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Eco-directed sustainable prescribing: feasibility for reducing water contamination by drugs

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HIGHLIGHTS

- Role of pollution prevention is examined for reducing drug entry to the environment.
- Eco-directed sustainable prescribing (EDSP) is proposed for reducing drug excretion.
- Drug loadings in environment via sewers are dictated by pharmacokinetics.
- Prescribing could be guided by selecting drugs that are poorly excreted.
- Do empirical environmental occurrence data for drugs correlate with pharmacokinetics?

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ABSTRACT

Active pharmaceutical ingredients (APIs) from the purchase and use of medications are recognized as ubiquitous contaminants of the environment. Ecological impacts can range from subtle to overt — resulting from multi-generational chronic exposure to trace levels of multiple APIs (such as in the aquatic environment) or acute exposure to higher levels (such as with wildlife ingestion of improperly discarded waste). Reducing API entry to the environment has relied solely on conventional end-of-pipe pollution control measures such as wastewater treatment and take-back collections of leftover, unwanted drugs (to prevent disposal by flushing to sewers). An exclusive focus on these conventional approaches has ignored the root sources of the problem and may have served to retard progress in minimizing the environmental footprint of the healthcare industry. Potentially more effective and less-costly upstream pollution prevention approaches have long been considered imprudent, as they usually involve the modification of long-established norms in the practice of clinical prescribing. The first pollution prevention measure to be proposed as feasible (reducing the dose or usage of certain select medications) is followed here by an examination of another possible approach — one that would rely on the excretion profiles of APIs. These two approaches combined could be termed eco-directed sustainable prescribing (EDSP) and may hold the potential for achieving the largest reductions in API entry to the environment — largely by guiding prescribers' decisions regarding drug selection. EDSP could reduce API entry to the environment by minimizing the need for disposal (as a consequence of avoiding leftover, unwanted medications) and reducing the excretion of unmetabolized APIs (by preferentially prescribing APIs that are more extensively metabolized). The potential utility of the Biopharmaceutics Drug Disposition Classification System (BDDCS) is examined for the first time as a guide for API prescribing decisions by revealing relative API quantities entering sewage via excretion.

1. Introduction

The practice of health care (the use of prescribed medications in particular) can have a broad spectrum of potential adverse health and economic consequences for both the environment and humans. Continuing to emerge is an understanding of the complex network of interconnected routes (Daughton, 2008; see Fig. 1 therein, also available: http://www.epa.gov/nerlesd1/bios/daughton/drug-lifecycle.pdf) that play active roles in the release to the environment of active pharmaceutical ingredients (APIs[1]) from the intended use and misuse of medications. These routes are especially important with respect to

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[1] Abbreviations — API: active pharmaceutical ingredient; BDDCS: Biopharmaceutics Drug Disposition Classification System; CAFO: confined animal feeding operation; EDSP: eco-directed sustainable prescribing; LOD: limit of detection; MEOC: Matthew Effect Orphaned Chemical; MQL: method quantitation limit; OTC: over the counter; PBT: persistent, bioaccumulative, and toxic; PK: pharmacokinetics.

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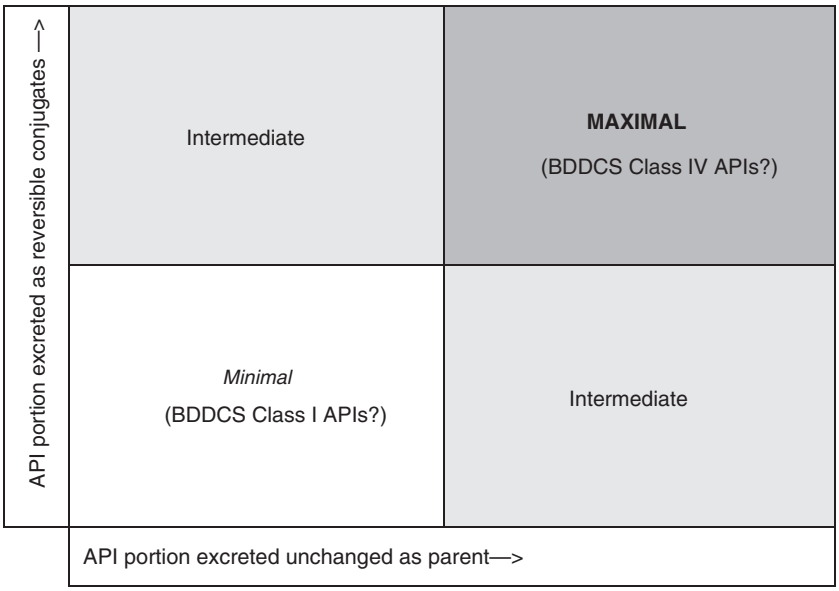

Fig. 1. Environmental loadings of APIs as a function of excretion and reversible conjugation. See Supplemental Table S-3 for a list of example APIs (and supporting references) that have shown "negative removals" during sewage treatment — often, perhaps, as a result of deconjugation. The possible predictive utility of the BDDCS is also indicated for Class I and Class IV APIs.

the aquatic environment [where many APIs have become ubiquitous trace contaminants — continuously present in many waters and displaying a pseudopersistence (Daughton, 2002, 2003; Mackay et al., in press); also see extensive list of references cited in Supplementary Tables S-1 and S-2] as well as for both the escalating defacto reuse of water (Rice et al., 2013) and the growing need for planned wastewater recycling, especially for potable use (Debroux et al., 2012). The potential for adverse impacts derives from two major routes: (1) the excretion of unmetabolized residues of APIs (as well as their active metabolites and "masked" derivatives such as metabolic reversible conjugates — the parent API linked to certain endogenous biomolecules) and (2) the accumulation of unwanted, leftover medications, whose safe and prudent disposal is often an onerous task for the consumer and rarely performed properly (Daughton, 2010a).

In general, excretion of API residues is the major route to the environment (especially for the aquatic domain), with adverse effects in the aquatic environment now known to be possible at extremely low API exposure levels. In contrast, the major concern regarding humans is non-therapeutic exposure and self-exposure to diverted leftovers via accidental, incidental, unintentional, or purposeful consumption — primarily via ingestion or dermal pathways (Bond et al., 2012; Budnitz and Salis, 2011; Burghardt et al., 2013; Daughton, 2010a). Morbidity and mortality among infants, toddlers, teens, and the elderly (from unintended exposure or non-medical self-exposure to diverted drugs, both of which are exacerbated by the incidence of leftovers) are well documented and largely preventable or avoidable. Mortality is especially notable and discouraging since it is often preventable. Additional routes for the entry of drug residues to the environment are bathing and dermal transfer. These routes could be more important than excretion for select drugs that are formulated primarily into topical preparations (such as high-content creams and transdermal devices) and for APIs that are extensively excreted via sweat; these routes may play significant roles in human bystander exposure. Bathing can transfer residues to sewers and ambient waters, while dermal contact may transfer significant residues to surrounding surfaces or directly to other people (Daughton and Ruhoy, 2009).

Historically, problems regarding chemical contaminants in the environment — especially those where sewage plays the major role — have been addressed with pollution control measures. End-of-pipe treatment is the long-established norm. Recognition has grown over the last decade, however, that myriad numbers of trace-level "emerging" contaminants (such as APIs) comprise the majority of the synthetic chemicals that remain in treated sewage, even with advanced treatment. Continual advancements needed for engineered treatment technologies capable of removing ever-lower levels of trace contaminants from solutions are resource intensive, and limits probably exist with regard to their economic sustainability (Jones et al., 2005).

Since the 1990s, various means of conventional and more advanced pollution control continue to be examined for reducing the ultimate entry of APIs to the aquatic environment, especially via treated sewage (e.g., Coday et al., 2014; Luo et al., 2014). But a singular focus on resource-intensive (and not fully effective) end-of-pipe approaches [such as improved treatment technologies for wastewater and drinking water, and "take-back" programs for collection of unwanted leftover medications to avert their disposal by flushing to sewers (e.g., Glassmeyer et al., 2009)] ignores the root origins of the problem and may actually serve to retard meaningful progress in minimizing the ecological and chemical footprints of the healthcare industry. In contrast, pollution prevention is a major unexplored approach for minimizing the impact of healthcare on the environment. Preventative measures would target the root factors that promote or facilitate the release of APIs to the environment. The most important routes for the release of APIs to the environment are excretion (unmetabolized API or active metabolites), bathing (topical APIs and sweat), and imprudent disposal of leftover, unwanted medications (especially to sewers). The key up-stream processes that dictate the scope and magnitude of excretion are the regulations, guidelines, behaviors, and customs surrounding the practice of prescribing and ultimate use, along with the associated activities of dispensing as influenced by the administration of healthcare and the insurance industry (Daughton, 2013; Ruhoy and Daughton, 2008).

1.1. Background

The practice of health care involves the widespread use of roughly 2500 distinct active pharmaceutical ingredients (APIs) in the US (roughly 4000 worldwide) formulated into tens of thousands of commercial pharmaceutical preparations (Daughton, 2013). The intended ultimate use of these APIs — some of which can elicit biological effects at the nanomolar level and below — often results in the excretion

(primarily via urine or feces, and secondarily via sweat) of unmetabolized APIs or bioactive metabolites. APIs can differ dramatically with regard to the extent of excreted dose — from practically nil to nearly complete; but there are few drugs for which metabolism (and excretion) are intermediate — i.e., between 30% and 70% (Benet et al., 2011). These two extremes encompass most APIs, which are either extensively metabolized or extensively excreted unchanged. Furthermore, portions of many oral dose forms are never absorbed systemically — a result of being excreted immediately and directly via the feces; this mechanism clearly serves to maximize the percentage excreted unchanged.

Excreted APIs enter the aquatic environment by way of both treated and untreated (raw) sewage; APIs in raw sewage enter unabated into surface and ground waters not just by wet-weather runoff and illegal discharges, but also by contributions from numerous point sources from defective sewer connections (Baum et al., 2013). Leftover, unwanted medications are also often disposed into sewers. Some APIs are formulated for external use (high-content topical drugs); some of these APIs have exclusive topical use (they are not administered systemically). For these APIs, bathing is a major route of entry to the environment (Daughton and Ruhoy, 2009). Both excretion and the need for disposal are partly driven by imprudent, unnecessary, or excessive prescribing, misuse, and overconsumption — all major problems in healthcare and the ones with many, complex causes (Daughton and Ruhoy, 2011).

Significantly, current approaches directed at reducing API levels in the environment have focused solely on pollution control — particularly improved wastewater treatment and take-back collection of unused consumer medications. These are end-of-pipe approaches, which for decades have been the hallmarks for controlling chemical contamination of the environment. These are not, however, approaches that can be relied upon to facilitate the sustainable use of medications. To the contrary, an argument may exist that pollution control measures might work counter to sustainability by deflecting the ongoing dialog surrounding drug residues in the environment away from possibly more effective measures addressing pollution prevention. The absence of a focus on pollution prevention fosters continued, unfettered prescribing and use of unnecessary drugs, for excessive durations, and often in excessive doses.

Many of the aspects of a drug's life cycle that have been identified as possible targets for optimizing to reduce API entry to the environment involve alterations to prescribing and dispensing practices. Some of these practices have already been undergoing examination for other purposes, such as improving patient adherence or compliance with medication regimens to reduce adverse events and improve therapeutic outcomes (Daughton, 2010a). Other prescribing modifications include drug substitution, reducing dispensed drug quantity (especially amounts suitable for short-term trials), easier or better-targeted delivery systems (e.g., transdermal systems), lower doses [e.g., achieved with alternative delivery routes or personalized doses (Daughton and Ruhoy, 2013)], dose timing (e.g., chronobiology), palatability (a factor that can strongly influence patient compliance and thereby raise or lower the incidence of leftovers), physician medication reviews with patients (and prevention of unnecessary polypharmacy), more informative and clearer labeling (which can directly promote patient compliance), elimination of unnecessary repeat prescriptions (especially automatic refills), improved coordination among prescriber, dispenser, and patient, and alternative treatments (exercise, physical therapy, diet, etc.). Numerous other approaches involve design of API chemical structure, drug formulation, and packaging. While many of the modifications to prescribing practices are intended to improve patient compliance and adherence, they may also coincidentally serve to reduce the incidence of leftovers and the subsequent need for disposal. Other potential approaches have included consideration of pharmEcokinetic factors [e.g., prescribing decisions partly based on selection of drugs having lower half-lives in the environment or reduced propensity to undergo bioaccumulation (Deblonde and Hartemann, 2013; Stockholm County Council, 2012)]. The spectrum of potential options for gaining better alignment with sustainability is clearly vast.

To minimize the potential for APIs to enter sewers in the first place, a wide array of measures designed to reduce or eliminate drug wastage have been under consideration or evaluation; these are partly designed to reduce the disposal of leftover medications in sewers. Up to now, the major approach widely assumed to lessen the occurrence of APIs in the aquatic environment has been the implementation of federal, state, and local guidelines for discouraging sewer disposal of leftover and unwanted drugs; this rationale persists despite the lack of evidence that sewer disposal contributes significant quantities of most APIs to the quantities already unavoidably entering sewage via excretion (Daughton, 2010a).

Potentially effective and less-costly upstream pollution prevention approaches have long been considered imprudent and impractical simply because they might conflict with long-accepted prescribing guidelines, norms, and tenets. But these are often influenced by behaviors, customs, attitudes, and traditions — of prescribers and patients alike. All these combined have contributed to an unfounded fear of jeopardizing the quality of delivered health care if prescribing guidelines are altered. Long-deemed infeasible has been the optimization of the therapeutic use of medications for preventing pollution at its source. This stance, however, has been shown to be unfounded in at least one instance, where some select drugs can be prescribed at off-label doses considerably lower but still prudent and efficacious; such lower doses could reduce wastewater loadings from excretion. Moreover, lower-doses hold the potential to also avoid the subsequent need for disposal of leftovers that would otherwise be generated as a result of patient non-compliance caused by adverse effects from higher doses (Daughton and Ruhoy, 2013). Many drugs are prescribed to segments of the population at doses that are unnecessarily or imprudently high. Imprudent drug prescribing and ultimate use are major aspects of escalating health care costs, which overall compose an unsustainable 17.6% of GDP (Curfman et al., 2013). Furthermore, by reducing the incidence of leftovers via lower doses, a concomitant reduction could result in drug diversion, abuse, and unintended poisonings (Daughton and Ruhoy, 2013). These are all major problems in the U.S. and a primary concern for the White House Office of National Drug Control Policy (ONDCP, 2013). To date, however, dose-reduction has been the only proposed approach for directly reducing the primary pathway (excretion) for API release to the environment, as well as for reducing the incidence of leftovers and the consequent need for their disposal. This proposed approach also suggests that patients and prescribers can consider more prudent medications and regimens; reducing the overuse and imprudent use of antibiotics is one example (Daughton, 2010a; Daughton and Ruhoy, 2013).

This first proposed approach to pollution prevention (lower-dose prescribing, see: Daughton and Ruhoy, 2013) is now followed here by an examination of a complementary but potentially more expansive approach for controlling the major route of API entry to the environment — excretion — which has escaped concerted attention as a target for control. Never before considered is a pollution prevention approach designed around the excretion profiles of APIs — favoring those that are more extensively metabolized to benign end products versus those known to be extensively excreted unchanged as the parent API or as reversible metabolic conjugates. Presented here is an examination of a concept for formally accommodating API pharmacokinetics (namely, API excretion parameters) in the decision process surrounding the practice of clinical prescribing. Such eco-directed sustainable prescribing (EDSP) could prove central to the advancement of a sustainable healthcare system while protecting the environment — treating the patient and the environment as an integral, interconnected whole.

Excretion profiles could also identify those APIs on the other end of the spectrum — those that are extensively excreted unchanged. For these APIs, the continued disposal of any unwanted leftovers to sewers could perhaps be justified on the basis that the quantities of excreted

residues may far surpass the incremental contributions from disposal. For these drugs as unwanted waste, their continued immediate disposal to sewers could be favored also because flushing remains the most effective practice uniformly accessible to consumers for ensuring that certain drugs are not diverted for abuse and for preventing unintended poisonings in humans and pets; leftover medications continue to be one of the leading causes of accidental mortality in children (Bond et al., 2012; Budnitz and Salis, 2011; Burghardt et al., 2013; Daughton, 2010a). Those APIs that are extensively metabolized could then be targeted as priorities for finding alternative pollution prevention approaches for disposal, since the contribution of their residues via other pathways (such as flushing leftovers into sewers) would pose a greater probability of adding significant portions to overall environmental loadings.

Examined here is the feasibility of factoring API excretion profiles into the decision process for prescribing and dispensing in order to optimize the selection of drugs posing minimal potential for environmental impact via excretion. Within given therapeutic classes, particular APIs may exist with more favorable metabolic profiles — those resulting in less excretion of bioactive residues. With an understanding of an API's pharmacokinetics (PK) that is more comprehensive than currently available (such as the routine PK data compiled in PK databases or provided in patient package insert documentation), an API within a given therapeutic class could be selected partly on the basis of reduced excretion. This approach could most easily be first implemented for those therapeutic groups where the APIs display minimal differences in therapeutic effectiveness. Certain drug classes (especially cytotoxic chemotherapeutics) may not be amenable to this approach; the best control measure for such highly toxic drugs may simply be the prevention of urine and feces from entering sewers.

1.2. Objectives

This project originally set out to provide a foundation for understanding the preventative measures that could be implemented for circumventing the entry of APIs to the environment. This could be accomplished first by reducing doses for certain APIs (when feasible and prudent) (Daughton and Ruhoy, 2013) and, now here in this article, by selecting medications whose APIs have more favorable excretion profiles. These two pollution prevention approaches combined could be called eco-directed sustainable prescribing (EDSP). The premise is that EDSP holds the potential for achieving the largest reductions in aquatic levels of API contaminants by reducing the major source (excretion) as well as a secondary source (disposal of leftovers to sewers). And at the same time, EDSP holds promise for improving the efficacy or healthcare while also reducing costs.

The objective in this paper is to determine what type of PK data would be needed (and how these data could be most readily obtained) to help in selecting APIs for two major purposes: (1) those APIs whose excretion is minimal (and could therefore be classified as having lower potential for environmental impact — when used as prescribed), and (2) those APIs whose excretion is maximal and therefore disposal of leftovers to sewers might have minimal comparative impact on the aquatic environment (versus the quantities normally excreted); for the latter group of APIs, disposal to sewers could possibly continue as a recommended practice when human safety and health are a priority (e.g., when drug diversion exacerbates human morbidity and mortality) (see list of APIs at: USFDA, 2009).

Ultimate objectives are to foster a better understanding among the healthcare communities as to how the use of pharmaceuticals impacts the environment — and indirectly may impact the general public via a number of routes — including de facto recycled drinking water (Daughton, 2010b; Debroux et al., 2012; Rice et al., 2013) — and to facilitate or catalyze discussion and further work among the many stakeholders regarding pollution prevention and environmental stewardship and how these impacts could be significantly reduced with EDSP. A major challenge in trying to catalyze change in society's relationship with pharmaceuticals is the sheer number of stakeholders concerned with the many aspects of the lifecycle of drugs — spanning from the point of manufacture and extending to prescribing, dispensing, ultimate usage, storage, diversion, disposal, and treatment (Daughton, 2008; see Fig. 1 therein, also available: http://www.epa.gov/nerlesd1/bios/daughton/drug-lifecycle.pdf).

A notable aspect of EDSP would be that improvements to the practice of conservative prescribing that are aimed at either reducing API excretion or the incidence of medication leftovers will at the same time also serve to improve aspects of healthcare and public safety. As previously argued for reduced doses (Daughton and Ruhoy, 2013), EDSP could have the same far-reaching collateral benefits, including reduced healthcare costs (by reducing dose and reducing medication waste), improved patient therapeutic outcomes (by reducing adverse events, thereby improving patient adherence, which in turn dictates in part what portion of a course of medication remains unused and thereby eventually requires disposal), and reduced morbidity and mortality from accidental poisonings caused by improperly stored or disposed medications. Leftover, unwanted medications are overt symptoms and direct measures of numerous inefficiencies and imprudence in the conduct and administration of healthcare. They directly reflect wasted resources (in terms of physician time and consumer expense), lost opportunities to achieve therapeutic outcomes (when leftovers are generated as a result of patient non-compliance or non-adherence), and pose significant but avoidable hazards to public safety and health (via diversion, abuse, and unintended poisonings) as well as to wildlife (Daughton and Ruhoy, 2011).

2. Materials, methods, and approach

Despite the ready availability of limited PK data for drugs, comprehensive PK data (sufficient to estimate API levels that would reach the environment after metabolism) can be surprisingly difficult to locate; the pharmacokinetics for many drugs are still not even sufficiently understood. This is because PK data needed for clinical trials and drug registration purposes do not need to account for the portion of a dose that passes directly through the gut unabsorbed and unmetabolized (sometimes exceeding the majority of a dose) or for reversible metabolic conjugates (those that can undergo deglucuronidation, via microbial or abiotic hydrolysis) versus total conjugates, which include non-reversible conjugates formed from phase I metabolites; conjugates of phase I metabolites do not yield the parent API upon hydrolysis (Hermening et al., 2000). The data cited in studies involving predicted environmental concentrations (PECs) for APIs often simply state that an API is “extensively metabolized” or “extensively excreted” and are insufficient to rule out whether the API has potential for occurrence in the environment via excretion.

The best available PK studies are those that strive to achieve stoichiometric mass balance around the parent API and all identified excreted metabolites (including all forms of metabolic conjugates) and unchanged parent API; these comprehensive studies usually involve mass-balance around radiolabeled APIs (White et al., 2013). But even then, these types of comprehensive studies involve few subjects. Within a population, many factors can dramatically modulate pharmacokinetics, resulting in enhanced or reduced excretion of parent API. Examples among numerous others include: dose, dose formulation (e.g., extended release; influence of excipients on absorption), duration of treatment, chronobiology, genetic polymorphisms (e.g., extensive versus poor metabolizers), gut microbiota, stress, exercise, diet, gender, age, physiology (especially intestinal physiology affecting motility and pH), health status (especially bowel disorders), and polypharmacy (e.g., drug–drug interactions, which can profoundly influence phase I metabolism, for example). Numerous drug-specific factors also influence the PK of APIs, notably including dissolution (e.g., Charkoftaki et al., 2010; Jamei et al., 2009; Macheras et al., 2013; McConnell et al.,

2008); the critical role of dissolution is shown by rifaximin, which is directly excreted, completely unchanged — almost exclusively in feces (Karanje et al., 2013). All of these variables can lead to considerable variance among individuals and across populations. This consequently imparts great uncertainty to predicting API input to sewers via excretion.

The original intent of this project was to compile comprehensive PK data on a wide spectrum of APIs. These APIs would be ranked according to the propensity of the parent API to be excreted. This ranking could then be used as an additional factor in guiding prescribing decisions — with the intent of reducing the overall loadings of APIs via sewers. For example, this excretion footprint could essentially serve as a fourth criterion, in addition to the three currently used for the Stockholm "Wise List" model of "Environmentally Classified Pharmaceuticals", created for the Stockholm City Council (Wennmalm and Gunnarsson, 2010). This represents the first and currently only formal system for classifying medications with respect to their potential for environmental impact. This system has been implemented in the form of "eco-labeling" and was designed to assist the prescribing process by considering the potential for environmental impact. A major limitation, however, is that the Stockholm criteria only comprise the three conventional factors (termed PBT) long-used in prioritizing chemicals for potential environmental harm: persistence (e.g., reflected by biodegradability), bioaccumulation (e.g., proxied by octanol-water partition coefficients), and aquatic toxicity. Importantly, however, these three factors only come into play if and when an API enters the environment. A more realistic approach needs to consider the potential for an API to gain entry to the environment to begin with. After all, an API with unfavorable PBT characteristics may actually have eco-friendly PK properties, imparting it with little potential to enter the environment — even if consumed by a large segment of the population. EDSP would add a fourth dimension to the Wise List — one that factors in PK excretion profiles — primarily the propensity for excretion of structurally unchanged APIs, reversible conjugates, and eco-toxic metabolites.

Quickly becoming apparent, however, is the difficulty in mining comprehensive PK excretion data for numerous APIs from the primary literature. The available data rarely are sufficient to account for reversible conjugates, which can serve as a major source of an API in the environment (beginning during transit of waste to an STP). This can be readily seen with studies of API levels in STPs where the concentrations in effluents are often significantly higher than in the influents (see discussion in Section 2.6: "Limitations to data — Factors influencing environmental occurrence and its measurement"). This also means that the excretion data used in published models to estimate API excretion to sewers are unable to accurately account for reversible conjugates (Lienert et al., 2007; Yan et al., 2014).

2.1. Proxy measure for API excretion: the BDDCS

Instead of an approach involving mining PK data from the literature, an alternative measure was evaluated in the study reported for the first time here. This approach makes use of what is called the Biopharmaceutics Drug Disposition Classification System (BDDCS) — an existing system used in the pharmaceutical industry for predicting various pharmacokinetic properties of APIs.

A discussion on the background and foundation of the BDDCS is beyond the scope of the work presented here but it is available from a number of articles (Benet, 2013; Benet et al., 2011; Custodio et al., 2008; Pham-The et al., 2013); the BDDCS serves as an extension of the predecessor work on the Biopharmaceutics Classification System (BCS) (Wu and Benet, 2005). Both systems attempt to classify APIs according to two major parameters. The BDDCS uses solubility and intestinal permeability — yielding four combinations of high and low (Classes I through IV); additional but small classes (e.g., Classes 0 and V) comprise a select few APIs whose PKs are extremely sensitive to pH profiles (e.g., amphetamine) or that display facile and ready degradation in the gut. It is important to note that class assignments for certain APIs are provisional and are subject to revision (Pham-The et al., 2013).

The APIs from only two of the four BDDCS classes were selected for the study reported here because they most likely represented two extremes with respect to the propensity of an API to be extensively metabolized (Class I) or to be extensively excreted unchanged (Class IV). This study did not evaluate Class II or Class III APIs, which probably would represent intermediate propensities. BDDCS Class I currently represents 40% of marketed drugs and 18% of new molecular entities (NMEs), while Class IV only represents 6% of marketed drugs and NMEs (Benet, 2013). This is the reason for the discrepancy in the number of APIs selected from these two classes.

On paper, the use of PK data for predicting the excretion of unchanged API should be a useful tool for predicting API entry to the environment. A host of factors would need to be considered, however, in evaluating the excretion efficiency of an API. Mining such data for each AP would be a time consuming task — made rather futile because the data may not be representative of reality (for any number of the reasons summarized earlier). Consideration of just one variable illustrates the complexity of the proposition. Consider carbamazepine, which is one of the most frequently detected APIs in the environment — despite the fact that it is extensively metabolized via the liver, with conjugation primarily of phase I metabolites. Carbamazepine might be gaining entry to sewers not because of any quirks of metabolism, but rather as a result of its slow, erratic, and highly variable rate of dissolution in the gut — a result of its poor aqueous solubility (a major limitation for BDDCS Class II APIs) (Hardikar et al., 2013). This can lead to substantial undissolved quantities passing directly through the gut — evading uptake during gastrointestinal transit. Poor dissolution of dose forms was proposed in 2001 as a factor promoting the entry of at least some APIs to the environment (Daughton, 2001). The compounding effects of meals (especially lipids) and non-homogeneous mixing within the gut add yet more variability (e.g., Schiller et al., 2005). Just by consideration of the unpredictable variability in excretion introduced by the dissolution of a drug during its transit through the gut, it becomes clear that the use of PK for predicting an APIs entry to the environment would be vulnerable to considerable error.

With this as a driver, the BDDCS was examined as a proxy measure for the relative extent of excretion of APIs unchanged. As a proxy measure for excretion, the BDDCS may not be as rigorous as compiling comprehensive PK data from the published literature, but it offers a number of advantages — the primary ones being its simplicity, ready accessibility, and recognition within the drug development community. The current study examined whether the published environmental occurrence levels of Class I APIs (measured in various environmental compartments but with emphasis on sewage and surface waters) trended lower than the levels for the Class IV APIs. That is, did the APIs belonging to the extensively metabolized group (BDDCS Class I) tend to have associated environmental monitoring levels that were clearly lower than the APIs in the group that was extensively excreted unchanged (BDDCS Class IV). The use of empirical field-monitoring data essentially accounted for the numerous variables involved with an API's entry to and transit through the aqueous environments of sewage and ambient waters.

2.2. Unanticipated outcome

A major collateral outcome resulted from this study in the course of mining the published environmental occurrence data for the APIs that were selected from the two BDDCS classes as presented in Benet et al. (2011). The result (compiled in Supplemental Tables S-1 and S-2) represents one of the larger and more comprehensive snapshots of the published data for the environmental occurrence of APIs; a number of prior efforts have also cataloged occurrence data for various APIs (e.g., Barnes et al., 2008; Daneshvar, 2012; Deo, 2014; Deo and Halden, 2013; Focazio et al., 2008; Hughes et al., 2013; Kolpin et al., 2002; Verlicchi et al., 2012; Williams and Cook, 2007; Zhou et al.,

2009). The data compiled in this current examination includes not just data of presence and data of absence, but in some respects more importantly it reveals those APIs for which data are completely lacking (absence of data). The published literature was examined for 374 APIs and involved the mining of data from over 500 articles (primarily from journals, book chapters, reports, and dissertations). Summaries of the data compiled in Tables S-1 and S-2 are provided in Section 3 (Results and conclusions) within Tables 1 and 2.

The importance of negative data and absence of data should not be underestimated. Consistent data of absence tells us which APIs might be lower priorities for future monitoring or what we might be able to ignore, thereby conserving resources. In contrast, the absence of data tells us what we might need to begin targeting for examination. With respect to the therapeutic use of drugs, data of absence in the environment (in conjunction with drug usage statistics and knowledge of metabolites of potential environmental concern) might tell us which APIs could continue to be used therapeutically with minimal environmental impact (although the potential for human poisoning from diverted drugs may still exist).

Table 1
The APIs from BDDCS Class I APIs (total of 322) for which environmental occurrence data seemed to exceed a threshold level of 1 μg/L in waters (or 1 mg/kg in solids) (for complete data, see Supplemental Table S-1).

Abundant occurrence data (57 APIs total in this group)
Acebutolol hydrochloride
Alprazolam
Aminophenazone
Amitriptyline (>5 μg/L; max 11.1 μg/L)
Bromazepam (>5 μg/L; max 15.5 μg/L)
Butalbital (>5 μg/L; max 5.3 μg/L)
Chloramphenicol (>5 μg/L; max 40 μg/L)
Cyclophosphamide (>5 μg/L; max 13.1 μg/L)
Diazepam
Diclofenac
Diltiazem
Diphenhydramine
Enalapril (>5 μg/L; max 10 μg/L)
Ethinylestradiol
Hydroxyzine
Ketamine
Meprobamate
Metoprolol
Metronidazole
Minocycline (>1 mg/kg)
Omeprazole
Phenobarbital
Risperidone
Sertraline
Temazepam
Tramadol (>5 μg/L; max 86 μg/L)
Venlafaxine

Limited occurrence data (41 APIs total in this group)
Escitalopram (>5 μg/L; max 32.2 μg/L)
Ramipril (>5 μg/L; max 5.4 μg/L)
Secobarbital (>5 μg/L; max 30 μg/L)
Zolpidem (=5 μg/L)
Zopiclone (=1 mg/kg)

Paucity of occurrence data (224 APIs total in this group)
Butabarbital
Chlordiazepoxide (>5 μg/L; max 6 μg/L)
Clorazepate (>5 μg/L; max 6.2 μg/L)
Doxorubicin (>1 mg/kg; max 5.6 mg/kg)
Indapamide (>5 μg/L; max 15.4 μg/L)
Linezolid (>5 μg/L; max 6 μg/L)
Levodopa
Phenylephrine
Valacyclovir (>5 μg/L; max 5.7 μg/L)
Valproic acid (>5 μg/L; max 9.3 mg/kg)
Zidovudine (>5 μg/L; max 9 μg/L)

Table 2
The APIs from BDDCS Class IV APIs (total of 52) for which environmental occurrence data seemed to exceed a threshold level of 1 μg/L in waters or 1 mg/kg in solids (for complete data, see Supplemental Table S-2).

Abundant occurrence data (13 APIs total in this group)
Ciprofloxacin (max 3.5 mg/kg)
Enoxacin (max 1.3 μg/L)
Erythromycin stearate (max 1 mg/kg)
Fleroxacin (max 1.84 mg/kg)
Furosemide (>1 μg/L; max 3.2–3.8 μg/L)
Norfloxacin (max 5.6 mg/kg)
Penicillin V (max 13.8 μg/L)
Roxithromycin (>1 μg/L; max 5 mg/kg)
Sulfamethizole (max 5.2 μg/L)
Valsartan (max >5 μg/L)

Limited occurrence data (8 APIs total in this group)
Acyclovir (max 1.76–2.4 μg/L)
Chlorothiazide (max 4.5–8.9 μg/L)
Chlorthalidone (max 20.1 μg/g)
Eprosartan (max 6.8 μg/L)

Paucity of occurrence data (31 APIs total in this group)
No data were available for 22 of the APIs in this group.
Of the few data available, none exceeded the threshold levels.

2.3. Literature search process

The primary source of data that was used to mine API environmental occurrence levels (or to verify the absence of data) is a bibliographic database maintained at the US EPA. The scope and coverage of this database are described here: http://www.epa.gov/ppcp/pdf/Synopsis-of-PPCPs.pdf. This database is one of the largest available that is devoted exclusively to all of the many and complex issues surrounding the interface between pharmaceuticals and the environment (Daughton and Scuderi, 2014); as of this report, this database contained over 18,500 records, including archival journal articles (published as well as in-press), book chapters, dissertations, reports, web pages, and the gray literature, among others; coverage dates back primarily to the 1980s, which coincides with the advent of concerted study of pharmaceuticals in the environment. All documents added to the database (compiled in EndNote X7, Thomson Reuters) were examined to ensure that their contents were digitized; when the main bodies of documents comprised scanned images, they were digitized (using Adobe Acrobat X Professional). Over 96% of the journal articles had complete digitized reprints allowing fast, full-text searching. This bibliographic database has been updated and curated on nearly a daily basis since 2008. Its articles are mined from commercial and public on-line databases, none of which provides comprehensive coverage on its own. These databases include ScienceDirect, American Chemical Society, Wiley, Springer, Taylor & Francis, Google Scholar, MedLine/PubMed, and the web itself. Hits from primary searches were expanded with reverse and forward citation analysis to accelerate location of additional relevant references and as a quality check on completeness. This database facilitates fast, full-text Boolean keyword searches. Most importantly, however, since the database content has already been triaged and curated for relevant articles, the searches avoid the major problem of numerous extraneous hits, which are inevitable whenever searching for data regarding pharmaceuticals within non-curated databases. The search strategy was not capable of locating articles where the spelling of the API search term was highly unusual (e.g., some non-English language spellings), nor could it locate references where the API spelling was consistently incorrect.

2.4. Caveats and comments regarding literature searching

Examination of the published literature surrounding the environmental occurrence of APIs reveals two distinct groups: (1) those APIs that have been specifically targeted for detection or quantitation in

any number of different matrices or environmental compartments, and (2) those APIs that have never (or rarely) been targeted for any type of environmental monitoring. The occurrence levels for APIs in the first group span the gamut from levels below the limits of analytical detection or quantitation, to the commonly reported levels encompassing the ppt–ppb range, and the less-common levels that span the ppb–ppm range. This first group therefore comprises both positive and negative data (i.e., data of presence and data of absence). The second group comprises APIs with an absence of data. These APIs have escaped targeted analysis in the environment for any number of reasons, ranging from the lack of suitable analytical methodologies to an outright lack of attention. Some of these APIs lacking data of occurrence may belong to a group referred to as Matthew Effect Orphaned Chemicals (MEOCs), as discussed in Daughton (2014), and therefore possibly merit future scrutiny.

For any individual API in the first group, the published occurrence data often do not cluster in clear or defined ranges. Instead, the occurrence data for an API often span the spectrum from non-detection to levels exceeding 1 μg/L in waters or 1 mg/kg in solids. This makes it difficult to generalize or to rank APIs according to their prevalence in the environment — whether by frequency of occurrence, geospatial distribution, environmental compartment, or especially concentration levels. Moreover, the reported levels among APIs are not intercomparable because limits of detection (LODs) or method quantitation limits (MQLs) can differ by one or more orders of magnitude. One consequence when comparing levels among APIs, for example, is that an API with abundant data of absence could actually occur at levels higher than an API that has a lower LOD and abundant positive data (albeit low levels).

In this current project, concentration data were mined from examination of publications covering environmental matrices — with a primary focus on waters (especially sewage and natural surface waters); groundwaters, source and finished drinking waters, and biota were of less interest because of the increased probability that the API levels had been yet further diminished by any number of transformation processes. Individual searches were performed for nearly every API compiled in the BDDCS evaluation that was performed by Benet et al. (2011). A small group of APIs (21 of the 346) from BDDCS Category I were excluded from evaluation because they have little toxicological relevance in the environment or they have major alternative contributory sources beyond that from bona fide human consumption of pharmaceuticals, such as from: endogenous biosynthesis (e.g., many of the estrogens, hydrocortisone, melatonin, vasopressin), food sources (caffeine, theophylline, niacin, cholecalciferol), illicit drug consumption (e.g., morphine, cocaine), widespread abuse (e.g., ethanol, nicotine), or domestic animal use (e.g., ivermectin). Occurrence data for these few APIs may therefore not reflect human excretion from ultimate therapeutic use.

The published occurrence data (both positive and negative) were organized into three somewhat subjective groups (see summaries below): APIs with: (1) abundant occurrence data, (2) limited data, and (3) paucity of data. These data can include non-detects (data of absence). The compiled data emphasized API occurrence in STPs and surface waters, while attempting to exclude data from locations possibly biased with contributions from hospitals or other healthcare facilities, manufacturing facilities, and confined animal feeding operations (CAFOs). No attempt was made to convert and standardize the reported units of concentration, such as ng/mL versus μg/L, or between ng/g, μg/kg, and mg/kg. The published literature was searched up through 8 May 2014 using the bibliographic database of Daughton and Scuderi (2014).

2.5. Three groups of API occurrence data

2.5.1. Abundant occurrence data

API is frequently detected in a wide range of matrices; levels reported by isolated studies are infrequently appreciable (greater than 1 μg/L or 1 mg/kg) but can also be low — probably a function of the quantity of drug locally prescribed or consumed. Numerous additional supporting references exist beyond the few examples cited in Supplemental Tables S-1 and S-2, which were selected primarily from the more recent literature. Asterisks in the column "Reported occurrence data" denote that published occurrence data supports an API's presence at substantial levels (i.e., levels in STPs exceeding 1 μg/L, or levels in sludges or sediments exceeding 1 mg/kg or 1 μg/g).

2.5.2. Limited occurrence data

API has been much less frequently targeted for monitoring and usually only in a limited number of matrices (primarily limited to STP wastewaters — raw influent or treated effluent). In contrast to the references cited for the "Abundant occurrence data" group, the references cited for "Limited occurrence data" are comprehensive, representing all that could be located in the published literature.

2.5.3. Paucity of occurrence data

A paucity of data does not imply that occurrence levels are low or below LODs, but rather that there have been at most very few studies that have targeted the API for monitoring (or multiple studies might exist but they are from the same authors); one or two isolated studies might report comparatively low or high levels but no sense of representativeness can be gained. With the exception sometimes of isolated reports, essentially no published occurrence data could be located (including data of absence). The cited references represent a comprehensive examination of the published literature. Many of these APIs are possibly Matthew Effect Orphaned Chemicals (MEOCs) (Daughton, 2014), and may therefore deserve attention as targets for future monitoring efforts.

2.6. Limitations to data — factors influencing environmental occurrence and its measurement

There are numerous complexities and limitations in interpreting the environmental occurrence data for APIs. Although these are important to understand, this section can be skipped by the reader without compromising an understanding of the subsequent sections.

Many of the higher API occurrence levels captured in Tables S-1 and S-2 were isolated reports and may have been erroneous or isolated excursions; for those in the group with abundance of data, there may have been additional data that could have further raised the maximum levels compiled in the tables. Note that an abundance of data does not necessarily correlate with widespread geographic occurrence, as very low levels (e.g., fluvoxamine) or non-detection (data of absence) is also often reported (e.g., cyclophosphamide). Other APIs may frequently have both data of absence and data of occurrence (examples include lorazepam and omeprazole).

Some APIs may be frequently detected (and at higher levels) in STP influent but not effluent (e.g., cortisone) and vice-versa. Apparently higher API levels in STP effluent versus the paired influent (so-called "negative removals") may often result from a variety of mechanisms, including deconjugation (hydrolysis of reversible metabolic conjugates, e.g., ketamine; budesonide). Reversible conjugates essentially serve as "masked" forms of APIs — serving as hidden reservoirs that when hydrolyzed are converted back to the parent form. Failure to account for reversible conjugates in predictive models can yield occurrence data that would point to much lower than actual environmental levels. See Supplemental Table S-3 for a listing of many examples of non-steroidal APIs for which so-called "negative removals" have been reported (such as resulting from hydrolysis of reversible conjugates) and Fig. 1 for the possible role of excretion in determining the environmental loadings of BDDCS Class I versus Class II.

The sewage-mediated deconjugation hypothesis emerged in the late 1990s, but the initial focus was steroids (Desbrow et al., 1998; Panter et al., 1999; Ternes et al., 1999). Many studies have since shown the incidence of higher levels for many APIs and endogenous hormones in STP

effluents versus influents result from deconjugation during sewage transit or treatment (e.g., D'Ascenzo et al., 2003; Kumar et al., 2012; Liu and Kanjo, 2012; Verlicchi et al., 2012); see listing of references providing data for various non-steroidal APIs (Supplemental Table S-3). Other instances of negative removals may result from the release of parent API from suspended fecal materials or flaws in sampling design or higher MQLs for influent than effluent (e.g., Blair et al., 2013; Gao et al., 2012; García-Galán et al., 2012; Snyder et al., 2007; Sui et al., 2011; van der Aa et al., 2011; Zhang et al., 2013).

Of the APIs in BDDCS Class I that have a paucity of environmental occurrence data, a portion may qualify as MEOCs (i.e., they have simply escaped notice), but others may have been actively ignored or overlooked for any of a wide spectrum of reasons. The occurrence data for others may be convoluted because of contributions from multiple sources (e.g., specific APIs originating from two or more related APIs, such as prodrugs). The following briefly summarizes some of these complicating factors.

Some APIs originate from their use as APIs in their own right but also from prodrug APIs. For example, the following APIs can originate as the major active metabolites from their respective prodrugs (shown in parentheses): fluorouracil (capecitabine), meprobamate (carisoprodol), prednisolone (prednisone), and primidone (phenobarbital). Some can also originate as metabolites from APIs not specifically designed as prodrugs. For example, clofibric acid is an active metabolite shared among multiple fibrate prodrugs; temazepam is also a metabolite of diazepam, and itself also yields the API oxazepam as a metabolite; nortriptyline is also the active metabolite of amitriptyline; nortilidine is also the active metabolite of tilitdine; oxymorphone is also the active metabolite of oxycodone; desalkylflurazepam is the major active metabolite of flurazepam and quazepam; and desipramine is the major active metabolite of imipramine.

Others yield related APIs as metabolic products (e.g., hydroxyzine yields the metabolite cetirizine). Still others are inactive themselves, serving as prodrugs for their active metabolites; as examples, the following APIs serve as the inactive prodrug esters of their respective APIs (shown in parentheses): benazepril (benazeprilat), bopindolol (pindolol), capecitabine (5-fluorouracil), cilazapril (cilazaprilat), enalapril (enalaprilat), imidapril (imidaprilat), olmesartan medoxomil (olmesartan), oseltamivir (oseltamivir carboxylate), perindopril (perindoprilat), ramipril (ramiprilat), temocapril (temocaprilat), valacyclovir (acyclovir), and valganciclovir (ganciclovir). For inactive APIs such as these, monitoring for the prodrug active metabolites would often be more useful than monitoring for the prodrugs themselves.

Although some of the APIs subject of this examination may be extensively excreted unchanged — and occur widely and frequently — their measured levels are very low (some below method detection limits, such as norgestimate) because of high potency and therefore low doses and low manufactured quantities (e.g., norethindrone, norgestrel). Some of these APIs have not been approved for use, have restricted use, or have been withdrawn from the market in some countries (e.g., benidipine, buflomedil, cerivastatin, chloral hydrate, chlordiazepoxide, dezocine, dilevalol, mianserin, rosiglitazone maleate, sibutramine, temocapril, tropisetron, urapidil, vorozole), perhaps explaining why they have not been targeted for monitoring; others are approved only for veterinary use in certain countries (e.g., phenylbutazone; promazine) or are no longer manufactured (e.g., molindone). Note, however, that even though some drugs have been removed from the market, they may still experience use. The widespread use of sibutramine in illicit supplements (Phattanawasin et al., 2012) serves as one example of how a withdrawn API could still make its way to the environment; hundreds of nutritional supplements are known to have undeclared additives comprising known pharmaceuticals and unregistered analogs (Cohen, 2014; USFDA, 2014).

Many APIs have limited occurrence data. Some of these are enantiopure APIs, including those that are eutomers (the enantiomer that possesses the desired pharmacologic effect); these stereoisomers are constituents of their corresponding racemic drugs (which comprise enantiomers in equal quantities). For example, the following APIs are enantiopure eutomers of the racemic APIs listed in parentheses: escitalopram (citalopram), esomeprazole (omeprazole), eszopiclone (zopiclone), and levonorgestrel (norgestrel); the enantiomer lacking the desired pharmacologic activity (distomer) might be ignored in environmental monitoring, even though it may be responsible for adverse effects. Monitoring data may exist for the racemic API but not the eutomer — or vice-versa; this may simply be a consequence of challenges posed by chiral analysis of complex matrices. Other APIs are enantiomers (but not necessarily eutomers), for example: dexmethylphenidate (methylphenidate), levobupivacaine (bupivacaine), dilevalol (labetalol); the racemic forms may have been targeted in environmental monitoring but not their enantiomeric constituents. Enantiomers can add a level of complexity in searching for published API occurrence data.

Lack of occurrence data for some APIs may be a consequence of inadequate analytical methodologies, such as excessively high method detection limits (e.g., 5-fluorouracil; valproic acid). Another factor that can affect measured levels is the great natural variability associated with sampling and variability in stream composition — especially sewage (Ort et al., 2010; Ort et al., 2014; Writer et al., 2013). This problem is magnified by the variabilities associated with STP design, which impacts efficiency and which, in turn, is modulated by microbial activity as affected by weather.

Other factors, which contribute to a dearth of occurrence data, include the following: chemical instability or suspected short environmental half-life (e.g., carbidopa, chlordiazepoxide, cisplatin, cyclobenzaprine, esmolol, isosorbide, nitroglycerin); natural variability and error associated with sampling (Writer et al., 2013); or simply the bona fide absence from the targeted matrix, such as via preferential partitioning to solids (e.g., suspended particulates, sludge, sediments, biofilms) thereby reducing their presence in a targeted dissolved phase (e.g., clemastine, clindamycin, minocycline, paroxetine, tamoxifen). Some matrices (such as sludge and sediments) are examined much less frequently than aqueous samples. This may negatively bias the occurrence data for those APIs that partition extensively to solids. Some APIs are polypeptides and might therefore be expected to become denatured (e.g., exenatide, goserelin, leuprolide, liraglutide, nafarelin, octreotide, pramlintide) and therefore are purposefully omitted from targeting, or they may pose analytical challenges (e.g., cyclobenzaprine), especially in particular matrices (e.g., 5-fluororacil). Some APIs have experienced dramatic declines in their usage, often because of widespread reported adverse reactions (e.g., thioridazine) or sometimes because of widespread controversy (e.g., thiopental). Some are natural products or endogenous biochemicals whose monitoring may not reflect exclusively the usage of medications (e.g., chloramphenicol, colchicine, dihydroquinidine, ergonovine, ergotamine, galantamine, levodopa, reserpine, scopolamine, vinblastine, vincristine). The data for some pharmaceutical APIs may be convoluted with contributions from illegal drug use (e.g., chloramphenicol in aquaculture; abusive use of flunitrazepam; sibutramine as an undeclared additive to diet aids).

The occurrence and levels of an API can be highly influenced by its primary or exclusive method of administration. For example, drugs that are intended exclusively for topical administration (including transdermal) can essentially be released to the environment in nearly stoichiometric quantities during bathing (Daughton and Ruhoy, 2009). Examples from BDDCS Class I include: betamethasone (and dexamethasone), bimatoprost, cortisone, hydrocortisone, imiquimod, lidocaine, minoxidil, rotigotine, and triamcinolone. For these APIs, pharmacokinetics may not be a determining factor in their release to the environment. One ramification is that an API for exclusive topical usage (depending on its rate of dermal absorption) might enter the environment in much greater quantities than an oral API — even one that is highly excreted. APIs that experience high topical usage might make high-probability targets for future monitoring.

Occurrence levels might also be elevated for some APIs even if they undergo extensive metabolism. This can occur for medications that have a higher propensity to accumulate unused (for example, those with poor patient compliance or adherence, such as resulting from adverse reactions or use in treatment of conditions that do not display overt symptoms) and later are disposed to sewers (Daughton, 2010a). Disposal to sewers may be a factor that could account for excursions or isolated reports of sporadically high levels in wastewaters.

Much published data on environmental occurrence results not from formal environmental monitoring activities designed with sampling plans, but rather from research designed to verify new analytical methodologies; the major objective of these studies is to demonstrate the utility of new analytical methods — generally by acquiring analytical figures of merit using isolated, unrepresentative samples (e.g., grab samples) collected from various environmental matrices. Monitoring data from multiple studies for a given API (or multiple APIs) usually cannot be directly compared because of the countless variables that impact sampling and analysis, including the use of disparate and non-standard methodologies, and even the effort that may or may not have been devoted to verifying molecular identity (e.g., via acquisition of accurate mass and the use of certified standards). No attempt was made in this assessment to distinguish a study or provide weighting to a study according to any number of possible criteria, including the number of samples collected, the sampling or analytical methodology or quality assurance (especially including the verification of analyte identification), or geographic location, which may play a major role in dictating the types and quantities of drugs consumed (e.g., as a result of contributions from medical facilities, CAFOs, or manufacturing, or as a result of prescribing customs, or season of year, which influences the usage of certain medications); some drugs are used almost exclusively at hospitals (e.g., ifosfamide, methohexital) or predominantly at CAFOs and therefore have limited geographic reach.

Finally, occurrence data can vary dramatically as a function of numerous factors associated with geography and governing boundaries, including gross differences in seasons (e.g., solar irradiance and temperature, which modify both biological and physical processes that act upon APIs, and seasonal distribution and incidence of diseases, which affects the types and doses of APIs prescribed). Many medications are not approved for use in all countries, and particular drugs may be withdrawn from markets in some countries but not others. Certain APIs may be readily available OTC in some countries but only via prescription in others. Likewise, the types and relative quantities of APIs can vary dramatically across geographic locales as a function of prescribing preferences, customs, and fads, as well as consumer preferences, beliefs, and behaviors (such as compliance and adherence, or drug popularity as influenced by consumer advertising). Recommended daily dose (which largely reflects potency and bioavailability) can vary among countries and often serves only as a guide to physicians. The age structures of populations also dictate the distribution and quantities of the types of APIs prescribed (with the incidence of polypharmacy increasing with age). All of these factors can introduce large geographic discrepancies in relative usage patterns and amounts, and thereby muddy the comparison of occurrence data across locales, regions, or countries — especially when the occurrence data are generated by disparate studies using different sampling and analytical methodologies.

3. Results and conclusions

The environmental occurrence data for the APIs in the two selected groups (BDDCS Class I and Class IV) as presented by Benet et al. (2011) are compiled in Supplemental Tables S-1 and S-2, respectively. These data are further organized into three somewhat subjective groups (as described in Approach) according to whether the availability of positive or negative occurrence data in the literature is Abundant, Limited, or scarce (Paucity of data). The APIs in each of these three groups for which occurrence data exceeded a threshold level of 1 μg/L (or 1 mg/kg) — as compiled in Supplemental Tables S-1 and S-2 — are summarized in Table 1 (for BDDCS Class I APIs) and Table 2 (for BDDCS Class IV APIs).

3.1. Occurrence data from Table 1 (BDDCS Class I)

The following summarizes the findings for each of the three groups of APIs (a total of 322) with respect to positive occurrence data:

Abundant occurrence data: A total of 57 APIs (18%) were in this group (Supplemental Table S-1). Of these APIs, there were 27 (47%) with data pointing to a routine occurrence exceeding 1 μg/L. And of these, only 8 (14%) had data pointing to a routine occurrence exceeding 5 μg/L or 1 mg/kg.
Limited occurrence data: A total of 41 APIs (13%) were in this group (Supplemental Table S-1). Of these APIs, there were 5 (12%) with data pointing to a routine occurrence exceeding 1 μg/L; these same five also had data pointing to a routine occurrence exceeding 5 μg/L. No study was located that reported an API level that exceeded 32.2 μg/L (i.e., for escitalopram) or 1 mg/kg (i.e., for zopiclone).
Paucity of occurrence data: A total of 224 APIs (69%) were in this group (Supplemental Table S-1). Of these APIs, there were 11 (5%) with but a few data pointing to the possibility of occurrence exceeding 1 μg/L. And of these, 8 (4%) had data pointing to the possibility of occurrence exceeding 5 μg/L or 1 mg/kg. No study was located that reported an API level that exceeded 15.4 μg/L (i.e., for indapamide) or 9.3 mg/kg (i.e., for valproic acid).

The number of APIs for which no data were available (not yet targeted in any study) totaled 176 (79% of the 224); the 224 APIs in the Paucity of data group could each be examined for whether it might be a Matthew Effect Orphaned Chemical — MEOC (as explained in Daughton, 2014). Note that for the 53 highly prescribed APIs that were first reported as possible MEOCs (Daughton, 2014), only 18 are also captured among these 224 APIs in BDDCS Class I: benazepril, carbidopa, colchicine, cyclobenzaprine, doxazosin, formoterol, hydralazine, hydroxychloroquine, isosorbide, nitroglycerin, olmesartan medoxomil, ondansetron, oxybutynin, ropinirole, sumatriptan, tamsulosin, terazosin, and valacyclovir. This means that 206 [224 minus 18] of the APIs captured in the Paucity of data group represent potentially new MEOCs. At the least, these APIs for which occurrence data do not exist could serve as targets for new monitoring studies.

3.2. Occurrence data from Table 2 (BDDCS Class IV)

The following summarizes the findings for each of the three groups of APIs (a total of 52) with respect to positive occurrence data:

Abundant occurrence data: A total of 13 APIs (25%) were in this group (Supplemental Table S-2). Of these APIs, the data for 10 (19%) pointed to a routine occurrence exceeding 1 μg/L or 1 mg/kg. Of these, only 5 (10%) had data pointing to occurrence exceeding 5 μg/L or 5 mg/kg. Ten of these APIs were antibiotics, and many of these preferentially partitioned to solids.
Limited occurrence data: A total of 8 APIs (15%) were in this group (Supplemental Table S-2). Of these APIs, there were 4 (8%) with data pointing to a routine occurrence exceeding 1 μg/L; of these four, 3 had levels exceeding 5 μg/L or 5 mg/kg. No study was located that reported an API level that exceeded 8.9 μg/L (i.e., for chlorothiazide) or 20.1 μg/kg (i.e., for chlorthalidone).
Paucity of occurrence data: A total of 31 APIs (60%) were in this group (Supplemental Table S-2). None had data pointing to the possibility of occurrence exceeding 1 μg/L.

The number of APIs for which no data were available (not yet targeted in any study) totaled 22 (71% of 31); most of the remainder had data from only one or two studies. The 31 APIs in the Paucity of data group could each be examined for whether it might be a MEOC.

Note that for the 53 highly prescribed APIs that were first reported as possible MEOCs (Daughton, 2014), only 3 are also captured among these 31 APIs in BDDCS Class IV: cefdinir, phenazopyridine, and nitrofurantoin (chlorthalidone is listed under Limited data in the study here). This means that 28 of the APIs captured in the Paucity of data group represent potential new MEOCs. At the least, these APIs for which occurrence data do not exist could serve as targets for new monitoring studies.

3.3. Overall comparison of occurrence data from BDDCS Class I and Class IV

For this study, BDDCS Class I and Class IV comprised very disparate numbers of APIs: 322 for Class I and 52 for Class IV; this discrepancy was discussed earlier in Section 2.1 (Proxy measure for API excretion: the BDDCS). Even so, one obvious commonality between the two classes is the large number of APIs for which no occurrence data were available (i.e., those having not yet been targeted in any published study). These numbers totaled 176 of 322 (55%) for Class I — and 22 of 52 (42%) for Class IV. So there were no occurrence data available (as of 8 May 2014) for roughly half of all the APIs subject to this examination.

The number of APIs with data pointing to elevated levels were 41 (13%) of the total number in Class I — or 41 of the 108 total (38%) having data. The number of APIs with data pointing to elevated levels were 14 (27%) of the total number in Class IV — or 14 of the 21 total (67%) having data. This weight of evidence points to a possible trend of higher incidence of elevated levels among BDDCS Class IV APIs; a disproportionate number of these data, however, derived from antibiotics that partition to solids. Of the APIs in the Abundant and limited data groups having the highest levels in solids, six were Class IV APIs (ciprofloxacin, erythromycin stearate, fleroxacin, norfloxacin, roxithromycin, and valsartan, with maximum levels ranging from 1 to 5.6 mg/kg), while only two were Class I (minocycline and zopiclone, with a maximum level of 1 mg/kg); these levels are roughly 3 orders of magnitude higher than the highest levels reported for aqueous samples (probably because of the surface-concentration effected by sorption and because levels in solids are often reported on a dry-weight basis). Higher occurrence levels for Class IV drugs would be expected not just by their poor metabolism but also by the need to administer higher doses (less potency), which leads to greater direct excretion (poor absorption).

The elevated levels among certain Class I APIs could be caused by any number of reasons, including the following: exceptionally high usage rates (e.g., several of these APIs are among the more highly prescribed drugs: diclofenac, diltiazem, metoprolol, propranolol); direct disposal to sewers (including consumers and hospitals, where unit-dose packaged injectables are frequently sent to sewers — a common practice, for example, with hydromorphone); substantial contributions from hospitals/healthcare facilities (e.g., ifosfamide); CAFOs (many antibiotics); possible illegal agricultural usage (e.g., chloramphenicol); abuse or recreational use (e.g., flunitrazepam, hydroxyzine, methadone, methylphenidate, oxycodone); exceptional environmental half-lives (e.g., clofibric acid); bias from time of day or season of sample collection (e.g., oseltamivir); geographic distribution of disease (e.g., zidovudine); and pharmacokinetics characterized by extensive metabolism but coupled with extensive excretion of reversible conjugates (e.g., zidovudine).

The data can also be examined from the other end of the spectrum — APIs with data of absence (negative data). Among the Class I APIs that have been targeted by monitoring, it is readily evident that at least 27 (8%) only have data reflecting very low levels (ng/L) or were not detectable: alprenolol, ambroxol, betaxolol, bromocriptine, cilazapril, clemastine, clomipramine, dexamethasone, dextromethorphan, doxazosin, duloxetine, fentanyl, finasteride, fluorouracil, fluvoxamine, ifosfamide, irinotecan, maprotiline, methylphenidate, midazolam, norgestimate, prochlorperazine, ribavirin, triamcinolone acetonide, triamcinolone, and vinorelbine. Of course, trends establishing data of absence can only be strengthened with additional targeted monitoring data; such data can be made more compelling but never be claimed as certain.

Likewise, among the Class IV APIs that have been targeted by monitoring, only about 5 (10%) have data supporting very low levels (ng/L) or were not detectable: cefdinir, iopanoic acid, medroxyprogesterone acetate, megestrol acetate, and meropenem. Furthermore, many of the Class I APIs in the Abundance group are frequently reported with mixed or conflicting findings (e.g., low levels or only sporadically at appreciable levels; bromazepam and secobarbital are but two examples). In contrast, all of the Class IV APIs in the Abundance group were frequently and consistently reported at appreciable or substantial levels. Since Class IV APIs may have the higher probability of elevated occurrence levels, they might serve as the more likely targets for future monitoring — especially those that are possible MEOCs.

APIs with compelling data of absence have significant implications with respect to medical prescribing. The loadings of these APIs in the environment would possibly be influenced the least as a result of ultimate use by patients. This points to the importance of diligence in the reporting of negative occurrence data for APIs from environmental monitoring (Daughton, 2014). APIs with abundant data of absence have the potential for the lowest environmental footprints (assuming direct disposal to sewers is avoided and bioactive metabolites are not a concern).

The weight of evidence (including the absence of evidence) that was revealed in this examination of environmental occurrence data tends to support the possible utility of using the BDDCS as a means of quickly informing medical practitioners as to the potential for environmental impact of an API. A more in-depth study would be needed to strengthen the trends that seemed to emerge — namely BDDCS Class I APIs being associated with reduced environmental presence compared with Class IV APIs. Additional APIs would need to be evaluated from both classes with respect to environmental occurrence. Yet more and ongoing literature searching is required for the substantial numbers of APIs that lack data. Alternatively, decisions should be made with respect to the possible MEOCs as to whether their targeted monitoring might be warranted. Additionally, consideration should be given to an analogous examination of BDDCS Class II APIs and Class III APIs (which are also poorly metabolized, like Class IV) to see if there are correlations regarding their environmental occurrence.

4. Future directions

An improved ability to predict the types and quantities of APIs that have the potential to enter the environment would certainly help guide the targeting of APIs to monitor in the environment. Access to real-time, geographic usage data is the major limitation to quantifying the scope (types, amounts, and locations) of API sources (Daughton, 2013). Comprehensive commercial informatics services are available in some countries. These databases compile detailed data on prescription sales, dispensing, and demographics, but access is often fee-based, which usually precludes their utility for modeling and predictive purposes. Even then, it is unknown what portions of dispensed drugs are ultimately used versus those that may be indefinitely stockpiled or disposed by end-users. Furthermore, the temporal delay between times of dispensing and ultimate use can range into the years. Disparities in spatial disconnects between the location of prescription sale and the geographic locale where the drug is ultimately used (due to population mobility) further complicates modeling; unknown portions of certain drugs are ultimately used in regions or countries where they were not originally dispensed, and a certain portion of some drugs that are legally dispensed only by prescription are widely purchased illegally. These and many other problems that impinge on the utility of modeling for predicting levels of APIs in the environment have been discussed (Daughton, 2013). Empirical monitoring data are critical for revealing which APIs to target for pollution prevention efforts and

for verifying the effectiveness of any prevention, control, or mitigation measures that have been implemented.

Pollution prevention approaches for reducing the entry of APIs to the environment must accommodate the interconnected whole — with the environment and patients essentially being treated as a single, integral system. Measures that might be protective for one may pose risks for the other. These tradeoffs require balancing — while at the same time ensuring that any alterations to the administration or practice of healthcare do not jeopardize human health or reduce economic efficiency. Ensuring an evidence-based approach for drug and dose selection is critical. An integrated approach will eventually require collaboration between environmental scientists and healthcare professionals — two groups that have historically never communicated; it also will require cooperation among disparate federal and state agencies involved with protection of the environment, administration of medical care, and regulation of medication sales and disposal (especially controlled substances).

EDSP marks the first time that API pharmacokinetics (using the BDDCS as a ready proxy) has been examined as a factor that could be used to guide decisions involving prescribing, dispensing, and end-use of drugs for the purpose of minimizing environmental impact. Changing the prescribing behavior of physicians would certainly be a major challenge. EDSP would represent the very first attempt at providing prescribers, dispensers, and users (patients) with pollution prevention information to consider in their selection of medications or dosages. The proposed approach would represent the first of undoubtedly multiple future steps required for changing behavior. At the least, the EDSP concept would serve to raise awareness that while excretion may represent the major source of most APIs in the environment, these levels can nonetheless be actively reduced — with no added infrastructure costs (such as entailed with improved wastewater treatment). The EDSP could mesh well with the emerging clinical movement of "conservative prescribing" (Schiff et al., 2011).

The proposed EDSP approach could be made even more effective with the eventual widespread implementation of personalized medicine ("precision" medicine), which is being accelerated with advances in pharmacogenomics. Not until the last couple of years had consideration been given to tailoring medications to patients with the intention of lowering the excretion of parent APIs or bioactive metabolites (see: Daughton and Ruhoy, 2011). By appropriate evaluation of the PK characteristics (absorption, distribution, metabolism, and excretion) for a particular API, better-informed decisions could be made regarding those APIs in a specific therapeutic class having less potential for environmental impact via excretion. For example, prescribing certain APIs could be avoided or reduced for individuals having non-optimal metabolism (e.g., heightened excretion of the API), for those taking other medications that inhibit the absorption or metabolism of the API, or for those who are simply poor therapeutic responders.

Excretion profiles would be useful not just for guiding the selection of drugs for prescribing but could also prove very useful for guiding decisions regarding whether a particular API could be prudently disposed to sewers. Excretion profiles could be used to assess the potential for whether the disposal of a particular drug would contribute significantly to the API's overall environmental loading. For example, some APIs are extensively excreted unchanged. For these APIs, disposal to sewers might add only small incremental portions to the already comparatively high ambient environmental levels continually contributed by excretion. In contrast, for those APIs that are extensively metabolized (little API is excreted unchanged or as reversible conjugates), sewer disposal holds the potential for contributing significant portions to ambient levels. This aspect of drug disposal has been under-recognized, especially in the formulation of regulations and guidance aimed at curbing sewer disposal. Despite the growing focus in the US on end-of-pipe pollution control programs for collecting leftover, unwanted drugs (and shunning their disposal to sewers), sewer disposal may well be the best option for the disposal of certain drugs (i.e., those excreted unchanged). This is especially true for those APIs with high acute toxicity (i.e., those with single-dose lethality) and those subject to diversion and abuse (certain synthetic opiates are but one example). Failure to immediately dispose or secure these leftover drugs (and associated delivery devices, such as used transdermal patches) is a documented cause of deaths in infants and young children (Daughton, 2010a; Daughton and Ruhoy, 2009); this has been a concern of the FDA regarding guidance for the sewer disposal of certain medications (USFDA, 2009). For those highly hazardous drugs that are extensively excreted unchanged, disposal of leftovers to sewers might continue to be the best means of preventing fatal poisonings. Furthermore, if sewer-disposal of a highly hazardous drug contributes only a small portion of the overall environmental burden of its API, then disposal may prove to have only nominal added impact on the aquatic environment.

The EDSP concept would need to be translated into clinical practice. Currently, the medical community receives little exposure to information regarding the environmental impact of their professions; environmental impact is not routinely incorporated in medical training. In the US, expertise in outreach medical education for translation, dissemination, and implementation resides at the AHRQ Effective Health Care Program (http://www.effectivehealthcare.ahrq.gov/), which operates under the HHS Agency for Healthcare Research and Quality (AHRQ). The AHRQ is the "lead Federal agency charged with improving the quality, safety, efficiency, and effectiveness of health care for all Americans", primarily through evidence-based decision making. The AHRQ has a number of mechanisms for communicating with doctors: spanning the spectrum from on-line continuing education to one-on-one in-office outreach visits with physicians (via the National Resource Center for Academic Detailing, NaRCAD: http://www.narcad.org/). One of few examples of pollution prevention being considered for reducing drug waste was the recognition by the pharmacy community for the need to develop actions to reduce the incidence of leftover drugs rather than focus on waste disposal, as formally proposed in 2009 by the National Association of Boards of Pharmacy: "Recommendation 3: Work with Appropriate Entities to Research Methods that Reduce the Amount of Unused Medications" (NABP, 2009).

A major objective of the work reported here is to foster increased recognition of the potential role for pollution prevention rather than pollution mitigation — particularly for reducing the many actions and behaviors in the healthcare communities that lead to the unnecessary and imprudent use of medications and generation and accumulation of avoidable drug waste. Prevention continues to remain an unused approach for dealing with the dual problems of drug waste and excreted residues and their resulting impacts on both human and environmental health.

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