Illicit Drugs and the Environment

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Introduction

The spectrum of chemicals recognized as contributing to widespread contamination of the environment began to be extended to pharmaceutical ingredients as early as the 1970s. But the topic did not begin to attract broader scientific attention until the mid-1990s (Daughton 2009a). Occurring generally at levels below 1 microgram per liter in ambient waters, the near ubiquitous presence of pharmaceuticals in a wide variety of environmental compartments serves as a stunning measure of advancements in analytical chemistry in expanding our understanding of the scope of environmental pollution.

The extent of progress and effectiveness of pollution regulation, mitigation, control, and prevention over the last 40 years is now reflected by a focus on trace-level chemical contaminants - a phenomenon only hypothesized as a possibility in the early 1970s. This focus is embodied particularly with the so-called "emerging" contaminants (Daughton 2009b) and the myriads of others not yet noticed or identified and which could be referred to as the "quiet contaminants."

Up through the 1990s, the emerging study of pharmaceuticals in the environment (PiE) inexplicably excluded from consideration the contributions by the so-called "illicit" drugs. Involving a structurally diverse group of chemical agents possessing extremely high potential for biological effects in humans and non-target organisms, the magnitude of worldwide illicit drug trafficking is presumably enormous but can only be very roughly estimated. The potential for illicit drugs to enter the environment should not differ markedly from that of medical pharmaceuticals – with contributions being from excretion, bathing, disposal, and discharge of manufacturing waste. While known for many decades that illicit drugs and metabolites (just as with medicinal pharmaceuticals) are excreted in urine, feces, hair, and sweat, not until 1999 (Daughton and Ternes 1999) and 2001 (Daughton 2001a; Daughton 2001c) was the scope of concerns surrounding PiE expanded to include illicit drugs. In characterizing and assessing risks incurred from PiE, both licit and illicit drugs need to be considered seamlessly.

Perhaps the first published indication that illicit drugs might be pervasive contaminants of our immediate surroundings and the larger environment was a 1987 FBI study in response to a newspaper report 2 years earlier that cocaine was present on money in general circulation (Aaron and Lewis 1987). Over the intervening 20 years, analogous seminal surveys of illicit drugs as ambient contaminants have been published for sewage wastewaters (Khan 2002), surface waters (Zuccato et al. 2005), air (Cecinato and Balducci 2007), sewage sludge (Kaleta et al. 2006) and biosolids (Jones-Lepp and Stevens 2007), and most recently drinking water (Huerta-Fontela et al. 2008b). An examination of the US EPA's bibliographic database on PiE (USEPA 2009a), shows that the core journal references having a major focus on illicit drugs in wastewaters, ambient waters, drinking water, or air total around 60 (this excludes those published on the topic of drugs on money). References (in any type of technical publication) dealing with illicit drugs in the environment total fewer than 200 – composing only 2% of the documents (approaching 10,000) surrounding the broader topic of PiE in general.

Presented here is a broad overview of illicit drugs as environmental contaminants. Perspectives are provided on their occurrence in various environmental compartments, what their occurrence might mean with regard to risk, and how their occurrence can be used as an analytical measurement tool to assess society-wide usage of illicit drugs.

A chronology of seminal publications on significant aspects of illicit drugs and the environment is presented in Table 1. The topic is trans-disciplinary, involving a variety of disparate but intersecting fields, including healthcare, pharmacology, criminology, forensic sciences, epidemiology, toxicology, environmental and analytical chemistry, and sanitary engineering, among others.

What Is an "Illicit" Drug?

Discussions regarding illicit drugs can become confused by the ambiguity in what exactly defines an "illicit" drug. Confusion stems from the fact that illicit drugs are not necessarily illegal. Many are licit medical pharmaceuticals having valuable therapeutic uses - two common examples being morphine and oxycodone. Instead, whether a drug is illicit is defined by international convention or national law, not necessarily by any inherent property of the drug. Some discussion is essential to better understand the scope of drug substances that can be considered illicit.

Terminology

There is no single, widely used term that accurately captures the myriad substances that become abused by habitual or addictive use. Although widely used, the term "illicit drug" is not accurate in the sense that most of the widely known abused drugs have bona fide medical uses as licit pharmaceuticals; the few that do not are incorporated in various listings or schedules of controlled substances maintained by various countries.

A variety of terms are used, often interchangeably, including: street drugs, designer drugs, club drugs, drugs of abuse, recreational drugs, clandestinely produced drugs, and hard and soft drugs. The term "designer" drug gained popularity in the 1980s when 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) was introduced to the black market; but perhaps the most notable first designer drugs were introduced in the 1920s - dibenzoylmorphine and acetylpropionylmorphine.

Regardless of the terminology, much overlap exists with licit pharmaceuticals (those with approved medical uses). This can lead to much confusion or ambiguity as to exactly what the scope of the topic is. Discussion of the confusion surrounding illicit drug terminology is provided by Sussman and Ames (2008). In the overview provided here, the guiding definition used is that of the United Nations Office on Drugs and Crime (UNODC), which focuses not on the chemical identity of the drug itself, but rather on the lifecycle pathway traveled by a drug. The UNODC does not recognize any distinction between the chemical identity of licit and illicit drugs - only the way in which they are used (UNODC 2009a). In this sense, the term "illicit" refers to the way in which these drugs are manufactured, distributed, acquired, and used, and by the fact that they are being used for non-medical purposes.

This definition allows the inclusion of legal pharmaceuticals - that is, when they are manufactured, distributed, trafficked, or used illegally, or diverted from legal sources. The wide spectrum of sources and routes by which legal drugs become diverted for illicit use range from the relatively large-scale diversion from pharmaceutical distributors, pharmacies, and healthcare facilities, to the smaller scale (e.g., "theft" from home storage locations, such as for teen "pharming"), and re-use of used medical devices, especially dermal medical patches, which present lethal hazards for both intentional and accidental exposures (Daughton and Ruhoy 2009).

Whether a drug is classified as illicit is a complicated function of mores and evidence-based health studies, which are sometimes at odds with one another and under increasing scrutiny and debate (e.g., see: Nutt 2009). Illicit substances (drugs and the precursors used for their manufacture) are captured on various government lists (controlled substance Schedules) that specify their allowable use. The primary criteria evaluated for listings are health risks, potential for abuse/addiction, therapeutic value, and utility as precursors for illicit manufacturing. The unifying worldwide scheme, used by the EU, for regulation comprises the Schedules of the three UN Conventions of: 1961 (United Nations Single Convention on Narcotic Drugs, New York, amended 1972), 1971 (Convention on Psychotropic Substances, Vienna), and 1988 (Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, introducing control on precursors, Vienna). Combined, these Schedules currently comprise about 250 explicitly named controlled substances (EMCDDA 2009a).

Showing how the lines of demarcation become blurred, prescription analgesic opioids have overcome heroin and cocaine in the US in leading to fatal drug overdoses (Leonard and Yongli 2008). Indeed, the use of certain licit drugs, including over-the-counter (OTC) medications, for non-medical purposes has recently surpassed the use of illicit drugs (NIDA 2008). For example, of the top 10 drugs misused by high-school seniors in the US, seven were legal prescription or OTC medications.

Numerous other illicit substances (such as structural analogs) exist but can only be captured implicitly by generalized chemical criteria that preemptively ban their synthesis; not all countries, however, have control acts that implicitly capture chemical analogs. Unknown numbers of additional substances exist but their chemical identities are elucidated only after they have experienced sufficient illegal use. A resource that provides the chemical structures for many of these substances (those listed by the Canadian Controlled Drugs and Substances Act) is maintained by Chapman (2009).

Adding further confusion regarding the distinctions between illicit drugs and medical pharmaceuticals, the laws dealing with illicit drugs vary dramatically from country to country. Long-standing drug policies in certain countries are also in a state of flux, as various changes are underway and adjustments under consideration. These range from "reducing harm" (e.g., via decriminalization of possession and use) to acknowledgment from the American Medical Association regarding the medical benefits of a Schedule I drug (namely, cannabis) and calling for its clinical research (AMA 2009). Beginning with Portugal in 2001 with the decriminalization of drug use, possession, and acquisition by drug end-users (Law no. 30/2000, which focuses on harm reduction) (see: Greenwald 2009), the array of laws dealing with illicit drugs has become

quite diverse; but growing, illegal manufacturing, and trafficking remain criminal offenses. Among the EU States, the spectrum of law is captured by EMCDDA (2009b).

Differences between Illicit and Licit Drugs as Environmental Contaminants

With respect to understanding their overall significance in the environment, seven aspects of illicit drug use contrast sharply with legitimate pharmaceutical use:

(1) For most illicit drugs, there are no accurate quantitative data available concerning production or usage. For regulated pharmaceuticals, sales figures and regional real-time prescribing data can be used in models to calculate predicted environmental concentrations (PECs); these values can then be compared with measured environmental concentrations (MECs).
(2) Although the chemical identities for the core group of illicit drugs are known, an ever-increasing number of new drugs (such as structural analogs with minor modifications of regulated pharmaceuticals and of previously known illicit drugs) can elude detection by forensics laboratories for years before they are noticed and identified. The myriad numbers of designer drugs and constant synthesis of new ones will pose challenges for mass spectrometrists for years to come and also introduce great uncertainty regarding the true scope of synthetic chemicals that contaminate the environment. Even though many of these unique chemicals are probably produced in relatively small quantities, the fact that they belong to relatively few chemical classes possibly means that they share only a few mechanisms of biological action. This makes additive action very likely, especially with substantial numbers of licit and illicit drugs often sharing the same mechanism of action. Since some have extremely low effective doses (e.g., in the range of one microgram per human use), this has relevance especially for aquatic exposure. As examples, cis-3-methylfentanyl and ß-hydroxy-3-methylfentanyl (as with carfentanyl, a large-animal tranquilizer) are extraordinarily potent designer drugs, being 3-5-orders of magnitude more potent than morphine.
(3) Drugs manufactured via illicit routes are commonly contaminated with unintended impurities and purposeful adulterants. These are often present at extremely high levels (e.g., sometimes more than half of the total mass, as opposed to mg/kg [ppm] levels for impurities in registered medicines) and are often more toxic than the sought-after drug.
(4) The manufacture of illicit drugs (particularly methamphetamine) can cause extensive ecological damage as well as irreversible damage to infrastructure such as buildings (USEPA 2009b).
(5) To date, the primary interest in residues of illicit drugs in the environment has been their occurrence in sewage (mainly untreated raw sewage) for use as a tracking tool to calculate community-wide consumption. This relatively new tool has been termed sewage (or sewer) forensics or epidemiology. In contrast to the licit use of pharmaceuticals, interest in their potential as biological stressors in the environment has been secondary, and very little is known.
(6) Much less is known regarding the toxicology (including pharmacokinetics) of most illicit drugs.
(7) With respect to environmental impact, numerous measures can be implemented to reduce the entry of licit pharmaceuticals into the environment. Routes of entry span an enormous spectrum of possibilities (Daughton and Ruhoy 2008). With illicit drugs, pollution

prevention measures are straightforward but more difficult to implement - namely, discourage their manufacture, distribution (e.g., via unapproved Internet pharmacies), and end use.

Note that the frequent changes in the introduction of new pharmaceuticals with potential for abuse, as well as new illicit substances, precludes any comprehensive definitive worldwide compilation of chemicals. The INCB (International Narcotics Control Board) maintains three major listings (INCB 2009): Yellow List (Narcotic Drugs under International Control), Green List (Psychotropic Substances under International Control), and Red List (Precursors and Chemicals frequently used in the Illicit Manufacture of Narcotic Drugs and Psychotropic Substances under International Control). A convenient listing of many of the corresponding chemical structures is provided by Chapman (2009).

The Core Illicit Drugs and the Environment

The types of drugs commonly abused are described in various ways, depending on their origin and biological effect. They can either be naturally occurring, semi-synthetic (chemical manipulations, such as analogs, of substances extracted from natural materials), or synthetic (created entirely by laboratory synthesis and manipulation). The primary categories are opiates, other CNS depressants (sedative-hypnotics), CNS stimulants, hallucinogens, and cannabinoids.

The scope of chemicals that could be considered illicit can be viewed in terms of the following categories of medical efficacy:
(1) no known medical use (and which are illegal in all circumstances according to various conventions) (e.g., benzylpiperazine; heroin in the U.S.),
(2) limited established medical use but which are also manufactured illegally and used primarily for non-medical purposes (e.g., methamphetamine),
(3) firmly established wide medical use but which are diverted illegally (e.g., theft; illegal prescribing such as via unapproved Internet "pharmacies"),
(4) firmly established wide medical use and which are obtained "legally" but for non-medical use (e.g., doctor/hospital shopping or by other con schemes),
(5) similar biological action to prescription drugs but synthesized as analogs (which are not individually and explicitly categorized as illegal; examples include the numerous analogs of phosphodiesterase type 5 inhibitors).

All of these categories comprise drugs with high potential for abuse or that enjoy recreational use. Methadone is usually included in these discussions even though most of its use is legal; it serves to track opiate addiction but is also used and abused as an analgesic.

Some drug residues in the environment have substantial multiple origins (both legal and illegal) making it difficult to ascribe monitored levels to illicit use. Morphine is one example. Morphine can originate from medical use of morphine itself or from codeine (via *O*-demethylation). It can also originate from diverted morphine or codeine as well as from heroin. By collecting data on other (and more unique) metabolites, these pathways can be teased apart. Using morphine as the

example, by monitoring for the heroin metabolite 6-AM (6-acetylmorphine), a more representative picture can be obtained for that portion of morphine originating from heroin.

While drug usage patterns and prevalence vary among countries as well as with time, those drugs in frequent use in the US can serve as an organizing framework for further discussion. The annual reports of the US DEA's National Forensic Laboratory Information System, NFLIS (USDEA 2008), provide the best insights regarding which known drugs are most used in non-medical circumstances (see Table 2).

Of all the samples analyzed in 2008 by US local and state forensic labs for the presence of non-medically used drugs, 25 controlled substances (Table 2) composed 90% of all samples. The most frequent four were tetrahydrocannabinol (THC), cocaine (benzoylmethylecgonine), methamphetamine, and heroin. Of these 25, only 15 have been targeted in environmental studies of illicit drugs: amphetamine, cocaine, codeine, heroin, hydrocodone, MDA, MDMA, methadone, methamphetamine, methylphenidate, morphine, oxycodone, PCP (phencyclidine), pseudo-ephedrine, and THC (D9-tetrahydrocannabinol).

Note that the top 25 detected by NFLIS are all among the most commonly abused drugs in the US. The major ones missing (but which are captured in the remaining 10% of samples analyzed by NFLIS) are barbiturates (e.g., seconal and phenobarbital; but whose rate of abuse has been declining), certain benzodiazepines (except flunitrazepam, such as librium, valium, and xanax), methaqualone, mescaline (3,4,5-trimethoxyphenethylamine), and dextromethorphan (NIDA 2009). Extensive statistics on rates of drug use worldwide (including those maintained by the UNODC) can be found on the ONDCP web page (ONDCP 2009). The UNODC World Drug Report (UNODC 2009b) provides comprehensive statistics on world illicit drug supply and demand.

From a comprehensive examination of the published literature on illicit drugs and their metabolites in a variety of environmental compartments (wastewaters, surface waters, drinking water, sewage sludge, sewage biosolids, air, and banknotes), positive occurrence data as well as indications of negative occurrence (data of absence) were compiled (data not shown here). From these data, those analytes with absence of data (i.e., those that have yet to be targeted in monitoring studies) can be deduced. For example, Postigo et al. (2008) noted that nor-cocaethylene and ecgonine ethyl ester have not been targeted in any monitoring study. Major reviews of illicit drugs in the environment are provided by Huerta-Fontela et al. (2010) and Zuccato and Castiglioni (2009).

The published data reveal that the drugs with the most positive occurrence data across all environmental compartments are among the top 25 detected by NFLIS - notably the following seven: codeine, morphine, methadone, amphetamine, methamphetamine, cocaine, and THC, and the primary metabolites of methadone (i.e., EDDP), cocaine (i.e., BZE, benzoylecgonine), and THC (i.e., 11-nor-9-carboxy- 9-THC [THC-COOH]). Although widely detected in drug screens, the occurrence of heroin (diacetylmorphine) in an environmental compartment is limited primarily to banknotes - because of its propensity to hydrolyze in water. Likewise, the cannabinoids are detected most frequently in air. Not surprisingly, no illicit drug (or metabolite)

frequently reported with environmental occurrence data is missing from the 25 most frequently identified by forensic labs.

Nine of the remaining 25 drugs most frequently identified by the forensic testing labs have not yet been targeted in environmental studies focused on illicit drugs: alprazolam, buprenorphine, BZP (1-benzylpiperazine), carisoprodol, clonazepam, diazepam, hydromorphone, lorazepam, and psilocin (4-hydroxy-dimethyltryptamine, 4-HO-DMT). Of these nine drugs, environmental occurrence data have been published in studies targeted at medical pharmaceuticals for: alprazolam, carisoprodol, diazepam, and lorazepam. Data do not exist for buprenorphine, BZP, clonazepam, hydromorphone, and psilocin. Depending on their pharmacokinetics and extent of excretion unchanged, these latter five drugs could be considered for targeting in future environmental monitoring.

Some illicit drug analytes when targeted are infrequently reported possibly as a result of their considerably higher detection limits. Normorphine and THC-COOH are examples, sometimes having limits of detection 1-2 orders of magnitude higher than other analytes. Other targeted analytes are not detected because they are extensively metabolized or excreted as conjugates. Conjugation undoubtedly plays a critical role in determining whether a free parent drug will be found in waters. Many drugs are extensively conjugated, and without a hydrolysis step in analysis, these will be missed (Pichini et al. 2008; Daughton and Ruhoy 2009).

Important to note is that some illicit drugs are metabolic/transformation daughter products of others, explaining why their concentrations in sewage or receiving waters are routinely higher than their parents. One example is heroin, which is quickly deacetylated to 6-AM followed by hydrolysis to morphine. This means that the probability is higher that these parent drugs, when detected in waters (especially waters distanced from impact by sewage), are present because they were directly flushed down the toilet (or excreted via sweat) - rather than being excreted via urine; an alternative source is run-off into streams, such as during clandestine manufacturing. Another example is fentanyl, which is extensively excreted as norfentanyl.

Environmental occurrence data from most of the major studies on illicit drugs have been captured in the reviews of Huerta-Fontela et al. (2010) and Zuccato and Castiglioni (2009).

Adulterants and Impurities

In contrast to pharmaceuticals produced under Good Manufacturing Practices, drugs made illegally contain myriad other chemical substances in addition to (or sometimes even in place of) the sought-after drug. Adulterants are often used to enhance desired biological effects. Included are diluents, which are added to mimic the physical appearance of the sought-after drug when the objective is economic gain (to extend the doses per mass). Impurities are sometimes integral to the natural chemistry of the native plant from which a drug is isolated, and other times a function of the synthetic route to the desired drug (as dictated by the skill of the operator/chemist).

Many dozens of impurities and adulterants are possible for any given drug synthesis. Impurities in turn can each yield numerous metabolites, most of which are not yet known. Adulterants can

range from common substances such as caffeine (albeit in very high concentrations), to more insidious chemicals such as the cytotoxic veterinary dewormer drug levamisole, which has led to a number of deaths; in this way, illicit drugs can serve as a route of entry to the environment for licit drugs that otherwise would never themselves experience non-medical use. Adulteration of illicit drugs has grown to become a major health risk for drug users.

These substances are often present at very high levels, especially in intentionally mislabeled drugs. They sometimes represent the bulk of the purported drug (e.g., noscapine can be present at levels up to 60% in heroin, or phenacetin at levels up to 50% in cocaine). These contaminants include products of synthesis or processing (precursors, intermediates, by-products), natural impurities (e.g., natural product alkaloids), products of degradation (e.g., oxidation during storage), and pharmacologically active adulterants (e.g., many licit drugs and other chemicals, obtained illegally, such as levamisole, xylazine, lidocaine, phenacetin, hydroxyzine, and diltiazem). Some of these impurities or adulterants are more potent than the sought-after drug (cocaethylene being one example - a synthesis by-product as well as a metabolite of cocaine when consumed together with ethanol). Some have considerable toxicity. In the course of reviewing the literature, over 90 common adulterants and impurities were noted just for the four illicit drugs cocaine, MDMA, methamphetamine, and heroin. These represent but a very small sampling of the variety of chemicals that can compose illicit drugs.

Large-scale Exposure or Source Assessments via Dose Reconstruction

Interest in illicit drugs in the environment has both prospective and retrospective dimensions. The prospective dimension concerns the questions surrounding the exposure of aquatic organisms and of humans to environmental residues. Of the environmental studies conducted, however, the major objective in collecting data on the presence and scope of illicit drugs in sewage and wastewaters has not been for prospectively assessing their significance as environmental contaminants and their potential for ecological or human health exposure. Rather, the objective has been use as a retrospective tool for reconstructing society-wide drug usage. This could be considered a large-scale version of exposure assessment called "dose reconstruction" (e.g., see: ATSDR 2009).

Separate but analogous approaches have also been attempted making use of the presence of drug residues on banknote currency and in airborne particulates. These could be more accurately referred to not as dose reconstruction, but rather as source reconstruction (deciphering the source and intensity of the origin of the drugs).

Sewage Epidemiology or Forensics

First proposed in 2001 (Daughton 2001a), the analysis of sewage for residues of illicit drugs unique to actual consumption (rather than originating from disposal or manufacture) for the purpose of back-calculating estimates of community-wide usage rates has since been discussed under a variety of terms, including: "sewage epidemiology" (a term first reported in the literature by Zuccato et al. 2008b), "sewage forensics," and "community-wide urinalysis" or "community drug testing". None of these terms, however, fully captures the multiple purposes that can be served by the methodology.

Epidemiology can be defined simply as the study of populations sharing similar characteristics of disease (or health status). Among its uses are identifying at-risk sub-populations, monitoring the incidence of exposure/disease, and detecting/controlling epidemics. Elements of illicit drug use fit all of these. In its simplest state, "forensics" involves the extraction of pertinent information to support an argument or investigation (Daughton 2001b). One of its best known modern renditions is to assist in resolving legal issues - and the worldwide legal system plays an integral role in all aspects of illicit drug use.

Since this still-evolving approach for measuring drugs in sewage to estimate collective drug usage has elements of both forensics and epidemiology, it would be more accurately captured under the newer term "Forensic Epidemiology," which integrates the principles and methods used in public health epidemiology with those used in forensic sciences (Goodman et al. 2003; Loue 2010).

With this in mind, a more accurate descriptive term should be considered in order to better unify the published literature. One possibility could be "Forensic Epidemiology Using Drugs in Sewage" (FEUDS). Use of a unique term and acronym would have the added benefit of more easily facilitating communication across disciplines and to greatly facilitate literature searches. In the remainder of this discussion, however, the shorthand term "Sewage (or Sewer) Forensic Epidemiology" (***SF/E***) will be used.

SF/E Used in Community-Wide Dose Reconstruction for Illicit Drugs

After its conceptualization in 2001 (Daughton 2001a), SF/E was first implemented in a field monitoring study by Zuccato et al. (2005). SF/E was originally proposed as the first evidence-based approach for measuring drug use because the long-practiced approaches that use population surveys are fraught with limitations, not the least of which involve numerous sources of potential error that are difficult to define, control, or measure (especially self-reporting bias) (Daughton 2001a). This has been corroborated in "concordance" studies (comparisons of self-report data with empirical bioanalysis data), which point to gross under-reporting by self-reports (often at rates as low as one-half). These conventional approaches to estimating illicit drug usage also suffer from two inherent limitations: extreme delays in times before results can be compiled and reported, and costs associated with data collection and interpretation.

Like public surveys, SF/E also suffers from a large number of sources of potential error. But SF/E is in its infancy, and its error derives from variables still under investigation and which

could be better controlled. While conceptually rather straightforward, the back-calculations used in SF/E are a function of numerous variables, including demographics, population flows (transient visitors and commuters) served by a sewage treatment facility, sewage flows, and pharmacokinetics. Combined, these pose a major challenge for modeling to accurately reconstruct dose. The numerous problems facing SF/E are discussed in Frost and Griffiths (2008). Most SF/E investigators couple drug concentrations in sewage with per-capita sewage flows to calculate what is sometimes called "index loads" or "per capita loads," expressed as mg/person/day. Many of the sources of uncertainty are covered by Banta-Green et al. (2009) and Zuccato et al. (2008b).

Despite the plethora of uncertainties in the many variables involved in SF/E back-calculations, the ability to provide estimates of near-real-time community-wide usage is something that is not possible with any other known approach. This also opens the possibility of detecting real-time trends or changes in drug use. Example applications include verifying reductions in drug use as a result of interdictions, or detecting the emergence of newly available drugs or overall changes in drug-use patterns. Data on real-time usage could better inform decisions regarding drug control and mitigation. Correlating policy actions with resulting society-wide impacts cannot be effectively done when collected data are significantly delayed in reporting.

Of great potential significance, there is also no apparent technical obstacle to designing automated continuous monitors for use in sewage collection/distribution systems. Implementing continuous monitoring to support SF/E would serve to better inform decisions regarding control and mitigation of drug use.

Another advantage with SF/E as opposed to population surveys is that not all drug use is necessarily known to the users themselves, who then unintentionally report to surveys incorrect drug identities and usage quantities. Illicit-drug users often do not know the identity or the quantity of the active substances they have consumed because the purity is unknown. Often the active substance or quantity is not what the distributor claims. Adulterants are often substituted, in part or in whole, for the purported drug. One general route of uninformed exposure is the surreptitious incorporation of designer drugs into otherwise legal OTC diet supplements or recreational or life-style products. An example is the relatively new (and probably incompletely characterized) synthetic analogs of the approved phosphodiesterase type 5 (PDE-5) inhibitors (used primarily in treating erectile dysfunction), such as sildenafil, vardenafil, and tadalafil (Poon et al. 2007; Venhuis and de Kaste 2008). The legal registered versions of PDE-5 inhibitors have only recently been detected in wastewaters (Nieto et al. 2010). The extent of such adulteration in the drug and supplements industry is unknown - largely because the targets for analysis are often not known to forensic analysts.

Hagerman (2008) provides a brief history of SF/E research in the US. The ONDCP performed the first SF/E monitoring in the US in 2006, targeting about 100 wastewater treatment plants (WWTPs) across two dozen regions in the US (Bohannon 2007). The first conference devoted to SF/E was organized by EMCDDA in Lisbon, Portugal in April of 2007 (EMCDDA 2007). It led to the first published overview of many of the aspects of the topic (including scientific, technical, social, privacy, ethical, and legal concerns), as provided by Frost and Griffiths (2008).

Summary of published research in SF/E

Overviews and discussion of the SF/E studies published up until 2008 are provided by Postigo et al. (2008) and Zuccato et al. (2008b). The major published articles regarding the SF/E approach are compiled in the chronology of Table 3. As of the beginning of 2010, there had been fewer than two dozen studies. All but a handful have been published after 2007.

Published SF/E studies have been conducted in a number of countries, with assessments at the local, regional, or national levels - primarily in Belgium, Germany, Ireland, Italy, Spain, Switzerland, the US (i.e., Oregon), and Wales. To date, SF/E assessments have focused on a select few parent drugs (primarily cannabis, cocaine, heroin, and MDMA) using various metabolites. They have been performed using a broad range of sampling methodologies ranging from single-event discrete grab sampling to longer-term (e.g., 12-month) integrative continuous sampling over numerous WWTPs or rivers, servicing regions with populations exceeding millions. Many of these studies have searched for temporal usage patterns - comparing yearly seasons or the day of the week (e.g., higher cocaine use on weekends). Usage rates are reported on various comparative bases, often involving per capita (e.g., g/day/1,000 population - usually ranging only up to several grams), total consumption (e.g., tonnes per year per geographic area), or flows (mass/river/day). Discrete monitoring must acknowledge the cyclic or episodic drug use pattern fluctuations in concentrations that can result from diurnal cycles, seasons, or day of the week. This can be particularly pronounced for recreational drugs. Limits of detection will dictate the extent to which a monitoring study will produce meaningful data-of-absence (negative data).

An enormous published literature surrounds the forensic chemistry of illicit drugs. The numbers of illicit drugs analyzed in the environment, however, is but a small fraction of those that have been targeted in countless studies published on biological tissues and fluids for the purposes of forensics and patient compliance monitoring and for the study of pharmacokinetics in animals. Accurate mass identification of unknowns (for example, via LC/TOF-MS) plays a central role especially when authentic reference standards are not available. While this conventional forensics literature can serve as a guide for environmental analysis, it is not directly relevant. There are numerous variables involved with (and impacting) the procedural steps used in analysis for SF/E - ranging from sampling design and matrix interferences to analyte determination and need for extremely low limits of detection. Some major overviews and discussion of the analytical approaches for measuring illicit drugs in wastewaters and other waters are available (Castiglioni et al. 2008; Postigo et al. 2008; Zuccato and Castiglioni 2009).

An issue little addressed in SF/E studies has been the complications posed by chirality. Possibly the majority of illicit drugs have at least one chiral center (Smith 2009). The alkaloid truxilline, as an example, occurs in coca leaf as 11 stereoisomers. Amphetamines can each have a pair of enantiomers, sometimes distinguishing the licit and illicit forms (as well as dictating toxicology). This may account for a portion of some of the large variance in estimated amphetamine usage across SF/E studies. While chiral isomers can pose difficult challenges for analytical chemists, they can also provide a wealth of forensics information in terms of chemical "fingerprinting" - for example, in distinguishing legal from illegal origins.

Illicit Drugs and Environmental Impact

With the exception of the immediate and overt (as well as hidden) environmental impacts from clan labs, little is known with respect to the potential actions of illicit drugs in the environment.

Compared with pharmaceuticals, little attention has been devoted to the environmental fate and transport of illicit drugs. Most illicit drugs have never been monitored in sewage biosolids or sediments. Domènech et al. (2009) used fugacity modeling to predict the fate of cocaine and BZE. The microbial degradation of methamphetamine has been reported by Janusz et al. (2003). Wick et al. (2009) examined biological removal in activated sludge and found rapid removal for morphine, codeine, dihydrocodeine, oxycodone, and methadone but not for tramadol. Two studies report on the sorption of illicit drugs to sediments (Stein et al. 2008; Wick et al. 2009). Wick et al. (2009) and Barron et al. (2009) acquired low distribution coefficients (Kd) for amphetamine, cocaine, cocaethylene, BZE, MDMA, morphine, codeine, dihydrocodeine, methadone, and tramadol, showing that removal via sorption to sewage sludge is probably negligible.

Far more is known regarding the ecotoxicology of licit pharmaceuticals than of illicit drugs, especially with regard to low-level mixed-stressor exposures. Almost nothing is known regarding the potential for biological effects in aquatic systems or the bioconcentration in biota of illicit drugs. Gagne et al. (2006) report some nominal effects data for morphine in mussels. The potential for effects from low-level exposure of fish is further complicated by the complexities in extrapolating across species. The first in-depth study of an ectotherm with any analgesic (i.e., morphine) comports with extreme variability between species (Newby et al. 2006).

The Future

Future work addressing the various environmental aspects of illicit drugs in the environment would benefit from a comprehensive assessment of what has been accomplished to date and what new research needs to be conducted. While the knowledge base regarding all aspects of illicit drugs in the environment is extremely small compared with that of pharmaceuticals, the body of published data is perhaps sufficiently large that we risk duplication of efforts while failing to address the more important remaining gaps or needs (Daughton 2009a). The first step in ensuring better-targeted research could be creation of a centralized, publically accessible database of results from research conducted worldwide. Such data could include environmental occurrence (sewage influent, effluent, and sludge/biosolids; surface and drinking waters; air; and money), ecotoxicity, and especially data generated from SF/E studies; occurrence data should include data-of-absence (with detection limits).

Advancing the Utility of SF/E

Advancement of SF/E as a topic of research as well as a survey tool could occur on two fronts. First, numerous improvements could be made to better define and control the many variables contributing to uncertainty in SF/E back-calculations for gauging collective drug usage. Needed are standardized methodologies with better understood and controlled sources of error. This is especially important for facilitating more meaningful inter-comparison of SF/E data.

For SF/E to succeed in gauging illicit drug usage, one variable in particular needs to be better understood - the pharmacokinetics (PK) of each drug, especially as it pertains to the excretion of parent drug and metabolites (especially conjugates). PK parameters are key to accurate dose reconstruction. While excretion rates for many pharmaceuticals are not well defined, even less is known regarding the PK of illicit drugs. PK and its poorly defined variance among a population contributes great uncertainty to the back-calculations used with SF/E. A comprehensive sensitivity analysis (which has yet to be performed) would probably reveal that small changes in variables such as excretion rates (especially for extensively metabolized drugs) can lead to large errors in SF/E calculations. For those drugs/metabolites with highly variable excretion rates, the error range could be substantial. As a case in point, with a study of 12 methamphetamine addicts, the urine ratio of amphetamine/methamphetamine ranged over 2 orders of magnitude - from 0.03 to 0.56 (Kim et al. 2008). This would also prove problematic for allocating amphetamine loadings in sewage to methamphetamine use versus medical use. A host of factors contributes to PK variability, including route and size of dose, gender, age, body mass, kidney and liver function, chronobiology, diet, polypharmacy interactions, and genetics/epigenetics (namely pharmacogenomics, which dictates the spectrum of PK variability). Similarly, it is important to be able to distinguish bacterial transformations in sewage (and the ambient environment) from those of human metabolism (Boleda et al. 2009).

Other ways to reduce the error boundaries in SF/E calculations could be viewed as analogous to internal-correction methods such as isotope dilution or standard additions. For example, instead of using correction factors based on modeling assumptions for dilution by waste streams and sewage transformations, correction factors could possibly be empirically derived by monitoring particular pharmaceuticals. Pharmaceuticals that would be most useful for "calibrating" a WWTP system would be those that: (i) are widely prescribed, (ii) are not abused or used recreationally, (iii) have real-time prescribing/sales data, (iv) are known to have high patient compliance (minimal leftovers, resulting in little disposal into sewers) and are used in short-term courses (not maintenance medications), (v) have a potential similar to that of the target illicit drug with regard to biodegradation and sorption to sewage solids, and (vi) have well understood pharmacokinetics (preferably poorly metabolized, resulting in extensive excretion unchanged). By comparing the known consumption rates of the pharmaceutical calibrant (from prescribing databases) with the levels actually detected in the sewage stream, more accurate correction factors could possibly be derived and then applied to the illicit drug. By gathering long-term time-course data for the calibrant pharmaceutical, even more uncertainty could possibly be removed from the calibration factor. This approach, however, cannot remove the confounding of dual inputs from excretion and disposal of the targeted illicit drug; the latter, however, probably leads to episodic spikes in underlying baseline levels, which would become clearer with sustained monitoring.

Second, the current scope of SF/E could possibly be expanded to tackle questions other than simply monitoring or gauging illicit drug consumption. Unexplored possibilities range from early-detection of emerging trends in abuse of mainstream pharmaceuticals and in their illegal trafficking (e.g., from diversion or Internet purchases) to better gauging medication compliance rates for patients. For example, with access to real-time local prescribing data, those pharmaceutical ingredients in sewage whose back-calculated usage rates are substantially higher than the prescribed rates could be targeted for investigating the possibility of illegal trafficking. A possible example can be seen in the data presented by Kasprzyk-Hordern et al. (2009a; see Table 7 therein), where calculated usage rates for over two dozen prescribed and OTC pharmaceuticals are compared with known nationwide (not local) dispensing rates. Of these drugs, the calculated average usage rates exceeded the national average sales by over an order of magnitude for only one drug - tramadol. Indeed, tramadol (an opioid) is recognized for its growing incidence of mis-use and abuse. Real-time prescribing data is greatly confounded, however, by the inability of current tracking systems to correlate location of dispensing with place of actual use (e.g., because of transient populations and mail-order prescribing). Another expanding source of data that could potentially be used to ground truth calculated usage rates is the growing network of collection programs that take back leftover medications (see: Glassmeyer et al. 2009).

An important aspect of SF/E for illicit drug use is that it has set the foundation for the use of SF/E for other purposes - some unrelated to drug use. A fascinating possibility would be the use of sewage monitoring for measuring indicators of community-wide health status via the presence of various biomarkers of health or disease.

TABLES

Table 1. Chronology of Some Selected Seminal Publications Regarding Illicit Drugs in the Environment

year	aspect	unique features of study	reference
1987	M	*first report in a journal confirming the presence of an illicit drug (cocaine) on banknotes in general circulation)* (objective to distinguish "drug" money from "innocent" money)	(Aaron and Lewis 1987)
1998	A	perhaps *first data on an illicit drug in the ambient environment*; *non-target analysis revealed cocaine associated with fractions of particulate matter in outdoor air* (Los Angeles)	(Hannigan et al. 1998)
2000	M	*first comprehensive overview of drugs on banknotes*	(Sleeman et al. 2000)
2001	F	*use of residues in sewage to reconstruct community-wide drug usage first proposed* (later to be termed "sewage epidemiology" or "sewage forensics", or sometimes "community drug testing" or "community urinalysis"); *first discussion to broaden the topic of drugs as environmental contaminants to include illicit drugs*	(Daughton 2001a)
2004	WW, mon	methamphetamine and MDMA in WWTP effluent; first report by US EPA of illicit drug in the environment; *first use of integrative time-weighted sampling for illicit drugs* in wastewaters	(Jones-Lepp et al. 2004)
2005	WW	*first report of widespread occurrence of an illicit drug in surface water and wastewater* (cocaine and BZE in WWTP influent and river)	(Zuccato et al. 2005)
2005	F	*first in-field implementation of "sewage epidemiology" to reconstruct community-wide drug usage*	(Zuccato et al. 2005)
2006	WW	*first study to target a spectrum of illicit drugs and metabolites (in WWTP influents and effluents)*; those not identified in prior studies: norbenzoylecgonine, norcocaine, cocaethylene, 6-acetylmorphine, morphine-3 -D-glucuronide, amphetamine, MDA, MDEA, EDDP, 11-nor-9-carboxy- 9-THC	(Castiglioni et al. 2006)
2006	SS	*first report in peer-reviewed literature of an illicit drug in sewage sludge* (amphetamine in sewage sludge)	(Kaleta et al. 2006)
2006	F, mon	*first nationwide monitoring in the US of illicit drugs in sewage*; study by ONDCP targeted about 100 WWTPs across two dozen regions in the US (results never published)	see: (Bohannon 2007)

2006	F	*first multi-country monitoring of cocaine in wastewaters to estimate usage*	see: (UNODC June 2007)
2007	A	*first targeted analysis of ambient air for an illicit drug*; cocaine quantified in particulates from all air sampled around Rome and several other Mediterranean locations (also in air samples archived several years prior	(Cecinato and Balducci 2007)
2007	SS	*first report of an illicit drug in biosolids* (methamphetamine in sewage biosolids)	(Jones-Lepp and Stevens 2007)
2007	R	*first conference devoted to topic of illicit drugs in the environment; led to first published overview of many of the aspects of the topic* (including scientific, technical, social, privacy, ethical, and legal concerns)	(EMCDDA 2007); (Frost and Griffiths 2008)
2008	DW	*first data on the occurrence and stepwise removal of illicit drugs at a municipal drinking water treatment plant*	(Huerta-Fontela et al. 2008b)
2008	F	*first use of the term "sewage epidemiology" in peer-reviewed literature*; perhaps first mentioned in a 2007 interview, by Fanelli (Bohannon 2007)	(Zuccato et al. 2008b)
2008	F	*creatinine in urine first assessed as means of normalizing drug concentrations across WWTPs* (and therefore to facilitate drug usage comparisons across communities); *creatinine first analyzed in sewage. Creatinine first proposed as a means for normalizing data by (Daughton 2001a)*	(Chiaia et al. 2008)
2008	WW, mon	*first systematic survey of illicit drugs in surface waters*	(Zuccato et al. 2008a)
2008	M, R	*first overview of an illicit drug (cocaine) from banknotes from multiple countries*	(Armenta and de la Guardia 2008)
2008-9	R	*first major overviews of illicit drugs in the environment*	(Kasprzyk-Hordern et al. 2009b); (Postigo et al. 2008); (Zuccato et al. 2008b); (Zuccato and Castiglioni 2009)
2008-9	R	*first major overviews of the analytical approaches used for illicit drugs in the environment*	(Castiglioni et al. 2008); (Postigo et al. 2008); (Zuccato and Castiglioni 2009)

2008-9	R, M	*first major overview of the analytical approaches used for illicit drugs on money*	(Armenta and de la Guardia 2008)
2008-9	EF	*first studies regarding the sorption of illicit drugs to sediments, soils, and sewage sludge*	(Barron et al. 2009); (Stein et al. 2008); (Wick et al. 2009)
2009	DW	*first data on the occurrence and stepwise removal of cannabinoids at a municipal drinking water treatment plant*	(Boleda et al. 2009)
2009	R	*first major overview of illicit drugs in airborne particulates*	(Postigo et al. 2009)
2009	WW	*first time that illicit drugs* (cocaine, BZE, and morphine) *monitored monthly in the sewage from an entire city over the course of a year*	(Mari et al. 2009)
2009	sw	*sweat first proposed as a means of general transfer of drugs not just to sewage* (via bathing and laundry) *but also to any object in the surrounding environment contacted by skin* (dermal transfer)	(Daughton and Ruhoy 2009)
2009	mon	*first geographic spatial surveys*; 24-hour composite WWTP influent samples representing 65% of population of State of Oregon analyzed for BZE, methamphetamine, and MDMA, and Belgium-wide survey of cocaine, BZE, and ecgonine methylester	(Banta-Green et al. 2009); (van Nuijs et al. 2009a); (van Nuijs et al. 2009b)
2009	A	*first qualitative report of cannabinols in ambient air aerosols* (in Rome)	(Cecinato et al. 2009b)
2009	A, mon	*first quantitative study of cocaine in ambient air across several continents*	(Cecinato et al. 2009a)

A=air; DW=drinking water; EF=environmental fate; F=forensics; M=money (banknotes); mon=monitoring; R=review; SS=sewage sludge (and biosolids); sw=sweat; WW=wastewater

Table 2. Drugs of Abuse Frequently Detected by US Forensics Labs[1]

Among the 25 abused drugs most frequently detected by US forensics labs

Most frequent
tetrahydrocannabinol (THC)
cocaine (benzoylmethylecgonine)
methamphetamine
heroin (diacetylmorphine; diamorphine)

Narcotic analgesics
buprenorphine
codeine
hydrocodone
hydromorphone
methadone
morphine
oxycodone

Benzodiazepines
alprazolam
clonazepam
diazepam
lorazepam

Others
1-benzylpiperazine (BZP)
3,4-methylenedioxyamphetamine (MDA)
3,4-methylenedioxymethamphetamine (MDMA)
amphetamine
carisoprodol
methylphenidate
phencyclidine (PCP)
pseudoephedrine
psilocin

Other abused drugs frequently detected by US forensics labs

Narcotic analgesics
butorphanol
dihydrocodeine
fentanyl
meperidine
nalbuphine
opium
oxymorphone
pentazocine
propoxyphene
tramadol

Benzodiazepines
chlordiazepoxide
flunitrazepam
midazolam
temazepam
triazolam

"club" drugs
1-(3-trifluoromethylphenyl)piperazine (TFMPP)
3,4-methylenedioxy-N-ethylamphetamine (MDEA)
5-methoxy-N,N-diisopropyltryptamine (5-MeO-DIPT)
gamma-hydroxybutyrate/gamma-butyrolactone (GHB/GBL)
ketamine

Stimulants
cathinone
ephedrine
phentermine

Anabolic steroids
methandrostenolone
nandrolone
stanozolol

[1]US DEA's National Forensic Laboratory Information System (USDEA 2008)

Table 3. Selected SF/E Studies (arranged roughly according to chronology)

Year	Title (and reference)
2001	Illicit drugs in municipal sewage: Proposed new non-intrusive tool to heighten public awareness of societal use of illicit/abused drugs and their potential for ecological consequence (Daughton 2001a)
2005	Cocaine in surface waters: New evidence-based tool to monitor community drug abuse (Zuccato et al. 2005)
2006	High cocaine use in Europe and US proven Stunning data for European Countries: First ever comparative multi-country study of cocaine use by a new measurement technique (Sörgel 2006)
2007	Using environmental analytical data to estimate levels of community consumption of illicit drugs and abused pharmaceuticals (Bones et al. 2007)
2008	Occurrence of psychoactive stimulatory drugs in wastewaters in north-eastern Spain (Huerta-Fontela et al. 2008a)
	Estimating Community Drug Abuse by Wastewater Analysis (Zuccato et al. 2008b)
2009	Cocaine and metabolites in waste and surface water across Belgium (van Nuijs et al. 2009b)
	Cocaine and heroin in waste water plants: A 1-year study in the city of Florence, Italy (Mari et al. 2009)
	Monitoring of opiates, cannabinoids and their metabolites in wastewater, surface water and finished water in Catalonia, Spain (Boleda et al. 2009)
	Can cocaine use be evaluated through analysis of wastewater? A nation-wide approach conducted in Belgium (van Nuijs et al. 2009a)
	Illicit drugs and pharmaceuticals in the environment – Forensic applications of environmental data, Part 1: Estimation of the usage of drugs in local communities (Kasprzyk-Hordern et al. 2009a)
	Assessing illicit drugs in wastewater: Potential and limitations of a new monitoring approach (Frost and Griffiths 2008)
	Municipal sewage as a source of current information on psychoactive substances used in urban communities (Wiergowski et al. 2009)
2010	The spatial epidemiology of cocaine, methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA) use: a demonstration using a population measure of community drug load derived from municipal wastewater (Banta-Green et al. 2009)
	Drugs of abuse and their metabolites in the Ebro River basin: Occurrence in sewage and surface water, sewage treatment plants removal efficiency, and collective drug usage estimation (Postigo et al. 2010)

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