# Illicit Drugs:
# Contaminants in the Environment and Utility in Forensic Epidemiology

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## 1 Introduction

The spectrum of chemicals recognized as contributing to widespread contamination of the environment was extended to pharmaceutical ingredients as early as the 1970s. The topic, however, did not begin to attract broader scientific attention until the mid-1990s (Daughton 2009b). Occurring generally at levels below 1 µg/L (1 part per billion) in ambient waters, recognition of the near ubiquitous presence of pharmaceuticals in a wide variety of environmental compartments serves as a stunning measure of advancements in analytical chemistry and of our still-emerging understanding of the scope and complexity of xenobiotic occurrence in the environment.

More so than with any other class of environmental contaminants, drugs have served to illustrate the intimate, inseparable, and immediate connections between the actions, activities, and behaviors of individual citizens and the environment in which they live (Daughton 2001a). Drug contaminants also highlight the profound changes that have occurred in how risk is perceived by the public. After all, it has now been 40 yr since the occurrence of an emblematic event that was a major catalyst for the creation of the US EPA (in 1971), and which was followed soon after by the Federal Water Pollution Control Amendments of 1972 and Clean Water Act of 1977, and later by the Water Quality Act of 1987. This event was the 1969 Ohio Cuyahoga River fire, which otherwise had little broad environmental significance because more than a dozen similar fires had occurred in the preceding 100 yr (with the largest occurring in 1952), all resulting from the river's continual accumulation of combustible floating debris and petroleum wastes.

Gross-level pollution of waterways had not been confined to the Cuyahoga River. But the 1969 fire was a landmark event and changed the way the environment was viewed. The extent of progress and effectiveness of pollution regulation, mitigation, control, and prevention over the last 40 yr is now reflected by a focus on trace-level chemical pollutants – an evolutionary change not contemplated in the early 1970s but made possible by continual advancements in instrumental analytical chemistry that began in the 1960s. This focus is embodied particularly with the so-called "emerging" contaminants (Daughton 2009a) and the myriad 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 one major aspect - the contributions to overall environmental loadings by the so-called "illicit" drugs. A structurally diverse group of chemical agents uniformly possessing extremely high potential for biological effects in humans and non-target organisms alike, illicit drugs are used in enormous quantities worldwide – but whose actual magnitude is unknown and can only be roughly estimated. The potential for illicit drugs to enter the environment via a wide array of pathways should not differ much from that of pharmaceuticals used in the practice of medicine. Although known for many decades that illicit drugs and their metabolites (just as with pharmaceuticals used in the practice of medicine) are excreted in urine, feces, hair, and sweat, the ramifications for the environment were basically ignored until 1999 (Daughton and Ternes 1999) and 2001 (Daughton 2001a; Daughton 2001c), when the scope of concerns surrounding PiE was 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 environment was a 1987 FBI study performed in response to a newspaper report 2 yr earlier that cocaine was present on money in general circulation (Aaron and Lewis 1987). Over the intervening 20 yr, analogous surveys of illicit-drug ambient contaminants have been attempted for the first time 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 pharmaceuticals in the environment (USEPA 2009b) shows that the core journal references having a major focus on illicit drugs in wastewaters, ambient waters, drinking water, or the air total about 70 (excluding those published on the topic of drugs on money). The number of references (in any type of technical publication) dealing with illicit drugs in the environment is fewer than 200; this number comprises only 2% of the roughly 10,000 documents that address the general topic of PiE.

Presented herein is the first broad overview of the topic of illicit drugs as environmental contaminants. Summary perspectives are provided of the published data on their occurrence in a spectrum of environmental compartments, what their occurrence might mean with regard to risk, and an historic perspective on how their occurrence can be used as an analytical measurement tool to assess society-wide usage of illicit drugs. An illustrated flowchart depicting the varied routes by which illicit drugs gain entry to our immediate surroundings and to the ambient environment is presented in Fig. 1.

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

This paper builds upon previous work, which is scheduled to be published in one of the only books to date devoted to the topic of illicit drugs in the environment (Daughton 2010 - in press-b).

## 2  What is an "Illicit" Drug?

Any discussion regarding illicit drugs can become confused by the ambiguity as to what exactly defines an illicit drug. Confusion stems from the fact that illicit drugs are not limited exclusively to illegal drugs - that is, drugs with no medical use. Illicit drugs can include active ingredients from bona-fide registered pharmaceuticals having valuable therapeutic uses - two common examples being morphine and oxycodone. They can also include active ingredients that are banned from all use under various international conventions or national law, as they are deemed as having no use in healthcare. Whether a drug is illicit (or illegal) can be dictated by a number of different characteristics, including the chemical structure of the active ingredient or the way in which the drug is manufactured, formulated, labeled, distributed, acquired, or used. Some further discussion is useful to better understand the circumstances under which a drug is considered "illicit."

## 2.1 Terminology

There is no single, widely used term that accurately captures the myriad numbers of substances that become abused by habitual or addictive use. The term "illicit drug," while widely used, 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 the listings of controlled substances maintained by various countries, such as Schedule I in the US.

A variety of terms are loosely used - often interchangeably - in discussions regarding illicit drugs. Major terms include: street drugs, designer drugs, club drugs, drugs of abuse, recreational drugs, clandestinely produced drugs, and hard and soft drugs. The term "research chemicals" had been used by the clandestine laboratory community as an alternative term for designer drugs - with the original intent being that the chemicals were for legitimate research purposes rather than human use (and therefore not subject to regulation); more recently, however, the manufacture of drug analogs as "research chemicals" has become a gray area of the law and is the bona-fide trade of those commercial laboratories synthesizing them for biomedical research. The term "designer" drug was first applied in the 1980s to various analogs of fentanyl and then gained popularity 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. A short history of designer drugs is presented by Freye (2009).

Rather surprisingly, no single term exists for capturing the full scope of intended meaning. 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. The confusion surrounding illicit drug terminology is discussed in papers authored by Sussman and Huver (2006) and Sussman and Ames (2008).

In the overview provided here regarding the environmental aspects of illicit drugs, 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 2009b). In this sense, the term "illicit" refers to the way in which these drugs are manufactured, formulated, distributed, acquired, and consumed, and by the fact that they are being used for non-medical purposes – that is, obtaining drugs without a bona fide prescription and using them in the absence of medical supervision.

This definition allows the inclusion of legal pharmaceuticals - that is, when they are manufactured, formulated, distributed, trafficked, or used illegally, or diverted from legal sources. For those illicit drugs that originate from diversion of legitimate pharmaceuticals, the many sources and the means for their control to reduce their entry to the environment have been discussed by Ruhoy and Daughton (2008). For those that have illegal origins, the sources and routes to the environment are illustrated in Fig. 1. 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 manufacturers, 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 transdermal medical patches, which present lethal hazards for both intentional and accidental exposures (Daughton and Ruhoy 2009).

A closely allied aspect of illegal drugs is counterfeiting. Counterfeiting can involve the repackaging of medical pharmaceuticals that have been either diverted from legitimate sources or manufactured illegally, or the substitution of the advertised ingredient with other substances. Counterfeit is therefore not necessarily synonymous with "fake." Counterfeiting can involve the addition of adulterants to the legitimate pharmaceutical, substitution with less-costly but illegally acquired active pharmaceutical ingredients, or substitution with non-pharmacologic substances, which can be highly toxic. Counterfeit drugs are recognized as a significant threat to human health as a result of the presence of an undeclared active ingredient, excessive dose of a declared ingredient, or absence of a declared active ingredient  (WHO 2008). Counterfeiting results in the entry of drugs to legal and illegal distribution channels; drugs can pretend to be either illicit or legitimate. The actual scope of counterfeiting worldwide is not known, but available data

indicate it to be enormous and escalating. Of the pharmaceuticals in the developed world, one estimate is that 1% are counterfeit, and in the developing world 10-50% might be counterfeit (Everts 2010). Although counterfeiting often produces drug ingredients that are illegal, it is excluded from the scope of the discussion here.

The scope of this discussion also includes all other chemicals associated with the illegal manufacture (including reformulation of divert pharmaceuticals) or trafficking of drugs, such as adulterants and impurities (Table 2). With these distinctions acknowledged, the following discussion will tacitly use a variety of terms very loosely. When the term "pharmaceutical" is used, the intention is to reference the active ingredients legally registered for use in drugs consumed for approved medical use and under formal medical supervision.

What constitutes an illicit drug is a complicated function of social mores and evidence-based health studies, which are sometimes at odds with one another. These conflicts and inconsistencies are reflected, for example, in the opinions expressed by Nutt (2009), which have served to catalyze increasing scrutiny and debate. Illicit substances (drugs and the precursors used for their manufacture) are captured on various government lists (controlled substance *schedules*) that attempt to control and limit their use. The primary criteria justifying inclusion on such listings are health risks, potential for abuse/addiction (partly based on actual data), therapeutic value, and utility as precursors for illicit manufacturing. The unifying worldwide scheme, used by the EU, for regulation of illicit substances 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 2009b).

The lines of demarcation between licit and illicit drugs have become blurred. To illustrate, prescription analgesic opioids (which are controlled prescription drugs – CPDs) have now superseded heroin and cocaine in the US in leading to fatal drug overdoses (Paulozzi and Xi 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 that are misused by high-school seniors in the US, seven were legal prescription - or OTC - medications.  Emergency room visits resulting from prescription opioid analgesics more than doubled from 2004-2008 and were highest for oxycodone, hydrocodone, and methadone (Cai et al. 2010).

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, implicitly capture chemical analogs in their regulations. For example, the US Analogue Act (21 U.S.C. § 813: http://www.justice.gov/dea/pubs/csa/813.htm) is a section of the United States Controlled Substances Act that specifies "A controlled substance analogue shall, to the extent intended for human consumption, be treated, for the purposes of any Federal law as a controlled substance in schedule I." Many additional substances are produced or used illicitly but their chemical identities are elucidated only after they have experienced sufficient illegal use (often, once adverse medical problems in the general population are documented). A central reference that provides the chemical structures for many of these substances (those listed by the Canadian Controlled Drugs and Substances Act) is maintained on a web page by Chapman (2009).

Adding further confusion to 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 being considered or are underway. 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 (i.e., namely cannabis) and calling for its clinical research (AMA 2009). Since Portugal began decriminalizing drug use, possession, and acquisition by drug end-users in 2001 (Law no. 30/2000, which focuses on harm reduction) (Greenwald 2009), the spectrum of laws dealing with illicit drugs has diversified; but growing, illegal manufacturing, and trafficking remain criminal offenses. Among the EU States, the spectrum of law is captured by the European Monitoring Centre for Drugs and Drug Addiction, EMCDDA (2009a). The approaches and

evidence used for classifying drugs as illicit are under increasing evidence-based scrutiny and debate (e.g., see: Nutt 2009).

## 2.2  Differences between Illicit and Licit Drugs as Environmental Contaminants

The primary factor distinguishing illegal from licit (registered) drugs is that the former have no legal (registered) uses, whereas the latter can experience illegal usage. 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 on their production or usage. For regulated pharmaceuticals, sales figures and regional real-time prescription 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 - so-called "designer" drugs or clandestinely produced 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 poses challenges for mass spectrometrists in the coming years and introduces great uncertainty to the true scope of synthetic chemicals that actually contaminate the environment; for examples, see the Psychonaut Web Mapping Research Group (2010) and EMCDDA (2010).  Although many of these unique chemicals are probably produced in relatively small quantities, the fact that they belong to relatively few chemical classes may mean that they share relatively few mechanisms of biological action (MOAs). This increases the probability of biological effects resulting from dose (or concentration) "additivity" – as opposed to acting independently.  When multiple chemical toxicants in a mixture share the same MOA, the dose or concentration of each toxicant can add to that of the others. Even if the concentration of each individual toxicant is below an effect threshold, the mixture's combined dose can act as a larger dose – a phenomenon

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informally referred to as "something from nothing" (Kortenkamp et al. 2009). Dose additivity is distinct from potentiation, where a chemical having no biological action of its own can enhance the action of another. Some designer drugs are highly potent, having extremely low effective doses (e.g., in the range of one microgram per human use), and this has environmental implications, 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 to 5 orders of magnitude more potent than morphine.

(3) Drugs manufactured via illicit routes are commonly contaminated with unintended impurities and purposeful adulterants (Table 2). 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 ingredient.

(4) The manufacture of illicit drugs (particularly methamphetamine) can cause extensive ecological damage as well as irreversible damage to infrastructure such as buildings (Cohen et al. 2007; Snell 2001; USEPA 2009a).

(5) The primary interest in residues of illicit drugs in the environment has not been their occurrence in the environment as contaminants, but rather their presence in sewage (mainly untreated raw sewage) for use as a tracking tool to calculate their community-wide consumption. This relatively new tool has been termed *sewage (or sewer) forensics (or epidemiology)*, but later in this document is referred to as FEUDS: "Forensic Epidemiology Using Drugs in Sewage." In contrast to the licit use of pharmaceuticals, interest in the potential for illicit drugs as biological stressors in the environment has been secondary, and very little is known.

(6) Compared with pharmaceuticals, much less is known about the toxicology (including pharmacokinetics), especially in the aquatic environment, of many illicit drugs (particularly designer drugs); for human research, there are added legal and ethical difficulties in performing studies. Knowledge of the scope of bioactive metabolites and extent of reversible conjugation is comparatively limited.

(7) Numerous measures are routinely implemented to reduce the entry of licit pharmaceuticals into the environment and moderate their potential for adverse effects. 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 "rogue" Internet pharmacies), and end use (==Fig. 1==).

The rate of introduction of new pharmaceuticals with potential for abuse and of new illicit substances precludes any comprehensive definitive worldwide compilation of such 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).

## 3  The Core Illicit Drugs and the Environment

The types of drugs commonly abused are categorized 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; or heroin in the US),

(2) limited established medical use but also manufactured illegally and used primarily for non-medical purposes (e.g., methamphetamine),

(3) firmly established with wide medical use but diverted for illegal use (e.g., theft; illegal prescribing such as via unapproved Internet "pharmacies"),

(4) firmly established wide medical use and legally obtained, but for non-medical use (e.g., doctor/hospital shopping or by other con schemes),

(5) biological action similar to prescription drugs but synthesized as analogs, which are not individually and explicitly categorized as illegal; examples include the numerous analogs of phosphodiesterase (PDE) type-5 inhibitors.

All of these categories tend to primarily comprise drugs with high potential for abuse or that enjoy recreational use.

Residues of some drugs in the environment have substantial multiple origins (both legal and illegal) making it difficult to ascribe or apportion monitored levels to illicit use. Morphine is one example. Morphine residues 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 reliable idea can be obtained to ascribe what portion of morphine originates from heroin usage.

While drug usage patterns and prevalence vary among countries and 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 NFLIS (Drug Enforcement Administration's National Forensic Laboratory Information System) (USDEA 2008) provide the best insights regarding which known drugs are most used in non-medical circumstances (Table 3). The NFLIS is a system operated by the DEA that collects data generated by state and local forensic laboratories in the US. Of all the samples analyzed in 2008 by US local and state forensic laboratories for the presence of non-medically used drugs, 25 controlled substances composed 90% of all the samples.

Of these 25 drugs, the most frequent four were tetrahydrocannabinol (THC), cocaine (benzoylmethylecgonine), methamphetamine, and heroin. Seven were narcotic analgesics (codeine, hydrocodone, oxycodone, methadone, morphine, buprenorphine, and hydromorphone), four were benzodiazepines (alprazolam, clonazepam, diazepam, and lorazepam), and others

included: 3,4-methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxyamphetamine (MDA), amphetamine, methylphenidate, phencyclidine (PCP), pseudoephedrine, carisoprodol, 1-benzylpiperazine (BZP), and psilocin. In addition to these top 25, other drugs frequently used for non-medical purposes included narcotic analgesics (butorphanol, dihydrocodeine, fentanyl, meperidine, nalbuphine, opium, oxymorphone, pentazocine, propoxyphene, and tramadol), benzodiazepines (chlordiazepoxide, flunitrazepam, midazolam, temazepam, and triazolam), "club" drugs [ketamine, 1-(3-trifluoromethylphenyl)piperazine (TFMPP), gamma-hydroxybutyrate/gamma-butyrolactone (GHB/GBL), 5-methoxy-*N*,*N*-diisopropyltryptamine (5-MeO-DIPT), and 3,4-methylenedioxy-*N*-ethylamphetamine (MDEA)], a number of stimulants (e.g., cathinone, ephedrine, and phentermine), and a number of anabolic steroids (e.g., methandrostenolone, nandrolone, and stanozolol). Many of these latter drugs (not the top-25) have never been routinely targeted for monitoring as environmental contaminants.

The top 25 detected by NFLIS (DEA's National Forensic Laboratory Information System) are all among the most commonly abused drugs in the US. The major ones missing from these top 25 (but which are captured in the remaining 10% of samples analyzed by NFLIS) are barbiturates (e.g., phenobarbital and seconal, whose rate of abuse has been declining), certain benzodiazepines (such as alprazolam, chlordiazepoxide, and diazepam, but excepting flunitrazepam), 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 located from the web page of the Office of National Drug Control Policy (ONDCP 2009). The  UNODC World Drug Report (UNODC 2009a) provides comprehensive statistics on world illicit drug supply and demand. The availability, use, and impacts of illicit drugs in the U.S. were most recently assessed by the National Drug Intelligence Center (NDIC 2010).

### 3.1  Environmental Occurrence

While drug usage patterns and prevalence vary among countries and through time, those drugs in frequent use in the US can serve as an organizing framework for further discussion. Of the top 25 most frequently identified non-medically used, controlled substances analyzed by US local and

state forensic laboratories in 2008, only 15 have been targeted in environmental studies of illicit drugs: amphetamine, cocaine, codeine, heroin, hydrocodone, MDA, MDMA, methadone, methamphetamine, methylphenidate, morphine, oxycodone, PCP, pseudo-ephedrine, and THC (Δ9-tetrahydrocannabinol). A summary of their occurrence in a variety of environmental compartments is shown in Table 4. Note that ground water is not listed. This is because of the dearth of groundwater monitoring studies that have targeted and identified illicit drugs. One of the only such studies identified codeine in recharged ground waters in Spain, at sub-ppb levels (Teijon et al. 2010).

Also shown in Table 4 is the occurrence information (as well as indications of negative occurrence – or data of absence) for nearly all of the other illicit drugs and metabolites that have been reported in the published literature. From these data, those analytes with absence of data (i.e., those that have yet to be targeted in monitoring studies) can be deduced. These substances with absence of data represent potential candidates for future monitoring, should they be of interest to environmental scientists, aquatic toxicologists, or for application with FEUDS. For example, Postigo et al. (2008b) note that nor-cocaethylene and ecgonine ethyl ester have not been targeted in any monitoring study.

The occurrence data are arranged in Table 4 according to the environmental compartments for which the data apply: wastewaters, surface waters, drinking water, sewage sludge, sewage biosolids, air, banknotes, wildlife tissue, and potential for dermal transfer. Dermal transfer is a potential route of transport to immediate physical surroundings (and to sewage during bathing) for drugs excreted via sweat or applied topically (Daughton and Ruhoy 2009)]. Other reviews of illicit drugs in the environment are provided by Huerta-Fontela et al. (2010) and Zuccato and Castiglioni (2009). It is important to note that parent drugs or their metabolites that have never been targeted for monitoring in the environment are not listed in Table 4. Some of these substances might make likely candidates for future screening. One example is the primary metabolite of methamphetamine, p-hydroxymethamphetamine, which is excreted as the sulfate and glucuronide conjugates (Boles and Wells 2010).

An examination of Table 4 reveals 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., 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine [EDDP]), cocaine (i.e., BZE [benzoylecgonine]), and THC (i.e., 11-nor-9-carboxy-9-THC [THC-COOH]). Although widely detected in clinical and forensic drug screens, the occurrence of heroin (diacetylmorphine) in an environmental compartment is limited primarily to banknotes, because of its propensity to hydrolyze in water. Similarly, 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 whose primary focus is illicit drugs. These are: 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 controlled prescription drugs (CPDs) for: alprazolam, carisoprodol, diazepam, and lorazepam. Data do not exist for buprenorphine, BZP, clonazepam, hydromorphone, and psilocin. Depending on their pharmacokinetics and the extent to which that are excreted unchanged, these latter five drugs might be likely targets for future environmental monitoring.

Alprazolam has been measured at low to high ng/L levels in treated sewage effluent (Batt et al. 2008). Although carisoprodol is extensively metabolized (primarily to the active metabolite meprobamate), it has been measured at sub-ppb levels in runoff from agricultural fields irrigated with treated wastewater (Pedersen et al. 2005).

Diazepam has been widely reported in a variety of wastewaters and surface waters; see summaries of Calisto and Esteves (2009) and Straub (2008). Most diazepam occurrence data from targeted monitoring, however, have been negative (Christensen et al. 2009). Diazepam resists biodegradation (Redshaw et al. 2008) and perhaps partitions to particulates.

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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 those of other analytes. This reiterates the importance of specifying limits of detection when presenting data of absence.

Other targeted analytes are not detected, probably 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 drug ingredients are extensively conjugated and, without a hydrolysis step to free the aglycone, will be missed (Daughton and Ruhoy 2009; Pichini et al. 2008). Conjugates could potentially serve as hidden reservoirs for drug ingredients in the environment (Daughton 2004), but, to date, published data are lacking to affirm the extent and magnitude of this phenomenon.

Lorazepam is extensively metabolized to its glucuronide conjugate, with negligible amounts excreted unchanged (Ghasemi and Niazi 2005). Nonetheless, it has been measured at levels up to 200 ng/L in treated sewage (Coetsier et al. 2009; Gros et al. 2009; Gros et al. 2010), perhaps reflecting an input from disposal to sewers or hydrolysis of the conjugate.

It is important to note that some illicit drugs are metabolic/transformation daughter products of others, which explains why their concentrations in sewage or receiving waters are routinely higher than those of their parents. One example is heroin, which is quickly deacetylated (both metabolically and in the environment) 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 removed from impact by sewage), are present because they were directly flushed into sewers (or excreted via sweat) - rather than being excreted via urine. An alternative source could be run-off into streams, such as during clandestine manufacturing. Another example is fentanyl, which is extensively excreted as norfentanyl.

*3.2 Adulterants and Impurities as Potential Environmental Contaminants*

In contrast to pharmaceuticals produced under Good Manufacturing Practices, drugs made illegally contain significant impurities and contaminants in addition to the sought-after drug (or sometimes even in place of the desired drug). These substances are often present at very high levels, especially in intentionally mislabeled drugs - sometimes representing the bulk of the purported drug. For example, noscapine can be present at levels up to 60% in heroin, or phenacetin at levels up to 50% in cocaine. Another example is the misrepresentation of MDMA by combining 1-benzylpiperazine (BZP) and 1-(3-trifluoromethylphenyl)piperazine (TFMPP), which can mimic its psychoactive effects. These adulterants and other contaminants also 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, 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 and metabolite of cocaine when consumed together with ethanol). In the course of reviewing the literature, more than 90 common adulterants and impurities were noted just for the four illicit drugs cocaine, MDMA, methamphetamine, and heroin (Table 2). These represent only a small sampling of the variety of chemicals that can compose illicit drugs.

Because some illicit drugs are natural products, they can inadvertently contaminate our food supply. The recent controversy regarding the presence of cocaine in a commercial energy drink (as residue from de-cocainized extract of coca leaf) (BfR 2009) demonstrates the power of analytical chemistry in revealing previously undetected levels of chemicals.

Adulterants are often used to enhance desired biological effects or make the drug more profitable. They include diluents, which are added to mimic the appearance of the sought-after drug (to extend the doses per mass) or enhance the biological effects. Impurities are sometimes integral to the natural chemistry of the native plant from which a drug is isolated, and at other times is a function of the synthetic route to the desired drug. The adulterants used are a function of the geographic locale of manufacture/distribution, or depend on what chemicals are available at the time of synthesis or what the clandestine manufacturer wishes to use. 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 known. Adulterants can range from common substances such as caffeine (very high concentrations) to more insidious chemicals such as the cytotoxic veterinary dewormer drug levamisole, which has led to a number of deaths from its inadvertent consumption. In this way, illicit drug use can serve as an alternative route of entry to the environment not just for drugs of abuse, but also for active pharmaceutical ingredients, such as levamisole, that have no potential for abuse. Adulteration of illicit drugs has grown to become a major health risk for drug users.

An expansive published literature exists for illicit-drug adulterants and impurities. This is driven largely by research and surveillance aimed at drug "profiling," a methodology for obtaining a chemical fingerprint or signature for individual batches of drugs. For example, determining illicit-drug impurities (and ratios of enantiomers) helps deduce the synthetic route or geographic locale of manufacture. An example of the profiling process (for methamphetamine) is presented by Inoue et al. (2008). Profiling data are potentially useful for targeting important adulterants or impurities for environmental monitoring.

Except for some registered pharmaceuticals that are used as adulterants in illicit drugs (to reduce cost or alter/mimic physiologic/psychotropic effects), these adulterants pose totally unknown risks for the environment. The ecological risks for some registered pharmaceuticals used as adulterants are similarly unknown. One example is levamisole, which is excreted largely unchanged and potentially poses risks for certain soil-dwelling organisms (McKellar 1997; Sommer and Bibby 2002). It is also known to be taken up by certain food crops such as lettuce (Boxall et al. 2006a), but has not yet been targeted in any environmental monitoring. Levamisole has, however, been identified as a high-priority compound for possible future environmental monitoring (Boxall et al. 2006b).

The general public may be unknowingly exposed to illicit drugs in the form of designer drugs as impurities in food or nutritional supplements. For example, common foods can contain residues of illegal analogs of legal drugs, particularly anabolic hormones (used in livestock), such as norbolethone, tetrahydrogestrinone, and desoxymethyltestosterone (Cunningham et al. 2009;

Noppe et al. 2008; Shao et al. 2009; Yang et al. 2009). Certain OTC supplements used for male erectile dysfunction can contain unregistered synthetic analogs of the approved phosphodiesterase type-5 (PDE-5) inhibitors (Poon et al. 2007; Venhuis et al. 2007; Venhuis and de Kaste 2008).

## 4  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 is concerned with the exposure of aquatic organisms and humans to environmental residues. Of the environmental studies conducted, however, this has not been the major thrust. Rather, the data obtained have been used as a retrospective tool for reconstructing society-wide usage of illicit drugs. Such data acquisition could be considered a large-scale version of exposure assessment called "dose reconstruction" (e.g., see: ATSDR 2009).

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

### 4.1  Sewage Epidemiology or Forensics - FEUDS

Daughton (2001c) first proposed analyzing 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.  Since 2001, this approach has been referred to as "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 could potentially be served by application of the methodology.

Epidemiology can be defined as the study of the occurrence, distribution, and causes of health effects in specific human populations, and the use of this study as the basis for interventions

targeted at re-establishing public health Epidemiology can be used for identifying at-risk sub-populations, monitoring the incidence of exposure/disease, and detecting/controlling epidemics. Elements of illicit drug use fit all of these categories. 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 applications 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).

Therefore, a more accurate descriptive term for "sewer epidemiology" should be considered 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 fields and to greatly simplify literature searches. The acronym FEUDS will be used as a shorthand in the remainder of the discussion here.

## 4.2 FEUDS for Community-wide Dose Reconstruction for Illicit Drugs

After its conceptualization in 2001 (Daughton 2001c; d), FEUDS was first implemented in a 2005 field monitoring study by Zuccato et al. (2005). FEUDS was originally proposed as the first evidence-based approach for measuring drug use because the long-practiced approaches that use oral or written 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 sampling bias and self-reporting bias) (Daughton 2001c). The limitations imposed by self-reporting bias have 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 of actual); the problems with profound underestimates derived from self-reporting are discussed by Magura (2010). Sampling bias inevitably results from the decision process used for selecting which segments of the general population to survey.

These conventional approaches to estimating illicit drug usage also suffer from two inherent limitations: extreme delays in time before results are compiled and reported, and costs associated with data collection and interpretation.

FEUDS, like public surveys, suffers from many sources of potential error. But FEUDS is in its infancy and its sources of error derive from variables still under investigation and which have not yet been optimized for better control. While conceptually rather straightforward, the back-calculations used in FEUDS are a function of numerous variables, including demographics, population flows through a locale (such as transient visitors and commuters) served by a given sewage treatment facility, route of dose administration, pharmacokinetics (including knowledge of extent of conjugation), constancy of usage, frequency of disposal (if the parent drug rather than a unique metabolite is targeted), and sewage flows. Combined, these pose a major challenge for modeling to accurately reconstruct dose. The numerous problems facing FEUDS are discussed in Frost and Griffiths (2008) and (van Nuijs et al. 2010 - in press). Most FEUDS 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/d. Many of the sources of uncertainty are covered by Banta-Green et al. (2009) and Zuccato et al. (2008b).

Despite the plethora of uncertainties attendant to variables involved in 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 public health campaigns, 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. Transient or episodic patterns are obscured when reports are on an annual basis.

Few systematic approaches to cataloging newly emerging recreational drugs (those not yet recognized in the published literature) have existed. One such attempt, conducted from 2008 through 2009, mined information collected from a broad spectrum of sources (Psychonaut Web Mapping Research Group 2010). As of March 2010, the project had categorized over 400 substances or mixtures not previously recognized in the published literature as having recreational use. One example is mephedrone (2-methylamino-1-$p$-tolylpropan-1-one; 4-methylmethcathinone; 4-MMC; MMCAT), a substance that has experienced wide and growing popularity as a street drug in the UK but which is sold in various guises, such as "plant food" and labeled "not for human consumption." By mid-April 2010, mephedrone had been banned in the UK, only to witness another drug enter the spotlight - 5,6-methylenedioxy-2-aminoindane (MDAI) - developed in the 1990s as an antidepressant. This exemplifies the speed at which a continual series of new chemicals is embraced by recreational drug users.

It is of great potential significance that there are no apparent technical obstacles to designing automated continuous monitors for use in sewage collection/distribution systems. Implementing continuous monitoring to support FEUDS could greatly enhance efforts to control and mitigate drug use. Such a hypothetical system could use a number of different approaches, generally based on the use of in-stream chemical sensors or automatic acquisition of discrete samples at pre-selected intervals followed by instrumented auto-analysis. The limiting factor would be cost. The foundation for continuous monitoring is already being established, especially for use in

clinical and forensics laboratories. One such automated method has been applied to 21 commonly abused drugs in urine, using on-line extraction coupled with tandem mass spectrometry (Chiuminatto et al. 2010); the main area of needed improvement is sufficiently low limits of detection.

Another advantage of FEUDS over population surveys is that not all drug use is necessarily known to the users themselves, who then unintentionally report 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 (e.g., counterfeit illicit drugs). Adulterants are often substituted (Table 2), in part or in whole, for the purported drug. One general route of such 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 still 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 et al. 2007; Venhuis and de Kaste 2008). In more than half of the OTC male erectile dysfunction health products examined, analyses revealed the presence of acetildenafil, hydroxyacetildenafil, hydroxyhomosildenafil, and piperidenafil - analogs of sildenafil and vardenafil not registered for pharmacologic use.  The legal registered versions of PDE-5 inhibitors have only recently been detected in wastewaters (Nieto et al. 2010). Since members of this class of drugs all share the same mechanism of biological action, the PDE-5 inhibitor analogs could contribute to dose additivity. Analogs are known to exist for various other classes of drugs, particularly psychoactives, anabolic steroids, and anti-obesity drugs. The toxicity of these analogs is largely unknown. 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 FEUDS projects in the US. The ONDCP performed the first FEUDS 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 FEUDS 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).

### 4.3 Quality Assurance and FEUDS

Two aspects of illicit drugs can have major impact on the quality and validity of any monitoring data used for FEUDS. The first is the contamination of samples during collection or analysis by transfer of residues from the skin of the analyst. Many drugs, especially illicit drugs, are readily excreted via sweat glands, including those on the fingers. This has the potential to result in contamination of samples during their collection or during various steps in analysis. Contamination of samples by analysts who are using prescribed or illicit drugs is an under-investigated potential source of erroneous data. The dermal excretion of drugs as a source of their transfer to immediate surroundings as well as to the environment was first examined by Daughton and Ruhoy (2009).

The second aspect is the stability of drug residues in samples in the absence of proper preservation. Little research has been done on the stability of illicit drugs in collected environmental samples; the extensive existing literature on the stability of residues in biological samples obtained for forensics and human drug monitoring purposes may be partly relevant and could serve as a starting point for environmental samples. Both cocaine and cocaethylene, for example, have been shown to readily degrade to benzoylecgonine (Castiglioni et al. 2006). González-Mariño et al. (2010) examined the preservation of raw sewage samples with sodium azide at $4^{o}$C (to inhibit microbial degradation). In time-course studies up to 7 d, large positive or negative changes in concentrations were noted for methadone, cocaine, benzoylecgonine, heroin, morphine, and THC-COOH. They concluded that sample preparation (e.g., solid phase extraction followed by any needed derivatization, and storage at low temperature) was best performed as soon as possible at the site of sample collection.

### 4.4 Summary of Published Research in FEUDS

Overviews and discussion of the FEUDS studies published up until 2008 are provided by Postigo et al. (2008b), van Nuijs et al. (2010 - in press), and Zuccato et al. (2008b). The major published articles regarding one or more aspects of the FEUDS approach are compiled in the chronology of Table 5. At the beginning of 2010, there had been fewer than two dozen studies, and most were published after 2007.

Published FEUDS analyses have been conducted in a number of countries, with assessments at local, regional, or national levels - primarily in Belgium, Germany, Ireland, Italy, Spain, Switzerland, the US (i.e., Oregon), and Wales. To date, FEUDS assessments have been focused on a select few parent drugs (primarily cannabis, cocaine, heroin, and MDMA) using various metabolites. They have been performed using a many sampling methodologies - ranging from 1-d single-event discrete grab sampling to longer-term (e.g., 12-mon) integrative continuous sampling over numerous WWTPs or rivers, servicing regions with populations exceeding millions. In many of these studies, temporal usage patterns were investigated, in which yearly seasons or the day of the week (e.g., higher cocaine use on weekends) were examined. Usage rates are reported on various comparative bases, often involving per capita (e.g., g/d/1,000 population - usually ranging only up to several grams), total consumption (e.g., tonnes per year per geographic area), or flows (mass/river/d). 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.

An enormous published literature surrounds the forensic chemistry of illicit drugs. The numbers of illicit drugs analyzed in the environment, however, is 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 (exact-mass) identification of unknowns (e.g., via time-of-flight mass spectrometry - 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 only indirectly relevant. There are numerous variables involved with (and impacting) the procedural steps used in the analyses required by FEUDS - ranging from sampling design and matrix interferences to analyte determination and the 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. 2008b; Zuccato and Castiglioni 2009).

With interest in trace environmental contaminants (or micro-constituents) continuing to grow, a critical and limiting factor in gaining a comprehensive and accurate picture is the limit of detection (LOD) – and allied figures of merit such as the limit of quantitation (LOQ). LOD and LOQ are functions of the individual analyte as well as the matrix in which it occurs; raw sewage, for example, is a particularly problematic matrix, giving significantly higher LODs than drinking water. As a key figure of merit, the LOD dictates the extent to which environmental monitoring produces meaningful data of absence (negative occurrence data); it is roughly defined as the lowest concentration that an analytical method can differentiate with statistical power from background signal. With discussions of the formal definition of the LOD aside, one ramification is that since LODs can differ widely among analytes (and among methods). Data of absence therefore cannot be directly inter-compared without providing the context of their respective magnitudes. The absence of two drugs in a sample, for example, has different meanings when their LODs differ by one, two, or even more orders of magnitude. To state that a drug is not found in a certain sample is rather meaningless without specifying its LOD. For most of the monitoring studies cited in this document, LODs were provided as part of the method development. For illicit drugs in sewage, LODs tend to settle in the 1-10 ng/L range, with excursions to either side. Some drugs have higher LODs – possibly a reason for sporadic occurrence data. One example is 6-acetylmorphine, whose LOD can be an order of magnitude higher than for others, such as cocaine and cocaethylene (Postigo et al. 2008a).

An issue little addressed in FEUDS studies has been the complications (and opportunities) posed by chirality. Only recently has attention begun to be directed to the speciation of enantiomers during environmental analysis (Kasprzyk-Hordern et al. 2010). 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 from the illicit form (as well as portending relative toxicity). This may account for a portion of some of the large variance in estimated amphetamine usage across

FEUDS studies. While chiral isomers can pose difficult challenges for analytical chemists, they also provide a wealth of forensics information in terms of chemical "fingerprinting" - for example, in distinguishing legal from illegal origins. Advancements in the application of chiral analysis to illicit drugs in the environment will most likely accelerate, especially in its use for FEUDS.

### 4.5  Legal Concerns Surrounding FEUDS

Application of FEUDS to analysis of co-mingled sewage (such as at a sewage treatment facility) clearly ensures the anonymity of individuals, which was one of its primary features when first proposed (Daughton 2001c; d). Even though FEUDS was conceptualized for public health purposes, the potential for its abuse in law enforcement was recognized early. An obvious scenario where privacy could be breached would be the implementation of sewage monitoring as close to individual sewer feeder lines as possible in order to trace the origin of illicit drug residues back to specific, individual neighborhoods or isolated buildings. Despite this tacit understanding as far back as 2001, there has been little formal discussion of legal or ethical issues in the published literature, even in law journals; interest in more specific, localized application of FEUDS is evident from statements such as whether it "can be used in smaller communities in which illicit drug use is especially unwanted such as drug rehabilitation centers, hospitals, prisons, military compounds and schools" (Verster 2010). One of the only, and certainly the most comprehensive, examinations of the legal concerns (in the US) was published by Hering (2009). The concerns center primarily on the Fourth Amendment (unreasonable searches) and the potential for violating  an individual's privacy. Although the historical summary of events behind FEUDS is not fully accurate, Hering presents a comprehensive examination of the pitfalls involving US law, using case law to substantiate the concerns. He concludes, however, that although FEUDS applied to the sewers of an isolated home might appear to constitute a search under the Fourth Amendment, the legal case would be "extremely tenuous."

## 5  Illicit Drugs in the Money Supply

Residues of illicit drugs have been known since the 1980s to occur on banknotes (e.g., Aaron and Lewis 1987; Table 1), primarily as a result of dermal transfer from drug users and transfer from contact with bulk drugs themselves. Highly contaminated banknotes can, in turn, cross-contaminate pristine banknotes in their proximity. Most studies have focused on cocaine, because of its propensity to become entrapped in banknote fibers and because of the use of banknotes for insufflation. Cocaine amounts exceeding 1 mg per banknote have been reported (Oyler et al. 1996) - more than 1% of a typical dose. The contamination may be so pervasive that large numbers of banknotes must be removed from general circulated each year (Thompson 2002). Bones et al. (2007a) pushed the limit of detection for cocaine into the range of a picogram per banknote. In addition to cocaine, other drugs studied on banknotes include: 6-AM, diacetylmorphine (DAM), Δ9-tetrahydrocannabinol, cannabinol, cannabidiol, 3,4-methylenedioxy-methamphetamine, methamphetamine, amphetamine, PCP, and codeine.

While the occurrence of illicit drugs on money in general circulation possibly serves as a minor source of exposure for the public - via dermal transfer and pulmonary exposure (but especially among those working with money sorting machines) - no exposure work has been done on these routes. Interest has been spurred instead by forensics - primarily with the potential to distinguish "drug money" from "innocent" money. Because of the widely varying drug-use practices and patterns across countries and cultures, very different patterns of money contamination by drugs occur. Correlations of contamination with the source of money, however, have been weak.  The degree of contamination is partly a function of the denomination of the banknote; in the US, for example, denominations $5 through $50 have contained higher cocaine residue levels than $1 and $100 denominations. While banknote contamination can give an indication of types of drugs in use and especially recent proximity to bulk drug supplies, it has not provided insights on societal usage rates.

The forensics aspects of drug-contaminated money have been advanced largely by the work of investigators with Mass Spec Analytical Ltd. (MSA 2007). Overviews are available from Sleeman et al. (2000) and  Armenta and de la Guardia (2008). Numerous papers have been

published, a few of which are: Bones et al. (2007a), Burton (1995), Carter et al. (2003), Ebejer et al. (2005), Ebejer et al. (2007), Jenkins (2001), Lavins et al. (2004), Luzardo et al. (2010), Sleeman et al. (1999), and Zuo et al. (2008).

This field will surely benefit from the rapid screening capabilities of ambient ionization mass spectrometry (e.g., Chen et al. 2009). Clearly, the potential exists for transfer of minute residues of illicit drugs from circulating money to the public; the ramifications of this, if any, are unknown.

## 6  Illicit Drugs in Ambient Air

Unlike the vast majority of pharmaceuticals, certain illicit drugs have the potential to escape to the ambient air, primarily because of the release of vapors and particulates from smoking and inhalation and from the generation of dusts; some of the only pharmaceuticals studied in air are the genotoxic chemotherapeutics used in the occupational setting (see references cited in: Daughton and Ruhoy 2009). Perhaps the first data on an illicit drug in the environment was the 1998 report of cocaine associated with particulates in Los Angeles ambient outdoor air (Hannigan et al. 1998). Since then, studies have actively targeted a limited array of illicit drugs in ambient air in several locales, primarily cities in Italy and Spain, but also in Serbia, Portugal, Algeria, Chile, and Brazil.

An overview of this topic is provided by Postigo et al. (2010). The major studies include: Balducci et al. (2009), Cecinato and Balducci (2007), Cecinato, Balducci, and Nervegna (2009a), Cecinato et al. (2009b), Cecinato et al. (2010), and Viana et al. (2010); another base of knowledge regarding analytical methodologies exists in the forensics literature, such as the work of Lai et al. (2008).  Residues are usually associated with airborne particulates. Concentrations of cocaine generally are in the low picograms per cubic meter but can range up to low nanograms per cubic meter. Levels within a geographic region can vary by two or more orders of magnitude and are sensitive to weather conditions and time of year (with higher concentrations in winter) (Cecinato et al. 2010).  These highest levels are roughly three orders of magnitude lower than commonly found for caffeine or nicotine. Also targeted in air studies have been other cocaine-

related chemicals such as BZE and cocaethylene, as well as amphetamines, cannabinoids, cocainics, heroin, lysergics, methadone, and opioids. Multi-analyte air analysis has been rare, the work of Viana et al. (2010) being a recent example, with eight analytes targeted; this is one of the only reports of 6-AM in air.

The objective of air monitoring for illicit drugs is more in line with forensics (as a tool in detecting trends in drug usage) than with concerns regarding public health impacts from chronic pulmonary exposure to trace ambient levels. This is because cumulative life-time doses (for example with cocaine), even in locales with higher contamination, are 2-3 orders of magnitude below that of a single recreational dose (Cecinato et al. 2010; Viana et al. 2010). Atmospheric levels of illicit drugs, however, may be more transient and variable than levels in wastewater, adding greater complexity to its use as a tracking tool for drug usage.

## 7  Other Routes of Illicit Drug Impact on the Environment

### 7.1  Clan Labs

Clandestine drug laboratories (clan labs) are a primary localized source of certain drugs to the environment. Acute and chronic human health risks have been documented via all major exposure routes: inhalation, dermal absorption, and ingestion. Clan labs have been a recognized environmental hazard since the late 1980s (Gardner 1989). Direct and collateral environmental impacts even from ephemeral production sites and facilities can be extensive (Cohen et al. 2007). Damage can result from negligent dumping of hazardous reagents and solvents, uncontrolled discharge of product chemicals and intermediates, alteration to watersheds (e.g., facilitation of erosion), and indiscriminate application of pesticides and fertilizers In the US, these impacts result primarily from cannabis and methamphetamine. Concerns are related not just to the synthesized parent drug (primarily methamphetamine in the US) but also to the numerous synthesis starting materials and by-products (Snell 2001). With methamphetamine clan labs, a particularly problematic aspect is the insidious contamination of building structures (National Jewish Medical and Research Center 2005), in which large amounts of product permeate porous materials, creating reservoirs that serve as a perpetual source for future exposure. Morbidity from

occupational and incidental human exposures is not trivial (Thrasher et al. 2009). The US EPA has issued new guidance for the cleanup of clan labs (USEPA 2009a).

Of particular interest is the financial liability and health risk posed by the purchase of contaminated real estate by unwary buyers (e.g., see: Jarosz 2009; Poovey 2009). Methamphetamine-contaminated real estate has grown sufficiently common that it has fostered commercial enterprises specializing in the detection of methamphetamine (and other illicit drugs) residues in real estate.

Worth noting is that wastewaters from pharmaceutical manufacturing facilities, which include both production and formulation facilities, had been largely ignored as a potential source of drug ingredients until the mid-2000s. The first survey of wastewaters from several manufacturing facilities in the US revealed the presence of several drugs of abuse at levels over 1,000 µg/L (Phillips et al. 2010 - in press). Historically, reported levels of APIs have generally been three or more orders of magnitude lower than this in wastewater streams from municipalities not receiving manufacturing waste. This raises the possibility that in some locales pharmaceutical manufacturing could be a major source of certain drugs of abuse in ambient waters.

## 7.2 *Livestock and Racing Animals*

A wide spectrum of pharmaceuticals are known or suspected of being used illegally in livestock, primarily as growth promoters. An extensive literature exists on this subject, but due to the clandestine nature of the practice, an accurate picture does not exist for its full scope and magnitude, which probably varies greatly among countries. Some of these drugs are also abused by humans, so they can serve as another source contributing to environmental residue levels; others are unique to veterinary practice. Among the drugs in use, many might be registered for veterinary use but not for the purposes actually employed. Others may not be approved for any purpose. Included are members from the following classes: anthelmintics (e.g., levamisole), a wide range of antibiotics, coccidiostats (e.g., nitrofurans), hormones (anabolic steroids, corticosteroids, and thyreostats such as the thiouracils), ß-agonists (e.g., clenbuterol), and tranquillizers (e.g., ketamine, haloperidol, xylazine) (Courtheyn et al. 2002; Stolker and Brinkman 2005).

Pharmaceuticals are known to contaminate much of the surroundings that race horses come into contact with (or which their urine or sweat contacts), including stalls and racetracks (Barker 2008). Although the drugs detected in this monitoring study were primarily conventional non-steroidal anti-inflammatories (phenylbutazone, flunixin, and naproxen),  analogous routes of contamination would not be unexpected for any illicit drugs that might be surreptitiously used.

### 7.3  Dermal Contact and Transfer

Dermal transfer as a route of exposure for drugs has been an under-recognized aspect of drugs and the environment. The first comprehensive review of the ramifications of transfer of drugs from humans to the surfaces of any items contacted in the immediate surroundings (and to other people) by way of dermal transfer is provided by Daughton and Ruhoy (2009). There are two contributing factors. One is the transfer of residues remaining from topically applied drugs (which are generally applied at very high levels). The second is the excretion of systemic residues in sweat. Both factors apply equally to drugs of abuse and illicit drugs, especially potent analgesics such as fentanyl. The overall significance of this route of transfer to the immediate environment is not yet known.

### 7.4  Diversion

Diversion of licit drugs is the major route by which licit pharmaceuticals enter illicit markets and illicit use. Major routes include purchase from Internet pharmacies and theft from manufacturers, distributors, brick and mortar pharmacies, healthcare facilities, and homes (e.g., for teen "pharming"). Pharmaceuticals still in clinical trials and not yet approved are even subject to diversion. A recent example is the selective androgen receptor modulator Andarine (a trifluoromethyl-arylpropionamide), which was being sold via the Internet to bodybuilders (Thevis et al. 2009).

Doctor/hospital shopping is also a form of diversion. A recent study of Internet pharmacies found that of nearly 3,000 online pharmacies (nearly half hosted in the US), with combined annual sales of nearly US$12B, only two were certified by the Verified Internet Pharmacy Practice Sites (VIPPS) program, which is run by the National Association of Boards of Pharmacy (Felman 2009), and 10% stated that no prescription was required. Evidence points to diversion (as well as counterfeiting) as major sources for many of these drug stocks. So-called rogue Internet pharmacies are documented as a significant source for diverted CPDs, especially Schedule III and Schedule IV drugs (NDIC 2009).

In addition to widespread outlets for illegally purchasing drugs of abuse, abusers have created a wide array of methods for "legally" diverting drugs. These include not just "doctor shopping" but also "hospital shopping." The latter is a practice in the US that involves using free emergency services to acquire drugs to support addiction (Sullivan 13 June 2009).

### 7.5 Disposal of Leftover Medications

One particular aspect of drug occurrence in the environment can add significant confusion to assessing whether the source is from illicit or legal usage. For those drugs that share both legal and illicit usage (namely, those controlled substances not listed on DEA's Schedule I), a potentially major route by which their active ingredients can directly enter the environment is by flushing into sewers. While prudent practice for disposal of leftover drugs has generally shifted away from flushing (a practice long favored in order to reduce the incidence of intentional and unintended poisonings in the home), current guidance in the US still recommends flushing a select list of drugs. As of June 2010, this list comprised 27 drugs, all of which are commonly abused or that pose inordinate risks of poisoning, and therefore are hazardous if disposed into trash; they primarily contain the active ingredients fentanyl, hydromorphone, meperidine, methadone, morphine, and oxycodone (USFDA 2009). Some of these drugs (especially fentanyl) are formulated in delivery devices such as transdermal patches. After these devices have been expended, a significant portion of the active ingredient remains. These devices often contain large amounts of active ingredient. A used drug device can contribute quantities of the active

ingredient that would exceed the amount that would otherwise be excreted after oral dosage. This is explained in Daughton and Ruhoy (2009).

## 8  Illicit Drugs and Environmental Impact

With the exception of the immediate and overt and hidden environmental impacts from clan labs, little is known about the potential actions of illicit drugs in the environment.

### 8.1  Fate and Transport

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 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.

In two studies, the sorption of illicit drugs to sediments was reported (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 possibly negligible.

### 8.2  Ecotoxicology

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. Aquatic exposures are the primary focus.

To date, bioconcentration data for drugs of abuse have been reported in two studies. Diazepam is one of the only drugs with substantial illicit usage whose presence has been targeted in aquatic tissues. Diazepam was measured in all 10 fish liver samples from turbot at wet-weight concentrations ranging from 23 to 110 ng/g (Kwon et al. 2009). And showing that its illicit use extends beyond humans, diazepam is commonly detected in wastewaters from slaughterhouses (in China), albeit at low levels up to 16 ng/L (Shao et al. 2009). Tramadol has been reported in the plasma of fish (up to 1.9 ng/g) exposed to treated sewage effluent (Fick et al. 2010).

The potential for effects from low-level exposure of fish is further complicated by the complexities in extrapolating across species. Data from the first in-depth study of an ectotherm with any analgesic (i.e., morphine) comport with extreme variability between species (Newby et al. 2006).

Gagne et al. (2006) report some nominal effects data from morphine in mussels. Scott et al. (2003) report on the absence of adverse effects on soil microbial enzyme activity by six substances used in amphetamine synthesis, including P2P (phenyl-2-propanone), ephedrine, methamphetamine, and 3,4-methylenedioxybenzaldehyde.

Pharmacological studies targeted at biological endpoints at ultra-low doses have relevance to the potential for both human and ecological effects from exposure to ambient residues in the environment, especially drinking water. Some of the pioneering studies relevant to ultra-low doses were conducted in the early 1990s and showed that biological effects could be obtained at doses many orders of magnitude lower than therapeutic doses; one example is the work of Crain and Shen (1995) who reported on the nociception in mice treated with doses as low as the femtomolar range. The subject of ultra-low dose effects has been discussed with respect to exposure to pharmaceuticals in drinking water (Daughton 2010 - in press-a).

**9  The future**

Future work to address 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 2009b). 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 should include both environmental occurrence data and data of absence (covering compartments such as sewage influent and effluent, sludge/biosolids, surface water, groundwater, and drinking water, air, wildlife tissues, and money), ecotoxicology (both field and controlled exposures), and especially data generated from FEUDS studies; metadata such as GIS, sampling and analytical methodologies, quality assurance, detection limits, and measures of range or variance are essential.

## 9.1 Advancing the Utility of FEUDS

Advancement of FEUDS as a topic of research as well as a population-level 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 FEUDS back-calculations for gauging collective drug usage. Needed are standardized methodologies with better understood and controlled sources of error. The methodologies currently used for analysis of environmental samples for illicit drug ingredients span a wide range; this can be readily seen just for amphetamine and methamphetamine (e.g., see: Boles and Wells 2010). Standardized methods are especially important for facilitating more meaningful inter-comparison of FEUDS data. Data from FEUDS studies also need to be assessed more rigorously against more comprehensive user surveys to better understand the accuracy and value of both approaches.

For FEUDS to succeed in gauging illicit drug usage for epidemiologic or forensic purposes, one variable in particular needs to be better understood - the pharmacokinetics (PK) of each drug, especially as it pertains to the excretion of unchanged parent drug and metabolites (especially

conjugates); the importance of thoroughly understanding PK and conjugate excretion has been covered in Daughton and Ruhoy (2009). PK parameters are key to accurate dose reconstruction. Although excretion rates for many pharmaceuticals are not well defined, even less is known about the PK of illicit drugs. PK and its poorly defined variation among a population contributes great uncertainty to the back-calculations used with FEUDS. Many factors contribute to the broad range of expression in population PK; genetic variability (such as single nucleotide polymorphisms) can even lead to interoccasion variability for the individual – partly as a function of environmental influences and physiological rhythms. The role of pharmacokinetics and environmental influence on drug metabolism is discussed in Daughton and Ruhoy (2010).

A comprehensive sensitivity analysis (which has yet to be performed) could possibly reveal that small changes in variables such as excretion rates (especially for extensively metabolized drugs) can lead to large errors in FEUDS 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 two 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 contribute 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 potential ways to reduce errors in FEUDS calculations could be viewed as analogous to using internal-correction methods such as internal standardization and isotope dilution. 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 for 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 prescription 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 profile 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, additional uncertainty could possibly be removed from the calibration factor. An example of a substance that might prove useful as a calibrant could be a metabolically refractory pharmaceutical such as iopromide – a widely used x-ray contrast agent with ubiquitous presence in sewage and natural waters.  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.

The second front for improving the utility of FEUDS would be to expand its scope 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 prescription 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. (2009b; see Table 7 therein), in which calculated usage rates for more than 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 prescription data are 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) (Ekedahl and Lindberg 2005). 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 consumer medications (see: Glassmeyer et al. 2009).

An important aspect of FEUDS is that it has set the foundation for the use of sewage monitoring 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 (discussed below).

## 9.2 Real-time Monitoring of Community-wide Health and Disease: Using Sewage Information-mining (SIM)

Within sewage is hidden a wealth of highly complex but chaotic chemical information about myriad aspects of biological processes. In the last 5 yr, we have witnessed probably only the beginning of the applications for which sewage data could prove useful - namely FEUDS. Possibly first noted in 2008, Zuccato et al. (2008b) briefly mentioned that monitoring sewage "has the potential to extract useful epidemiologic data from qualitative and quantitative profiling of biological indicators entering the sewage system."

Perhaps the most important information contained in sewage resides with the countless biomarkers - substances that could serve as collective measures of community-wide health or disease. Biomarkers could serve as composite measures of exposure, stress, vulnerability to disease or overt disease, or health. Biomarkers include endogenous biochemicals produced in response to stress or indicative of health; they also include adducts of endogenous chemicals and xenobiotics. And of course, they include metabolites of significant detoxication or intoxication processes from xenobiotic exposure. Suitable markers could not have pharmaceutical equivalents, which would add great complexity to the modeling process because of the need to distinguish natural from anthropogenic sources; an example of an endogenous biomarker that has exogenous pharmacological use is cortisol (hydrocortisone).

As community-wide measures of health or disease status, a new discipline of SIM could provide, for the first time, the ability to gauge collective population-wide health and disease in real-time.

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SIM would constitute the first true application of sewage chemistry to epidemiology, and provide a means for conducting epidemiology in near-real time. SIM could also create the opportunity to view communities from a new perspective - "communities as the patient" - perhaps eventually leading to the paradigm of combining human and ecological communities as a single patient – as an interconnected whole. SIM could greatly expand our limited abilities for examining associations between human health and a host of environmental variables and stressors. It could hold the potential for greatly reducing the time and expense involved with establishing linkages between human disease and any stress imposed by the environment - or for gauging the effectiveness of new health-care measures. SIM could prove invaluable in more efficiently informing and targeting limited healthcare resources. Illicit drugs have certainly provided insights for new ways to monitor the health of entire populations.

## 10  Summary

The published literature that addresses the many facets of pharmaceutical ingredients as environmental contaminants has grown exponentially since the 1990s. Although there are several thousand active ingredients used in medical pharmaceuticals worldwide, illicit drug ingredients (IDIs) have generally been excluded from consideration. Medicinal and illicit drugs have been treated separately in environmental research even though they pose many of the same concerns regarding the potential for both human and ecological exposure. The overview presented here covers the state of knowledge up until mid-2010 regarding the origin, occurrence, fate, and potential for biological effects of IDIs in the environment.

Similarities exist with medical pharmaceuticals, particularly with regard to the basic processes by which these ingredients enter the environment - excretion of unmetabolized residues (including via sweat), bathing, disposal, and manufacturing. The features of illicit drugs that distinguish them from medical pharmaceuticals are discussed. Demarcations between the two are not always clear, and a certain degree of overlap adds additional confusion as to what exactly defines an illicit drug; indeed, medical pharmaceuticals diverted from the legal market or used for non-medicinal purposes are also captured in discussions of illicit drugs. Also needing consideration as part of the universe of IDIs are the numerous adulterants and synthesis

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impurities often encountered in these very impure preparations. Many of these extraneous chemicals have high biological activity themselves.

In contrast to medical pharmaceuticals, comparatively little is known about the fate and effects of IDIs in the environment. Environmental surveys for IDIs have revealed their presence in sewage wastewaters, raw sewage sludge and processed sludge (biosolids), and drinking water. Nearly nothing is known, however, regarding wildlife exposure to IDIs, especially aquatic exposure such as indicated by bioconcentration in tissues. In contrast to pharmaceuticals, chemical monitoring surveys have revealed the presence of certain IDIs in air and monetary currencies - the latter being of interest for the forensic tracking of money used in drug trafficking. Another unknown with regard to IDIs is the accuracy of current knowledge regarding the complete scope of chemical identities of the numerous types of IDIs in actual use (particularly some of the continually evolving designer drugs new to forensic chemistry) as well as the total quantities being trafficked, consumed, or disposed.

The major aspect unique to the study of IDIs in the environment is making use of their presence in the environment as a tool to obtain better estimates of the collective usage of illicit drugs across entire communities. First proposed in 2001, but under investigation with field applications only since 2005, this new modeling approach for estimating drug usage by monitoring the concentrations of IDIs (or certain unique metabolites) in untreated sewage has potential as an additional source of data to augment or corroborate the information-collection ability of conventional written and oral surveys of drug-user populations. This still-evolving monitoring tool has been called "sewer epidemiology" but is referred to in this overview by a more descriptive proposed term "FEUDS" (Forensic Epidemiology Using Drugs in Sewage). The major limitation of FEUDS surrounds the variables involved at various steps performed in FEUDS calculations. These variables are summarized and span sampling and chemical analysis to the final numeric calculations, which particularly require a better understanding of IDI pharmacokinetics than currently exists. Although little examined in the literature, the potential for abuse of FEUDS as a tool in law enforcement is briefly discussed.

Finally, the growing interest in FEUDS as a methodological approach for estimating collective public usage of illicit drugs points to the feasibility of mining other types of chemical information from sewage. On the horizon is the potential for "sewage information mining" (SIM) as a general approach for measuring a nearly limitless array of biochemical markers that could serve as collective indicators of the specific or general status of public health or disease at the community-wide level. SIM might create the opportunity to view communities from a new perspective - "communities as the patient." This could potentially lead to the paradigm of combining human and ecological communities as a single patient – as an interconnected whole.

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# TABLES

1. Chronology of Some Selected Seminal Publications Regarding Illicit Drugs in the Environment
2. Adulterants and Impurities in Illicit Drugs (a very small sampling)
3. Drugs of Abuse Frequently Detected by US Forensics Laboratories
4. Drugs of abuse targeted and identified in environmental compartments
5. Major FEUDS Studies (arranged roughly according to chronology)

# FIGURE

Illicit Drugs in the Environment (relative significance of routes indicated by intensity of lines).

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**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 2001c) |
| 2002 | WW | morphine, methamphetamine, and methadone in sewage | (Khan 2002) |
| 2004 | WW, monit | 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) |
| 2004 | M | THC, cannabinol, and cannabidiol on banknotes from US and other countries | (Lavins et al. 2004) |

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| 2005 | WW | morphine and methamphetamine is sewage sludge and WWTP influent; methadone and morphine in aqueous phase of digested sludge | (Khan and Ongerth 2005) |
|---|---|---|---|
| 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 implementation of "sewage epidemiology" to reconstruct community-wide drug usage* | (Zuccato et al. 2005) |
| 2005 | M | diacetylmorphine on banknotes | (Ebejer 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 (3,4-methylenedioxyamphetamine), MDEA (3,4-methylenedioxy-N-ethylamphetamine), EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine), 11-nor-9-carboxy-9-THC | (Castiglioni et al. 2006) |
| 2006 | WW | codeine, dihydrocodeine, hydrocodone, oxycodone, tramadol in WWTP influents and effluents, and surface water | (Hummel 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, monit | *first nationwide monitoring in the US of illicit drugs in sewage*; study by the Office of National Drug Control Policy (ONDCP) targeted about 100 WWTPs across two dozen regions in the US (results never published) | see: (Bohannon 2007) |

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| 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 | WW | norcodeine, THC, THC-COOH in WWTP influents and effluents and surface water | (Boleda et al. 2007) |
| 2007 | M | BZE and heroin on banknotes | (Bones et al. 2007a) |
| 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 | WW | methadone, EDDP, and cocaethylene in surface waters | (Zuccato et al. 2008a) |
| 2008 | WW | cocaethylene, LSD (and nor-LSD and 2-oxo-3-hydroxy-LSD), heroin, Δ9-THC (and 11-hydroxy-THC and nor-THC), (R,R)(-)-pseudoephedrine and (1S,2R)(+)-ephedrine hydrochloride in WWTP influents and effluents | (Postigo et al. 2008a) |
| 2008 | F, monit | weekly temporal wastewater fluctuations in various drug classes | (Zuccato 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 2001c)* | (Chiaia et al. 2008) |
| 2008 | WW, monit | 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. 2009a; Postigo et al. 2008b; 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. 2008b; 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) |

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| 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 | ecgonine methyl ester (EME) in WWTP influents; EME possibly in surface water | (van Nuijs et al. 2009c; Vazquez-Roig et al. 2010) |
| 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 | monit | *first geographic spatial survey*s; 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 | $\Delta$9-tetrahydrocannabinol, cannabidiol, and cannabinol identified in ambient air particulates | (Balducci et al. 2009) |
| 2009 | A, monit | *first quantitative study of cocaine in ambient air across several continents* | (Cecinato et al. 2009a) |
| 2009 | WW | cannabinoids in surface waters | (Boleda et al. 2009) |

| 2009 | WW | nor-LSD, O-H-LSD, THC-COOH, OH-THC identified in surface waters (river) | (Postigo et al. 2010) |
|------|-----|-----|-----|
| 2010 | A | *first use of existing air quality monitoring sites for detection of multiple drugs of abuse*; including amphetamines, cannabinoids, cocainics, lysergics, and opioids (Spain) | (Viana et al. 2010) |
| 2010 | WW | *first enantiomeric speciation analysis of illicit drugs in wastewater*; including amphetamines, ephedrines, and venlafaxine | (Kasprzyk-Hordern et al. 2010) |
| 2010 | WW | *first identification of buprenorphine in sewage*, with concentrations ranging up to 20 ng/L in WWTP influents (France) | (Karolak et al. 2010 - in press) |
| 2010 | WW | *first survey of wastewaters from US pharmaceutical manufacturing facilities* reveals relatively high levels (sub-mg/L) of a range of drugs of abuse: butalbital, carisoprodol, methadone, and oxycodone | (Phillips et al. 2010 - in press) |
| 2010 | WW | *comprehensive review of FEUDS* | (van Nuijs et al. 2010 - in press) |

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

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## Table 2  Adulterants and impurities in illicit drugs (a very small sampling)

**Cocaine**

α- and ß-truxillines (probably photodimers of cinnamoyl cocaines)

3,4,5-trimethoxycocaine

benzoyl pseudotropine

benzoyltropine

*cis*- and *trans*-cinnamoyl ecgonine (hydrolysis of *cis*- and *trans*-cinnamoyl cocaine)

*cis*- and *trans*-cinnamoyl cocaine (aka methylecgonine cinnamate) (up to 5% by weight)

cuscohygrine (pyrrolidine alkaloid in coca)

diastereomers of synthetic cocaine (pseudococaine, allococaine, allopseudococaine, d-enantiomer of cocaine)

diltiazem (adulterant)

ecgonine methyl ester (hydrolysis of cocaine)

ecgonine (hydrolysis of cocaine)

hydroxytropacocaine

methylecgonine

*N*-formyl-cocaine

norcocaine

tropacaine

phenacetin (up to 50% by weight) (adulterant)

xylazine (adulterant)

hydroxyzine (adulterant)

hygrine (pyrrolidine alkaloid in coca)

levamisole (up to 4% by weight) (adulterant)

lidocaine (adulterant)

**MDMA (ecstasy: 3,4-methylenedioxy-methamphetamine)**

1-(3,4-methylenedioxy)phenylpropanol-2

1-(1,2-dimethyl-1-azacyclopropyl)methyl-3,4-methylenedioxybenzene

1,2-(methylenedioxy)-4-methylbenzene

1,2-(methylenedioxy)-4-(2-*N*-methyliminopropyl)benzene

1,2-(methylenedioxy)-4-propylbenzene

1,2-dimethoxy-4-propenylbenzene

3,4-methylenedioxyphenyl-2-propanol (MDP)

3,4-methylenedioxy-phenyl-2-propanone (MDP2P)

3,4-methylenedioxy-amphetamine (MDA)

3,4-methylenedioxy-*N*-methylbenzylamine (MDB)

3,4-(methylenedioxy)benzaldehyde

4-methoxy-*N* -dimethyl-benzeneethanamine

4-methyl-5-phenyl pyrimidine

dextromethorphan (adulterant)

dimenhydrinate (adulterant)

isosafrole

safrole

*N*-formyl-3,4-methylenedioxymethamphetamine (*N*-formyl-MDMA)

*N*-formyl-amphetamine

*N*-formyl-methamphetamine

*N*-ethyl-3,4-MDA (MDEA)

*N,N*-dimethyl-MDA

*N*-ethyl-*N*-methyl-(1,2-methylenedioxy)-4-(2-aminopropyl)benzene

*N,N*-dimethyl-(1,2-methylenedioxy)-4-(2-aminopropyl)benzene

piperonal

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**Methamphetamine**

1-benzyl-3-methylnaphthalene

1,2-dimethyl-3-phenylaziridine

1,3-dimethyl-2-phenylnaphthalene

3,4-dimethyl-5-phenyloxazolidine

*cis*-1,2-dimethyl-3-phenylaziridine

*cis*-3,4-dimethyl-5-phenyl-2-oxazolidone

dimethyl amphetamine

dimethylsulfone (adulterant)

*N*-benzyl amphetamine

*N*-acetyl methamphetamine

*N*-methyl ephedrine

*N*-methyl pseudoephedrine

*N*-acetyl methamphetamine

*N*-ethyl methamphetamine

*N*-formyl amphetamine

*N*-acetyl ephedrine

*N*-ethyl amphetamine

*N*-formyl methamphetamine

*N,N*-dimethyl amphetamine

*p*-bromotoulene

phenyl-2-propanone (P2P)

**Heroin**

(Z)-*N*-acetylanhydronornarceine

6-acetylmorphine

3-*O*,6-*O*,*N*-triacetylmorphine

3,6-dimethoxy-4,5-epoxyphenanthrene

4-*O*-acetylthebaol

4,6-diacetoxy-3-methoxyphenanthrene

4-*O*-thebaol

6-*O*,*N*-diacetylnorcodeine

(E)-*N*-acetylanhydronornarceine

acetylcodeine

meconine

clenbuterol (adulterant)

*N*-acetylnorlaudanosine

*N*-acetylnornarcotine

noscapine (up to 60% by weight)

papaverine (up to 20% by weight)

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [during synthesis of 1-methyl-4-propionoxypyridine (MPPP), an analog of meperidine]

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## Table 3  Drugs of abuse frequently detected by US forensics laboratories[a]

**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

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

# Table 4 Drugs of abuse targeted and identified in environmental compartments[a]

| | Waste-waters | surface waters | drinking water | sewage sludge | biosolids | air | banknotes | wildlife tissue | dermal transfer [b] |
|---|---|---|---|---|---|---|---|---|---|
| *Analgesics* | | | | | | | | | |
| 6-AM (6-acetylmorphine; deacetylated heroin) | ×✓ | ×✓ | × | | | | ✓ | | ▲ |
| 6-AC (6-acetylcodeine) | | × | | | | | | | |
| codeine** | ✓✓✓ | ✓✓ | ××✓ | | | | × | | ▲ |
| dihydrocodeine* | ✓ | ✓ | | | | | | | |
| heroin (diacetylmorphine)** | ××✓ | × | × | | | ✓ | ✓✓ | | ▲ |
| hydrocodone** | ✓✓ | ×✓ | | | | | | | |
| morphine** | ✓✓✓ | ✓ | × | ✓✓ | | × | ✓ | | ▲ |
| morphine-3ß-D-glucuronide | ×✓ | × | | | | | | | |
| norcodeine | ✓ | ✓ | ××✓ | | | | | | |
| normorphine | ✓ | × | × | | | | | | |
| fentanyl* (excreted mainly as norfentanyl) | ×× | ×× | × | | | | | | ▲ ‡ |
| norfentanyl | × | | | | | | | | |
| oxycodone** | ✓✓ | | | | | | | | |
| tramadol* | | ✓ | | | | | | ✓ | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Methadone*** | | | | | | | | | | |
| methadone** | ✓✓✓ | ✓ | ✓✓ | ✓✓✓ | | × | | | | ▲ |
| EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine) | ✓✓✓ | ✓✓ | ✓✓ | | | | | | | |
| ***Stimulants*** | | | | | | | | | | |
| amphetamine** | ✓✓ | ×✓ | ××✓ | ✓✓ | | ×✓ | ✓ | | | ▲ |
| ephedrine*/pseudo-ephedrine** | ✓✓✓ | ✓ | | | | × | | | | |
| methamphetamine** | ✓✓✓ | ✓ | ××✓ | | ✓ | ×✓ | ✓ | | | ▲ |
| MDA** | ✓ | ×✓ | ××✓ | | | | | | | |
| MDBD | × | | | | | | | | | |
| MDEA* | ×✓ | × | | | | | | | | |
| MDMA** | ✓✓ | ✓ | ✓ | | | ×✓ | | | | ▲ |
| methylphenidate** | | | | | | | | | | ‡ |
| ***Cocainics*** | | | | | | | | | | |
| benzoylecgonine (BZE) | ✓✓✓ | ✓ | ✓ | | | ✓ | ✓ | | | ▲ |
| cocaethylene | ×✓ | ✓ | | | | × | | | | |
| cocaine** | ✓✓ | ✓ | ×✓ | | | ✓✓ | ✓✓✓ | | | ▲ |
| ecgonine methyl ester (EME) | ×✓✓ | | | | | | | | | ▲ |
| norbenzoylecgonine | ✓ | ✓ | | | | | | | | |
| norcocaine | ×✓ | ✓ | | | | | | | | |

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| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ***"Club" Drugs*** (e.g., Dissociative Anesthetics) | | | | | | | | | |
| ketamine* | ××✔ | × | × | | | | | | |
| norketamine | × | | | | | | | | |
| PCP (phencyclidine)** | ×✔ | × | × | | | | ✔ | | |
| ***Hallucinogens*** | | | | | | | | | |
| LSD | ××✔ | × | × | | | × | | | |
| Nor-LSD (*N*-demethyl-LSD) | ×✔ | ××✔ | | | | × | | | |
| O-H-LSD (2-oxo-3-hydroxy-LSD) | ×✔ | ××✔ | | | | × | | | |
| ***Cannabinoids*** | | | | | | | | | |
| cannabinol (CNB) | | | | | | ✔✔ | ×✔ | | |
| cannabidiol (CND) | | | | | | ×✔ | ×✔ | | |
| OH-THC (11-hydroxy-Δ9-tetrahydrocannabinol) | ×✔ | ××✔ | | | | × | | | |
| nor-THC | ✔ | | | | | × | | | |
| THC (Δ9-tetrahydro cannabinol)** | ✔✔ | ✔✔ | × | | | ✔✔ | ×✔ | | ▲ |
| THC-COOH (11-nor-carboxy- Δ9-tetrahydro cannabinol) | ✔✔✔ | ✔✔ | × | | | | | | |
| ***Other*** | | | | | | | | | |
| flunitrazepam* | × | | | | | | | | |
| testosterone | | | | | | | | | ‡ |

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a The references providing the data for this table are listed below for each of the columns. Wastewaters include both raw sewage influent and treated sewage effluent. Note that this table does not include drugs or metabolites that have never been targeted in monitoring studies; p-hydroxymethamphetamine is one example.

b Potential for transfer from skin to surroundings (Daughton and Ruhoy 2009): ▲ = known to be excreted via sweat; ‡ = available in high-concentration dermal transfer devices.

"×": frequency of negative occurrence data (data of absence); supporting data are stronger with more "×" (up to two total).
✓: frequency of positive occurrence data; supporting data are stronger with more "✓" (up to three total).
grayed-out cells denote lack of any type of supporting data (absence of data)

** 15 of top 25 most frequently identified non-medically used, controlled substances - as analyzed and reported by US local and state forensic laboratories in 2008 (see: USDEA 2008) and which comprised 90% of all drugs identified (USDEA 2008).

* among the other most frequently identified non-medically used, controlled substances - as analyzed and reported by US local and state forensic laboratories in 2008 (see: USDEA 2008); the other nine most frequently identified 25 drugs, but not yet targeted in more than a single environmental study focused expressly on illicit drugs are: alprazolam, buprenorphine, BZP (1-benzylpiperazine), carisoprodol, clonazepam, diazepam, hydromorphone, lorazepam, and psilocin.

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## Table 4 *(con't)*: Supporting References

**wastewaters**

(Bartelt-Hunt et al. 2009; Bijlsma et al. 2009; Boleda et al. 2007; 2009; Bones et al. 2007b; Castiglioni et al. 2006; Castiglioni et al. 2007; Chiaia et al. 2008; Frost and Griffiths 2008; Gheorghe et al. 2008; González-Mariño et al. 2009; González-Mariño et al. 2010; Huerta-Fontela et al. 2007; Huerta-Fontela et al. 2008a; Huerta-Fontela et al. 2008b; Hummel et al. 2006; Jones-Lepp et al. 2004; Karolak et al. 2010 - in press; Kasprzyk-Hordern et al. 2007; Kasprzyk-Hordern et al. 2008a; b; 2009a; Kasprzyk-Hordern et al. 2010; Khan 2002; Loganathan et al. 2009; Mari et al. 2009; Postigo et al. 2008a; Postigo et al. 2010; Terzic et al. 2010 - in  press; van Nuijs et al. 2009c; Zuccato et al. 2005; Zuccato et al. 2008b)

**surface waters**

(Bartelt-Hunt et al. 2009; Bijlsma et al. 2009; Boleda et al. 2007; 2009; Bones et al. 2007b; Gheorghe et al. 2008; González-Mariño et al. 2010; Huerta-Fontela et al. 2007; Huerta-Fontela et al. 2008b; Kasprzyk-Hordern et al. 2007; Kasprzyk-Hordern et al. 2008b; Postigo et al. 2010; Zuccato et al. 2005; Zuccato et al. 2008a)

**drinking water**

(Boleda et al. 2009; Huerta-Fontela et al. 2008b)

**sewage sludge**

(Kaleta et al. 2006; Khan 2002)

**biosolids**

(Jones-Lepp and Stevens 2007)

**air**

(Balducci et al. 2009; Cecinato and Balducci 2007; Cecinato et al. 2009a; Cecinato et al. 2009b; Cecinato et al. 2010; Hannigan et al. 1998; Postigo et al. 2009; Viana et al. 2010)

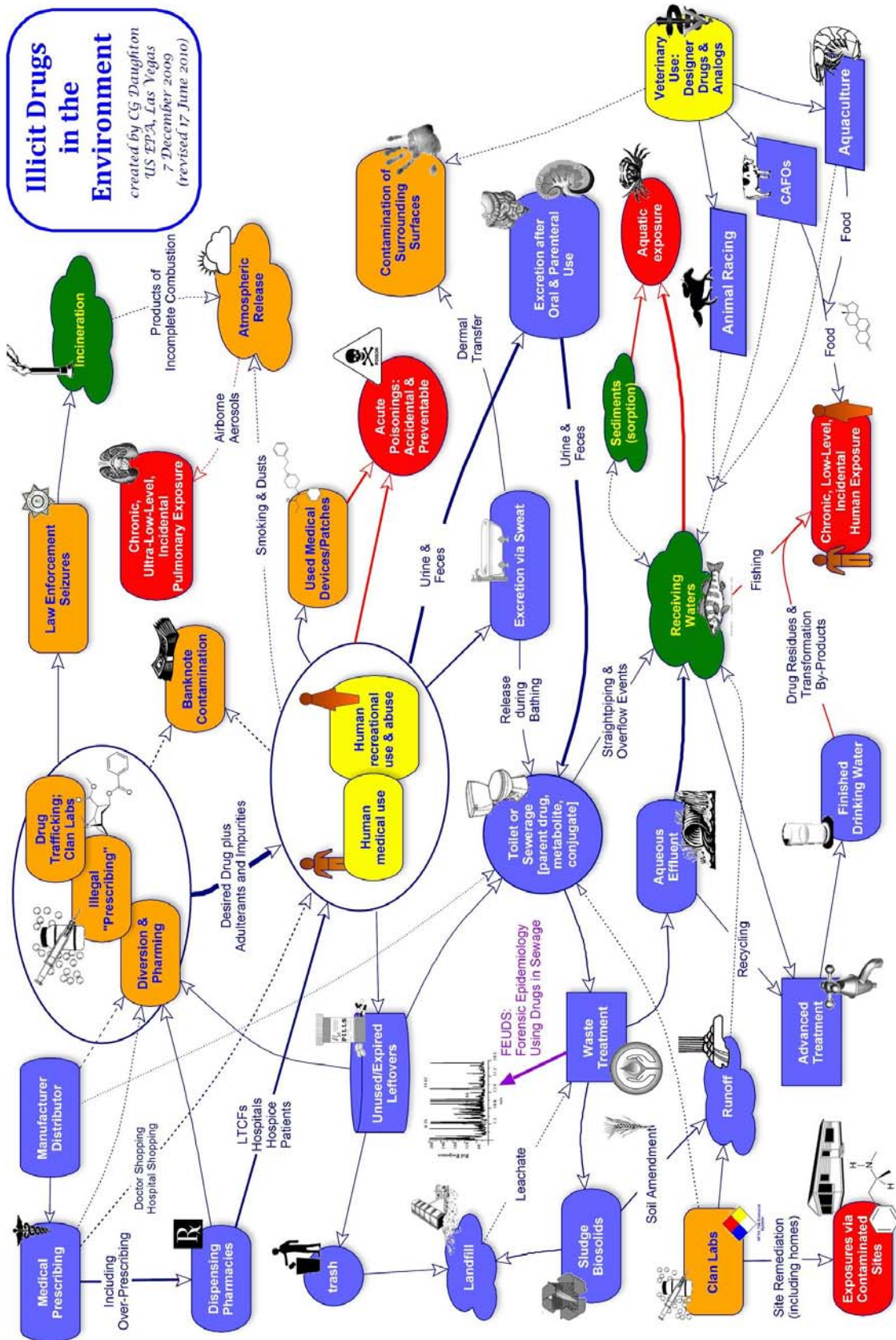**banknotes** (small sampling of published works)

(Aaron and Lewis 1987; Armenta and de la Guardia 2008; Bones et al. 2007a; Carter et al. 2003; Ebejer et al. 2005; Ebejer et al. 2007; Felix et al. 2008; Jenkins 2001; Lavins et al. 2004; Sleeman et al. 2000; Zuo et al. 2008)

## Table 5  Major FEUDS studies (arranged according to chronology)

| Year | Title (citation) |
|---|---|
| 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 2001c) |
| | Commentary on Illicit Drugs in the Environment: A Tool for Public Education - Societal Drug Abuse and Its Aiding of Terrorism (Daughton 2001d) |
| 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. 2007b) |
| 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) |
| | Assessing illicit drugs in wastewater: Potential and limitations of a new monitoring approach (Frost and Griffiths 2008) |
| 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. 2009b) |
| | |
| | Municipal sewage as a source of current information on psychoactive substances used in urban communities (Wiergowski et al. 2009) |
| | 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) |
| **2010** | |
| | 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) |
| | Estimation of illicit drugs consumption by wastewater analysis in Paris area (France) (Karolak et al. 2010 - in press) |
| | Illicit drugs in wastewater of the city of Zagreb (Croatia) - Estimation of drug abuse in a transition country (Terzic et al. 2010 - in press) |
| | Illicit drug consumption estimations derived from wastewater analysis: A critical review (van Nuijs et al. 2010 - in press) |

# Illicit Drugs in the Environment

created by CG Daughton
US EPA, Las Vegas
7 December 2009
(revised 17 June 2010)

Veterinary Use: Designer Drugs & Analogs

Aquaculture

CAFOs

Animal Racing

Aquatic exposure

Sediments (sorption)

Receiving Waters

Fishing

Chronic, Low-Level, Incidental Human Exposure

Food

Food

Drug Residues & Transformation By-Products

Finished Drinking Water

Advanced Treatment

Recycling

Runoff

Waste Treatment

FEUDS: Forensic Epidemiology Using Drugs in Sewage

Soil Amendment

Leachate

Sludge Biosolids

Landfill

trash

Clan Labs

Site Remediation (including homes)

Exposures via Contaminated Sites

Aqueous Effluent

Straightpiping & Overflow Events

Toilet or Sewerage [parent drug, metabolite, conjugate]

Release during Bathing

Excretion via Sweat

Urine & Feces

Urine & Feces

Excretion after Oral & Parenteral Use

Dermal Transfer

Contamination of Surrounding Surfaces

Human recreational use & abuse

Human medical use

Desired Drug plus Adulterants and Impurities

Unused/Expired Leftovers

LTCFs Hospitals Hospice Patients

Doctor Shopping Hospital Shopping

Including Over-Prescribing

Medical Prescribing

Dispensing Pharmacies

Manufacturer Distributor

Drug Trafficking; Clan Labs

Illegal "Prescribing"

Diversion & Pharming

Banknote Contamination

Law Enforcement Seizures

Used Medical Devices/Patches

Acute Poisonings: Accidental & Preventable

Smoking & Dusts

Chronic, Ultra-Low-Level, Incidental Pulmonary Exposure

Airborne Aerosols

Atmospheric Release

Products of Incomplete Combustion

Incineration

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