECs), specifically pharmaceuticals and illicit drugs, have been identified in multiple environmental compartments [i.e., soils, plants, fish, surface waters, source waters, drinking water, and influents and effluents from wastewater treatment plants (WWTPs)]. Several insightful reviews covering general topic knowledge, analytical methods, and reports of occurrence of these ECs have been published (Jones-Lepp et al. 2009; Kümmerer 2009a; Kümmerer 2009b; Martinez 2009; Turkdogan et al. 2009; Kümmerer 2010; Deblonde et al. 2011; Pal et al. 2012; Richardson 2012).

There are a wide variety of antibiotics that are available for the treatment of bacterial diseases in humans and other animal species, see Table 1. Usually the antibiotics used in the treatment of human diseases are not identical to those used in treatment of animal diseases, but instead are isomers, or isobars, to prevent cross-reactivity of antibiotic resistant bacteria (ARB) between humans and other animal species. However, some antibiotic classes, i.e., macrolides, quinolones, sulfonamides, tetracyclines, and β-lactams, are used in the treatment of disease in both human and other animal species.

Methamphetamine, methylenedioxy-methamphetamine (MDMA, Ecstasy), heroin, and cocaine are considered illicit substances in the United States (US), as listed in the Code of Federal Regulations (CFR) Title 21 United States Code (USC) Controlled Substances Act (http://www.deadiversion.usdoj.gov/21cfr/21usc/index.html). While other narcotics, and habit-forming prescription drugs, such as, hydrocodone, oxycodone, morphine, and diazepam (valium), are not considered illicit substances, they are considered controlled substances. Controlled substances are compounds that the US Drug and Enforcement Agency (DEA) lists as

schedule III and IV drugs, substances that have a potential for abuse, (http://www.deadiversion.usdoj.gov/21cfr/21usc/index.html).

This chapter is intended as an updated review focusing on the occurrence, effects, and methodologies encompassing antibiotics and illicit substances in the environment.

5.2 Environmental Occurrence – routes of exposure

There are several routes of possible exposure from human-use antibiotics and illicit drugs into the environment. Probably the most prevalent exposure route is through consumer consumption and subsequent excretion into the municipal sewer systems and transport through the WWTP process into surface waters (Batt et al. 2006a; Batt et al. 2006b; Choi et al. 2008; Feitosa-Felizzola et al. 2009; Kümmerer 2009b; Kümmerer 2009a; Loganathan et al. 2009; Le-Minh et al. 2010; Zuccato et al. 2010; Murata et al. 2011; de la Torre et al. 2012; Jones-Lepp et al. 2012; K'Oreje et al. 2012; Lupo et al. 2012; Zheng et al. 2012).

Other possible routes of exposure can be through leaking septic systems, non-seweraged systems (e.g., boat privies, outhouses), land-use of reclaimed wastewater (Jones-Lepp et al. 2010; Lapworth et al. 2012), and application of biosolids onto agricultural fields, (Jones-Lepp 2006; Kinney et al. 2006; Jones-Lepp et al. 2007; Sabourin et al. 2009; Xu et al. 2009; Tso et al. 2011; Lapworth et al. 2012; Rosi-Marshall et al. 2012; Kolpin et al. 2013; Li et al. 2013).

A unique route of environmental exposure to antibiotics is through the practice of aquaculture (fish farming). Many countries, particularly in Southeast Asia (Hoa et al. 2011; Zheng et al. 2012), use the intensive practice of aquaculture for food production, and this can lead to inadvertent introduction of antibiotics into surrounding surface waters. In Vietnam, they use an integrated farming practice – vegetable, aquaculture, caged animal (VAC), which can

directly lead to contamination of surface waters from antibiotics used in swine farming, as well as aquaculture, (Hoa et al. 2011). Here in the US, catfish and salmon aquaculture are practiced, whereby only sulfadimethoxine (a sulfonamide) combined with ormetoprim, is allowable for treating bacterial infections (APHIS 2003) in catfish and salmon aquaculture [US Food and Drug Administration (FDA) Green Book, last accessed 28-May-13]. Sulfadimethoxine is closely related to sulfamethoxazole, which is combined with trimetoprim, to treat bacterial infections in humans (Rxlist.com, last accessed 28-May-13). Ormetoprim and trimetoprim are isobaric antibiotic compounds ($C_{14}H_{18}N_4O_3$, MW 290.1379 Da), used for veterinary and human use, respectively. Other types of sulfonamides, and drug combinations, are permissible in swine farming in Southeast Asia and the US (Hoa et al. 2011; Apley et al. 2012), again increasing their likelihood of entering the environment through integrated farming practices. Having related antibiotics released together into the environment increases the chances of developing ARB in the environment that could cross over between species. The topic of ARB will be discussed later in this chapter.

In 2003, Khan and Ongerth (Khan et al. 2003) reported, for the first time, at the 2003 National Ground Water conference, the presence of an illicit substance, methamphetamine, in wastewater effluent from a large US city in California. Jones-Lepp et al. (2004) reported for the first time in the peer-reviewed literature, the detection of two illicit drugs, methamphetamine and MDMA, collected from wastewater treatment plant (WWTP) effluent streams in Nevada and South Carolina, US (Jones-Lepp et al. 2004). Since 2004, numerous articles have been published regarding the environmental occurrence of illicit drugs (Chiaia et al. 2008; Bartelt-Hunt et al. 2009; Petrovic et al. 2010; Jones-Lepp et al. 2012; Aguilar et al. 2013).

Besides release via WWTPs, smaller contributions of illicit drugs into the environment are from clandestine drug laboratories. For example, during the illegal manufacturing of methamphetamine well over 50 hazardous chemicals are either used, or produced, as methamphetamine by-products (USEPA 2008). All of those hazardous compounds, including methamphetamine, have the potential to enter the environment through improper disposal into the city sewer or individual septic systems, via shallow drainage ditches directly onto surrounding soils (commonly used in remote methamphetamine operations), or through burn or burial pits (USEPA 2008).

5.3 Ecotoxicological Effects

While there have been many papers regarding the finding of antibiotics and illicit drugs in the environment, there have been very few papers written with regards to ecotoxicological consequences. Santos et al. (2010) published a very good review of ecotoxicological effects from a wide variety of drugs, including antibiotics (Santos et al. 2010). In this review, they look at various toxicological endpoints such as, growth inhibition, adverse reproductive effects, histopathological changes, and other adverse effects. An article by Rosi-Marshall and Royer (2012) provides a brief review of sources of pharmaceuticals into aquatic ecosystems and ecological effects. They outline a broad-plan for future research efforts regarding the consequences of ecosystem-level exposure for those in the scientific community studying aquatic ecology (Rosi-Marshall et al. 2012).

5.3.1 Antibiotics. The introduction and use of antibiotics in the early 20th century has led to a decrease in mortality from common bacterial infections, but there are adverse

consequences due to their overuse and misuse. Unexpected ecotoxicological effects can come from indirect exposure to antibiotics that are essentially designed for one purpose - treatment of human and domestic livestock for illness and disease (Isidori et al. 2005). For example, it is now recognized that the increasing use of human antibiotics can lead to an increase in ARBs in the environment, which is an unintended negative consequence (Schwartz et al. 2003; Da Silva et al. 2006; Pruden et al. 2006; Schwartz et al. 2006; Auerbach et al. 2007; Felmingham et al. 2007; Kim et al. 2007a; Lindberg et al. 2007; Schlüter et al. 2007; Baquero et al. 2008; Martinez 2009; Rosenblatt-Farrell 2009; Szczepanowski et al. 2009; Turkdogan et al. 2009; Knapp et al. 2010; Hoa et al. 2011; Merlin et al. 2011; Munir et al. 2011; Gao et al. 2012; Lupo et al. 2012; Vignesh et al. 2012; Maal-Bared et al. 2013; Michael et al. 2013; Shi et al. 2013). Kümmerer gives two very good overviews of antibiotics in the aquatic environment that touch upon nearly every aspect of origin, fate and affects of antibiotics, as well as the rise of ARBs, in the aquatic environment (Kümmerer 2009a; Kümmerer 2009b).

Besides the development of ARB, other ecological toxic effects from exposure to antibiotics in the environment have been shown. For example, the sulfonamide, sulfamethoxazole, and the fluoroquinolone, levofloxacin, elicit strong phytotoxic responses in two aquatic plants, *Myriophyllum sibiricum* and *Lemna gibba* (Brain et al. 2004). Ciprofloxacin, a fluoroquinolone, has been shown to inhibit photosynthesis through interference in the photosynthetic pathway through inhibition of DNA gyrase (Aristilde et al. 2010). Garcia-Käufer et al. (2012) demonstrated that ciprofloxacin, and its photodegradation products, while not cytotoxic do elicit genotoxic effects upon human cell cultures (Garcia-Käufer et al. 2012). González-Pleiter et al. (2013) tested five different antibiotics individually, and as mixtures, for their toxicity towards two representative aquatic organisms; cyanobacterium *Anabaena*

CPB4337, and green alga *Pseudokirchneriella subcapitata* (González-Pleiter et al. 2013). Their study showed that the cyanobacterium were more sensitive to exposure than the green alga, and that erythromycin (a macrolide antibiotic widely used in Europe; the counterpart drug is azithromycin in the US) was shown to be highly toxic to both organisms. Macrolides, and the other classes of antibiotics tested (i.e., tetracycline, quinolones and amoxicillin), as well as other antibiotic classes, like the sulfonamides, have all been detected in US waters (e.g., source, well, drinking) (Yang et al. 2003; Alvarez et al. 2005; Batt et al. 2006a; Batt et al. 2006b; Jones-Lepp 2006; Barnes et al. 2008; Bhandari et al. 2008; Benotti et al. 2009; Loganathan et al. 2009; Jones-Lepp et al. 2012), and throughout the world (Nageswara Rao et al. 2008; Chang et al. 2010; García-Galán et al. 2010; Hoa et al. 2011; Murata et al. 2011; Al Aukidy et al. 2012). The Gonzalez-Pleiter (González-Pleiter et al. 2013) study supports earlier toxicity studies that had determined the toxicity of various antibiotics to aquatic organisms (Isidori et al. 2005; Kim et al. 2007b).

5.3.2 Illicit drugs. Illicit drugs have been detected in environmental waters from around the industrialized world (Castiglioni et al. 2011). However, there is very little in the literature regarding the impact of illicit drugs in the environment on aquatic organisms. Binelli et al. (2012) and Parolini et al. (2013) have both shown cytotoxicity in zebra mussels (*Dreissena polymorpha*) from exposure to cocaine (Binelli et al. 2012) and its metabolite benzoylecgonine (Parolini et al. 2013). What little is known regarding the ecotoxicology of illicit drugs has been reported in a review by Domingo et al. (Domingo et al. 2010). A recent article by Thomas and Klaper (2012) proposed that there is a possible pathway between unmetabolized psychoactive compounds that have been found in source waters, sewage effluent, and drinking waters and

consequent exposure of the unborn to these compounds and the development of autism (Thomas et al. 2012).

5.4 Analytical Methodologies

5.4.1 Extraction. The majority of the extraction techniques for antibiotics and illicit drugs in aqueous environmental matrices use solid phase extraction (SPE) cartridges. For solid environmental matrices, a variety of other techniques are employed like pressurized liquid extraction (PLE) and liquid-liquid extraction (LLE). Typical concentrations of antibiotics and illicit drugs found in the environment are in the nanogram per liter (ng L^{-1}) range, making pre-concentration, and cleanup, prior to detection an important step. Several methods of extracting and concentrating antibiotics and illicit drugs from environmental matrices in both aqueous and solid matrices are listed as follows:

- liquid-liquid micro-extraction (LLME) (Lin et al. 2008),
- solid phase extraction (SPE) (Batt et al. 2006a; Batt et al. 2006b; Jones-Lepp et al. 2012; Zhou et al. 2012a; Zhou et al. 2012b; Dorival-García et al. 2013)
- tandem-solid-phase extraction (where two, or more, SPE cartridges are used in tandem for separation and clean-up) (Zhou et al. 2012b)
- ultra-sonication (Yang et al. 2010; Zuccato et al. 2010; Hu et al. 2011)
- microwave assisted extraction (MAE) (Chen et al. 2009; Hu et al. 2010; Sanchez-Prado et al. 2010; Azzouz et al. 2012; Speltini et al. 2012)
- molecularly imprinted polymers (MIP) (Turiel et al. 2007; Chen et al. 2010)
- pressurized liquid extraction (PLE) (Jones-Lepp et al. 2007; Lillenberg et al. 2009; Vazquez-Roig et al. 2010)

- large volume injection (LVI) (Thompson et al. 2009; Backe et al. 2012)
- magnetic nanoparticles dispersive-SPE (dSPE) (Herrera-Herrera et al. 2011; Xu et al. 2012).

5.4.2 Detection. Most environmental matrices are complex, and only the mass accuracy and specificity given by mass spectrometry can overcome the large amounts of interferences found in environmental matrices. Although simpler detectors are sometimes used, such as ultra-violet/visible (UV/Vis), fluorescence, diode array (DAD), etc., the majority of the detection techniques used to identify the very low levels (ppb and lower) of antibiotics and illicit drugs in complex environmental matrices are mass spectrometry based (Petrovic et al. 2005; Hao et al. 2007; Richardson 2010; Richardson 2012).

5.4.2.1 *Gas Chromatography/mass spectrometry*

Initially, gas chromatography/mass spectrometry (GC/MS) was an analytical approach used for detecting non-polar pharmaceuticals, polar pharmaceuticals (with derivatization), and steroids and hormones in environmental matrices (Garrison et al. 1976; Moeder et al. 2000). In general, substances that vaporize < 300 °C (and; therefore, are stable up to that temperature) can be measured by GC/MS. Unlike non-specific detection techniques [e.g., ultra-violet/diode array detection (UV/DAD), or fluorescence], GC/MS offers the ability to produce multiple fragment ions from a given analyte, via electron impact ionization, giving an unequivocal mass spectral fingerprint.

5.4.2.2 *Liquid chromatography/mass spectrometry.*

From almost the beginning of the finding of pharmaceuticals in the environment (Hirsch et al. 1999), there was also the realization that liquid chromatography/mass spectrometry (LC-MS) would be the better analytical detection technique than GC/MS because most of the classes of pharmaceuticals (i.e., antibiotics and illicit drugs) are polar and have low volatility making them ideal candidates for LC/MS. The coupling of LC to MS has been utilized for over 30 years (Niessen 2006).

Briefly, the mobile phase of the LC is nebulized via electrospray ionization (ESI) into a MS source. LC/MS is a technique that usually only creates a single ion in the source, typically the molecular ion plus or minus a hydrogen; if in the positive ionization mode, $(M+H)^+$, or if in the negative ionization mode, $(M-H)^-$. However, the formation of a single ion is also a limitation of LC/MS, for without more than one ion for identification, misidentification of analytes in complex environmental matrices can occur. Therefore, when using LC/MS, tandem MS, or MS/MS, techniques must be used for more specific identification. Tandem MS is a MS technique whereby the precursor ion formed in the MS source [in the case of LC/MS this is typically the $(M+H)^+$ or $(M-H)^-$ ion] is energized and collided, either in a triple quadrupole, ion trap, or a magnetic sector, mass spectrometer; thereby, producing product ions. Product ions are typically the loss of various functional groups from the analytes, for example $(M+H-OH)^+$ or $(M+H-CH_3)^+$.

5.5 Conclusions

There are now numerous articles demonstrating methods for detecting and reporting on the occurrence and fate with regards to antibiotics and illicit drugs. However, continued research

efforts are still necessary for better understanding of the complexity of continual low-level environmental exposures to these chemicals either singly or as mixtures, and their subtle effects not only on aquatic organisms, but ultimately, the consequences to those higher up in the food chain, i.e., humans. The ability to understand the potential for adverse effects from environmental exposure from antibiotics and illicit drugs on human and ecological health is becoming more important due to the increasing multi-use character of wastewater effluent (e.g., snowmaking, golf course irrigation, landscape irrigation, crop irrigation, etc.), and in some cases where it is continuously recycled in a closed-loop, such as in Singapore, and Scottsdale, Arizona (US). This multi-use and recycling of wastewater effluent increases the potential for cumulative increases of antibiotics and illicit drugs into water supply sources. Water reuse is becoming especially important in densely populated arid areas where there is an increasing demand to supply water from limited sources. Human well-being in a future world will depend more heavily upon a sustainable source water resource and the characterization of antibiotics and illicit drugs will become important for ecological and human health risk assessments and commodities valuation of water resources (Young 2005). Through improved understanding of environmental exposures, and greater knowledge of their chemical fate, better models of risk assessment can be made. Ideally, the information gathered will provide better models could be developed for predicting occurrence, fate and effects; leading to proactive responses, instead of reactive responses to environmental exposures from new emerging contaminants (Kostich et al. 2008). Improvements in limits of detection and specificity are fundamental to advancing our understanding of the sources, transport, and the ultimate fate of these contaminants.

NOTICE: The United States Environmental Protection Agency through its Office of Research and Development funded and managed the research described here. It has been subjected to Agency's administrative review and approved for publication.

Table 1. Classes of antibiotics and illicit drugs: Analytical methods, environmental matrix, country, reference.

Classes of antibiotics – illicit drugs	Analytical Methods Extraction - Detection	Environmental matrix	Country	Reference
Sulfonamides	SPE HPLC-MS/MS	wastewater	Italy	(Al Aukidy et al. 2012)
	POCIS HPLC-MS/MS	wastewater	US	(Alvarez et al. 2005)
	SPE HPLC-LC-MS	groundwater	US	(Barnes et al. 2008)
	POCIS HPLC-MS/MS	surface water	US	(Bartelt-Hunt et al. 2009)
	SPE HPLC-MS/MS	wellwater	US	(Batt et al. 2006b)
	SPE HPLC-MS/MS	wastewater	US	(Batt et al. 2006a)
	SPE HPLC-MS/MS	drinking water	US	(Benotti et al. 2009)
	SPE HPLC-fluorescence and photodiode array	wastewater	US	(Bhandari et al. 2008)
	Tandem SPE HPLC-MS/MS	wastewaters and source waters	China	(Chang et al. 2010)
	MAE-SPE HPLC-MS/MS	soils	China	(Chen et al. 2009)
	SPE HPLC-MS/MS PLE HPLC-MS/MS	surface water, sediments	France	(Feitosa-Felizzola et al. 2009)
	on-line SPE-HPLC-MS/MS	surface water, groundwater wastewater, influent	Spain	(García-Galán et al. 2010)
	SPE HPLC-MS/MS	source waters	Vietnam	(Hoa et al. 2011)
	SPE HPLC-MS/MS	soils	China	(Hu et al. 2011)
	MAE HPLC-MS/MS	Manure	China	(Hu et al. 2010)
	SPE HPLC-MS	wastewater	Korea	(Choi et al. 2008)
	SPE HPLC-MS/MS	source water	Kenya	(K'Oreje et al. 2012)
	PLE HPLC-MS	soils	US	(Kinney et al. 2006)
	SPE HPLC-MS/MS	wastewater lagoon	US	(Li et al. 2013)
	PLE HPLC-MS/MS	sewage sludge	Estonia	(Lillenberg et al. 2009)
	LLME HPLC/UV	waters	Taiwan	(Lin et al. 2008)
	SPE HPLC-MS/MS	waters	Japan	(Murata et al. 2011)

	SPE HPLC-MS/MS	surface waters	India	(Nageswara Rao et al. 2008)
	SPE and PLE, HPLC-MS/MS	runoff waters and biosolids	Canada	(Sabourin et al. 2009)
	SPE and PLE, HPLC-MS/MS	runoff waters and biosolids	US	(Tso et al. 2011)
	SPE and PLE HPLC-MS/MS	soils and sediments	Spain	(Vazquez-Roig et al. 2010)
	SPE HPLC-MS/MS	waters	China	(Xu et al. 2007)
	sonication-SPE rapid resolution (RR)LC-MS/MS	sediments	China	(Yang et al. 2010)
	SPE HPLC-MS/MS	seawater	China	(Zheng et al. 2012)
	sonication SPE RRLC-MS/MS	sediments, manure, sludge, surface water, lagoon wastewater, wastewater	China	(Zhou et al. 2012b)
Fluoroquinolones	SPE HPLC-MS/MS	wastewater	Italy	(Al Aukidy et al. 2012)
	POCIS HPLC-MS/MS	wastewater	US	(Alvarez et al. 2005)
	SPE HPLC/MS	groundwater	US	(Barnes et al. 2008)
	SPE HPLC-MS/MS	wastewater	US	(Batt et al. 2006a)
	MIP HPLC-UV	soils		(Turiel et al. 2007)
	SPE HPLC-fluorescence and photodiode array	wastewater	US	(Bhandari et al. 2008)
	Tandem-SPE HPCL-MS/MS	wastewaters and source waters	China	(Chang et al. 2010)
	Magnetic-MIP HPLC-MS/MS	environmental waters	China	(Chen et al. 2010)
	SPE UPLC-MS/MS	wastewater	Spain	(Dorival-García et al. 2013)
	SPE HPLC-MS/MS PLE HPLC-MS/MS	surface water, sediments	France	(Feitosa-Felizzola et al. 2009)
	magnetic nanoparticles dSPE capillary zone electrophoresis (CZE)-DAD	waters	Spain	(Herrera-Herrera et al. 2011)
	SPE HPLC-MS/MS	soils	China	(Hu et al. 2011)
	MAE HPLC-MS/MS	Manure	China	(Hu et al. 2010)
	SPE HPLC-MS/MS	source water	Kenya	(K'Oreje et al. 2012)
	PLE HPLC-MS/MS	sewage sludge	Estonia	(Lillenberg et al. 2009)

	Ultrasonic L/S HPLC-MS/MS	Sewage sludge	Sweden	(Lindberg et al. 2007)
	SPE HPLC-MS/MS	surface waters	India	(Nageswara Rao et al. 2008)
	MAE HPLC-fluorescence	soils	Italy	(Speltini et al. 2012)
	SPE and PLE HPLC-MS/MS	soils and sediments	Spain	(Vazquez-Roig et al. 2010)
	SPE HPLC-MS/MS	waters	China	(Xu et al. 2007)
	sonication SPE RRLC-MS/MS	sediments	China	(Yang et al. 2010)
	sonication SPE RRLC-MS/MS	sediments, manure, sludge, surface water, lagoon wastewater, wastewater	China	(Zhou et al. 2012b)
Macrolides	SPE HPLC-MS/MS	wastewater	Italy	(Al Aukidy et al. 2012)
	POCIS HPLC-MS/MS	wastewater	US	(Alvarez et al. 2005)
	SPE HPLC/MS	groundwater	US	(Barnes et al. 2008)
	POCIS LC-MS/MS	surface water	US	(Bartelt-Hunt et al. 2009)
	SPE HPLC-MS/MS	wastewater	US	(Batt et al. 2006a)
	LLE HPLC-fluorescence and photodiode array	wastewater	US	(Bhandari et al. 2008)
	Tandem SPE HPCL-MS/MS	wastewaters and source waters	China	(Chang et al. 2010)
	SPE HPLC-MS/MS PLE HPLC-MS/MS	surface water, sediments	France	(Feitosa-Felizzola et al. 2009)
	SPE HPLC-MS/MS	source waters	Vietnam	(Hoa et al. 2011)
	SPE HPLC-MS/MS	source water	US	(Jones-Lepp et al. 2012)
	PLE HPLC-MS/MS	vegetables, bermuda grass	US	(Jones-Lepp et al. 2010)
	SPE HPLC-MS/MS	source water	Kenya	(K'Oreje et al. 2012)
	PLE HPLC-MS	soils	US	(Kinney et al. 2006)
	SPE HPLC-MS/MS	wastewater lagoon	US	(Li et al. 2013)
	SPE HPLC-MS/MS	waters	Japan	(Murata et al. 2011)
	SPE HPLC-MS/MS	waters	China	(Xu et al. 2007)
	sonication SPE RRLC-MS/MS	sediments	China	(Yang et al. 2010)
	SPE HPLC-MS/MS	seawater	China	(Zheng et al. 2012)
	sonication SPE RRLC-MS/MS	sediments, manure, sludge, surface	China	(Zhou et al. 2012b)

		water, lagoon wastewater, wastewater		
Tetracyclines	POCIS HPLC-MS/MS	wastewater	US	(Alvarez et al. 2005)
	SPE HPLC/MS	groundwater	US	(Barnes et al. 2008)
	SPE HPLC-MS/MS	wastewater	US	(Batt et al. 2006a)
	Tandem SPE HPCL-MS/MS	wastewaters and source waters	China	(Chang et al. 2010)
	SPE HPLC-MS/MS PLE HPLC-MS/MS	surface water, sediments	France	(Feitosa-Felizzola et al. 2009)
	SPE HPLC-MS/MS	soils	China	(Hu et al. 2011)
	MAE HPLC-MS/MS	manure	China	(Hu et al. 2010)
	SPE and PLE, HPLC-MS/MS	runoff waters and biosolids	US	(Tso et al. 2011)
	SPE and PLE HPLC-MS/MS	soils and sediments	Spain	(Vazquez-Roig et al. 2010)
	sonication SPE RRLC-MS/MS	sediments	China	(Yang et al. 2010)
	sonication SPE RRLC-MS/MS	sediments, manure, sludge, surface water, lagoon wastewater, wastewater	China	(Zhou et al. 2012b)
Amphenicols	MAE-SPE GC-MS	sewage sludge	Spain	(Azzouz et al. 2012)
	SPE HPLC-MS/MS	waters	China	(Xu et al. 2007)
	sonication SPE RRLC-MS/MS	sediments, manure, sludge, surface water, lagoon wastewater, wastewater	China	(Zhou et al. 2012b)
β-lactams	SPE HPLC-MS/MS	source water	Kenya	(K'Oreje et al. 2012)
	SPE HPLC-MS/MS	surface waters	India	(Nageswara Rao et al. 2008)
	SPE HPLC-MS/MS	waters	China	(Xu et al. 2007)
Illicit drugs	SPE LC-MS/MS	wetland waters	Spain	(Aguilar et al. 2013)
	POCIS HPLC-MS/MS	surface water	US	(Bartelt-Hunt et al. 2009)
	LVI HPLC-MS/MS	wastewater	US	(Chiaia et al. 2008)
	SPE HPLC-MS/MS	source water	US	(Jones-Lepp et al. 2012)
Opiates	SPE HPLC-MS/MS	wetland waters	Spain	(Aguilar et al. 2013)
	SPE HPLC/MS	groundwater	US	(Barnes et al. 2008)

	LVI HPLC-MS/MS	wastewater	US	(Chiaia et al. 2008)
	SPE HPLC-MS/MS	source water	US	(Jones-Lepp et al. 2012)
	PLE HPLC-MS	soils	US	(Kinney et al. 2006)
Psychiatric drugs	SPE HPLC-MS/MS	wastewater	Italy	(Al Aukidy et al. 2012)
	SPE HPLC/MS	groundwater	US	(Barnes et al. 2008)
	SPE HPLC-MS/MS	drinking water	US	(Benotti et al. 2009)
	LVI HPLC-MS/MS	wastewater	US	(Chiaia et al. 2008)
	SPE HPLC-MS	wastewater	Korea	(Choi et al. 2008)
	SPE HPLC-MS/MS	source water	Kenya	(K'Oreje et al. 2012)
	PLE HPLC-MS	soils	US	(Kinney et al. 2006)
	SPE HPLC-MS/MS	wastewater lagoon	US	(Li et al. 2013)
	SPE and PLE HPLC-MS/MS	runoff waters and biosolids	Canada	(Sabourin et al. 2009)
	SPE and PLE HPLC-MS/MS	soils and sediments	Spain	(Vazquez-Roig et al. 2010)

REFERENCES

Aguilar, J. A. P., V. Andreu, et al. (2013). Presence of Illicit Drugs in Surface Waters of Protected Natural Wetlands Connected to Traditional Irrigation Systems and Urban Areas. Management of Water Resources in Protected Areas. H. Farfán González, J. L. Corvea Porras, I. de Bustamente Gutiérrez and J. W. LaMoreaux, Springer Berlin Heidelberg**:** 277-283.

Al Aukidy, M., P. Verlicchi, et al. (2012). "Monitoring release of pharmaceutical compounds: Occurrence and environmental risk assessment of two WWTP effluents and their receiving bodies in the Po Valley, Italy." Science of The Total Environment **438**(0): 15-25.

Alvarez, D., P. Stackelberg, et al. (2005). "Comparison of a novel passive sampler to standard water-column sampling for organic contaminants associated with wastewater effluents entering a New Jersey stream." Chemosphere **61**: 610-622.

APHIS (2003). ESC and vaccination practices, USDA.

Apley, M., E. Bush, et al. (2012). "Use Estimates of In-Feed Antimicrobials in Swine Production in the United States." Foodborne Pathogens and Disease **9**(3): 272-279.

Aristilde, L., A. Melis, et al. (2010). "Inhibition of Photosynthesis by a Fluoroquinolone Antibiotic." Environmental Science & Technology **44**(4): 1444-1450.

Auerbach, E. A., E. E. Seyfried, et al. (2007). "Tetracycline resistance genes in activated sludge wastewater treatment plants." Water Research **41**(5): 1143-1151.

Azzouz, A. and E. Ballesteros (2012). "Combined microwave-assisted extraction and continuous solid-phase extraction prior to gas chromatography–mass spectrometry determination of pharmaceuticals, personal care products and hormones in soils, sediments and sludge." Science of The Total Environment **419**(0): 208-215.

Backe, W. J. and J. A. Field (2012). "Is SPE Necessary for Environmental Analysis? A Quantitative Comparison of Matrix Effects from Large-Volume Injection and Solid-Phase Extraction Based Methods." Environmental Science & Technology **46**(12): 6750-6758.

Baquero, F., J.-L. Martínez, et al. (2008). "Antibiotics and antibiotic resistance in water environments." Current Opinion in Biotechnology **19**(3): 260-265.

Barnes, K. K., D. W. Kolpin, et al. (2008). "A national reconnaissance of pharmaceuticals and other organic wastewater contaminants in the United States — I) Groundwater." Science of The Total Environment **402**(2–3): 192-200.

Bartelt-Hunt, S. L., D. D. Snow, et al. (2009). "The occurrence of illicit and therapeutic pharmaceuticals in wastewater effluent and surface waters in Nebraska." Environmental Pollution **157**(3): 786-791.

Batt, A. L., I. B. Bruce, et al. (2006a). "Evaluating the vulnerability of surface waters to antibiotic contamination from varying wastewater treatment plant discharges." Environmental Pollution **142**(2): 295-302.

Batt, A. L., D. D. Snow, et al. (2006b). "Occurrence of sulfonamide antimicrobials in private water wells in Washington County, Idaho, USA." Chemosphere **64**(11): 1963-1971.

Benotti, M. J., R. A. Trenholm, et al. (2009). "Pharmaceuticals and Endocrine Disrupting Compounds in U.S. Drinking Water." Environmental Science & Technology **43**(3): 597-603.

Bhandari, A., L. Close, et al. (2008). "Occurrence of Ciprofloxacin, Sulfamethoxazole, and Azithromycin in Municipal Wastewater Treatment Plants." Practice Periodical of Hazardous, Toxic, and Radioactive Waste Management **12**(4): 275-281.

Binelli, A., A. Pedriali, et al. (2012). "Illicit drugs as new environmental pollutants: Cyto-genotoxic effects of cocaine on the biological model Dreissena polymorpha." Chemosphere **86**(9): 906-911.

Brain, R. A., D. J. Johnson, et al. (2004). "Microcosm evaluation of the effects of an eight pharmaceutical mixture to the aquatic macrophytes Lemna gibba and Myriophyllum sibiricum." Aquatic Toxicology **70**(1): 23-40.

Castiglioni, S., E. Zuccato, et al. (2011). Illicit drugs in the environment: occurrence, analysis, and fate using mass spectrometry, Wiley.

Chang, X., M. T. Meyer, et al. (2010). "Determination of antibiotics in sewage from hospitals, nursery and slaughter house, wastewater treatment plant and source water in Chongqing region of Three Gorge Reservoir in China." Environmental Pollution **158**(5): 1444-1450.

Chen, L., Q. Zeng, et al. (2009). "On-line coupling of dynamic microwave-assisted extraction to solid-phase extraction for the determination of sulfonamide antibiotics in soil." Analytica Chimica Acta **648**(2): 200-206.

Chen, L., X. Zhang, et al. (2010). "Determination of fluoroquinolone antibiotics in environmental water samples based on magnetic molecularly imprinted polymer extraction followed by liquid chromatography–tandem mass spectrometry." Analytica Chimica Acta **662**(1): 31-38.

Chiaia, A. C., C. Banta-Green, et al. (2008). "Eliminating Solid Phase Extraction with Large-Volume Injection LC/MS/MS: Analysis of Illicit and Legal Drugs and Human Urine Indicators in US Wastewaters." Environmental Science and Technology **42**(23): 8841-8848.

Choi, K., Y. Kim, et al. (2008). "Seasonal variations of several pharmaceutical residues in surface water and sewage treatment plants of Han River, Korea." Science of The Total Environment **405**(1–3): 120-128.

Da Silva, M. F., I. Tiago, et al. (2006). "Antibiotic resistance of enterococci and related bacteria in an urban wastewater treatment plant." FEMS Microbiology Ecology **55**(2): 322-329.

de la Torre, A., I. Iglesias, et al. (2012). "An approach for mapping the vulnerability of European Union soils to antibiotic contamination." Science of The Total Environment **414**(0): 672-679.

Deblonde, T., C. Cossu-Leguille, et al. (2011). "Emerging pollutants in wastewater: A review of the literature." International Journal of Hygiene and Environmental Health **214**(6): 442-448.

Domingo, G., K. Schirmer, et al. (2010). Illicit Drugs in the Environment: Implication for Ecotoxicology. Illicit Drugs in the Environment: Occurrence, Analysis, and Fate using Mass Spectrometry. S. Castiglioni, E. Zuccato and R. Fanelli. Singapore, John Wiley & Sons, Inc**:** 253-274.

Dorival-García, N., A. Zafra-Gómez, et al. (2013). "Simultaneous determination of 13 quinolone antibiotic derivatives in wastewater samples using solid-phase extraction and ultra performance liquid chromatography–tandem mass spectrometry." Microchemical Journal **106**(0): 323-333.

Feitosa-Felizzola, J. and S. Chiron (2009). "Occurrence and distribution of selected antibiotics in a small Mediterranean stream (Arc River, Southern France)." Journal of Hydrology **364**: 50-57.

Felmingham, D., R. Canton, et al. (2007). "Regional trends in β-lactam, macrolide, fluoroquinolone and telithromycin resistance among *Streptococcus pneumoniae* isolates 2001-2004." Journal of Infection **55**: 111-118.

Gao, P., D. Mao, et al. (2012). "Occurrence of sulfonamide and tetracycline-resistant bacteria and resistance genes in aquaculture environment." Water Research **46**(7): 2355-2364.

García-Galán, M. J., M. S. Díaz-Cruz, et al. (2010). "Determination of 19 sulfonamides in environmental water samples by automated on-line solid-phase extraction-liquid chromatography–tandem mass spectrometry (SPE-LC–MS/MS)." Talanta **81**(1–2): 355-366.

Garcia-Käufer, M., T. Haddad, et al. (2012). "Genotoxic effect of ciprofloxacin during photolytic decomposition monitored by the in vitro micronucleus test (MNvit) in HepG2 cells." Environmental Science and Pollution Research **19**(5): 1719-1727.

Garrison, A., J. Pope, et al. (1976). GC/MS Analysis of organic compounds in domestic wastewaters. Identification and Analysis of Organic Pollutants in Water. C. H. Keith. Ann Arbor, Michigan, Arbor Science Publishers**:** 517-556.

González-Pleiter, M., S. Gonzalo, et al. (2013). "Toxicity of five antibiotics and their mixtures towards photosynthetic aquatic organisms: Implications for environmental risk assessment." Water Research **47**(6): 2050-2064.

Hao, C., R. Clement, et al. (2007). "Liquid chromatography–tandem mass spectrometry of bioactive pharmaceutical compounds in the aquatic environment—a decade's activities." Analytical and Bioanalytical Chemistry **387**(4): 1247-1257.

Herrera-Herrera, A. V., L. M. Ravelo-Pérez, et al. (2011). "Oxidized multi-walled carbon nanotubes for the dispersive solid-phase extraction of quinolone antibiotics from water samples using capillary electrophoresis and large volume sample stacking with polarity switching." Journal of Chromatography A **1218**(31): 5352-5361.

Hirsch, R., T. Ternes, et al. (1999). "Occurrence of antibiotics in the aquatic environment." Science of The Total Environment **225**(1–2): 109-118.

Hoa, P. T. P., S. Managaki, et al. (2011). "Antibiotic contamination and occurrence of antibiotic-resistant bacteria in aquatic environments of northern Vietnam." Science of The Total Environment **409**(15): 2894-2901.

Hu, W., L. Ma, et al. (2011). "Simultaneous extraction and determination of fluoroquinolones, tetracyclines and sulfonamides antibiotics in soils using optimised solid phase extraction chromatography-tandem mass spectrometry." International Journal of Environmental Analytical Chemistry **92**(6): 698-713.

Hu, X., Y. Luo, et al. (2010). "Simultaneous Analysis of Selected Typical Antibiotics in Manure by Microwave-Assisted Extraction and LC–MS n." Chromatographia **71**(3-4): 217-223.

Isidori, M., M. Lavorgna, et al. (2005). "Toxic and genotoxic evaluation of six antibiotics on non-target organisms." Science of the Total Environment **346**(1-3): 87-98.

Jones-Lepp, T. L. (2006). "Chemical markers of human waste contamination: analysis of urobilin and pharmaceuticals in source waters." Journal of Environmental Monitoring **8**(4): 472–478.

Jones-Lepp, T. L., D. A. Alvarez, et al. (2009). Pharmaceuticals and Hormones in the Environment. Encyclopedia of Analytical Chemistry, John Wiley & Sons, Ltd.

Jones-Lepp, T. L., D. A. Alvarez, et al. (2004). "Polar Organic Chemical Integrative Sampling and Liquid Chromatography–Electrospray/Ion-Trap Mass Spectrometry for Assessing Selected Prescription and Illicit Drugs in Treated Sewage Effluents." Archives of Environmental Contamination and Toxicology **47**(4): 427-439.

Jones-Lepp, T. L., C. Sanchez, et al. (2012). "Point sources of emerging contaminants along the Colorado River Basin: Source water for the arid Southwestern United States." Science of The Total Environment **430**(0): 237-245.

Jones-Lepp, T. L., C. A. Sanchez, et al. (2010). "Method Development and Application To Determine Potential Plant Uptake of Antibiotics and Other Drugs in Irrigated Crop Production Systems." Journal of Agricultural and Food Chemistry **58**(22): 11568-11573.

Jones-Lepp, T. L. and R. Stevens (2007). "Pharmaceuticals and personal care products in biosolids/sewage sludge: the interface between analytical chemistry and regulation." Analytical and Bioanalytical Chemistry **387**(4): 1173-1183.

K'Oreje, K. O., K. Demeestere, et al. (2012). "From multi-residue screening to target analysis of pharmaceuticals in water: Development of a new approach based on magnetic sector mass spectrometry and application in the Nairobi River basin, Kenya." Science of The Total Environment **437**(0): 153-164.

Khan, S. and J. Ongerth (2003). Mass-Balance Analysis of Pharmaceutical Residues Within a Sewage Treatment Plant. National Ground Water Association, Minneapolis, MN.

Kim, S. and D. S. Aga (2007a). "Potential Ecological and Human Health Impacts of Antibiotics and Antibiotic-Resistant Bacteria from Wastewater Treatment Plants." Journal of Toxicology and Environmental Health, Part B: Critical Reviews **10**(8): 559 - 573.

Kim, Y., K. Choi, et al. (2007b). "Aquatic toxicity of acetaminophen, carbamazepine, cimetidine, diltiazem and six major sulfonamides, and their potential ecological risks in Korea." Environment International **33**(3): 370-375.

Kinney, C. A., E. T. Furlong, et al. (2006). "Presence and distribution of wastewater-derived pharmaceuticals in soil irrigated with reclaimed water." Environmental Toxicology and Chemistry **25**(2): 317-326.

Knapp, C. W., J. Dolfing, et al. (2010). "Evidence of Increasing Antibiotic Resistance Gene Abundances in Archived Soils since 1940." Environmental Science and Technology **44**: 580-587.

Kolpin, D. W., V. S. Blazer, et al. (2013). "Chemical contaminants in water and sediment near fish nesting sites in the Potomac River basin: Determining potential exposures to smallmouth bass (*Micropterus dolomieu*)." Science of the Total Environment **443**: 700-716.

Kostich, M. S. and J. M. Lazorchak (2008). "Risks to aquatic organisms posed by human pharmaceutical use." Science of The Total Environment **389**(2–3): 329-339.

Kümmerer, K. (2009a). "Antibiotics in the aquatic environment – A review – Part I." Chemosphere **75**(4): 417-434.

Kümmerer, K. (2009b). "Antibiotics in the aquatic environment – A review – Part II." Chemosphere **75**(4): 435-441.

Kümmerer, K. (2010). "Pharmaceuticals in the Environment." Annual Review of Environment and Resources **35**(1): 57-75.

Lapworth, D., N. Baran, et al. (2012). "Emerging organic contaminants in groundwater: A review of sources, fate and occurrence." Environmental pollution **163**: 287-303.

Le-Minh, N., S. J. Khan, et al. (2010). "Fate of antibiotics during municipal water recycling treatment processes." Water Research **44**(15): 4295-4323.

Li, X., W. Zheng, et al. (2013). "Occurrence and removal of pharmaceutical and hormone contaminants in rural wastewater treatment lagoons." Science of The Total Environment **445**: 22-28.

Lillenberg, M., S. Yurchenko, et al. (2009). "Simultaneous determination of fluoroquinolones, sulfonamides and tetracyclines in sewage sludge by pressurized liquid extraction and liquid chromatography electrospray ionization-mass spectrometry." Journal of Chromatography A **1216**(32): 5949-5954.

Lin, C.-Y. and S.-D. Huang (2008). "Application of liquid–liquid–liquid microextraction and high-performance liquid-chromatography for the determination of sulfonamides in water." Analytica Chimica Acta **612**(1): 37-43.

Lindberg, R. H., K. Björklund, et al. (2007). "Environmental risk assessment of antibiotics in the Swedish environment with emphasis on sewage treatment plants." Water Research **41**(3): 613-619.

Loganathan, B., M. Phillips, et al. (2009). "Contamination profiles and mass loadings of select macrolide antibiotics and illicit drugs from a small urban wastewater treatment plant." Chemosphere **75**(1): 70-77.

Lupo, A., S. Coyne, et al. (2012). "Origin and evolution of antibiotic resistance: the common mechanisms of emergence and spread in water bodies." Frontiers in Microbiology **3**.

Maal-Bared, R., K. H. Bartlett, et al. (2013). "Phenotypic antibiotic resistance of Escherichia coli and E. coli O157 isolated from water, sediment and biofilms in an agricultural watershed in British Columbia." Science of The Total Environment **443**(0): 315-323.

Martinez, J. L. (2009). "Environmental pollution by antibiotics and by antibiotic resistance determinants." Environmental Pollution **157**(11): 2893-2902.

Merlin, C., S. Bonot, et al. (2011). "Persistence and dissemination of the multiple-antibiotic-resistance plasmid pB10 in the microbial communities of wastewater sludge microcosms." Water Research **45**(9): 2897-2905.

Michael, I., L. Rizzo, et al. (2013). "Urban wastewater treatment plants as hotspots for the release of antibiotics in the environment: A review." Water Research **47**(3): 957-995.

Moeder, M., S. Schrader, et al. (2000). "Solid-phase microextraction–gas chromatography–mass spectrometry of biologically active substances in water samples." Journal of Chromatography A **873**(1): 95-106.

Munir, M., K. Wong, et al. (2011). "Release of antibiotic resistant bacteria and genes in the effluent and biosolids of five wastewater utilities in Michigan." Water Research **45**(2): 681-693.

Murata, A., H. Takada, et al. (2011). "Nationwide monitoring of selected antibiotics: Distribution and sources of sulfonamides, trimethoprim, and macrolides in Japanese rivers." Science of the Total Environment **409**: 5305-5312.

Nageswara Rao, R., N. Venkateswarlu, et al. (2008). "Determination of antibiotics in aquatic environment by solid-phase extraction followed by liquid chromatography–electrospray ionization mass spectrometry." Journal of Chromatography A **1187**(1–2): 151-164.

Niessen, W. (2006). Liquid Chromatography-Mass Spectrometry. New York, New York, Marcel Dekker, Inc.

Pal, R., M. Megharaj, et al. (2012). "Illicit drugs and the environment — A review." Science of The Total Environment(0).

Parolini, M., A. Pedriali, et al. (2013). "Sub-lethal effects caused by the cocaine metabolite benzoylecgonine to the freshwater mussel Dreissena polymorpha." Science of The Total Environment **444**(0): 43-50.

Petrovic, M., M. D. Hernando, et al. (2005). "Liquid chromatography-tandem mass spectrometry for the analysis of pharmaceutical residues in environmental samples: a review." Journal of Chromatography A **1067**(1-2): 1-14.

Petrovic, M., C. Postigo, et al. (2010). Occurrence and Fate of Pharmaceuticals and Illicit Drugs Under Water Scarcity. Water Scarcity in the Mediterranean. S. Sabater and D. Barceló, Springer Berlin Heidelberg**:** 197-228.

Pruden, A., R. Pei, et al. (2006). "Antibiotic Resistance Genes as Emerging Contaminants: Studies in Northern Colorado†." Environmental Science & Technology **40**(23): 7445-7450.

Richardson, S. D. (2010). "Environmental Mass Spectrometry: Emerging Contaminants and Current Issues." Analytical Chemistry **82**(12): 4742-4774.

Richardson, S. D. (2012). "Environmental Mass Spectrometry: Emerging Contaminants and Current Issues." Analytical Chemistry **84**(2): 747-778.

Rosenblatt-Farrell, N. (2009). "The landscape of antibiotic resistance." Environmental Health Perspectives **117**(6): A244-A250.

Rosi-Marshall, E. J. and T. V. Royer (2012). "Pharmaceutical Compounds and Ecosystem Function: An Emerging Research Challenge for Aquatic Ecologists." Ecosystems **15**(6): 867-880.

Sabourin, L., A. Beck, et al. (2009). "Runoff of pharmaceuticals and personal care products following application of dewatered municipal biosolids to an agricultural field." Science of the Total Environment **407**(16): 4596-4604.

Sanchez-Prado, L., C. Garcia-Jares, et al. (2010). "Microwave-assisted extraction: Application to the determination of emerging pollutants in solid samples." Journal of Chromatography A **1217**(16): 2390-2414.

Santos, L. H. M. L. M., A. N. Araújo, et al. (2010). "Ecotoxicological aspects related to the presence of pharmaceuticals in the aquatic environment." Journal of Hazardous Materials **175**(1–3): 45-95.

Schlüter, A., R. Szczepanowski, et al. (2007). "Genomics of IncP-1 antibiotic resistance plasmids isolated from wastewater treatment plants provides evidence for a widely accessible drug resistance gene pool." FEMS Microbial Review **31**: 449-477.

Schwartz, T., W. Kohnen, et al. (2003). "Detection of antibiotic-resistant bacteria and their resistance genes in wastewater, surface water, and drinking water biofilms." FEMS Microbiology Ecology **43**(3): 325-335.

Schwartz, T., H. Volkmann, et al. (2006). "Real-time PCR detection of Pseudomonas aeruginosa in clinical and municipal wastewater and genotyping of the ciprofloxacin-resistant isolates." FEMS Microbiology Ecology **57**(1): 158-167.

Shi, P., S. Jia, et al. (2013). "Metagenomic insights into chlorination effects on microbial antibiotic resistance in drinking water." Water Research **47**(1): 111-120.

Speltini, A., M. Sturini, et al. (2012). "Microwave-assisted extraction and determination of enrofloxacin and danofloxacin photo-transformation products in soil." Analytical and Bioanalytical Chemistry **404**(5): 1565-1569.

Szczepanowski, R., B. Linke, et al. (2009). "Detection of 140 clinically relevant antibiotic resistance genes in the plasmid metagenome of wastewater treatment plant bacteria showing reduced susceptibility to selected antibiotics." Microbiology: mic.0.028233-028230.

Thomas, M. and R. Klaper (2012). "Psychoactive Pharmaceuticals Induce Fish Gene Expression Profiles Associated with Human Idiopathic Autism." PLoS ONE **7**(6): e32917.

Thompson, T. S., D. K. Noot, et al. (2009). "Large volume injection for the direct analysis of ionophores and avermectins in surface water by liquid chromatography–electrospray ionization tandem mass spectrometry." Analytica Chimica Acta **633**(1): 127-135.

Tso, J., S. Dutta, et al. (2011). "Simultaneous Analysis of Free and Conjugated Estrogens, Sulfonamides, and Tetracyclines in Runoff Water and Soils Using Solid-Phase Extraction and Liquid Chromatography−Tandem Mass Spectrometry." Journal of Agricultural and Food Chemistry **59**(6): 2213-2222.

Turiel, E., A. Martín-Esteban, et al. (2007). "Molecular imprinting-based separation methods for selective analysis of fluoroquinolones in soils." Journal of Chromatography A **1172**(2): 97-104.

Turkdogan, F. I. and K. Yetilmezsoy (2009). "Appraisal of potential environmental risks associated with human antibiotic consumption in Turkey." Journal of Hazardous Materials **166**(1): 297-308.

USEPA (2008). RCRA Hazardous Waste Identification of Methamphetamine Production Process By-products, report to Congress under the USA PATRIOT Improvement and Reauthorization Act of 2005. OERR. Washington D.C.

Vazquez-Roig, P., R. Segarra, et al. (2010). "Determination of pharmaceuticals in soils and sediments by pressurized liquid extraction and liquid chromatography tandem mass spectrometry." Journal of Chromatography A **1217**(16): 2471-2483.

Vignesh, S., K. Muthukumar, et al. (2012). "Antibiotic resistant pathogens versus human impacts: A study from three eco-regions of the Chennai coast, southern India." Marine Pollution Bulletin **64**(4): 790-800.

Xu, J., W. Chen, et al. (2009). "Leachability of some emerging contaminants in reclaimed municipal wastewater-irrigated turf grass fields." Environmental Toxicology and Chemistry **28**(9): 1842-1850.

Xu, S., C. Jiang, et al. (2012). "Magnetic nanoparticles modified with polydimethylsiloxane and multi-walled carbon nanotubes for solid-phase extraction of fluoroquinolones." Microchimica Acta **179**(3-4): 257-264.

Xu, W.-h., G. Zhang, et al. (2007). "Determination of selected antibiotics in the Victoria Harbour and the Pearl River, South China using high-performance liquid chromatography-electrospray ionization tandem mass spectrometry." Environmental Pollution **145**(3): 672-679.

Yang, J.-F., G.-G. Ying, et al. (2010). "Simultaneous determination of four classes of antibiotics in sediments of the Pearl Rivers using RRLC–MS/MS." Science of The Total Environment **408**(16): 3424-3432.

Yang, S. and K. Carlson (2003). "Evolution of antibiotic occurrence in a river through pristine, urban and agricultural landscapes." Water Research **37**: 4645-4656.

Young, R. A. (2005). Determining the economic value of water : concepts and methods. Washington, DC, Resources for the Future.

Zheng, Q., R. Zhang, et al. (2012). "Occurrence and distribution of antibiotics in the Beibu Gulf, China: Impacts of river discharge and aquaculture activities." Marine Environmental Research **78**(0): 26-33.

Zhou, J. L., K. Maskaoui, et al. (2012a). "Optimization of antibiotic analysis in water by solid-phase extraction and high performance liquid chromatography–mass spectrometry/mass spectrometry." Analytica Chimica Acta **731**(0): 32-39.

Zhou, L.-J., G.-G. Ying, et al. (2012b). "Simultaneous determination of human and veterinary antibiotics in various environmental matrices by rapid resolution liquid chromatography–electrospray ionization tandem mass spectrometry." Journal of Chromatography A **1244**(0): 123-138.

Zuccato, E., S. Castiglioni, et al. (2010). "Source, occurrence and fate of antibiotics in the Italian aquatic environment." Journal of Hazardous Materials **179**(1–3): 1042-1048.