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Types and Quantities of Leftover Drugs Entering the Environment via Disposal to Sewage – Revealed by Coroner Records

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ABSTRACT

Pharmaceuticals designed for humans and animals often remain unused for a variety of reasons, ranging from expiration to a patient's non-compliance. These leftover, accumulated drugs represent suboptimal delivery of health care and the potential for environmentally unsound disposal, which can pose exposure risks for humans and wildlife. A major unknown with respect to drugs as pollutants is what fractions of drug residues occurring in the ambient environment result from discarding leftover drugs. To gauge the significance of leftover drugs as potential pollutants, data are needed on the types, quantities, and frequencies with which drugs accumulate. Absence of this data has prevented assessments of the significance of drug accumulation and disposal as a contributing source of drug residues in the environment. One particular source of drug accumulation is those drugs that become "orphaned" by the death of a consumer. A new approach to acquiring the data needed to assess the magnitude and extent of drug disposal as a source of environmental pollution is presented by using the inventories of drugs maintained by coroner offices. The data from one metropolitan coroner's office demonstrates proof of concept. Coroner data on leftover drugs are useful for measuring the types and amounts of drugs accumulated by consumers. This inventory also provides an accurate measure of the individual active ingredients actually disposed into sewage by coroners. The types of questions these data can address are presented, and the possible uses of these data for deriving estimates of source contributions from the population at large are discussed. The approach is proposed for nationwide implementation (and automation) to better understand the significance of consumer disposal of medications.

Keywords: Coroner; disposal; pharmaceuticals; patient compliance; environmental pollution; sewage

Introduction

Understanding the scope and magnitude of medication disposal is required for providing: (1) more accurate and comprehensive data for models used for predicting amounts or concentrations of active pharmaceutical ingredients (APIs) introduced to the environment, and (2) a better understanding of the prescribing, dispensing, and consumer consumption practices that lead to the accumulation of leftover (unwanted or unneeded) drugs and which then contribute to human morbidity and mortality via poisonings (Watson et al., 2005). There are two major reasons that leftover drugs are not immediately disposed: (1) inadvertent household accumulation (resulting from drugs languishing unnoticed past their expiry), and (2) purposeful stockpiling (because the consumer is awaiting a satisfactory means for disposal) (see Figure 1).

This paper introduces a methodology for collecting data to provide evidence-based estimates on the types and quantities of APIs disposed to the environment. Coroner offices in many locales maintain detailed inventories of medications remaining at sites visited for investigation and acquisition of decedents. These drug stockpiles can serve as a means of obtaining maximum and minimum ranges on the quantities and types of drugs that might have ordinarily been disposed by this subpopulation. These inventories also become an accurate record of the types and quantities of APIs that are actually disposed by coroner offices. This is the first time that an extensive dataset of disposed drugs has ever been compiled for a well-defined population whose sewage is known to be handled by particular sewage treatment facilities. Such a dataset should permit calculations of average (or minimum) concentrations of APIs introduced via sewage. We propose this as a general approach that can be widely implemented. The types of data collected using this new approach are useful for quantifying or estimating source contributions of pharmaceuticals introduced to the environment and which subsequently could play roles in ecological as well as human exposure, via the natural or artificial recycling of water.

Residues of a wide array of pharmaceuticals are known to occur as contaminants in the environment (Daughton and Ternes, 1999; Halling-Sorensen et al., 1998; Kolpin et al., 2002). A major research gap continues to be an understanding of the relative contributions to these ambient residues resulting from their intended use (such as from excretion and bathing) versus the direct disposal of unwanted, leftover medications. The significance of contributions from direct disposal compared with excretion remains controversial, largely because there have been no easy means of determining the quantities of medications that are directly disposed, for example to sewage or trash.

The topic of pharmaceuticals as environmental pollutants continues to foster increasing discussion and debate. Various groups, including regulatory agencies, independent organizations, water

utilities, and public advocacy groups, have placed high priority on determining whether the existence of APIs in the environment, albeit at low concentrations, pose exposure risks for humans or the environment (Fent et al., 2006). One of the outgrowths of this concern in the U.S. has been increasing interest from local and regional agencies in the implementation of programs designed to take back medications stockpiled by consumers, thereby obviating their disposal directly to the environment. Several states, cities, and counties have successfully implemented both single and recurring collection events for unwanted medications (IISG, 2007). The intention of these "take-back" programs has been to reduce the introduction of APIs to sewerage and trash, from where they can enter the environment as contaminants. The key unknown with these pollution prevention efforts, however, is whether they can significantly reduce the individual or overall loadings of APIs to the environment (Daughton, 2007).

An additional development is the recent federal guidelines for drug disposal. In an effort to combat the rising rates of prescription drug abuse, the White House Office of National Drug Control Policy (ONDCP, 2007) has established the first Federal guidelines for proper disposal of unused drugs. These guidelines, released in February 2007, direct consumers to adulterate unwanted medications by mixing with an unpalatable substance and then disposing into the household trash (except those few whose labels require disposal to sewage because of the acute risk of diversion resulting in human poisonings). While adulterating medications in this manner does not remove the API's potential to enter the natural environment, the intent of these recommendations is to prevent purposeful introduction of medications into sewage while also rendering them unpalatable for those who attempt to reclaim the drugs from the trash for inappropriate use. The guidelines also suggest returning leftover drugs to local "take-back" locations, when available. This demonstrates the Federal government's interest in reducing the availability of drugs to those who seek to misuse or abuse prescription medication, while also reducing environmental pollution.

Pharmaceuticals are ubiquitous compounds that have the ability to alter innate human physiological mechanisms. Studies of these compounds as they occur in the environment are unique in various ways. First, these compounds are often detected at such low concentrations (ng L^{-1}) that detection is usually limited to more recent, advanced analytical techniques employed at research laboratories (Daughton, 2007). Second, recent studies (e.g., Heberer, 2002; Radjenovic, 2006; Snyder et al., 2006) have indicated efficient and effective methods (e.g., ozone oxidation) of removing, if not all detectable amounts, a significant percentage of the more commonly studied APIs; note, however, that "removal" can refer to the structural transformation of the API or it can simply refer to the physical relocation or partitioning of the API from the aqueous phase to the solids (sludge) phase. It is important to note that most wastewater treatment plants (WWTPs) in the U.S. do not possess the resources required for the best available treatment technology. Third, the controversy remains over whether acute or chronic exposure to

pharmaceuticals in our water supply results in detectable human health effects. Finally, and with reference to the study presented here, while there have been a number of studies that have measured levels of APIs and their metabolites in wastewater, there has been no ready source of data that characterizes the types and masses of APIs disposed via flushing to sewage and whether these amounts are significant with respect to overall environmental loadings (Daughton 2007).

Chemical monitoring studies have provided evidence of the presence of drugs in the aquatic environment (e.g., Fent et al., 2006; Heberer, 2002; Hignite and Azarnoff, 1977; Hirsch et al., 1999), and less frequently in drinking waters, but the sources and their correlations with disposed quantities have proved difficult to determine. Coroner offices compile drug disposal data during the ordinary course of investigating and taking custody of the bodies of decedents. A survey of this inventory provides a snapshot and some insights as to the potential extent of unused pharmaceuticals and their disposal. The information gleaned from these under-recognized databases can help guide the identification of drugs to be monitored in the environment and better target where pollution-prevention or source-control efforts should be directed.

Often overlooked are other important possible outcomes from obtaining comprehensive data on leftover drugs and their disposal. Such data could foster the optimization of prescribing and dispensing practices within the healthcare communities, along with improving communication with patients to improve their adherence to medication regimes. These outcomes, by reducing leftover medications, would lessen the consequent need for disposal, and possibly improve healthcare outcomes (Daughton, 2003a). In the ideal world, perfectly functioning prescribing and dispensing systems, coupled with perfect medication adherence by the patient (while noting that one cause of non-adherence is unanticipated adverse effects), would lead to zero drug wastage and completely eliminate the need for disposal of leftovers. Although probably not a realistically achievable goal, any progress in this direction might also improve the quality of healthcare.

The presence of pharmaceuticals in our environment is by no means unexpected. Pharmaceuticals owe their accumulation in the environment to their universal and highly dispersed but cumulative usage by multitudes of individuals (Daughton, 2001). From 1993 to 2003, the number of prescriptions purchased in the U.S. increased 70% (from 2 billion to 3.4 billion) (Kaiser, 2004), while the population increased only 13% (from 257,782,608 to 290,796,023) (U.S. Census Bureau, 2006). The elderly consume an ever-increasing number of medications – some prescribed to counteract the effects and responses of other prescribed medications. At any given time, 40% of those older than 65 years use five or more drugs, and 50% of all adults in the US (greater than 18 years of age) take at least one prescription medicine (Kaufman et al., 2002). In 2005, among the 300 most frequently prescribed pharmaceuticals in the U.S., more than 2.5 billion prescriptions were written (RxList, 2007). Prescription rates for opioids,

benzodiazepines, diuretics, monoamine agonists, anti-infectives, and corticosteroids were the highest among all the medications prescribed.

Unused pharmaceuticals not only pose exposure risks for both the environment and humans, they also reflect lost opportunities for proper therapeutic treatment and wasted healthcare resources. In the U.S. alone, an estimated \$1B (US) of prescription drugs are discarded each year (Strom, 2005) from healthcare institutions such as hospitals, pharmacies, hospices, and long-term care facilities; figures for consumers do not exist. Although procedures are available in the healthcare sector (such as hospitals, pharmacies, hospices and long-term care facilities) for the proper disposal of unused pharmaceuticals, especially for the low percentage that are regulated as hazardous waste, generally these substances are simply disposed to drains (and sometimes to trash) or disposed along with regulated medical waste (Burke and Smith, 2006). These unwanted and unused drugs represent a costly wasted resource for the healthcare system and indicate the growing problem of what to do with unused and unwanted medications or how to minimize their creation. With regard to public health, this wasted resource may reflect inefficiencies in prescribing practices and may indicate sub-optimal delivery of healthcare, impairing or diminishing therapeutic outcomes. Unused, unwanted drugs in consumer homes inadvertently accumulate past expiry or are stockpiled (awaiting disposal) and are therefore available for those (including children) who seek to abuse them or who might ingest them accidentally (Figure 1). Unwanted drugs, moreover, represent a source from where a spectrum of biologically active anthropogenic chemicals can enter the environment. That human health and the health of the environment can be inextricably tied (Daughton, 2003b) is demonstrated perhaps in no better way than the fact that the non-optimum delivery of health care is, in part, a contributing source for pharmaceuticals in the environment, which in turn may play a role in affecting the environment and, therefore, quality of life.

Prior to the approach described here for mining coroner data, the only means available for obtaining inventories of drugs destined for disposal was from take-back events or from time-consuming, dirty physical investigation of municipal trash. Obtaining data from take-back events requires the efforts of a pharmacist (under the vigilance of law enforcement) to identify and record the identity of the medication, the dosage of the API(s), and the dosage units. These data are already meticulously collected during the course of coroner investigations, requiring no additional work.

Decedent populations could be biased in terms of age and health status, although many decedents are younger and probably represent the norm in terms of health and drug consumption. The drugs inventoried during coroner investigations could therefore possibly be biased in terms of the types of drugs or their formulations, and perhaps biased somewhat high in terms of the quantities on-hand (for those with declining health). In contrast, the drugs returned at local take-back events held on sporadic schedules

very possibly represent accumulations over long periods of time (where the consumer had accumulated a backlog of drugs for an entire household while waiting to eventually find out how they could be disposed). This means that the quantities of drugs initially received from a particular individual during a take-back event may be biased high - - not representing the amounts that would be returned if take-backs occurred on a continual basis; it is also very difficult to extrapolate to the general population. For the decedent population, the types and quantities of drugs on hand represent the types and amounts that would be found at any point in time for a decedent. For take-backs, however, the quantities of drugs returned cannot easily be used to calculate population accumulation rates because the quantities that any one individual returns could decline over time. Data would need to be collected over sufficiently long periods of time to obtain representative data.

It is important to note that coroner investigations do not select for inherently biased populations - - namely individuals who were necessarily purposefully saving unwanted drugs. Most decedents had probably been living lives unconnected to any focus on accumulating drugs. In contrast, the population attending take-back events is biased in terms of those who have purposefully been accumulating leftover drugs while waiting to figure out how to dispose of them.

Another consideration with respect to coroner data is the ability to collect more information regarding the individual, such as age, sex, patient non-compliance, illicit drugs (usually available from police investigation reports), and location of residence. Location is important should it be desired to estimate quantities of APIs that are introduced to sewage within a particular sewage district (in order to calculate concentrations or quantities entering a given WWTP). Compliance is extremely useful to know in order to better design approaches to pollution prevention, such as more vigilant and appropriate prescribing.

Attempts at identifying and quantifying the types and amounts of wasted drugs have often been inadequate in terms of accuracy, consistency, and breadth. Most of the information amassed has been from various one-time local take-back events. Data collection from these events has never been standardized, and there is no current consensus on the most efficient way to inventory the types and quantities of drugs received over the course of these events. Often reported are just the gross weight and/or volume of the complete, formulated medications, sometimes including the retail packaging (without note of actual API content), because identifying and measuring the types and amounts of drugs was labor intensive and frequently cost prohibitive. The Unused Medicine Registry (CRG Medical Foundation, 2006) was recently established by the Community of Competence organization in Bellaire, TX to collect information about drugs remaining in the home. The Registry is designed to collect information from community-based drug return programs (“take-backs”) on the medications received from consumers. While the Registry demonstrates some important trends in unused medication, the data

received are from a variety of events, many with different organizational structures and different methodologies used to collect the data. Another major limitation of data collected from take-backs is that the subpopulations of those who return their medications cannot be correlated with the WWTPs that receive their waste, making calculation of API masses introduced to known sewage flows inaccurate or impossible. Other methods of acquiring similar types of data generally focus on waste from institutions such as hospitals and long-term care facilities, which are not necessarily representative of the general population.

The methodology described here allows for the identification and quantification of the APIs actually disposed from a previously unrecognized but common source -- coroner offices. Comprehensive data on medications disposed within one metropolitan county for an entire year were compiled. These data provide for the first time some insights and measures regarding the contribution to ambient environmental residues of human drugs that result from disposal. If this type of data were to be collected on a nationwide basis, the means for improving the practices for prescribing and dispensing of drugs could eventually lead to minimization of the accumulation of leftover drugs. A major outcome of this new methodology would be an increased understanding of the scope of disposed pharmaceuticals. Such an understanding could lead to new approaches for reducing drug diversion, abuse, and accidental poisonings, as well for improving therapeutic outcomes at lower cost.

Background

It is considered standard protocol by most coroner offices in the U.S., as described by the National Association of Medical Examiners (NAME, 2007), that when a medical investigator from the coroner's office arrives upon the scene of a decedent, following the standard procedures regarding the approach to the body and the scene, the investigator will then search for medications present on the scene, in case drugs may have contributed to the cause of death. There are some cities, however, where law enforcement services are called to the scene rather than investigators from the coroner's office; in these cases, the coroner's office medical investigator plays no role in analyzing or removing anything from the scene and therefore does not have any role in the disposal of leftover medication -- they simply receive the expired body. There currently are no accessible statistics that describe how many cities primarily use law enforcement instead of coroner services, nor is the process of collecting and inventorying medications standardized among them. However, a survey is under preparation to effectively assess the prevalence of coroner offices that operate under these guidelines (Ruhoy, in preparation).

A death becomes a coroner's case when the decedent has either expired alone or the death is considered suspicious by law enforcement. The majority of the coroner cases are due to those deaths that occurred without a witness present. The investigator at the scene records the information found on the

medication vial or submits them to Poison Control Services for help in identification. This information includes the prescription number (as labeled by the dispensing pharmacy), the date the prescription was filled, the name of the medication (generic or brand name), the dosage, the directions for taking the medication as prescribed by the physician, the prescribed number of pills (which refers to both tablets and capsules but does not include powders, liquids or alternative drug delivery systems), and the name of the prescribing health care professional. The final and important piece of information recorded by the investigator is the number of pills remaining in the prescription vial. A facsimile of a typical coroners' site-investigation record is shown in Figure 2.

Following the collection of these data on an inventory sheet, the investigator then disposes of the remaining prescription pharmaceuticals. This is done most often via the toilets at the locations of the decedents and always done in the presence of a witness. Occasionally, the medications are disposed of in the garbage of the home, either because of faulty toilet systems or at the request of family. Disposal is manually recorded along with the signatures of the disposer (usually the investigator) and the witness (usually a family member or a local police officer). These factors all contribute to ensuring a high standard of quality for the collected data.

The medical investigators are “deputized” and, therefore, act as representatives of law enforcement. This is necessary due to US Drug Enforcement Administration (DEA) enforcement of the Controlled Substances Act (CSA) (U.S. DOJ, 1970). The CSA was enacted into law by the Congress of the United States as Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970. This law prohibits the transference of any controlled substance from the prescribed individual to any entity other than law enforcement (see summary in Daughton, 2007). The consumer is considered the end user and cannot transfer the controlled medication to anyone, including a physician or a pharmacist. All pharmaceuticals identified by the medical examiner are required to be disposed of by the investigator, as opposed to allowing family members to take possession of the leftover drugs. Law enforcement officers are permitted to seize controlled substances. It would be permissible, however, for consumers to return unused and unwanted pharmaceuticals to their local police stations.

Medications collected and disposed of by coroner offices are themselves a measurable source of drugs in the environment. Of more interest, however, is the fact that these inventories provide information regarding the categories and dosage amounts of medications that accumulate and require disposal. At the least, coroner disposal data can be used to calculate minimum known introductions to sewage for an individual water treatment plant or watershed; additional sources would include excretion and bathing, as well as disposal from a wide array of additional sources, including consumers (Ruhoy, in preparation). For the purposes of the model scenarios developed in this paper, the assumption is that the sole source of an API in sewage would be from direct disposal by coroner offices. At the maximum, these data could be

used to estimate upper boundaries for these introductions (by assuming similar drug disposal rates across a community's entire population, not just from the coroner). The empirically measured load for any given drug targeted by a monitoring study of sewage influent would fall below or near this imputed upper bound if excretion were a minor source. An empirically measured concentration for a drug that is extensively metabolized (i.e., resulting in excretion of minimal parent API) and that fell near the imputed maximum range would indicate the possibility that disposal was a significant contributing source.

Knowledge of the categories, types, and quantities of drugs being disposed can help guide the selection of targets for environmental monitoring and for study of the potential impacts on both the environment and human health (from inadvertent exposure to ambient residues from the environment). In this particular study, the disposed drugs were introduced to sewage known to be treated by particular WWTPs, making possible the calculations of minimum amounts of APIs introduced to sewage. The data can also be used, in conjunction with requisite demographics data, to derive virtual predicted introduction concentrations (PICs) for disposed drugs (concentrations smoothed over time), for the first time allowing evaluation of the actual impact or significance of drug disposal on total environmental loads of pharmaceuticals.

Furthermore, the relevant data may prove valuable to gain insights regarding use, nonuse, and misuse of medications, which can then serve healthcare practitioners in their approach to treatments prescribed. The coroner data also provides some insight to what categories of drugs accumulate due to patient non-compliance, and therefore which drugs have the highest potential for accumulating unused, eventually requiring disposal.

Interpretations that could be derived from the data include patient compliance rates and abuse rates. Patient compliance (adherence) is an extremely important issue in the medical community, as it greatly impacts therapeutic outcomes and is a major factor in health care cost (Foxhall, 2007; Haynes, 2006). Compliance is also a major factor leading to the accumulation of drugs in households, and therefore, has direct ramifications for the environment (because of consequent disposal). The rate of compliance is frequently discussed in the medical and pharmacy communities, and wide ranges of rates (ranging essentially from 0% to 100%) are often stated with little supporting data. A report released by the National Community Pharmacists Association and Pharmacists for the Protection of Patient Care, states that 38% of consumers questioned had forgotten to take a prescription medication, and 29% of those surveyed said that they had at least once stopped taking a drug before the prescribed period was over (NCPA, 2006). The same survey found that 74% of respondents admitted to non-adherent behaviors including skipping doses, taking less than the recommended dose, or forgetting to take medication. In a survey by Abahussain et al. (2006), 25.8% of the respondents reported self-discontinuation of treatment

regimens. A persisting, unanswered question is determining what percentage of accumulated, unwanted medications derives from non-compliant behavior.

Methods

The data as described above were collected from the Clark County Coroner's Office (CCCO) in Clark County, Nevada. The total available data were selected from the 13-month period of January 2005 through January 2006 as this was the most recent accessible data for an entire calendar year. In this period, there were 1,632 coroner cases having drugs that were inventoried and therefore suitable to evaluate in this study. The most recent census for Clark County estimates a population of 1.7 million people (U.S. Census Bureau, 2006). Data were then entered into a spreadsheet, reviewed for accuracy by comparing computer records with manual file records, and analyzed.

There were 13,761 deaths reported in Clark County in 2005. Of this total, 10,135 deaths were reported to the Clark County Coroner. The total number of cases accepted as coroner cases was 3,393. Some of these cases, however, were not deaths in the home environment. For example, coroner cases include traffic accidents or bodies found outdoors. For obvious reasons, these case files usually did not include medication inventories. Certain other cases, while located in a home environment, did not have any unused medications to report. Often these cases were deaths of minors or young adults. The 1,632 cases reviewed (48% of the total coroner cases) represent those cases that contained a medication inventory log. Fifty-eight of the cases reviewed were from January 2006. To consider the data on the basis of a complete calendar year, 1,574 cases therefore contained medication inventory logs during 2005. The cases reviewed represent approximately 11% of all 2005 deaths reported in Clark County (detailed statistics, including demographic data, will be presented in a subsequent paper; Ruhoy, in preparation). Note that this frequency of occurrence of drug-inventory data may not be representative of the frequency at other locales, but would have no influence on data that might be collected in other locales.

The 2005 death rate for Nevada is comparable with that on a national basis. In 2005, the 13,761 deaths in Clark County's population of 1.7 million represented a rate of 0.008. In the U.S., during 2005, there were 2,432,000 deaths in a population of 297.8 million (NCHS, 2006), also a rate of 0.008. This is significant in terms of relating the populations and extrapolating the data.

The data compiled by the coroner office in Clark County resides in handwritten and/or digital notations recorded by case number. Each case was reviewed for data regarding pharmaceuticals located and disposed of. The listing of the specific pharmaceutical information (such as name of drug, prescription dosage, prescription date, and directions for use) is originally recorded on a written inventory sheet included in each case file; a facsimile example is shown in Figure 2. The information is then entered as a narrative parameter within the coroner database. However, not all cases had been entered into the

case database, often due to time constraints of entering multiple medications found in a particular case. Therefore, each case, including its inventory sheet and digital file, was evaluated manually in order to compile all pharmaceuticals disposed during the research period. Each paper file was reviewed for accuracy and thoroughness.

For the study reported here, this information was recorded in an Excel spreadsheet, and masses of APIs disposed of were calculated using the number of doses identified and the dosage strengths reported. The information was alphabetized by API name as well as sorted by pharmaceutical category as listed in the Tarascon Pharmacopoeia (Tarascon, 2007).

It is important to note that sometimes the brand name was listed in the coroner records as opposed to the generic name. For example, furosemide, an oft-prescribed diuretic, was frequently listed as Lasix®. The data were scoured for these inconsistencies, and all brand names were replaced with generic names for proper chemical distinction; for the future, the spreadsheet will be converted to a relational database, and CAS Registry Numbers will be used to ensure consistency. In addition, combination drugs, which are developed and prescribed with increasing regularity, were separated into their component APIs. For example, Lortab® was entered into the spreadsheet as both hydrocodone and acetaminophen, with appropriate dose amounts applied.

Results

The 13-month CCCO dataset contained greater than 5,000 discrete entries, representing on average a little over three APIs per decedent. Each entry represented a single API from a medication identified at the scene. A medication is most often identified by the label on the prescription bottle. In some cases, no pills were remaining from a prescription, and the entry then showed zero doses disposed. As described above, those medications that were dispensed as combinations of APIs were separated in the spreadsheet into their components. Therefore, one entry does not necessarily correlate with just one medication inventoried. A complete discussion of all results and population demographics will be elaborated in future publications (Ruhoy, in preparation). Some representative data are presented here for illustrative purposes.

The most prevalent method of disposal for the CCCO was to flush the inventoried medications into the sewage system. Greater than 92% of the medications found at decedent sites were flushed. Approximately 7% of the medications were disposed of in the household trash of the home of the decedent. Less than 1% was incinerated by law enforcement service. This latter disposal route usually occurred when loose, unidentified pills were found. These pills would be collected and transported to the offices of the Coroner and subsequently identified by Las Vegas Poison Control and inventoried. Following this, the Coroner would apply for a court order to dispose of the drugs, since the act of taking

them into possession then made these drugs evidence. The court order would allow cremation of the drugs in the possession of the Coroner.

During the 13-month period of this pilot study, at least 325,000 doses of a wide array of drugs were disposed of into the sewage system by the CCCO; in Clark County, this system is serviced by three tertiary treatment plants. This estimate does not include the multitude of other medication formulations (such as powders and liquids) and delivery systems (such as inhalers, patches, and syringes). The powders and liquids were also disposed of into the toilet but were not quantified in this study. The inhalers, patches, and syringes were disposed in the household trash and were not quantified in this study. The 325,000 doses represent greater than 102,000,000 milligrams of APIs disposed of into the sewage system over the 13-month period. These 102 kg are specific to the route of toilet disposal. Considering the similarities in death rates between Nevada and the country, it is not unreasonable to extrapolate these data to obtain an estimate of at least 17.9 billion milligrams (17.9 metric tons) of APIs disposed of annually into the national sewage systems by the deceased population alone (mass disposed by CCCO multiplied by the ratio of the U.S. population to the Clark County population).

The following two examples illustrate the utility of the Coroner dataset. First is an API that serves as a contaminant archetype because of its frequency of occurrence in environmental monitoring studies – the anticonvulsant, carbamazepine (CBZ). The second comprises the beta-blocker cardiac medications. Analogous data exist in the dataset for 200 other APIs (Ruhoy, in preparation).

The anticonvulsant CBZ is considered the primary drug for partial and tonic-clonic seizures and is also used in other treatments. While a low percentage (1-3%) of CBZ is excreted unchanged, another portion is excreted as conjugates, which can be hydrolyzed back to the parent CBZ, once released to sewage (Bendz et al., 2005). Therefore, the effluent concentrations often may not be much reduced from influent concentrations. The efficiency of CBZ transformation in WWTPs and in the environment is not high, leading to widespread persistence of measurable ambient, environmental residues (Bendz et al., 2005).

During the 13-month period of the collected data, there were 1,755 tablets of CBZ identified and disposed of in the homes of the decedents. These tablets represented 307,300 milligrams (307 g) of pharmaceutically active CBZ introduced directly into the Clark County sewage system. Since the most common dose prescribed was 200 mg, it would take roughly between 51,000 and 154,000 oral doses of CBZ for excretion to contribute the equivalent of 1,755 tablets of the pharmaceutically active CBZ disposed of by the CCCO (assuming an excretion rate ranging from 1 to 3%). The Clark County sewage system has average sewage flows of 144.4×10^6 gal/day (MGD) (LVWCC, 2007). Assuming a hypothetical, uniform and consistent daily disposal to sewage, a minimum averaged concentration of 1.4

ppt CBZ (see Equation 1) could be expected in the influent, as well as possibly the effluent, from the disposal of CBZ by the CCCO alone.

Equation 1: $(307 \text{ g}/13 \text{ months}) \times (12 \text{ months}/\text{year}) \times (1 \text{ year}/365 \text{ days}) \times (1 \text{ day}/144 \times 10^6 \text{ gal}) \times (1 \text{ gal}/3.7854 \text{ L}) = 0.0014 \times 10^{-6} \text{ g/L} = 1.4 \text{ ng/L} = 1.4 \text{ ppt CBZ in WWTP influent}$

It is important to note that in reality the disposal of medications does not take place at a uniform, constant rate, but rather episodically. This will result in plug-flows that have higher transient concentrations; this is one of the variables involved with fluctuating levels in sewage (Daughton, 2007).

Assuming CCCO serves the entire Las Vegas basin, this population is served by the Clark County Sewage District. The U.S. Census Bureau estimates 1.2 million adults over the age of 18 in Clark County in 2005 (U.S. Census Bureau 2007). However, more specifically, and perhaps more accurately since not only are most prescriptions written for older adults (a result of a greater incidence of polypharmacy), there are approximately 183,000 people in Clark County over the age of 65 (U.S. Census Bureau, 2007). The CCCO data derive from 1,632 cases (over the course of 13 months) and represent approximately 0.0089 of this sub-population. This estimate can be used roughly to correct the estimate of 1.4 ppt (in STP influent) to 157 ppt CBZ disposed by the proportion of the sub-population aged 65 or older in Clark County.

The 1,632 cases represent approximately 307 g of CBZ identified and disposed annually. This is roughly 0.19 g of CBZ per case. As explained above, these deaths represent 11% of all deaths reported in Clark County in 2005. Assuming similar coroner statistics across all 50 states, 11% of all deaths in the country would be 267,500 yielding a potential 50.8 kg of CBZ being disposed nationwide on an annual basis just by coroner offices.

For the second example, consider the β -adrenergic blockers, commonly referred to as beta-blockers, which are used in the treatment of hypertension, systemic, and ophthalmic disorders. The compiled CCCO data set indicates almost 10,000 leftover beta-blocker pills that were disposed of, translating into greater than 600,000 milligrams (600 g) of beta-adrenergic antagonist APIs disposed into sewage.

By using the prescription date listed in the coroner records, dose-frequency instructions, doses remaining, and the date of death, compliance or noncompliance can be ascertained. The data for beta-blockers represented an approximate 33% rate of noncompliance among the decedents for all the medications listed in the inventory. Of great clinical interest, in almost 70% of those noncompliant cases, the cause of death listed by the medical examiner was the precise disease the unused drugs were intended

to treat. The cause of death listed due to acute toxicity of prescribed drugs, which by definition does not include illicit drugs, was listed in 7% of the cases.

The decedents possessed an average of seven prescriptions. These medications were the same pharmaceuticals that are commonly prescribed in the general population (RxList, 2007) and were not present in inordinate quantities. While one might expect that those near the end of life would be taking larger quantities of, for example, opiates for pain, this did not appear in the CCCO data. The number of hydrocodone prescriptions for this data set was 692. This did not necessarily represent one prescription per case since often more than one hydrocodone prescription was listed for a single decedent. While details regarding the number of specific pharmaceutical prescriptions per decedent will be elucidated in future articles, this basic information can be used to assess the comparability of local, state, and national prescribing and dispensing practices. There were an estimated 1.8 million hydrocodone prescriptions in Nevada during 2005 (Haynes, 2005), a state with almost 2.5 million people (U.S. Census Bureau, 2007). In the same year, there were greater than 101 million hydrocodone prescriptions written in the U.S. (RxList, 2007), a country of almost 300 million people (U.S. Census Bureau, 2006). While the ratios of prescriptions to population count in Clark County (42%) and Nevada (72%), are higher than national figures (33%) , they most likely represent the upper range, and may be due to local practices and demographics. This information is valuable because it serves to establish the relevance and representativeness of the data with regard to its overall representation of the U.S. population. In addition, it may be easier to address, and alter, prescription and dispensing practices on a local basis. Comparing local prescription behaviors with similar localities and communities may provide information and recommendations for more efficient, effective, and prudent prescription handling.

Discussion

The data collected from the records of coroner offices regarding the quantities and disposal of unused drugs can be used as a comprehensive and accurate data set from which to derive a wealth of information regarding the extent of environmental disposal of pharmaceuticals that span all therapeutic classes; some example applications for these data are summarized in Table 1. The data can provide insights to answer questions such as, in what quantities are specific medications disposed of, and what categories of medication are commonly found in the coroner offices inventories. The coroner inventory is useful because it includes data on specific drugs with dosage information that were left over following a death, and that are directly disposed into the sewage systems by the coroner staff. The disposed dosage amounts could prove very valuable in better understanding the sources and their relative contributions of drug residues as measured in STP influents or effluents. As additional water monitoring studies are

conducted, this information could be helpful in correlating water concentrations and usage patterns among local populations.

The same dataset provides insight into noncompliant behaviors among the population including the abuse and misuse of prescribed medications and prescription trends of the representative geographic area. Combined with the information on disposal, these factors need further evaluation for various scenarios that would have an effect on ambient environmental concentration levels, as well as indicating the efficiency of prescribing and patient education by medical care providers.

Further analysis can reveal those medications that accumulate at rates disproportionate to their dispensed frequencies and those that accumulate at the highest absolute rates and in the highest quantities. Data such as these would be useful, for example, in indicating which drugs experience high non-compliance or are prescribed in excessive quantities. With these data as a guide, it is possible to target these drugs for emphasizing better prescribing (or dispensing) practices, as well as more prudent disposal practices. An additional use for this inventoried data would be to identify those drugs that have not been the target of monitoring efforts, but yet exist in the coroner data at significantly high rates. For example, greater than 80,000 milligrams of lisinopril, an angiotensin-converting enzyme (ACE) inhibitor, was disposed of. The ACE inhibitors have never been routinely targeted in monitoring studies.

There are two major approaches for ameliorating the disposal issue – source control and pollution prevention. The first would focus on an effective and environmentally friendly way to dispose of pharmaceuticals that go unused. The second reduces the size of the source by reducing the quantities of medications that accumulate and which would have then required disposal. The supply and distribution of medications coupled with the behavior patterns of patients and physicians dictate the amounts of pharmaceuticals having the potential to accumulate. Patient noncompliance to treatment regimens and physician prescription patterns could be addressed to better optimize patient care and reduce accumulations. These approaches may help to limit the accumulation of pharmaceuticals and reduce the ready source of those drugs that are highly addictive and which are abused, misused, or targets of diversion.

Minimizing the need for drug disposal will need to bring together professionals from the health care and insurance industries, government, environmental sciences and policy, and engineering. The research described here, and to be delineated in upcoming publications, begins to address some of the long-standing uncertainties in science that will need to be resolved. It also exposes other areas of a complex web of pharmaceutical sources that are in need of individual disposal strategies, and potential ways in which the amounts of accumulated drugs can be reduced. In addition, the research introduces a source of data that has previously been overlooked -- where a potentially large source of drugs introduced into the environment is already being inventoried and cataloged. This information is valuable for

furthering discussions regarding human medication behavior and also provides a basis for future research into determining what quantities of APIs are disposed, and which then serve as a source of APIs that can enter the environment.

A project creating a unified network of inventoried-drug databases from coroner offices around the country could prove highly useful. Such an effort could first compile existing coroner data, and then automate for future collection. This data could be used to improve patient outcomes and reduce costs of health care. In turn, improved prescribing practices will automatically reduce the quantities of medications needing disposal. The purpose of this paper is to provide some examples of the types of inferences and deductions that can be derived from coroner data. An overarching objective is to catalyze consideration for adoption of a more comprehensive version of this approach on regional or national scales. No obstacle to developing a central nationwide database employed by all coroners offices has yet been identified.

Note Added: Soon after the conclusion of the project reported here, the Clark County Coroner Office began discussions with local hazardous waste transporters regarding the feasibility of removal and transport of their collected leftover decedent drugs to incinerator facilities. The intent is to cease disposal of the pharmaceuticals into sewage. These discussions were partly a result of the information provided by this research project, as well as the desire of local water authorities to comply with the newly issued federal guidelines. The CCCO hopes to develop a model for proper and safe disposal of pharmaceuticals acquired by the coroner.

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Table 1: Potential Applications for Coroner Drug Inventories

Coroner drug inventories can be used to:

DETERMINE:

- Types and relative amounts of APIs disposed
- Actual quantities of APIs disposed
- Fraction of APIs disposed by various routes (e.g., sewage vs. trash)
- Minimum limits on amounts of individual APIs disposed
- Putative maximum limits on amounts of individual APIs disposed
- Predicted concentrations introduced to STPs
- Relative significance of disposal with respect to the overall environmental occurrence of an individual API
- Those APIs for which disposal is insignificant with respect to their overall environmental occurrence
- Those APIs for which disposal might play a significant role in their overall environmental occurrence
- Those medications for which patient compliance rates are low

GUIDE:

- Selection of APIs for targeted monitoring in sewage streams and the environment in specific geographic locales
- Recognition of APIs that are being over-prescribed
- Recognition of medications with poor patient compliance

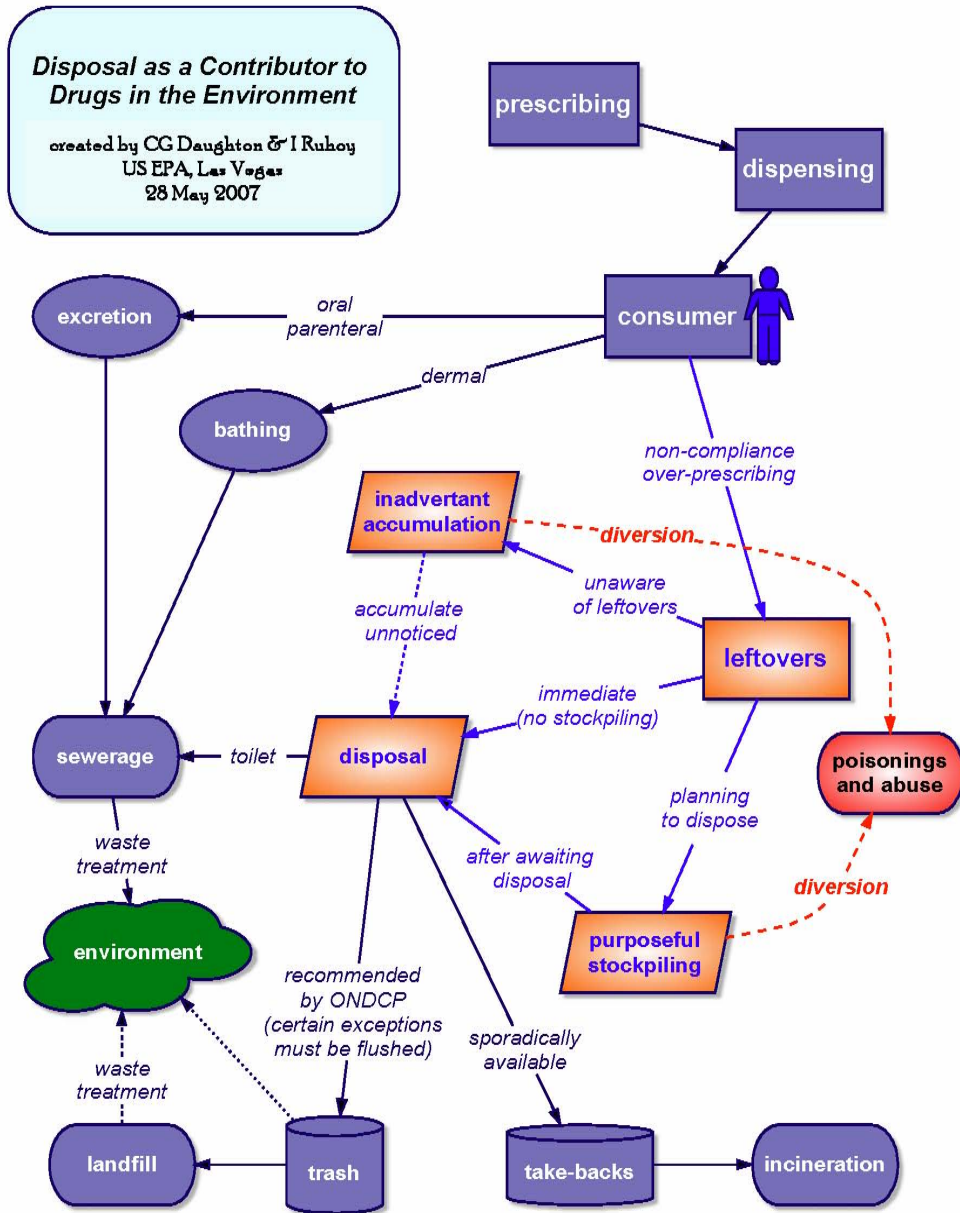


Figure 1. Role of Leftover Drugs in the Exposures of Humans and the Environment

NAME:		CLARK COUNTY CORONER'S OFFICE						CASE#:		
Thomas, CHRIS		MEDICATION ACTIVITY LOG						DATE:	01-04-06	
Rx Number	Rx Date	Description	Mg/MI	Where found	Rx Amount	Amount left	Dosage	Physician	Pharmacy	
M629522	8-11-05	THIAMINE	50mg	KITENED	60	21	2X	DR. A. MILLE	AFB	
M629822	8-11-05	THIAMINE	50mg	"	60	59	2X	"	"	
M622856	7-27-04	LISINAPRIL	10mg	"	90	31	1X	"	"	
M622856	7-27-04	LISINAPRIL	10mg	"	90	0	1X	"	"	
M629822	8-11-05	FOLIC ACID	1mg	"	30	12	1X	"	"	
M629822	8-11-05	FOLIC ACID	1mg	"	30	20	1X	"	"	
M609120	5-15-03	PIROXYTINE	30mg	"	90	60	1X	"	"	
M609052	5-6-03	PLENYTIN	100mg	"	270	270	3X	"	"	
M622947	10-19-04	LANSOPRAZOLE	30mg	"	90	88	1X	"	"	
02710690658	10-27-05	LISINAPRIL	10mg	"	30	20	1X	"	WALGREEN	
M603343	10-15-02	Celecoxib	100mg	"	60	19	2X	"	AFB	
M601340	5-6-03	DILTIAZEM	100mg	"	180	17	3X	"	"	
M532062	4-6-00	PLENYTIN	100mg	"	270	37	3X	DR. T. ALABO	"	
F04535	4-19-00	ALENDRONATE	10mg	"	90	44	1X	DR. F. SMITH	"	
M16335	12-21-00	VICODIN	5mg	"	30	2	12X	DR. F. CHU	"	
B34703	3-15-95	HALOPERIDOL	2mg	"	14	14	2X	DR. S. ARDAUB	WALGREEN	
M578661	11-29-99	ALENDRONATE	10mg	"	90	101	1X	DR. F. SMITH	AFB	

Disposal of Medications		
Disposal Time: 0930hrs	Witnessed By: DUKE, Sam-10-Lea	Signature: [Signature]

CCCO 11/04

Figure 2. Facsimile of Coroner Inventory Case Record for Medications Remaining from One Decedent. The names of the actual physicians and Rx numbers, as well as the name of the patient, have been changed.